DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
139th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 6-7, 2006

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

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BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 139th regular meeting on Wednesday, September 6, 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, September 6, 2006, from 8:30 a.m. to 4:30 p.m. The meeting was closed to the public from 4:30 p.m. until adjournment at 5:30 p.m. The meeting was open to the public on Thursday, September 7, from 8:00 a.m. until adjournment at 12:00 noon. NCAB Chair Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members

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

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. Allen Dearry, NIEHS
Ms. Diane Jones, OSTP (absent)
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. T. G. Patel, VHA
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Anita Schill, NIOSH (absent)
Dr. Donald Wright, OSHA

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Ms. Nelvis Castro, Acting 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. Carolyn Aldige, National Coalition for Cancer Research
Dr. Eve I. Barak, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Nancy Riese Daly, American Society of Clinical Oncology
Ms. Georgia Decker, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Mr. John Huber, American Urologic Association
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Ms. Alexine Clement Jackson, Intercultural Cancer Council
Dr. W. Marston Linehan, Society of Urologic Oncology
Ms. Jennifer Padberg, American Society of Therapeutic Radiology and Oncology
Ms. Christy Schmidt, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Mr. Douglas Ulman, National Cancer Institute, Director's Consumer Liaison Group
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists

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THURSDAY, SEPTEMBER 7, 2006

WEDNESDAY, SEPTEMBER 6, 2006

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 139th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, staff, and guests. New members to the Board were introduced. They are: Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, and Professor and Chairman, Department of Urology, Wake Forest University School of Medicine; Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center; Dr. Donald Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Johns Hopkins University School of Medicine; Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated; Dr. Judah Folkman, Director, Vascular Biology Program, Children's Hospital of Boston, and Julia Dyckman Andrus Professor of Pediatric Surgery and Professor of Cell Biology, Harvard Medical School; Mr. Robert Ingram, Vice Chairman, Pharmaceuticals, GlaxoSmithKline; and Dr. Karen Meneses, Professor, School of Nursing, and Beat M. and Jill L. Kahli Endowed Chair in Oncology, University of Central Florida. Dr. Runowicz called attention to a recent *Wall Street Journal* article entitled "Patients with Rare Diseases Work to Jump Start Research," which chronicled the work of NCAB member Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc. 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.

Motion. A motion was made to approve the minutes of the June 14, 2006, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

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

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

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

Dr. John Niederhuber announced the official appointment of Dr. Runowicz as Chairperson of the NCAB, and he extended congratulations. He welcomed the new NCAB members who had been introduced earlier by Dr. Runowicz and expressed satisfaction that the group of knowledgeable and dedicated individuals nominated by the NCI had been selected to join the other sitting members in providing advice and leadership to the NCI.

Honors and Appointments. Dr. Niederhuber announced the most recent honors accorded NCI staff and appointments within the NCI. Drs. John T. Schiller and Douglas Lowy, Laboratory of Cellular Oncology, Center for Cancer Research (CCR), received the Department of Health and Human Services (DHHS) Honor Award for research on the human papillomavirus. Dr. Norman Coleman, Radiation Oncology Branch, CCR, and Dr. Lee J. Helman, Pediatric Oncology Branch, CCR, received the DHHS Honor Award for contributions to NCI's Katrina Relief Team. Dr. Dan Gallahan was appointed Deputy Director, Division of Cancer Biology, and Dr. Lenora Johnson was appointed Acting Director, Office of Liaison Activities.

Fourth Quarter Budget Update. Dr. Niederhuber reported that the NCI in this final quarter is making final adjustments in its allocation of the Fiscal Year (FY) 2006 budget, moving unused resources to areas where it was hoped earlier that additional funding could be provided. He noted that the NCI received a mid-year increase in taps of almost $4 M for direct utility costs to the NIH. In regard to the status of other budget lines, he reported that the Research Project Grant (RPG) payline is running about the 11th percentile, with 15 percent of the competing pool in reserve for exceptions; Type 5 grants have been funded at about 2.35 percent below the commitment of record in accord with the NIH-wide policy; funding for the Special Programs of Research Excellence (SPOREs) has been about 2 percent below the FY 2005 commitment; funding for the Cancer Centers has been essentially flat with FY 2005 with the exception that some additional money was identified and applied in a graded scale to the six Centers that were reviewed this year; and funding for training is 1 percent above the FY 2005 level. At its June 26, 2006, meeting, the NCI Executive Committee (EC) decided that sufficient resources were available to raise the payline for R01 grants to the 12th percentile and for *R01s (the new investigator mechanism) to the 18th percentile. The total of additional funds committed was $8.3 M.

Budget Planning for FY 2007. Next, Dr. Niederhuber reviewed the process by which leadership of the NCI is coming together to evaluate programs with an eye toward reduced or flat budgets for the foreseeable future. At a June 7-8, 2006, EC retreat, Division Directors presented and discussed each scientific program in their research portfolios to provide a background for future funding decisions. Dr. Niederhuber noted that the exercise produced a better understanding of what each Division was doing and planning and how collaborations could be effected across Divisions for a trans-NCI approach for the efforts. As part of the process, each Director was asked to rank each program by anonymous ballot as to whether the program should be reduced, maintained, or expanded. A prearranged scoring mechanism was used as a guide. In an ongoing process through early November, the information gained from the tabulated results of the balloting is being addressed in repeated meetings to create a prioritization list of scientific programs. Phase 2 of the planning process occurred in August when infrastructure-like programs, many of which are housed within the Office of the Director (OD), were reviewed. In Phase 3 from now until January, all scorings will be revisited multiple times and reprioritized toward a monetary target. Members were informed that both the scientific and infrastructure reviews are being conducted to identify areas where efforts can be consolidated and cost savings realized to ensure that every dollar is counted. Dr. Niederhuber noted that the RPG pool could come under similar scrutiny in the future as part of an ongoing process throughout the NIH.

To explain the current budget pressures, Dr. Niederhuber reviewed the pattern of NCI's Congressional appropriations from FY 1998 to the projection for FY 2007. Members were reminded that the significant increase in the budget from 1998 to 2003 (NIH doubling and NCI 80 percent increase) was followed by appropriate increases in 2003 and 2004 and essentially flat budgets since then. Dr. Niederhuber pointed out that, because of the higher inflation index for biomedical research, flat budgets represent an actual 3 to 5.5 percent decrease (about $150 M) in the operating budgets for those years. Projections are that a similar or greater decrease in the operating budget could become a reality in FY 2007. Strategies to address the situation that were developed in working with colleagues across the NIH include keeping the number of competing awards (about 1,280 for the NCI) and the average dollar amount per award at the same level as the previous year. Members were reminded that appropriations bills for Labor/DHHS have been passed in both the House and Senate Subcommittees, but neither bill has come up for a vote by the full House or Senate. A vote in either house is unlikely before the November elections; therefore, the NCI will be operating on a continuing resolution after October 1 at about 80 percent of the FY 2006 level.

Dr. Niederhuber reviewed the status of the FY 2007 appropriations bill. The House version, which is essentially equal to the President's Budget, allocates $4.754 B for the NCI, $40 M less than the

FY 2006 budget. In the Senate, the Appropriations Subcommittee added $200 M to the NIH request and specifies $4.799 for the NCI, $9 M more than the FY 2006 budget.

Roadmap Trans-NIH Strategic Initiative Drive. Dr. Niederhuber reported that Dr. Elias Zerhouni, Director, NIH, and NIH leadership have begun planning for a new cohort of Roadmap initiatives to begin in FY 2008. He explained that the Roadmap fund comprises about 1.7 percent of the FY 2008 budget across the NIH, and that an agreement has been reached that growth of the fund would not exceed 1 to 1.1 percent of the NIH budget as long as flat or negative budgets continue to be enacted. In Phase 2 of the planning process, which occurred during July and August, five consultation meetings were held to solicit ideas for initiatives from the extramural community. The goal at these meetings was to identify scientific priorities that would be enabling for biomedical research across diseases. During August, ideas for initiatives were also solicited from Institute and Center (IC) Directors and program officers in the OD, NIH. In Phase 3 of the process, the identified initiatives will be brought to the larger stakeholder community via a Web-based Request for Information (RFI) to be released in October. The process of reviewing and prioritizing the proposed initiatives will continue through fall, and Dr. Zerhouni will select up to five to be developed into concepts in December. Roadmap development teams will than conduct pre-RFA activities to produce initiative-focused science and business plan packages between January and May 2007. A final review of the proposed initiatives will be conducted in May by IC Directors and the Advisory Council to the NIH Director, with final selections to be made by Dr. Zerhouni, also in May.

Oncology Biomarkers Qualification Initiative (OBQI). Dr. Niederhuber presented an update on the OBQI, which began in February 2006 and was developed collaboratively by the NCI, Food and Drug Administration (FDA), and Center for Medicare and Medicaid Services (CMS). NCI's contribution to the initiative is to develop biomarker technologies and validation protocols to improve detection, diagnosis, treatment, and prevention of cancer. The FDA responsibility will be to develop guidance for the use of the biomarkers to facilitate cancer drug development, and the CMS task will be to make informed decisions about reimbursement for new or existing cancer treatment regimens based on biomarker-guided knowledge. Members were reminded that the OBQI was developed to implement the biomarker discovery and development objective of the NCI/FDA Interagency Oncology Task Force (IOTF). The IOTF was established in 2003 to enhance efficiency of clinical research and scientific evaluation of new cancer treatments. Other IOTF objectives were to establish joint training and fellowships, utilize the Cancer Bioinformatics Grid (caBIG™) to support standardized and organized clinical trials data reporting and to support electronic filing to speed regulatory review, and address specific regulatory barriers impeding cancer drug development. The two initial OBQI projects are studies of FDG-positron emission tomography (PET) as a biomarker. The first project is studying the efficacy of FDG-PET as a predictor of tumor response and patient survival in lymphoma; the second is a Phase II study of FDG-PET as a predictive marker of tumor response and patient outcome in non-small cell lung cancer. Dr. Niederhuber noted that the OBQI also represents a first step in the effort to develop a biomarkers consortium that will be a public-private partnership involving the NIH, FDA, CMS, pharmaceutical and biotechnology companies, and the NIH Foundation. The consortium will work through individual projects, and the FDG-PET studies will be the lead projects. An announcement about the consortium is expected in October.

Scientific Updates. Dr. Niederhuber called attention to the recently published advances in immunotherapy made intramurally in the Surgery Branch, CCR, by Dr. Steven Rosenberg, Chief, and colleagues. Gene therapy has been shown to enhance adoptive cell transfer, which, until now, had been shown to mediate a 50 percent objective response only in patients with advanced melanoma and only in those who have a population of tumor reactive lymphocytes. The Rosenberg group has developed a method to transfect T-lymphocytes retrovirally with T-cell receptors that recognize cancer antigens. With

this method, normal human resting peripheral blood lymphocytes can be converted into cells capable of recognizing tumor antigens *in vitro* and capable of mediating cancer regression *in vivo*. This work suggests the therapeutic potential of genetically engineered cells for biologic therapy of cancer. Although the response rate in early-phase trials is lower than in the conventional adoptive cell transfer, the method increases the number of patients eligible for ACT. Further modification of the transfection procedure may produce greater persistence of the modified lymphocytes and thus increase response. Dr. Niederhuber briefly described the procedure and presented the results of early-phase trials in two cohorts of patients. In a cohort of patients with metastatic melanoma, two individuals demonstrated regression of their tumors at more than 18 months after treatment with the engineered T-lymphocytes. Dr. Niederhuber noted that the intramural immunology group is holding a symposium this fall, and more than 1,000 registrations were received shortly after announcement of the event, attesting to the recognition accorded the program and the strength of the intramural program.

Dr. Niederhuber closed by reiterating the common mission and the dedication of the Board and the NCI to making a difference in cancer as a disease in terms of prevention, treatment, and survival. He reminded members of data that demonstrate a sustained slow decline in mortality from this disease despite a rapidly aging population and other factors that would predict otherwise, as well as a recent study indicating that every 1 percent decrease in the mortality of cancer translates to a savings of about $400 B in the U.S. economy. He articulated the belief that the NCI and community of cancer researchers across the country have led advances in biomedical research for the past several decades and must continue to provide such scientific leadership, both intramurally and through the extramural program. Toward that end, he cited trans-NIH initiatives, such as that in angiogenesis, in which the NCI has a lead role for the NIH. In addition, the NCI is working on trans-NCI programs in areas such as the environment and prevention and computational biology.

Questions and Answers

Dr. Runowicz recalled discussions among members as to how the Board can help the NCI in its advisory capacity, in areas such as financing and research direction. Dr. Chabner commended the comprehensive review that has been undertaken by the NCI. He expressed interest in hearing the outcome of the review in terms of programs that are deemed the top priorities with potential for contributing to the future and those that may be left behind or reduced in scope. Dr. Niederhuber gave assurance that the process would continue to be transparent, and he welcomed feedback from all sources, including the scheduled meetings of the advisory boards, the annual joint retreat, visits at the various universities, and discussions with members of the professional societies. Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD) and Dr. Robert Wiltrout, Director, CCR, commented on the rigor and transparency of the intramural review and its value in promoting understanding of the work and resources of the other divisions. Dr. Wiltrout noted also that the review provided an opportunity in this large organization to see where resources can be leveraged within one division for the benefit of another and where trans-NCI activities can be initiated, as well as partnerships within the NCI and with the extramural community. Dr. Niederhuber expressed his intention to have the intramural enterprise serve as a resource to the extramural research community, citing the computational facility on the Frederick campus and the Clinical Center as examples of available and valuable resources.

Dr. Coffey commended the recent presentation to Congress about the financial savings realized from cancer research and the demonstrated reduction in cancer deaths, a savings, he noted, that was equal to more than 100 years of financing for the NCI. He called attention to the Harris Report and the public's perception that there is a 1 in 100 chance of getting cancer, whereas the real odds are 1 in 3. He recommended that all of this information be communicated proactively in defense of the NCI budget. In that regard, Ms. Giusti pointed out that some groups have begun working together to create one voice

against cancer and that more work is needed among the 8,500 or so cancer foundations to be one voice for the purpose of educating philanthropic organizations and the public about cancer issues. She commended the NCI for going beyond the critical funding issues and addressing other obstacles such as access to tissue, how to work with the biotechnology industry to bring their drugs to patients more quickly, and legal issues associated with intellectual property (IP) and getting discoveries into the public domain. She asserted the importance of speaking with a unified voice against all obstacles to drug development and achieving better patient outcomes. Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, OD, affirmed the needs and difficulties identified by Ms. Giusti. She cited her 4 years of work in the biospecimen area and the fact that guidelines for specimen collection and access are becoming a reality only now. She pointed out that science and policy have merged and that scientists have not stepped into that arena to inform policy, so they are facing obstacles such as the need for genetic privacy laws. She expressed the view that advocacy groups are taking a leadership role that will inform and enable science in the future.

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

On behalf of members Dr. Margaret Kripke and Mr. Lance Armstrong, Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel, and Charles R. Drew Professor of Surgery, Howard University College of Medicine, congratulated Drs. Niederhuber and Runowicz on their recent appointments and articulated the Panel's desire to continue to work closely with them. He reported that the Panel has been working since the June meeting to prepare for the upcoming series of meetings entitled "Promoting Healthy Lifestyles to Reduce the Risk of Cancer." This 2006-2007 series of 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 and overweight, lack of physical activity, and an unhealthy diet on cancer risk. Dr. Leffall stated that, in this series, the Panel will be seeking the views of a wide range of invited participants that will include government officials, state and local public health officials, academic and institution representatives and scientists, practitioners, community-based organizations, private industry representatives, advocates, and consumers.

At the first meeting at the University of Minnesota Cancer Center on September 11, 2006, the Panel will explore current research on obesity, physical activity, and nutrition as well as learn about current programs in these areas relevant to reducing the risk of cancer. Areas of particular interest will include: (1) ongoing research and identification of knowledge gaps; (2) the influence of culture, geography, and community structure on lifestyle choices and behaviors; (3) the impact of technology advances on lifestyle and activity levels; (4) economic costs associated with unhealthy lifestyles; and (5) potential policy changes and implementation strategies. Other meetings in the series include another meeting on obesity, physical activity, and nutrition and two meetings on issues related to the impact of tobacco use and environmental tobacco smoke on cancer risk.

Dr. Leffall presented background information related to the 2006-2007 series, noting that new research continues to increase understanding and awareness of the issues created by unhealthy lifestyle choices. Current statistics indicate that this year the percentage of obese adults increased in all states but Nevada. The opportunity to achieve tangible results through research and prevention activities in this area is significant. Some believe that the next biggest threat facing the developed world is the growing epidemic of obesity. According to a 2003 *New England Journal of Medicine* article, current patterns of obesity and overweight conditions in the U.S. population could account for up to 14 percent of all cancer deaths in adult men and 20 percent in adult women. A recent study published by two economists from Emory University revealed that the rate of obesity among Medicare patients doubled from 1987 to 2002 and health care spending on those individuals more than doubled. Other recent studies have added obesity and physical inactivity to the list of factors that increase cancer risk.

Dr. Leffall noted that the health consequences of tobacco use are well known; however, this knowledge has not remedied the problem of widespread tobacco use. Despite declines in smoking rates, according to the Centers for Disease Control and Prevention (CDC), 46.2 million United States adults were current smokers in 2001, the most recent year for which numbers were available. A report issued by the Surgeon General in 2004 stated that tobacco use is responsible for 30 percent of cancer deaths, including 87 percent of lung cancer deaths. Second-hand smoke, also known as environmental tobacco smoke, increases the risk of lung and nasal sinus cancer and is associated with numerous other health conditions. Prevention campaigns aimed at altering lifestyle can achieve success as demonstrated by large-scale campaigns that promote sun screen use to prevent skin cancer. Dr. Leffall stated that the Panel believes that research into factors linking obesity, physical activity, and nutrition, as well as tobacco use and environmental tobacco smoke, to cancer risk can inform future initiatives to prevent such risks. Other 2006-2007 meeting dates and locations are: October 23 in Lexington, KY; December 5 in Portland, OR; and February 12 in Jackson, MS.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response (OPAR), OD, reviewed the status of appropriations for FY 2007. The President's Budget was announced on February 6 and called for $28.6 B for the NIH and $4.70 B for the NCI. The House version of the bill was reported by Committee on June 13, with $28.3 B for the NIH and $4.75 B for the NCI. The Senate version was reported by Committee on July 20, with $28.6 for the NIH and $4.8 for the NCI. Ms. Erickson noted that the Appropriations Subcommittees then wrote their Labor, HHS, and Education appropriations bills (the source of NIH funding) and issued their accompanying reports to express opinions and provide guidance to agencies about programs funded by the appropriations in the bills. The House report language commended the NCI in the areas of the American-Russian Cancer Alliance (ARCA), Cancer Centers program, The Cancer Genome Atlas (TCGA), and the Community Cancer Centers program. The House report also encouraged the NCI to: (1) support translational research in the area of gynecological cancers; (2) coordinate the federal effort in lung cancer with other agencies, including the CDC, CMS, FDA, and Department of Defense; (3) add a minority institution to the Cancer Centers program; and (4) provide support for a HALT-C clinical trial in lung cancer. Areas in the House report language in which specific recommendations or concerns were expressed include gynecologic cancer, the SPOREs program, and strategic plans. In the first area, the NCI was asked to include a gynecologic cancer in the pilot program for TCGA. In the second, the NCI was encouraged to fund the SPORE program at the FY 2004 level, which saw the highest level of funding to date. In the third area, all NIH ICs were asked to link strategic plans closely with specific initiatives in their Congressional justification documents for the benefit of new committee staff.

Ms. Erickson noted that the Senate report language also commended the NCI for the Cancer Centers program and TCGA. In addition, the Senate commended NCI's support of prostate cancer research but encouraged more research on screening and early detection. In the area of antimicrobial resistance research, the NCI was commended for its collaboration with the National Institute for Allergy and Infectious Diseases (NIAID). Also in the Senate report, the NCI was encouraged to: (1) continue leadership of the trans-NIH angiogenesis group; (2) add a minority institution to the Cancer Centers program; (3) develop a vaccine for tobacco addiction as a means to reduce lung cancer; (4) conduct more research in the area of lymphedema; (5) accelerate the translation of lymphoma research and dedicate additional funds to survivorship research; and (5) bring together nanotechnology, systems biology, and molecular imaging. In its report language, the Senate recommended that the NCI: (1) develop a strategic plan for melanoma; (2) provide more funds for the Children's Oncology Group (COG) clinical trials; (3) fund the SPOREs at the FY 2004 level; (4) increase utilization of the Small Business Innovation Research (SBIR) mechanism; (5) develop a professional judgment budget in the area of pancreatic cancer;

(6) place more emphasis on developing treatments and translating discoveries in the area of blood cancers; (7) increase research in the area of chronic lymphocytic leukemia (CLL); and (8) focus more on quality-of-life (QOL) issues for patients with breast cancer and accelerate the advances in breast cancer screening techniques. The Senate report also expressed concern about the NCI decision to cancel the Academic-Public-Private Partnership Program (AP4).

Next, Ms. Erickson reviewed the status of NIH reauthorization legislation. Two drafts of the bill written last year were never introduced, but there has been much discussion on a possible new draft. Discussion points were generated by the House Energy and Commerce Committee in several areas. In terms of authorization of appropriations, the Committee is discussing the authorization of an overall funding level for the NIH with a 5 percent increase. A Common Fund would be established as a permanent funding mechanism to encourage collaboration among the ICs and as a reflection of the growing trend toward interdisciplinary research. The set-aside amount for this fund would be capped at 5 percent of the NIH budget and would be administered through the Office of Program Analysis and Strategic Initiatives (OPASI), OD, NIH. Another area for discussion in the purported new draft bill was the need for periodic organizational review in which scientific and lay advisors and some Directors would review the structural design of the NIH and make recommendations about the optimal structure of the NIH. Ms. Erickson observed that this provision would replace the one in the previous draft bills calling for a mission-specific reorganization of the ICs. In other discussions, the OPASI would be the body with responsibility for analyzing activities across the NIH and the Director, NIH, would have additional authority, with OPASI guidance, to identify areas of research that were over- or underemphasized and make adjustments in the research portfolio. Ms. Erickson stated that no written document has yet been seen and there has been no opportunity for NCI input. She observed that, although the House Energy and Commerce Committee Chair has identified NIH reauthorization as a priority, there are limited days left in the legislative calendar for introduction of such a bill and Congressional action. In conclusion, Ms. Erickson noted that the number of areas covered in the House and Senate reports is an indication that the Congress is very much aware of the work of the NIH and the NCI and that they are responsive to feedback from advocacy groups and professional society representatives.

Questions and Answers

In response to a question from Ms. Lydia Ryan, Service Line Clinical Director, Children's Healthcare of Atlanta, AFLAC Cancer Center, Ms. Erickson reviewed the prospects for passage of the FY 2007 appropriations bill before September 30, 2006, and noted that a continuing resolution would be needed to fund activities after that time if Congress does not act on the bill. Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, asked if Congress had given any indication of addressing the harmonization of federal laws that relate to human research. He observed that the lack of harmonization of federal codes that govern the FDA, Office of Health Research Policy (OHRP), and civil rights impedes the collection of tissues and data. He referred to the fact that questionnaires have been sent to investigators soliciting opinions, and he asked whether the information gathered as a result might eventually lead to legislative action. Ms. Erickson replied that she was not aware of any pending legislation but would check into the matter. Dr. Chabner expressed interest in hearing, at some point during the year, NCI's plan for dealing with the SPORE and Cancer Centers programs in the current fiscal environment.

VI. AMERICAN SOCIETY FOR CLINICAL ONCOLOGY REPORT—DR. GABRIEL N. HORTOBAGYI

Dr. Gabriel N. Hortobagyi, Professor and Chairperson, Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, and American Society for Clinical Oncology (ASCO)

President, reminded members that the five-fold ASCO mission is to improve cancer care and prevention, advance education and training, foster communication among the subspecialties, advocate public policy, and assist practicing oncologists. ASCO, now in its 42nd year, is the largest professional organization related to oncology professions, having more than 24,000 members. ASCO membership consists primarily of medical oncologists but also serves as the umbrella organization to surgical, radiation, and pediatric oncology services, and head and neck oncologists; urologists, nurses, oncology advocacy group representatives, and other professionals related to oncology.

As an international organization, with more than 29 percent of the members living outside the United States, ASCO has an opportunity to influence oncology practice, research, and policy worldwide. To that end, the International Affairs Department and Committee was organized several years ago with representation from oncology organizations throughout the world. Initiatives developed through this committee include grants such as: (1) the IDEA Award, which brings oncologists from underdeveloped countries to the ASCO annual meeting and for a visit to a comprehensive cancer center; (2) a multidisciplinary cancer management course; (3) the Best of ASCO, a 1- or 2-day review of annual meeting highlights, which is presented in various parts of the world every year; (4) and support for a technology idea transfer fellowship in collaboration with the International Union against Cancer (UICC).

ASCO is governed by an 18-member Board of Directors, and its activities are fostered by 22 committees and a number of task forces, with support from 200 staff members. Dr. Hortobagyi briefly reviewed the rich and longstanding collaboration with the NCI through members who serve on a variety of NCI committees and advisory boards and NCI staff who serve on various ASCO committees and the Board of Directors. In addition, NCI and ASCO leadership and staff meet regularly.

Dr. Hortobagyi highlighted current ASCO research priorities in the areas of translational research, clinical trials, ASCO grants, and legislative advocacy. In the area of translational research, Biomarker and Imaging Task Forces have been created to advise the Board of Directors on strategies to improve the translational content of ASCO educational activities, as well as translational research to be fostered through ASCO. Recommendations of the Task Forces were reviewed in February, and an Implementation Task Force met in early summer to initiate implementation. Some initiatives in this regard are the increase in the translational content of ASCO annual meetings; expansion of support for training and the development of translational investigators; contacts with organizations and societies that represent research in biomarkers and molecular imaging to enhance the ability to incorporate these approaches to new drug development and clinical research; the development of a professorship in translational research within ASCO; interaction with the FDA in the Critical Pathway Initiative; and participation in the Uniform Protocol for Imaging in Clinical Trials (UPICT) to expand the application of PET, magnetic resonance imaging (MRI), and other forms of functional imaging in translational research and clinical trials. Dr. Hortobagyi indicated that ASCO also is working toward reform of the Health Information Portability and Accountability Act (HIPAA) and similar legislation that are roadblocks to effective and efficient clinical research. Factual data are being collected so that the process can be reexamined and solutions proposed. He noted that it has been 10 years since HIPAA was enacted and 3 years since the last review, and that some of the DHHS Secretary's recommendations have not yet been implemented. He expressed the view that HIPAA could be refined to provide a better approach to both protection of confidential information and effective conduct of research.

In the area of clinical trials, Dr. Hortobagyi emphasized ASCO awareness of and support for the highest level of integrity in the research process. ASCO has paid substantial attention to the avoidance of conflict of interest (COI) policy or effective management when avoidance is impossible. ASCO's COI policy was first implemented in 1994 and has been updated several times since then. At the most recent Board meeting, the various ASCO COI policies for members, volunteers, and employees have been

harmonized. In addition to disclosure for highest level officers and staff members, the policy has specific provisions about ownership and financial interactions, and it applies to guidelines and to the ASCO *Journal of Clinical Oncology (JCO)*. Dr. Hortobagyi stated that ASCO believes that the prospect for translational research advances in coming years requires a revisiting and restructuring of clinical trials and the development of creative endpoints to expedite and streamline the process of drug discovery. To that end, ASCO is working with the FDA and other professional societies to organize workshops for the consideration of optimal endpoint selection for the approval of cancer drugs. Results of the workshops are periodically presented to the Oncology Drug Advisory Committee, FDA, and other relevant organizations to enhance the process of drug development.

Dr. Hortobagyi noted that ASCO for several years has supported the concept of central review of clinical trials, particularly for multicenter or cooperative group trials. The ASCO Cancer Research Committee has discussed what the barriers for full utilization of the central IRB are and how they could be overcome and believes this is an area where ASCO could interact effectively with the NCI to identify barriers and work through the process of eliminating them. To address the low level of participation in clinical trials in comparison with some European countries, ASCO has developed a Clinical Trials Participation Award to reward community practices that make effective contributions to clinical trials. A final initiative in the area of clinical trials as a research priority is ASCO's involvement in the issue of Medicare coverage of routine patient care costs. At the request of CMS, the issue has been considered by ASCO and recommendations have been sent for consideration by CMS in its review of the 2000 national coverage decision for clinical trials for Medicare participants. In addition, ASCO's government policy component has communicated a number of other thoughts to the CMS.

Dr. Hortobagyi reported that ASCO supports a number of grant awards through the ASCO Foundation. These include the Advanced Clinical Research Award (ACRA), Young Investigator Award (YIAs) for last-year fellows and first-year junior faculty, and the Career Development Award (CDAs) for individuals in their second, third, and fourth years of faculty positions at an academic institution. Acting out of concern that young investigators be competitive in writing applications, ASCO has expanded a previous initiative and will hold a 5-hour course on writing effective grant applications at the next annual meeting. Plans are to invite CDA and YIA awardees to present the results of their grant-supported research for the benefit of future applicants.

Dr. Hortobagyi noted that, in gratitude for the work of the NCI and the cancer research enterprise during the past 40 years, ASCO membership intends to highlight their accomplishments over the coming year to raise awareness within the public, the group of political representatives, and other medicine specialties. For this purpose, the ASCO Clinical Cancer Advances Report was published in 2005 as a review of the most significant clinical research presented or published across the area of cancer. ASCO has used the Report to inform Congress and other organizations and is working on strategies to highlight the report and spread the information throughout the medical and scientific communities at large. Dr. Hortobagyi stated that ASCO believes continued funding for the NIH and NCI is critical and has supported the process by contacting members of Congress and continuing to interact with advocacy and other professional organizations. In another area of legislative advocacy, ASCO concern about the NIH reauthorization legislation has led to contact with Chairman Joe Barton (R-TX) and House Energy and Commerce Committee staff regarding the first two drafts. This legislative advocacy will continue in the hope that NCI's authorities and responsibilities will be preserved in the reauthorization process.

Dr. Hortobagyi noted that quality of cancer care and quality of cancer research are important ASCO priorities and that a number of initiatives have driven this area of interest. The National Initiative on Cancer Care Quality (NICCQ) was based on the 1999 report of the National Cancer Policy Board entitled "Ensuring Quality Care." The NICCQ initiative was the retrospective cohort study of incident

breast and colorectal cancers conducted in collaboration with the Harvard School of Public Health and the Rand organization. The survey, which included 61 quality measures, was completed and analyzed and the results were presented at the 2005 annual meeting. The results demonstrated that the quality of cancer care overall was higher than previously thought, but areas were identified where improvement was needed and possible. Dr. Hortobagyi explained that the ASCO-NCCN quality measures were derived from the NICCQ initiative. Three breast cancer quality measures and four in the area of colorectal cancer have been identified as major determinants of outcome in those diseases. These quality measures were published online, and ASCO will pilot their use and promote their implementation in future activities. ASCO also participates in the Cancer Quality Alliance through a committee chaired by Dr. Patricia Ganz, ASCO Board member. Alliance initiatives include the dissemination of information to the public, policymakers, commercial and public payers, patients, and survivors. Another ASCO quality initiative is the Quality Oncology Practice Initiative (QOPI), which is based on ASCO-NCCN quality measures and provided as an online self-assessment program for community practices. Additional uses of QOPI data are being explored.

To address concerns about health disparities, a task force of volunteers was created within ASCO to explore health disparities and define strategies for overcoming them. As a result of task force activities, the educational content of various ASCO meetings and publications has been enhanced to highlight health disparities and the opportunities for improvement in this area. In addition, the development of a YIA and a CDA was approved this year to focus specifically on health disparities and encourage research to improve this problem. ASCO also is a member of the American Medical Association Commission to End Health Disparities.

Acting on the conviction that efforts in cancer prevention are important to move the field forward, ASCO created a freestanding Cancer Prevention Committee in 2002. The Committee promotes increased integration of cancer prevention science into all ASCO educational content and publications, and a track that emphasizes cancer prevention activities has been created within the ASCO annual meeting. Other cancer prevention initiatives include a survey among U.S. and international members of ASCO focused on cancer genetics; the development of a cancer genetics curriculum, which will form one of the bases for future cancer prevention activities; and the creation of a cancer prevention and control curriculum. One objective of these activities is to ensure the appropriate reimbursement for clinical prevention services. Dr. Hortobagyi stated that ASCO collaborates with other tobacco control coalitions to advocate for tobacco control. The ASCO tobacco control policy statement was updated in 2003 and calls for rapid worldwide reduction and ultimate elimination of tobacco products and their use. ASCO is engaged in further enhancing its tobacco control efforts and identifying proven educational programs and practical tools to assist oncologists in working with their patients on the cessation of tobacco use.

In the area of education and training, Dr. Hortobagyi highlighted the Methods in Clinical Cancer Research workshop held annually in association with the American Association for Cancer Research (AACR), with partial support from the NCI. This week-long course emphasizes individual mentorship and presents all of the basic information needed for development of effective clinical trials. At the end of the week, participants are required to have a fully developed clinical trial that is reviewed and approved by their mentors. Each year, about 75 fellows and 25 junior faculty members are trained in this program. A similar program is conducted annually in Europe in collaboration with AACR and the Federation of European Cancer Societies. In addition, ASCO was involved in the intellectual input and structure of a methods workshop held this year for the first time in the Australia-Pacific basin. For the first time this year, ASCO is participating as a sponsor, together with the NCI and the European Organization for Treatment of Cancer (EORTC), of the international Biomarkers Meeting to be held this year in the United States.

Dr. Hortobagyi then summarized the areas where there is potential for ASCO and NCI collaborations. These include: (1) enhancing the visibility of federally funded cancer research and advocating for continued support; (2) working to ensure that conflict-of-interest policies are effective yet fair and equitable; (3) promoting the central review of clinical trials and working to understand and remove obstacles if possible; (4) understanding the consequences of HIPAA and ensuring that the research process is efficient and devoid of obstacles and yet protects the individual's right to confidentiality; and (5) working toward expanded Medicare coverage of clinical trials. In terms of the future, Dr. Hortobagyi expressed the view that cancer research is beginning to harvest the tangible results of 40 years of intensive research and that the momentum must be maintained. He stated, therefore, that collaborations in research, access to care and high-quality research, and training for the next generation of investigators are paramount and will be a critical focus of ASCO future effort.

Questions and Answers

Dr. Coffey asked for specific issues included in the informative review of ASCO activities to which the Board can contribute. Dr. Hortobagyi replied that the intent of his presentation was to provide information to NCAB members who are not aware of the extent of ASCO activities, but he identified access to high-quality clinical trials and high-quality care as areas where ASCO and the NCI can work together. Another area for emphasis would be interaction among the NCI, FDA, and ASCO on translational research to make drug development and the clinical trials process more effective. Dr. Runowicz agreed that areas where collaboration is critical to success in solving the cancer problem are improving discovery, prevention, access to care, and training for the next generation of researchers. Dr. Hortobagyi observed that several hundred new drugs are being discovered throughout industry and that the NCI systems and the current rate of accrual to clinical trials will preclude developing those drugs effectively. He cited insurance reimbursement and issues related to various regulatory activities as two of a number of obstacles to clinical trials accrual that must be worked through collaboratively and eliminated.

From the patient perspective, Ms. Giusti expressed the view that synergies are needed between community centers, which are gateways to care for many people, and the academic centers, where many of the trials are initiated, to create feeder systems that would be beneficial in both clinical trial accrual and tissue acquisition. Dr. Chabner recommended central review for clinical trials as an area where ASCO and the NCI should collaborate and reach consensus on the kind of review necessary for clinical protocols. He cited the conflicting messages that Cancer Centers receive, and he observed that trials could be activated earlier and questions answered more quickly for FDA review purposes. Dr. Doroshow cited the issue of so many trials and so few patients as one to be addressed, and he noted that work is proceeding on a prioritization process for all NCI-supported trials. The process brings together all stakeholders to focus available resources and enhance the system. He expressed the view that the rate of accrual is the issue rather than total accrual so that trials can be finished earlier and the next question addressed. Dr. T.J. Patel, Program Director, Oncology and Kidney Diseases, Veterans Health Administration (VHA), discussed the recent charge received at the VHA to write a policy on colorectal cancer screening, with timelines for moving through the various tests to biopsy then to surgery or radiation or chemotherapy. A search for a model ended at the National Health Service in the United Kingdom. He expressed the view that guidelines and timelines for cancer would enhance the quality of cancer care and that the NCI should take the lead in creating different timelines and sets of standards and performance measures.

VII. NCI COMMUNITY-BASED CANCER CENTERS PILOT PROGRAM—DR. JOHN NIEDERHUBER

Dr. Niederhuber reminded members that the impetus for a community-based cancer centers program came from the concern that there is no way at present of delivering the science of today to people in the community where they live, as well as the belief that access to state-of-the-art care will be a greater determinant of cancer patient mortality than any other risk factor, including tobacco. He cited the success of the NCI-designated Cancer Centers in 61 major academic and research institutes in making significant contributions each day to advances in the understanding, prevention, and treatment of cancer. He pointed out that many geographical gaps exist, however, where the public is unable to receive the kind of care available in the Cancer Centers. Moreover, more than 80 percent of patients with cancer actually are cared for in their local communities.

Dr. Niederhuber reviewed current trends in community-based cancer care that make the NCI Community-based Cancer Centers Pilot (NCCCP) a viable option at this time, as well as the reasons why most cancer patients are treated in hospitals in their communities. The mission statement developed across the NCI over the past year for the NCCCP is to enable the provision of state-of-the-art multispecialty care and early-phase clinical trials in community-based locations to meet the needs of people. The goal of the pilot is to anticipate and sponsor multiple pilot sites for a 3-year period to identify critical factors that would be incorporated into a future Request for Applications (RFA), which would establish this initiative as a permanent program. Members were reminded of the House Appropriations Subcommittee FY 2007 report commending the development of a program to translate the most promising advances in cancer treatment to community hospitals around the country.

Dr. Niederhuber acknowledged and commended the work of the Guiding Coalition and the many Division and Office staff members who collaborated in the development of the NCCCP. Considerations in developing this pilot was to select from among community sites that have: (1) early-phase programs with significant outreach to racial and ethnic minorities and address health care disparities; (2) well-established programs with experience in clinical trials research and some infrastructure in place; (3) strong state-funded support indicating a relationship between the community effort and the regional or state health care structure; (4) hospital-based programs that reach large uninsured populations; or (5) programs that primarily address rural issues. Dr. Niederhuber noted that NCI-designated Cancer Centers that have community networks already in place have been consulted and have provided valuable advice. In addition, NCI program developers have talked with other national health systems to explore the possibility of utilizing their rapid knowledge transfer capabilities for replication of the program.

Baseline components that are considered important for sites selected in the NCCCP are: (1) evidence of a community cancer program, including a minimum of 1,000 new cases a year, cancer screening programs, accreditation, and appropriate staffing, technology, clinical programs, and expertise; (2) clinical trials experience; (3) disparities and community outreach capability; (4) information technology capacity that includes plans for electronic medical records (EMRs) and implementation of caBIG™ infrastructure and components; (5) commitment and capability to describe and assess implementation requirements for the *First-Generation Guidelines for NCI-Supported Biorepositories*; and (6) emphasis on hospice and palliative care. Dr. Niederhuber briefly reviewed areas that will be of special interest in implementing the pilot program, such as linkages with NCI-designated Cancer Centers and successful approaches to increase accruals to NCI-sponsored clinical trials.

Next, Dr. Niederhuber described the NCCCP assessment structure. An external and independent program evaluator will be employed for this demonstration project. Year 1 would be devoted to infrastructure development, refinement of the pilot program, and beginning to address the research

questions. Years 2 and 3 would be used for implementation of the more expanded model and evaluation of the metrics and research questions around the pilot program. In regard to funding, Dr. Niederhuber explained that it is the intent to support multiple sites through the NCI's prime contract with SAIC-F, at a level of $9 M for the 3-year period. Supplemental funding models would be considered in support of goals as they evolve. Guidelines for allocation of resources would be 40 percent for health care disparities and 20 percent each for information technology, the biospecimen initiative, and clinical trials. Next steps are a Development Committee review of comments obtained from the RFI issued in mid-August, drafting of the Request for Proposal (RFP), and a strong communication effort to educate stakeholders in the cancer community regarding this proposal and elicit feedback. The proposed timeline for this initiative includes closing the RFI period in September, RFP release in mid-October, pre-proposal conference in mid-November if needed, RFP response deadline in mid-December, RFP response evaluation in mid-January, and pilot selections completed early in 2007.

Questions and Answers

Dr. Diana Lopez, Professor, Department of Microbiology and Immunology, University of Miami Miller School of Medicine, suggested that the recommendations of a Project Review Group (PRG) commissioned by the former Secretary, DHHS, could be used in formulating guidelines for the NCCCP inasmuch as community-based health care delivery was a major focus of the report. Dr. Niederhuber replied that many issues and ideas generated by the PRG were brought to the discussions of the NCCCP Development Committee, as well as research in the various NCI Divisions. He suggested that the community site can be viewed as a laboratory that provides an opportunity to implement many different programs at one site for the improvement of health care delivery. As a result, it will be possible to evaluate whether conducting activities in an integrative fashion is a more effective approach than doing them in isolation. Ms. Ryan commented that the NCCCP is comprehensive and ambitious, and she asked whether the NCI had conducted a national snapshot of the landscape to determine what programs may exist in the areas of interest to the program, such as access to health care. She also commented that, from a research perspective, there may be a question of feasibility, for example, the time needed for a community center to operate effectively. Dr. Niederhuber gave assurance that options and resources that could play into the program were extensively researched during the program development phase. Dr. Moon Chen, Professor, Public Health Sciences, and Associate Director, Cancer Disparities and Research, University of California, expressed enthusiasm for the NCI vision of linking together a nationwide cohort to address health care issues.

Dr. Everson applauded the NCI for the vision embodied in the NCCCP, and he noted that it is a vision that his institution's network of more than 1,000 practicing oncologists try to emulate. He volunteered to help in any way and share his experience base. Dr. Chabner recounted his institution's experience in attempting to develop a similar program in a largely Portuguese and Hispanic hospital system, and he described unexpected challenges that were encountered, including the need for a very strong program for translation to put patients on complex protocols such as the current Phase I protocols. Another challenge was encountered in trying to find the right trial for the right person. He expressed the view that much thought must be given to the feasibility of matching the trial to the local expertise and patient population on a larger scale. Ms. Ryan agreed that feasibility questions are valid, but she cited the challenges facing the COG in getting aphaeresis done in institutions nationwide for its massive Phase III trials in neuroblastoma, and she commented that success in achieving that was a valuable learning experience.

VIII. UPDATE: HUMAN CANCER GENOME ATLAS PROJECT—DR. ANNA BARKER

Dr. Barker prefaced the update by stating that The Cancer Genome Atlas Project (TCGA) is an example of the convergence of science and technology to achieve insights into the cancer cell that have the potential to produce valuable dividends for cancer research. She reminded members that the TCGA is a 3-year pilot project of the NCI and the National Human Genome Research Institute (NHGRI) to increase the Nation's comprehensive understanding of the genetic basis of cancer. It is anticipated that TCGA's integrated database of molecular and clinical information will provide scientists with unprecedented opportunities to discover and develop a new generation of targeted diagnostics, therapies, and preventives for cancer. Conversations with the NHGRI on this project began about 2.5 years ago as NCI's Cancer Genome Anatomy Project (CGAP) was coming into maturity. The intent of the conversations was to ascertain next steps in this research area, and NCI's interests coincided with NHGRI interest in medical sequencing. Dr. Barker noted that cancer is the first disease that will have dedicated to it over the next 3 years the largest contingent of molecular and clinical scientists ever brought together to look at the genomic basis of specific diseases.

The enabling rationale for TCGA was based largely on achievements of CGAP, and other programs which include the identification of gene families and pathways, development of robust genomic analysis technologies and early indications that somatic mutations are important potential targets. Dr. Barker pointed out that the real impact of these various achievements already has been felt, and it is known that some of these targets can lead to the creation of a new generation of targeted interventions. She gave assurance that this initiative is not a technology project; rather it has been designed to integrate the work of biologists and genomicists in the most optimal way. TCGA development milestones since September 2003 have included many meetings about the project, involving large contingents of researchers and other stakeholders from across the community. This was supplemented and reinforced by the report of the Ad Hoc Subcommittee's report to the NCAB in February 2005 and the NCAB recommendation to proceed with the project. The NCI-NHGRI Working Group was formed, and meetings were held to solicit input from the extramural community in preparation for designing TCGA.

During the last year, significant progress has been made in developing the project and issuing parts of it to the public in the form of RFIs, RFAs, and RFPs. The Biospecimen Core Resource RFA was issued in February 2006, proposals in response have been reviewed, and the selection process is final. An RFA for the Cancer Genome Characterization Centers (CGCCs) was issued in March, and applications were received from the major academic medical centers around the country. These Centers constitute the biggest part of this project in that they will be delving into the biology and starting to integrate the genomic changes that are found with the biology. Issues arose in regard to the possibility that patients could be identified in the process of integrating sequencing and clinical data. A Data Release Workshop was held with representatives of the scientific and patient advocate communities, and reasonable and effective solutions have been identified. Another of the biggest issues that arose was selecting the first tumors that are sequenced in the Cancer Genome Atlas. Dr. Barker noted that that selected tumor types to be sequenced in the TCGA pilot will be announced in the coming week as will the award for the Biospecimen Core Resource. The selections for the Cancer Genome Characterization Centers and bioinformatics support will be finalized and the awards announced in October. NHGRI will finalize the selection and announce the award of its high-throughput Sequencing Centers in December, and plans are to launch the project in early 2007.

Dr. Barker explained that a systems approach has been applied to address the challenges associated with moving from R01-type science to science that integrates biology and technology. The Biospecimen Core Resource will receive all tissue donated for study by the patient community and will have responsibility for quality control (QC) of every biomolecule that goes to the Centers to ensure that

robust data emerge from this project. She pointed out that the Genome Sequencing Centers and the Genome Characterization Centers can be considered two sides of a coin in that they are the group that will work on such areas as copy number changes, expression profiling, and resequencing. Data management, bioinformatics, and computational analysis will constitute the fourth component of the TCGA network. Underlying everything is technology development that will be funded by both the NHGRI and NCI. Dr. Barker observed that the patient, patient advocacy, research, and medical communities will be engaged in various aspects of the project.

Because it is central to TCGA Pilot success, the Biospecimen Core Resource will: (1) receive the tissue samples, verify all of the biologic and clinical data, and perform the pathologic QC; (2) perform central processing of specimens to provide uniform biomolecules for distribution to both Genome Characterization and Sequencing Centers; (3) track and quality assure all specimen-related operations, including ensuring that specimens are appropriately consented; (4) provide "standard" samples for technology platform comparisons; (5) develop (with the Office of Biorepositories and Biospecimen Research) and monitor the standard operating procedures for prospective specimen collection; and (6) serve as a member of the TCGA's Steering Committee, which will be composed of the principal investigators from the Cancer Genome Sequencing Centers and the Genome Characterization Centers.

Dr. Barker described the complications associated with the selection of categories of biospecimen collections to initiate the TCGA Pilot. In the end, it was decided one tumor type will be selected from qualifying biorepositories in three categories: (1) a tumor representing a major public health problem, because TCGA is about creating new interventions for patients; (2) a tumor type that demonstrates a high degree of homogeneity; and (3) a collection that derives from a completed clinical trial where patients were treated in the same manner. Next, Dr. Barker described the robust evaluation process for selecting the biorepositories to be included in TCGA, which began with the issuance of an RFI and notification to Cancer Centers. Rigorous primary and secondary criteria will be applied in the evaluation process. She announced that three tumors have been selected for the specified categories, and she commended the altruism displayed by the institutions that will be providing the specimens for TCGA.

Qualifications sought in the Cancer Genome Characterization Centers were: (1) technology platforms for high throughput genome characterization; (2) the capacity and willingness to work on improving and developing existing technologies; and (3) concurrence with the requirement for real-time data release into a public database. Dr. Barker noted that the cooperative agreement mechanism (U24) will be used to promote collaboration and cooperation and provide for the governance structure that is represented by the TCGA Steering Committee. Peer review of the applications has been completed and awards will be announced in October. Similarly, U24 applications for NHGRI's Genome Sequencing Centers have been reviewed, and the awards will be announced in December. Members were reminded that the NHGRI is dedicating $50 M from its sequencing budget for this project. NCI's caBIG™ will provide a bioinformatics platform for TCGA. All molecular and clinical data from both the Genome Characterization and Sequencing Centers will be deposited in the public TCGA database that is under development through caBIG™. The data will be made available through caBIG™ and through the National Library of Medicine's National Center for Biotechnology Information (NCBI).

In the course of organizing this project, according to Dr. Barker, it became apparent the TCGA and other large-scale medical genomics efforts must address several ethical, legal, and policy issues (ELPIs). These include: the level of detail in the informed consent; who should have access to data; how to leverage and capitalize on the potential for progress and ensure privacy protection; and whether new forums of patients, clinicians, researchers, and ethicists will be needed to discuss these issues and inform policy. Dr. Barker noted that the NCAB has considered these ELPI and informed consent issues in the past and that the NIH is taking a lead in the effort to develop policy in this area because of TCGA and the

other NIH projects dealing with these issues. As an indication of the difficulty of arriving at a universally acceptable informed consent, Dr. Barker noted that a draft informed consent for TCGA use that was 9 months in the making was critiqued and dismissed in a recent workshop.

Looking ahead, the expectations are that the TCGA Pilot will succeed in completing the genomic analysis of three tumors, and will make it possible to identify some alterations in genes that are associated with cancer and differentiate tumor subtypes based on genomic alterations. The ultimate goal is the establishment of a database with all data from the TCGA Pilot that scientists can access for followup experiments. It is expected that this will empower and enable a whole new era of science for cancer that will create hypothesis testing similar to that seen shortly after the genome itself was sequenced. Expectations for TCGA in the long term include the ability to identify those somatic changes in cancer genomes that could establish the molecular basis for each cancer and establish molecular oncology as the approach to personalized medicine. A new era of oncology could be envisioned—one that is preemptive and preventive as well as targeted in terms of new therapies, adds to knowledge in the biomarker area, and improves the ability to stratify patients for clinical trials.

Dr. Barker directed those interested in knowing more about TCGA or receiving automated updates to the Web site http://cancergenome.nih.gov. She acknowledged and thanked the many people responsible for bringing TCGA through the 4 years of planning to a place where the project is now in the hands of the extramural world that is going to execute it.

Questions and Answers

Dr. Peter Kirchner, Senior Scientist, Office of Biological and Environmental Research, Department of Energy, asked whether TCGA would be sampling early metastases sequentially over time to see if there are genomic subtype changes following therapy or just as an evolution of time. Dr. Barker replied that the intent was to choose tumors that would lessen that concern. The tumors chosen for this project in the three categories are primary tumors, not metastases. However, biologists might be expected to look for those kinds of indicators in the data over time. Dr. Everson suggested, based on experience in his institution's network, that TCGA should ensure that there is a dedicated resource at the site collecting the tissue. In response, Drs. Barker and Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research, OD, reviewed the rigorous criteria for locating specimens to ensure that those identified for TCGA are of very high quality and will fulfill the technological needs of the project in regard to providing meaningful biologic and clinical data. Dr. Coffey asked whether alternate splicing, where one gene can make hundreds of different proteins, is covered in TCGA; whether any karyotyping would be done; and whether TCGA investigators would be looking at the RNA pattern. Dr. Barker replied in the affirmative to the first and last query and noted that she did not think any of the TCGA centers would be doing karyotyping.

Dr. Barker stated that TCGA has benefited from the experience gained in the mini-genome program organized by the Multiple Myeloma Research Consortium shortly after planning for the NCI project began. Ms. Giusti recounted lessons learned: (1) it was necessary to station coordinators at each of the 11 sites submitting tissue to ensure that the standard operating procedures developed for the project were followed and tissue was collected only from untreated patients; (2) it was beneficial for the 11 sites and for the overall project to track metrics and distribute a monthly report as to amount of tissue collected and sent, number of patients accrued, and speed of the IRB review at each site; (3) it was deemed valuable to hire a contract research organization to conduct a review of the data that are being accumulated; (4) it may be necessary to expand the collection process to Europe to access enough tissue from untreated patients; (5) it was necessary to adjust quality standards over time when an old standard was found to be

unworkable; and (6) patients require the answers to many questions and the education process is extensive.

Dr. Chabner asked how the TCGA information would be used to look at outcomes. Dr. Barker explained that TCGA would create the databases, and scientists and clinicians will be able to begin asking those kinds of questions. She noted, however, that one of TCGA tumor choices is from a well-orchestrated clinical trial so it will be possible to take that data and work back to outcomes. Moreover, different portals are envisioned for the Atlas, and it is hoped there will be groups of clinicians who make up different portals for the data so that questions can be asked and answered in real time about some of the kinds of trials that will be part of the Atlas. Dr. Freedman stated that he has had reservations about the ELPI issues related to TCGA, and he expressed the view that the data must be de-linked, not anonymized, to be of value. He asked how the ELPI issues were being addressed. Dr. Barker explained that they currently are being dealt with at the levels of the NCI through the implementation of its *First Generation Guidelines for Biorepositories* and the NIH through a couple of projects, one called the Gene Environment Interaction Project. Guidelines from the NIH project were recently published in the *Federal Register*. Dr. Barker noted that, initially, a limited or two-tier access to TCGA data will be necessary, that opening access in the future will require action at the Department or Congressional level, and that the scientific community will have a chance to respond.

IX. TAMOXIFEN AND STAR TRIAL RESULTS—DRS. LESLIE FORD AND LARRY WICKERHAM

Dr. Leslie Ford, Acting Deputy Director, Division of Cancer Prevention (DCP), reminded members of the initial report in 1998 of the National Surgical Adjuvant Breast and Bowel Project (NSABP) tamoxifen trial, NCI's first breast cancer prevention initiative. That trial compared tamoxifen to placebo and led to the first FDA approval of a drug for risk reduction in women at increased risk for breast cancer.

The Study of Tamoxifen and Raloxifene (STAR) was the second prevention trial and was reported in 2005 at ASCO and in the *Journal of the American Medical Association.* She introduced Dr. Lawrence Wickerham, Associate Chairman, NSABP, and Associate Professor of Human Oncology, Drexel University School of Medicine at Pittsburgh, to present an update on the NSABP breast cancer prevention program.

Dr. Wickerham reminded members that the NSABP is now close to a 50-year history of conducting cooperative group studies in the treatment of breast and bowel cancers, and these have had a major impact on the standard of care in those diseases. NSABP trials were largely responsible for the transition from true radical mastectomy to lumpectomy, and adjuvant trials have looked at therapy in node-positive and node-negative patients with ductal carcinoma *in situ* (DCIS).

Therapies in adjuvant trials have included both hormonal therapies and chemotherapies. The NSABP prevention network now comprises 200 sites and an additional 300 satellite centers located throughout the United States, Canada, and Puerto Rico. This includes more than 50 of the Cancer Community Oncology Program (CCOP) institutions, and they have been a key component to NSABP prevention activities. Other keys to success have been the wide distribution of sites throughout North America and the time and effort spent making certain that the quality of trial participation at these centers is distributed equally. Dr. Wickerham pointed out that American Cancer Society (ACS) figures for 2006 estimate more than 212,000 new diagnoses of invasive breast cancers and, despite improvements in treatment and screening, more than 40,000 deaths, indicating the potential for prevention to have a significant impact on the public health related to this topic.

Dr. Wickerham briefly reviewed the structure and results of the NSABP B14 trial of tamoxifen, which he described as the most commonly prescribed breast cancer drug in the world. The design was among the first node-negative/receptor-positive trials in the world. It began in 1981 and arguably is a landmark study in oncology, not just breast cancer oncology. With 2,800 who were randomized to placebo or tamoxifen, NSABP was able to demonstrate that tamoxifen improved both disease-free survival and survival in general and that those benefits now have gone through 15 years of followup. In addition, it was found that women taking tamoxifen had a 50 percent reduction in new primaries in the opposite breast. This had been seen also in other trials around the world and in the PETO overview of all the tamoxifen studies, and led to the design of the first NSABP breast cancer prevention trial (BCPT-P1).

BCPT-P1 enrolled otherwise healthy individuals at an increased risk for the future development of breast cancer and assigned them to either tamoxifen or placebo for a 5-year period in a double-blinded trial. Gail Model variables were used to quantify their breast cancer risk. The minimum score to be eligible for BCPT-P1 was a 1.66 percent risk of developing breast cancer in the next 5 years. BCPT-P1 began in 1992 with more than 13,000 women entered in the study. Premenopausal (35 years of age and older) women were included in the trial, 39 percent were under the age of 50, and family history accounted for most of the risk. Three-quarters of them had one more first-degree relative, which translated into an average Gail risk of a little more than 3 percent. Seventeen percent had a risk of 5 percent or greater. Only 6 percent had a prior history of lobular carcinoma *in situ* (LCIS), and 9 percent had atypical hyperplasia. BCPT-P1 results were announced in 1998 and were able to show that tamoxifen was highly effective in reducing the risk of invasive breast cancer (mediating a 49 percent reduction in invasive disease). The benefits were demonstrable in all of the subgroups, but the groups that appeared to benefit the most were those who came into the trial with a prior history of LCIS or atypical hyperplasia. The LCIS group has a risk of about 13 cases per 1,000 per year and the tamoxifen dramatically reduced that. The atypical hyperplasia reduction by 86 percent holds at the 4-year point. An unexpected reduction in noninvasive cancers also was seen.

Dr. Wickerham stated that these results have been updated through 7 years of followup and, despite unblinding and in some cases crossover, there is still a continued and durable benefit for both invasive and noninvasive disease. He noted also that a durable benefit in NSABP treatment trials where there were reductions in opposite breast cancer now go out to 20 years. Detrimental events included endometrial cancer and thromboembolic events. These were clearly a factor in the acceptability of tamoxifen for this indication. Although the drug has FDA approval as well as endorsement from various societies and organizations, the use of tamoxifen for prevention has not been overwhelming.

Next, Dr. Wickerham described how the Multiple Outcome of Raloxifene (MORE) trial led to the design of NSABP's P-2 STAR trial.

Raloxifene, another selective estrogen receptor modulator (SERM), is approved in this country for the treatment and prevention of osteoporosis. The results of the MORE trial for postmenopausal women with osteoporosis were announced at the same ASCO plenary session in 1998 where BCPT-P1 results were announced. Women in the raloxifene-treated group demonstrated a 72 percent reduction in invasive breast cancer compared with the placebo group, with no excess of endometrial cancer. This was a group of women with histories of osteoporosis, however, not a group at known increased risk for breast cancer. MORE was a fracture prevention trial, but it did lead to the design of NSABP's STAR, which studied risk-eligible women based on the Gail score, and only postmenopausal women. Patients were assigned to either tamoxifen and its proven benefits or the promising results from raloxifene as shown in the MORE trial. The objectives were to evaluate the effect of raloxifene versus tamoxifen in reducing the incidence of primary invasive breast cancer. Secondary endpoints included the evaluation of noninvasive

disease, endometrial cancer, ischemic heart disease, and fractures. Of the 184,000 women screened for this study, 96,000 were found to be risk-eligible and 20,000 were randomized over a 5-year period. Dr. Wickerham attributed the success of P-2 STAR to the rigorous screening process in which all individuals received an individualized risk/benefit estimate based on the Gail model and discussion about breast cancer and screening.

Characteristics of the STAR population were: (1) age distribution—9 percent under age 50, 50 percent in their 50s, 32 percent in their 60s, and 9 percent above age 70; (2) racial/ethnic distribution—93.5 white and 6.5 minority; (3) 5-year predicted Gail scores—25 percent with a 5 percent or greater risk, with an average score of more than 4 percent; (4) 70 percent with one or more first-degree relatives with breast cancer; (5) 51.5 percent with prior hysterectomy; and (6) compared with BCPT-P1, an increase in the percentage of LCIS and atypical hyperplasia (more than 22 percent of the women with atypia). Dr. Wickerham presented the overall results of the STAR trial showing that tamoxifen and raloxifene were equally effective in reducing the risk of invasive breast cancer by approximately 50% from an estimated 8/1000/year to 4/1000/year. The cancers that did occur in the tamoxifen or raloxifene groups were of equivalent size, stage, receptor, and nodal status. Raloxifene was not as effective as tamoxifen in reducing the incidence of non-invasive breast cancers (DCIS and LCIS combined), but raloxifene-treated women had fewer deep vein thrombosis, pulmonary emboli, cataracts, endometrial cancers, and hysterectomies for benign disease. He noted that Quality of Life (QOL) was monitored closely in this population, and there were no significant differences in the primary QOL endpoints and overall minimal symptom severity across the board. In summary, raloxifene was demonstrated to be as effective as tamoxifen in the prevention of primary invasive breast cancer, but less effective in the prevention of noninvasive disease (LCIS and DCIS combined). Compared with tamoxifen, raloxifene use was demonstrated to result in fewer thromboembolic events, fewer endometrial cancers, and fewer cataracts. This analysis was based on 76,000 patient years or followup, just short of 4 years on average.

Dr. Wickerham observed that, as a result of P-2 STAR, postmenopausal women at increased risk for this disease now have a new, effective option for breast cancer prevention and one that comes with fewer serious side effects. The option also is an attractive one inasmuch as there are 500,000 women in the United States today on this medication for the treatment and prevention of osteoporosis; those women tend to be older and tend to have a lower breast cancer risk than the group in the STAR trial, and they already are receiving the benefits relative to breast cancer risk reduction. Dr. Wickerham noted estimates that breast cancer has been prevented in as many 10,000 to 14,000 women of that 500,000. Moreover, primary care providers are comfortable prescribing raloxifene and know what to expect. He predicted that, if the FDA approves raloxifene for this indication, broader use of it will be seen for primary breast cancer prevention.

Dr. Wickerham itemized other benefits already leveraged by both BCPT-P1 and P-2 STAR: (1) serum and lymphocytes on more than 30,000 of these women have been stored from the baseline exams; (2) formalin-fixed tumor blocks have been banked, not only of their breast cancers but also their endometrial and other cancers; and (3) access to these is not restricted to NSABP investigators; an open process allows that to occur across the board and the availability has been promoted through the various breast and GI SPOREs, as well as to the general scientific community.

Dr. Wickerham observed that P-2 STAR is an important step and, although much progress has been made since 1990 with the BCPT-P1, P-2 STAR, and Women's Health Initiative, there clearly is more work to be done. True to its history of doing trials that build on the results of prior studies, the NSABP has proposed the P4 trial, a study of letrozole and raloxifene. Members were reminded that the aromatase inhibitors (AIs) are rapidly replacing tamoxifen in the adjuvant treatment of receptor-positive postmenopausal women. In those large adjuvant trials, the AIs on average have reduced the risk of new

primaries of the opposite breast 50 percent more than the tamoxifen treatment. Considering that tamoxifen had reduced that risk by 50 percent, the potential exists for a 70-75 percent reduction in primary invasive breast cancer compared with an untreated control group. Letrozole was capable of doing that in both the traditional adjuvant setting and the so-called extended adjuvant setting compared to placebo, but after 5 years of tamoxifen therapy. The P-4 proposal has already gone through peer review, and the hope is to initiate P-4 this calendar year.

In conclusion, Dr. Wickerham reminded everyone that the breast cancer stamp is one way to thank the women who have participated in the prevention trials. He acknowledged that the breast cancer prevention program of the NSABP owes its worldwide reputation to the thousands of women willing to enter its various prevention trials.

Questions and Answers

Dr. Runowicz asked for comment on the number of DCIS incidences that would have been expected on a placebo arm versus what was seen on the raloxifene arm alone, noting that she understood that raloxifene-mediated decrease was lower than that for tamoxifen. Dr. Wickerham replied that it would be necessary to refer to the P-1 trial and because the populations were somewhat different, it would be hard to say whether the few per thousand seen in the raloxifene group has no effect at all as in the expected population effect or a little bit lower. Dr. Chabner observed that, according to the Gail model, people above age 60 are at increased risk. He asked for an opinion on whether every woman without another factor that would proscribe its use should be on raloxifene to prevent breast cancer. Dr. Wickerham replied that the Gail score is used as a way to quantify risk within this clinical trial, but could conceivably be used as a tool to select individuals who may or may not be candidates when people become comfortable with it. He expressed the view that it is not an absolute criterion but simply a starting point in a reasonable risk benefit assessment that takes into account the Gail score but other things as well. Dr. Chabner pointed out that the estrogen receptor positivity findings represent an opportunity to try to understand tamoxifen resistance. Dr. Wickerham agreed and noted that NSABP already has begun to look at the molecular profile of the breast cancers that occurred in both trials while these women were on tamoxifen. One Pittsburgh group has begun that process to see whether a profile can be identified that would provide an insight into why resistance occurred.

Dr. Freedman asked about excluding patients where there was use of estrogenic substances in the past that might have influenced the progression, whether a history of that use was obtained, and whether the arms of the study were balanced. Dr. Wickerham replied that concurrent estrogen use was excluded. Women were permitted to enter the trial after a 3-month washout period of any of those products; all medications were characterized at the time of entry. In answer to the balance query, he observed that 20,000 people in the study would likely ensure a balance no matter what is examined. Dr. Meneses asked about overall adherence to the regimens. Dr. Wickerham explained that much time and effort was focused on adherence and compliance of both NSABP investigators or coordinators and the women coming into the trial. The goal was to make certain those coming into the trial knew what would be happening and the extent of the commitment they would be making. The original estimate for the STAR trial was that the level of noncompliance (i.e., dropping off medication but not out of the trial) would be 7.2 percent per year, but the actual level was lower. He stated that those figures are important because the sample size was defined based on those levels of assumptions; therefore, compliance was tracked carefully during the course of the study.

Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, commended the NSABP and NCI for spearheading these prevention efforts, noting that they provide evidence that an emphasis on prevention could lead to a significant health benefit in women and in other

diseases as well. He noted the concern that has been expressed regarding the group differences in the DCIS results in this trial and what the biology might be. He asked whether the estrogen receptor status of the DCIS lesions had been investigated and whether there had been an analysis to characterize the differences between the two groups. Dr. Wickerham replied that the groups had not been analyzed for differences, but the tumors are on hand and an analysis could be done. He alluded to the fact that there was a review of the histologic characteristics of the tumor from the original pathology report, with no excess of necrosis, and surmised that there would be the expected 75/25 split. Dr. Cowan asked whether any differences in the prognostic features of the invasive tumors were identified in the characteristics review. Dr. Wickerham stated that all of the histologic characteristics have not yet been analyzed, but the staging criteria suggest no difference. Dr. Cowan referred to the concern that AIs and SERMs may not be best when used in combination and questioned the choice of the combination in the P-4 study as opposed to a sequential use in the prevention. Dr. Wickerham clarified that the schema calls for raloxifene plus a letrozole/placebo and raloxifene or letrozole plus a raloxifene/placebo, so participants are on either the AI or the SERM.

Dr. Cowan observed that in the original trial the 5 years of tamoxifen regimen was based on adjuvant data that were carefully worked out by NSABP, but data for an additional 5 years do not exist. He asked whether there are plans for studying that. Dr. Wickerham replied that a formal study is not planned, but data exist in the osteoporosis setting for women taking the drug in a structured way through 8 years. No impact or detrimental effect to the bone was identified, nor were there unexpected or cumulative toxicities, and the benefits relative to breast cancer risk reduction were continued; so extrapolation would be necessary to find an answer. Dr. Runowicz observed that the results of P-2 STAR make raloxifene sound like an ideal preventive strategy but the Ruth trial and the editorial about raloxifene suggest that a better, safer drug may be needed, and she asked for comment. Dr. Wickerham briefly reviewed the design hypothesis and study results of the Ruth trial and expressed the view that the STAR results suggest that if a population at low risk for thromboembolic disease is selected as P-4 proposes, overall risk can be reduced, as well as death due to stroke. This becomes part of the risk/benefit equation and needs to be part of that informed consent process. Dr. Chabner alluded to the past concern about the possibility that the strokes and the increased thrombotic events occurred in a subset of women who had a predisposition because of inherited deficiencies in their anticoagulant factors, and he asked whether this threat had materialized. Dr. Wickerham replied that some of the serum and lymphocyte bank material was used to look at Factor V and prothrombin mutation. The finding was that Factor V and prothrombin did increase the risk of clot, but they increased it independent of tamoxifen. The risk increased in both groups equally and there was no justification for screening for those abnormalities for women receiving tamoxifen, either for prevention or for treatment, which would have even a greater impact.

X. ADOLESCENT AND YOUNG ADULT ONCOLOGY REPORT—MS. CHERI NICHOLS AND DRS. BARRY ANDERSON, KAREN ALBRITTON, AND MICHAEL CALGIURI

Ms. Cherie Nichols, Director, Office of Science Planning and Assessment (OSPA), OD, reminded members that the OSPA has led a number of PRGs, and she introduced members of the Adolescent and Young Adult Oncology (AYAO) PRG to present its report entitled "Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer." She observed that the themes of the report coincide with earlier discussions about the need for making a difference in this disease, continuing to provide scientific leadership, developing trans-community efforts, and ensuring access. The need for a PRG for this age group was proposed a year ago to Dr. Andrew von Eschenbach, then-Director, NCI, by Mr. Doug Ulman, Liaison Representative, Director's Consumer Liaison Group (DCLG). His proposal was accompanied by an offer from the Lance Armstrong Foundation (LAF) to match NCI funding for the effort. Presenters of the AYAO PRG report are: Dr. Barry Anderson, PRG Executive Director, and

Senior Clinical Investigator, Cancer Therapy Evaluation Program (CTEP), NCI; Dr. Karen Albritton, PRG CO-Chair, and Director, Adolescent and Young Adult Oncology, Dana-Farber Cancer Institute; and Dr. Michael Caligiuri, Nationwide Professor and Director, Comprehensive Cancer Center and Division of Hematology and Oncology, Ohio State University. Ms. Nichols acknowledged and thanked NCI and contractor staff who contributed to this report.

Overview. Dr. Anderson began by reviewing the rationale for the AYAO PRG: (1) cancer in the AYAO age range is a significant problem—almost 68,000 individuals ages 15 to 39 years were diagnosed with the disease in 2002 and there were more than 10,000 deaths; (2) AYA patients lack a health care niche; medicine and society are largely unaware of that population; and (3) survival in the AYAO age group has not improved in more than 2 decades, according to Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 1998. Dr. Anderson explained that the AYAO PRG's decision to define the adolescent and young adult population as comprising ages 15 through 39 was based on several issues: the gap in survival improvement is most pronounced in that population; the LIVE**STRONG** Young Adult Alliance came to the same conclusion based on a number of social and developmental factors; and young adult advocacy groups (Planet Cancer, Young Survival Coalition, Life Lab, and Fertile Hope) consider individuals in the 18-39 age range as their target population. Moreover, although AYAs are a heterogeneous population, programs at institutions serving them recognize this and use developmentally appropriate interventions for subsets within the group.

The charge to the AYAO PRG was threefold: (1) define and describe the issues that are unique to the cancers that occur in the AYA population and which distinguish that group from younger pediatric and older adult cancer patients; (2) assemble a cadre of experts in AYA medicine, biology, psychosociology, behavior, and business to identify what needs to be learned and implemented to promote cancer prevention and improve the survival and QOL of this population; and (3) facilitate the adoption and implementation of cancer research, social and health policy, community programs, and clinical interventions focused on AYA cancer prevention and treatment, and evaluate the impact of these efforts. Dr. Anderson reminded members that the AYAO PRG is a unique partnership between the NCI and LAF created as a result of the mutual interest of the NCI Pediatric Oncology Group and the LAF's LIVE**STRONG** Young Adult Youth Alliance. Benefits to the NCI derived from the collaboration include the opportunity to leverage NCI resources and facilitate the PRG process. Moreover, the Alliance's commitment to the PRG enhances the potential of realizing many of its recommendations. For the LAF, the collaboration has provided the opportunity to address a top priority issue through a process that is firmly established and well recognized.

Dr. Anderson reviewed the organizational structure of the PRG and described the three-phase PRG process. Leadership includes two non-federal Co-Chairs and the Executive Director from the NCI; membership includes 27 representatives of all major areas of expertise across the AYAO spectrum. At its initial all-hands meeting, the AYAO PRG planned a roundtable meeting, which was held this past spring. At the roundtable, 74 participants worked with the PRG to identify areas of need and opportunities to advance research and practice. In regard to the process, the AYAO PRG currently is implementing the final segment of Phase I, which is focused on developing recommendations. The PRG report has been prepared and is being presented to sponsoring agency leaders and the NCAB. Phase II will focus on implementation and begin with the establishment of an implementation group, and Phase III will be the reporting phase.

In regard to the AYAO Roundtable deliberations, Dr. Anderson reported that the participants were organized into 11 breakout groups, which reflected the issues that needed to be addressed. Core topic groups focused on biology, prevention/cancer control/epidemiology/risk, insurance, clinical care models, psychosocial/behavioral factors, and long-term effects. The Cross-Cutting Breakout Groups dealt

with issues such as access, clinical trials and research, health-related QOL, special populations, and awareness. Dr. Anderson reviewed the unique ways many of these issues affect patients in this age range.

Priority Recommendations. Dr. Albritton presented the first three recommendations of the AYAO PRG report and reviewed some of the underlying rationale for their development. Recommendation 1 is to identify the characteristics that distinguish the unique cancer burden in the AYAO patient. More specifically, the recommendation is to elucidate the unique biologic characteristics of AYA cancers and AYAO patients, elucidate life-stage and developmental characteristics, and identify and work to ameliorate health disparities. The priority tumors for this population were defined as sarcoma, leukemia, lymphoma, breast cancer, and colorectal cancer. Recommendation 2 is to provide education, training, and communication to improve awareness, prevention, access, and quality cancer care to AYAs. More specifically, the recommendation is to: raise awareness of AYA issues as a first step toward increasing the national focus and resource allocation; provide targeted education to patients, families/caregivers, and the public; and educate multidisciplinary providers to improve referrals and services. Recommendation 3 is to create the tools to study the AYA cancer problem. More specifically, the recommendation is to create a large prospective database to facilitate research, increase the number of annotated specimens to support research progress, create and modify the needed assessment tools, improve grant coding and search term standardization for evaluation purposes, and expand clinical trials to increase AYA treatment choices and accelerate treatment advances.

Dr. Caligiuri presented and briefly discussed the final two recommendations. Recommendation 4 is to ensure excellence in service delivery across the cancer control continuum. This includes developing, evaluating, and disseminating standards to improve outcomes and establishing a network or coalition of providers and advocates seeking to achieve a standard of excellence in AYA cancer care. Recommendation 5 is to strengthen and promote advocacy and support of the AYA cancer patient. More specifically, the recommendation is to address the subjective experience of AYA patients, build the capacity of existing resources to address AYA psychosocial needs, and evaluate existing programs and develop new interventions. Dr. Caligiuri cited Planet Cancer as a valuable resource for addressing psychosocial needs, but noted the need for broader dissemination. In regard to program evaluation, he emphasized the need for outcomes research to better understand what the best interventions are.

Dr. Caligiuri concluded by outlining steps that will be taken in Phase II of the AYAO PRG process. An Implementation Meeting is scheduled for November 10-12 in Austin TX, sponsored and organized by the LIVE**STRONG** Young Adult Alliance. The cross-disciplinary nature of the process will be maintained as diverse stakeholders from all backgrounds meet to provide a focused and structured approach to improving cancer prevention, cancer care, and QOL for adolescents and young adults with cancer.

Questions and Answers

Dr. Chabner questioned whether data had been presented to establish a survival problem in this group, noting that survival appeared to be high in comparison with older people and even younger people. In discussion it was noted that the reason could be that this is a group of diseases that have good prognoses, and that there is a need to gain understanding on a disease-by-disease basis. Dr. Albritton agreed that a biology- and disease-specific study would be needed for optimal understanding of the AYAO situation. Dr. Chabner cautioned against balkanization of the research area and for ensuring that there is enough understanding of the problem to warrant a special research effort. Dr. Meneses commended the fact that the AYAO problem was approached also from a developmental perspective in terms of the needs of this particular group. She suggested that contemporary communications vehicles be employed for disseminating educational materials. Dr. Runowicz questioned the age parameters chosen

by the AYAO PRG, and she suggested that there are two different groups of patients in that range of ages. Ms. Ryan agreed and suggested this could become an issue in developing research to explore issues. Dr. Niederhuber noted that, from NCI's perspective, there is a need for this PRG process to identify important biologic differences or scientific questions that are currently not being invested in or addressed.

XI. SCIENTIFIC UPDATE: CENTER FOR CANCER RESEARCH—DRS. ROBERT WILTROUT, MARY CARRINGTON, JAVED KHAN, DAVID WINK, AND STEVEN K. LIBUTTI

Dr. Niederhuber introduced the CCR update by noting that one of the perks of being part of the NCAB is to be able to hear some very exciting science. He said that he came to the NCI with a real passion about the intramural program and the importance of the intramural program to the extramural research community, as a resource in terms of the laboratory science and technology, for opportunities for translational research in the Clinical Center and also the opportunities for partnerships between the extramural community and NCI's intramural scientists. The intramural program has become one of the most rigorously and scientifically reviewed programs with which he has been associated. Dr. Niederhuber lauded Dr. Wiltrout's overall leadership, as well as Dr. Helman's efforts on the clinical side.

Introduction—Dr. Robert Wiltrout

Dr. Wiltrout expressed appreciation for the opportunity to present details about CCR's ongoing intramural research. He concurred with Dr. Niederhuber's comments regarding the process of reengineering the intramural program, which has resulted in a somewhat leaner organization with fewer principal investigators that hopefully is making even greater progress and inroads based on its ability to form partnerships within the NCI, across the NIH, and between intramural and extramural investigators.

NCI's intramural research is distinctive based on its critical mass of highly integrated basic and clinical scientists who work to solve complex scientific problems. The review and reward structure, which is somewhat different than the standard R01 type of approach, allows a quicker redeployment of resources in support of the NCI mission and goals to meet urgent public health needs and new opportunities. One example of this is the creation of an intramural laboratory focused on nanobiology to work in close concert with the efforts emanating from Dr. Gregory Downing and colleagues in the IMAT Program. In the past, this has been accomplished in the HIV and AIDS arena. Another recent success story from the intramural program is its work on the human papillomavirus (HPV). When NCI investigators are reviewed by the Board of Scientific Counselors (BSC), they must be able to defend their choices of projects. This rigorous process involves a retrospective review based on an investigator's work during the past 4 years. Dr. Wiltrout expressed the belief that most of the BSC would agree that the current portfolio contains high-quality projects. Another important aspect of the intramural program is providing access to the new clinical center. Having basic, translational, and clinical scientists working in close proximity in this new facility and surrounding buildings is a tremendous opportunity—and obligation—to translate basic science into clinically applicable breakthroughs on behalf of cancer patients.

The CCR is also comprised of four areas: discovery, basic research, clinical research, and translational research. A variety of training programs, ranging from basic science through clinical applicability and technology development, overlap these areas. A significant portion of funding comes to the CCR from the NIH, Office of AIDS Research. In the past, the NCI intramural program made seminal contributions to the identification of the AIDS virus, including the development of diagnostic tests and some of the drugs that continue to be used today in terms of providing care for these patients. This has led to another generation of research centering on the ability to profile the disease to inform better

treatments, particularly in the drug resistance area. Because patients are living longer, many of these patients are coming down with a higher frequency of malignancies; for this reason, a significant component within the CCR deals with AIDS-associated malignancies.

The CCR is also a comprehensive translational research program. It addresses nine areas: (1) cancer biology and etiology also; (2) HIV/AIDS research; (3) molecular targets and molecular oncology; (4) immunology, immunotheraphy, and immunoprophylaxis; (5) genetics and genomics; (6) imaging and biomarkers; (7) advanced biomedical technologies; (8) clinical infrastructure and support; and (9) CCR infrastructure. Dr. Wiltrout next presented a graphic to illustrate the infrastructure used to support translational multidisciplinary research across these nine areas. The infrastructure included: training, faculty, Center of Excellence, drug development, imaging, programs and initiatives, cores, HIV/AIDS, and epidemiology.

The CCR's mission includes the establishment of partnerships, such as between CCR laboratories and branches, across the NCI and the NIH, and between intramural and extramural investigators. Collaborations also are fostered with industry, pharmaceutical companies, other federal agencies, and national and international consortia, among others. Dr. Wiltrout shared a list of areas in which CCR funds are leveraged in support of intramural-extramural partnerships. Several of these include the Leukemia and Lymphoma Molecular Profiling Project, the HPV vaccine, and the Phase O initiative.

Dr. Wiltrout next introduced several of NCI's mid-career scientists to present to the NCAB some of the exciting investigations that are occurring in their laboratories. Dr. Mary Carrington will discuss hosting genetic variation and dramatic consequences for HIV disease. Dr. Javed Khan will talk about his studies with artificial neural networks, as well as a new, multi-agency initiative to develop approaches for gene discovery and analysis. Dr. David Wink will describe NCI's Redox Faculty. Finally, Dr. Steven K. Libutti will talk about the trans-NIH angiogenesis research program.

Influence of Immunogenetic Variation on HIV Disease—Dr. Mary Carrington

Dr. Carrington presented a scientific update on research concerning the influence of immunogenetic variation on HIV disease. Host genetic variation can influence the likelihood of HIV infection as well as disease progression after HIV seroconversion. The HLA class I genes, located in the major histocompatibility complex on chromosome 6, and the killer immunoglobulin-like receptor (KIR) gene cluster, located in the leukocyte receptor complex on chromosome 19, appear to play roles in this process. The products encoded by the HLA Class I genes and KIR genes serve as receptors and ligands for one another and are highly polymorphic. HLA Class I genes show extreme allelic polymorphism—there are many forms of a single gene. The KIR genes also show substantial allelic polymorphism and are polygenic in nature as well. Across haplotypes in humans, the number and type of KIR genes that present on chromosome 19 varies.

Natural killer (NK) cells represent the first line of defense against viral infection as well as tumor development. NK cells express a number of different receptors that regulate their activity, including KIRs. When inhibitory KIRs interact with their ligands, which are a specific HLA Class I allotype, a signal is sent to the NK cell not to kill the target because it has healthy, normal Class I expression. Some virally infected cells and tumor cells downregulate HLA Class I ligands; lack of inhibitory KIR ligands allows an activating receptor to send a signal to the NK cells to kill these cells.

Two genes that have been of particular interest regarding HIV infection are HLA-B and KIR3DL1, which encode molecules that serve as ligand and receptor. HLA-B is the most polymorphic gene in the human genome identified to date and KIR3DL1 also is highly polymorphic. In both cases, the polymorphism has been shown to have functional significance, resulting in differential binding between

KIR3DL1 and HLA-B subtypes. For example, KIR3DL1001 interacts with high affinity with a certain set of HLA-B allotypes, including B57, the most protective HLA allotype against HIV disease. The same KIR3DL1 subtype interacts with low affinity with a different group of HLA-B allotypes, including B27, another allotype that is protective against HIV. There also is a set of HLA-B allotypes that do not serve as ligand for KIR3DL1, for example B45; this group of alleles is known as Bw6. Individuals homozygous for Bw6 have no ligand for KIR3DL1 and thus serve as a control group for studying protective effects between specific combinations of KIR3DL1 and HLA-B subtypes.

Five AIDS cohorts, in which dates of seroconversion are known for each participant, have been used to study the effects of compound genotypes of KIR3DL1 and HLA-B on progression from seroconversion to an AIDS-defining illness. Individuals with specific combinations of KIR3DL1 and HLA-B progress slowly to AIDS relative to those who do not have the ligand for KIR3DL1 (individuals homozygous for Bw6). There are multiple distinct, independent effects of KIR3DL1 and HLA-B subtypes on HIV disease. The most protective HLA-B allele is B57; a combination of specific KIR3DL1 alleles plus B57 confers greater protection against HIV disease progression relative to any other genetic variant identified to date in these cohorts. The protection conferred by this combination of KIR3DL1 and HLA-B alleles also appears to apply to cervical neoplasia, which may indicate that combinations of these genes could offer varying degrees of protection against multiple diseases. These complex, abundant, epistatic or synergistic effects between KIR3DL1 and HLA-B are unprecedented with regard to any pair of genetic loci in human disease.

Questions and Answers

Dr. Daniel Von Hoff, Director, Translational Drug Development Division, Translational Genomics Research Institute, University of Arizona, asked about the sample size for the populations used in this study. Dr. Carrington answered that there were 1,400 seroconverters from the five cohorts, with perhaps 20 individuals per low frequency genotype or several hundred individuals for higher frequency genotypes. There were 67 individuals who had the highly protective combination of KIR3DL1 and HLA-B alleles.

Dr. Chabner asked if Dr. Carrington had worked with Dr. Bruce Walker, who has reported a cohort of men who seroconverted but never developed AIDS. Dr. Carrington responded that her laboratory is currently working with Dr. Walker to genotype these "elite controllers" with regard to KIR and HLA typing. She mentioned working with Dr. Mark Connors at the National Institute of Allergy and Infectious Diseases (NIAID), who also has identified a group of individuals who have controlled their HIV infections well. The protective KIR3DL1 and HLA-B genotypes have been found at high frequency among these patients, and it is likely that the same will be true for Dr. Walker's group. Dr. Freedman asked whether there was evidence that vaccines might work better in people with the protective genotypes. Dr. Carrington replied that currently there is no evidence for this, because there are no strongly protective vaccines. She added that developing therapies that increase NK cell activity probably would be useful; experiments performed *in vitro* and in macaques suggest that increased NK cell activity is beneficial for viral control.

Microarrays and Artificial Intelligence for Diagnosis, Prognosis, and Selection of Therapeutic Targets in Cancer—Dr. Javed Khan

Dr. Khan explained investigative work underway to use microarrays and artificial intelligence in the diagnosis, prognosis, and selection of therapeutic targets for cancer. Cancer artificial neural networks (ANNs) can be used to diagnosis cancers using gene expression profiles and to predict prognosis. ANNs are powerful pattern recognition algorithms modeled on the human brain. These algorithms are highly

adaptable and can "learn" from prior experience by error minimization. Input into ANNs can be any type of data, for example gene expression data or a combination of gene expression and clinical data. Output is numeric and there can be a number of clinical or diagnostic categories within the algorithms. There also are hidden layers to the algorithms that allow for nonlinearity in the data. ANNs are used in defense, weather prediction, and voice, handwriting, and fingerprint recognitions. Clinical applications include using ANNs in defibrillators to detect arrhythmias and give the correct shock, to detect myocardial infarctions, and for interpreting mammograms and other radiographs such as MRI scans.

A number of different cancers appear histologically similar—referred to as the small round blue cell tumors. Despite current modern diagnostic techniques, incorrect diagnoses of these cancer types continue to be made. ANNs could provide a useful tool for distinguishing between these types of cancer. ANNs were used to analyze expression of thousands of genes in tumor cells. A novel algorithm was developed to rank the genes and resulted in identification of 96 genes (out of 6,000) that could be used to correctly classify the small round blue cell tumors. Using expression profiles, the 96 genes were clustered based on diagnosis. For example, MIC2 was found to be overexpressed in Ewing sarcoma, but because it also is highly expressed in some rhabdomyosarcomas, it is thus by itself insufficient for making a correct diagnosis. Several other genes characteristic of certain tumor types also were identified, including IGF2 and a tyrosine kinase receptor. One gene in particular, CDK6, has been shown in siRNA knockdown studies to have a role in tumor growth; knockdown of CDK6 in a neuroblastoma cell line profoundly suppresses new growth. This work provided evidence that ANNs could be used to develop diagnoses and prognoses, and to identify potential target genes.

Neuroblastoma is another small round blue cell tumor that is heterogenous and has a poor prognosis. Gene expression arrays and analysis with ANNs were used to develop gene profiles or signatures that could be used to distinguish between patients with poor or better prognoses. The signature for predicting survival involved 19 genes and distinguished patients that survived from those who died with high significance.

The ultimate goal of this research is to develop clinical applications. The NanoBioSensor Initiative, a joint effort between the NCI, the University of Maryland, and National Aeronautics and Space Administration (NASA), has been started to develop applications. This initiative is developing technology to detect gene expression patterns as electrical output. DNA hybridization to an oligonucleotide probe results in an increase in current; this electrical output can be directly analyzed using algorithms such as ANNs and the information can be used for activities that include developing diagnoses and prognoses as well as gene sequencing and identification.

Combining genomics and machine learning algorithms will lead to the development of powerful tools for diagnosis, prognosis, and identification of target genes. The NanoBiosensor Initiative will further this work through a collaboration that involves multiple disciplines, including physicians, biologists, biochemists, mathematicians, and physicists. In the future, this technology may be useful for measuring drug levels and protein levels in tumors as well as gene expression.

Research Program of the Redox Faculty—Dr. David Wink

Dr. Wink described redox biology as very complicated and intricate. The Cancer Redox Biology Faculty is working to understand how redox biology—particularly oxidative stress, radicals, antioxidants, and nitrosative stress—plays a role in carcinogenesis, inflammation, cancer treatment, and cancer prevention. Oxidative stress occurs during the act of breathing. Humans use oxygen, which then can be reduced simply and chemically to species such as hydrogen peroxide. This, in turn, can be converted to a very reactive chemical species called hydroxyl radicals and metallo-oxo species, which are known to

damage cells. Oxidative stress plays a role in almost every single disease or degenerative processes such as aging, heart disease, and a variety of acute and chronic neuronal diseases. On the other side, however, oxygen can produce other molecules, such as nitric oxide, which is associated with air pollution, cigarette smoke, and all the deleterious effects witnessed in brown smog over cities. Around 1980, nitric oxide, which is an active ingredient in nitroglycerin, was discovered to regulate blood pressure. This changed the perception about toxic intermediates; hydrogen peroxide and NO may be important in regulating a number of physiological processes. Other molecules also have been discovered to influence body regulations. Carbon monoxide, for example, recently has been found to serve as a key regulatory molecule of inflammation. Hydrogen sulfide, the compound that makes eggs stink, is found in μM levels in the human brain.

The goal of the faculty is to bring together researchers within CCR/NIH and the extramural community to provide a vehicle to discuss and facilitate collaboration in redox biology. The Steering Committee agreed on three objectives to foster cooperation: (1) establish a course in "Redox Biology in Cancer," with complementary seminars; (2) hold workshops to expand on promising areas identified by the Steering Committee (two workshops have been held on the topics of imaging and biomarkers for oxidative stress, and redox-based non steroidal anti-inflammatory drugs (NSAIDs); and (3) focus collaborative research on identified areas of need. Measurement remains the most controversial issue in redox biology. Dr. Wink shared the lecture topics and speakers for the redox biology course that has been taught for the past 3 years. He noted that, even with a relatively young faculty, a number of different collaborative papers have been published during the past 2 years.

The current Redox Faculty is focusing on redox-based NSAIDs, which alleviate the gut toxicity of conventional NSAIDs. Another advantage of these novel compounds is that some moieties offer anti-thrombotic properties; this is important because chronic use of NSAIDs can lead to drug toxicity, and NSAIDs have thrombotic properties that can lead to stroke and heart attack. Dr. Wink mentioned that common NSAIDs include aspirin, indomethicin, sulindac, and diclofenac. Redox-active moieties include nitrogen oxide, thiol-based NSAIDs (e.g., ADT and oltipraz), and superoxide (SOD) mimetics (e.g., nitroxides). Collaborators working with these compounds include Drs. Piero Del Soldato (CTG), Bruce King (Wake Forest University), Larry Keefer (LCC/CCR/NCI), and the Division of Cancer Prevention.

The redox-based NSAIDs have been examined for potential use in chemoprevention, treatment, and imaging. Dr. Wink described chemoprevention properties of redox-based NSAIDs, as studied by Dr. Grace Yeh, LM/CCR. Dr. Yeh has been interested in polyaromatic hydrocarbons and how they can be used to block the activation of the polyaromatic hydrocarbons. She studied Phase I enzymes extensively, in which, when a polyaromatic hydrocarbon is present, the xenobiotic responsive element is activated, which in turn activates the p450. The p450s oxidize the polyaromatic hydrocarbons to form the carcinogen, which ultimately labels the DNA. She has screened a number of compounds and natural products and has demonstrated that some compounds can block this pathway. There also is another strategy that can be employed to block the carcinogens, which is a focus on Phase II enzymes. Phase II enzymes upregulate other enzymes that scavenge the carcinogen and detoxify it. The redox faculty is aiming to discover agents that help to block Phase I and increase Phase II. Dr. Yeh's group surveyed a variety of NSAIDs and found that some worked whereas others did not. The thiol-based NSAIDs, as well as the nitro-aspirin, for instance, would knock down Phase I, and both of these sets of compounds increased Phase II. Tumor biology studies will be examining mammary and lung tumors in animals. Further work also is planned to use compounds provided by the Division of Cancer Prevention to synthesize a better molecule.

Regarding the use of redox-based NSAIDs in cancer treatment, the goal was to identify agents that can help increase efficacy of conventional therapies, particularly radiation and chemotherapy. The

first objective was to determine whether or not they maintained their NSAID efficacy; they all inhibited the PGE2 synthesis. Dr. Wink observed that a very preliminary result with the S-NSAID revealed an 80 percent reduction of one of the compounds for the growth rate of the PC3 cells; additional studies will utilize a number of different cellular- and tissue-based assays by Dr. Dave Roberts. The redox faculty also is drawing on the work of Dr. Robert's group (*Matrix Biol* 2005), who has grown a tumor in media and seen new vessel formation; pro-angiogenic or anti-angiogenic potential can be determined by measuring the growth or the width of the growth. Salient conclusions reached to date include that: (1) S-NSAIDs have anti-angiogenic properties and (2) NO-based NSAIDs have pro-angiogenic properties.

Dr. Wink next explained Drs. Murali Krishna and James Mitchell's work on oxygen and redox EPR and MRI imaging with nitroxides. They focused on imaging free radicals in tissue. They can take the relative rates of induction of these nitroxides, and they can decipher the different pixels. Dr. Wink showed this through an oxygen map and a redox map, illustrating the benefit of imaging as a diagnostic tool. Dr. Wink said that Dr. Larry Marnett, Vanderbilt University, was able to derivatize indomethicin with a fluorophore and, upon feeding it to the animal, found that in cells that were specifically expressing COX-2, the fluorophore was taken up. He measured the concentration and found it to be up to 100 μM, which is similar to the range for imaging.

Dr. Wink concluded with a model for testing redox-based compounds. He noted the enthusiasm of all the people who have been involved. The redox faculty and collaborators have been able to ask basic biology questions and then translate them into cellular models. The faculty now has the capacity to now screen different therapeutic agents, and serves as a fulcrum for this science.

The Trans-NIH Angiogenesis Research Program—Dr. Steven K. Libutti

Dr. Libutti explained that he would describe the Trans-NIH Angiogenesis Research Program (TARP) in general, and then highlight the CCR's contribution to the program. TARP began in 2003, when representatives of the Juvenile Diabetes Research Foundation met with then NCI Director, Dr. Andrew von Eschenbach. They postulated that angiogenesis and perturbations of vascular development underpin a number of different diseases, and are important for cancer progression and metastases, diabetic retinopathy, heart disease, rheumatoid arthritis, and other disease processes. They suggested a collaboration to leverage information across disciplines and to speed the progress of the understanding of vascular biology. That meeting became the impetus for a working group that discussed areas of possible collaboration. Initially comprised of the NCI, Juvenile Diabetes Research Foundation International (JDRF), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the working group quickly incorporated other institutes, such as the National Heart, Lung, and Blood Institute (NHLBI), the National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Child Health and Human Development (NICHHD). The working group held a workshop in the spring of 2004, and experts from various disciplines, in both the extramural and intramural communities, attended to discuss where there might be collaboration and how to move the field forward. This workshop resulted in suggestions for a number of initiatives, from which a mission statement for the TARP was formulated.

TARP's mission is to: (1) encourage and facilitate the study of the underlying mechanisms controlling blood vessel growth and development; (2) identify specific targets and to develop therapeutics against pathologic angiogenesis to reduce the morbidity due to abnormal blood vessel proliferation in a variety of disease states; (3) better understand the process of angiogenesis and vascularization to improve states of decreased vascularization; (4) encourage and facilitate the study of the processes of lymphangiogenesis; and (5) achieve these goals through a multidisciplinary approach, bringing together

investigators with varied backgrounds and varied interests. In the FY 2005 House Report 108-636 of the committee that oversees the NCI budget, the committee had been aware of the workshop and encouraged the continued establishment of collaborations and the pursuit of some of the findings of that workshop.

TARP has had notable accomplishments over the past 2 years. It has organized and sponsored the aforementioned workshop on opportunities for cross-discipline collaboration for vascular developmental biology research. A Web site, www.tarp.nih.gov, has been established. New collaborative RFAs, which involve the NIDDK, JDRF, NINDS, NHLBI, NEI, and the NCI, have been initiated. TARP has organized and co-sponsored a Nature Insight publication on angiogenesis, performed a review of the angiogenesis grant portfolios for five member ICs, and convened a panel to review the current angiogenesis portfolio and to offer opinions on new directions and opportunities. Finally, it opened an Angiogenesis Core Facility at the CCR Advanced Technology Center (ATC) in May 2006.

The Angiogenesis Core Facility has as its mission to: (1) validate existing angiogenesis assays and reagents so that investigators can be speaking the same scientific language in various institutions; (2) develop new assays focusing on molecular pathways and systems biology; (3) develop animal models to study the biology of angiogenesis on a molecular or cellular scale; (4) provide clinical trial support to measure changes in angiogenesis in patients on clinical studies; and (5) expand its capabilities over time to provide support services to other investigators. The core facility occupies approximately 1,500 square feet of laboratory space at the Advanced Technology Center where *in vitro* and *in vivo* assays can be performed. It operates under the leadership of Dr. Frank Cuttitta, and has a number of investigators who have implemented a number of existing assays, such as the directed *In Vivo* Angiogenesis Assay, which was developed in the laboratory of Dr. William Stetler-Stevenson.

One of the new assay approaches to measuring angiogenesis involves microvascular endothelial cells. Investigators in the field of vascular biology have been using various preparations of these cells, whether they be from human umbilical veins, so-called HUVECs or dermal or lung microvascular endothelial cells, to study the effects of various agents on angiogenesis, and have assumed that these cells are pure populations of vascular endothelial cells. Dr. Cuttitta and his team in the Core found that most of the commercial preparations that are available to investigators are a mix of both vascular and lymphatic angiogenesis progenitors, endothelial cells that can line both lymphatic and vascular networks. He made the observation by staining some of these commercial preparations and found that up to 20 to 30 percent of the cells are of lymphatic origin based on their LYVE-1 positivity. The receptor profiles on these cells are very different with respect to different VEGF receptor moieties. Dr. Cutitta developed a flow through methodology to separate those agents that affect lymphatic biology by using magnetic beads with antibodies against LYVE-1, as well as beads that are a positive selection, he came up with a flow through that is purely positive for vascular endothelial cells and eliminates the lymphatic cells. Based on the validation of this methodology, Cambrex, which is one of the more common companies that make available endothelial cells, now uses this technology to make available pure populations of vascular endothelial cells for use by investigators across the country.

The facility's short-term goals aim to standardize investigative approaches by: (1) establishing reliable *in vitro* and *in vivo* angiogenesis assays; (2) identifying commercial sources of primary human blood vessel endothelial cells with low lymphatic contamination; and (3) identifying commercial sources of potent angiogenic factors, such as VEGF, to use as standards and respective suppressor compounds for that activity. Long-term goals target bench to bedside applications. These include the development of new *in vitro* and *in vivo* angiogenesis and lymph angiogenesis assays, which better mimic the clinical setting, and the modification of existing assays to measure patient endpoints when patients are on pro or antiangiogenic therapies. The identification of new angiogenic, both anti and pro, as well as lymphangiogenic drugs using established assays is a further objective. Finally, the facility aims to serve

as a training center for the intramural and extramural communities and propagate standardization in the field.

Dr. Libutti closed with an acknowledgement of the members of the TARP steering committee, which represent a number of different institutes, as well as the efforts of Ms. Kathleen Schlom, Office of the Director, NCI.

XII. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 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 2,164 applications were reviewed requesting support of $ 591,824.139. The subcommittee adjourned at 5:30 p.m.

THURSDAY, SEPTEMBER 7, 2006

XIII. NCI CANCER CENTERS DIRECTOR'S REPORT—DRS. JOHN MENDELSOHN AND MARTIN D. ABELOFF

Drs. John Mendelsohn and Martin D. Abeloff presented recommendations from the NCI-designated Cancer Center directors to accelerate successes against cancer. The recommendations resulted from two meetings and a number of teleconferences between the Cancer Center directors and the NCI Director, and were shared in a report that aimed to diminish confusion over goals and expectations regarding the 2015 target, provide a blueprint for achieving what is possible, cope with frustration over the reduction in NCI funding at a time of great opportunity for increased successes, and recognize the advantages of increased collaboration and joint activities. Key points from the report include: (1) NCI-designated Cancer Centers have implemented programs that lead the way in each of the three initiatives of the NIH Roadmap; (2) Cancer Centers, unlike the NCI, have dual missions: research and dissemination of improved care to patients; (3) deaths from cancer can be reduced substantially by broadening the application of current knowledge, and Cancer Centers can lead the way; and (4) the promise of "personalized" medicine is achievable.

The Cancer Center Directors' Working Group identified four goals: (1) reduce the burden of cancer through research in the areas of prevention, detection, treatment, and survivorship, and create a strategy for success; (2) identify ways in which NCI-designated Cancer Centers can enhance collaboration with each other and with other stakeholders in the pursuit of our shared mission; (3) suggest initiatives that will enable the Cancer Centers to extend their research beyond their local communities and to provide leadership in the wide dissemination of best practices in cancer and prevention; and (4) create a realistic vision of the potential for future successes and identify the roadblocks.

Notable progress has been made. The ACS, for example, has performed a midpoint analysis of the goal of 50 percent reduction in deaths, 1990-2015, and projected the success rate to be 23 percent

(Byers et al., *Cancer* 2006;107(2):396-405). Additionally, the projected decrease in breast, male lung, and colon cancers is tracking at 50 percent. Prevention and early detection are more important than treatment in these successes, and more can be achieved by increased participation. Collaboration and synchronization with stakeholders (e.g., other Cancer Centers, state care providers, professional organizations, pharmaceutical and biotechnology companies, patient advocacy groups, and government agencies) remains important. This exercise has succeeded in energizing the directors of NCI-designated Cancer Centers to collaborate in research and dissemination of best practices, and to advocate aggressively for increased public awareness and governmental funding.

Regarding prevention, there is a need for uniform dissemination and an educated and motivated public. Because cancer is a disease that starts as a premalignant clone of cells and progresses, early interventions should be effective. In addition, endorsement of the recommendations of the National Cancer Policy Board should be a priority. Immediate strategies address the importance of acting on risk factors that reflect lifestyle (e.g., tobacco use, obesity, physical inactivity, and diet), as well as intervention by health care providers (e.g., colonoscopy, mammography, PSA, Pap smear, vaccination, chemoprevention, and smoking abatement). Approaches to the long-term resolution include: clinical trials to discover molecular targets for early detection of high-risk and precancerous lesions and identification of targets for chemopreventive therapy; chemoprevention clinical trials (i.e., risk-based interventions); clinical research in behavioral sciences; and the need for databases and powerful informatics to establish risk profiles for individuals and for high-risk populations. Other issues to take into consideration with prevention are the length and cost of clinical studies, the epidemic of childhood obesity, disparities in provision of and payment for health care, and the thought that scientific knowledge does not guarantee clinical implementation.

Cancer clearly is more curable when it is detected early. Research results will come in faster if the focus is on high-risk populations: cancer survivors, genetic predisposition, environmental exposure, and family history. The technology involved in early detection includes genomics, proteomics, and immunohistochemistry; X-ray and MRI imaging; molecular imaging; and informatics and computational biology. Immediate strategies involve partnering with: (1) government agencies and providers to expand the clinical use of validated screening methods; (2) advocacy groups to pursue payment from Centers for Medicare and Medicaid Services (CMS), insurance, and health plans; (3) state public health departments and health care providers to disseminate information on health benefits and on points of access; and (4) other Cancer Centers to share tissue resources and advance technology platforms. The report identifies several long-term strategies, including collaboration in large-scale clinical trials to discover and validate biomarkers and the application of new technologies in genomics, proteomics, immunohistochemistry, and molecular imaging. It also is important to continue fundamental, basic research on genetic and molecular abnormalities in cancer. Finally, it was recommended that, through the NCI and governmental agencies, a standardized electronic database of medical and scientific information and patient medical records be created.

Systemic treatment is contributing significantly to the decrease in the mortality rate in breast cancer and probably in other common solid tumors. Recent advances in targeted therapy are not yet reflected in encouraging mortality statistics. There is an urgency to make progress in cancers refractory to current therapeutic approaches, but obstacles to collaboration and coordination must be overcome. One of the immediate strategies to address treatment in the short term is to work with the NCI as Cancer Center directors to activate the Clinical Trials Working Group (CTWG)'s recommendations to improve NCI's role in supporting innovative clinical research. Additionally, top priority should be placed on training, recruiting, and supporting clinical investigators, and redundancy in clinical research should be reduced by a more effective sharing of services, technologies, and tissue specimens. Further collaboration between government agencies, industry, and Cancer Centers across the spectrum of clinical

research also can help accelerate progress in the short term. Longer term approaches involve the implementation of the extensive CTWG recommendations on collaboration, coordination, standardization, and infrastructure support in clinical research; the creation of a unified, standardized national Web-based clinical trials information system; and the investigation of new technologies and targeted therapies with the goal of achieving personalized treatments for cancer. Other considerations that are important are the ideas that: (1) continued and enhanced support for fundamental research, particularly on the genetics and biology of cancer, is necessary to accelerate the pace of treatment advances; and (2) the regulatory environment and inadequate health care system threaten the translation of science to clinical innovation, particularly in underserved populations.

Survivorship is an area that needs a comprehensive approach. In particular, the increasing mobility of the U.S. population has created a need for uniform guidelines and electronic summaries of patient records, and longitudinal research is needed to better serve cancer survivors. To address this in the short term, Cancer Centers should collaborate with NCI's Office of Cancer Survivorship on the data warehouse and with the American Society of Clinical Oncology (ASCO) in developing clinical practice guidelines; moreover, they should broaden already established educational and support programs for patients and families. Key issues to be dealt with over the long term include: Cancer Centers working more closely and effectively with the community providers in terms of followup care and their leadership role in developing a clinical research focused on understanding, detecting, avoiding, and treating late complications of cancer and its treatment. The appendix of the full report contains material on current survivorship activities of the Cancer Centers, as well as reports to the President's Cancer Panel and some very good reports by the Institute of Medicine's (IOM) Survivorship Report.

Key ideas about collaboration are that optimizing collaboration is essential to accelerating successes against cancer, and collaborations involving individuals (micro-scale) within or outside a Cancer Center are frequent and productive. Moreover, there is a great need to enhance institution to institution collaboration (macro-scale), and true translational science is, by its nature, a much larger undertaking than discovery science. The Working Group suggested five immediate strategies for Cancer Centers: (1) form a collaborative chemoprevention trial consortium of Cancer Centers and academic medical centers; (2) expedite research on biomarkers by multiplexing hundreds of candidates; (3) facilitate collaboration in therapeutics between industry and academia by developing shared licensing agreements; (4) develop and implement standardized databases for Cancer Centers' collection and analyses of survivorship information; and (5) take the lead in disseminating cancer care guidelines in collaboration with state health departments and cancer plans. Longer term efforts should engage the interest and involvement of pharmaceutical and biotechnology companies in chemoprevention and engage health economics experts to overcome barriers to development of translational discoveries. Moreover, a commercial consortium (similar to the SNP consortium) could be formed to invest jointly in the discovery of new technologies in proteomics. Research strategies could be implemented to identify problems experienced by a large cohort of cancer survivors and to explore interventions and treatments. Finally, the Cancer Centers could bring together fragmented efforts of the NCI, Centers for Disease Control and Prevention (CDC), CMS, and other DHHS agencies to coordinate funding and dissemination of cancer control efforts. Other considerations for collaboration are that a more effective use of shared resources in Cancer Centers could be fostered throughout the country, and that cultural changes across academia, industry, government, and the financial community are required to achieve the level of collaboration noted in the report.

Regarding dissemination, there is striking heterogeneity in the U.S. population in knowledge of best practices and evidence-based approaches to cancer interventions. Furthermore, the disparities are greatest in communities not directly proximal to or traditionally linked with Cancer Centers. A major barrier is the limited CMS and private payor reimbursement for cancer prevention, screening, early

detection, or survivorship issues. The immediate strategies recommend the development of an infrastructure to link Cancer Center expertise with community hospitals, clinical oncologists, and primary care physicians to utilize electronic technology to provide information for Cancer Centers to the diverse communities. Better use of the state cancer registries, Surveillance, Epidemiology, and End Results (SEER) data, and geographic information systems (GIS) mapping could help identify areas and populations of disproportionate need. An additional approach is to supplement Cancer Center Support Grants (CCSG) to link Cancer Centers in a regional network with community hospitals, clinical oncologists, and primary care physicians. Longer term strategies in dissemination involve: CMS support for demonstration projects, led by Cancer Centers, to test implementation strategies for population-based cancer control efforts; the development of metrics to continuously monitor effectiveness of efforts; and the planning and support of national outcomes studies through a national cancer data system working in connection with SEER and the National Cancer Data Base (NCDB).

Questions and Answers

Dr. Niederhuber expressed his appreciation for Dr. Mendelsohn's leadership, as well as Drs. Abeloff's and Johnson's work, in fostering good dialogue among the leadership of the cancer community. He requested that Dr. Mendelsohn continue as a point person in the effort to extend the recommendations in the NCI Cancer Centers Directors' Report through the American Association of Cancer Institutes (AACI) to non-NCI-affiliated cancer institutions. Dr. Coffey affirmed the importance of the Cancer Centers. He offered several ways to affect prevention, treatment, and the other areas discussed by the report; these included adding cancer preventive agents to food and water, and considering the development and use of cancer vaccines.

Ms. Giusti raised the issue of NCI funding and wondered what NCI's message to decision makers should be about its funding, and what the NCI should do to make the message consistent and uniform; she also suggested that the NCI should consider how to take advantage of the industry's support of oncology, and she described issues involving philanthrophy and cancer. She commented on the critical importance of collaboration across the cancer centers, especially in the uncommon cancers. Ms. Giusti noted that the patients and advocacy groups are willing to help the NCI in any way possible.

Dr. Chen requested further information about the role of disparities in Cancer Centers. Dr. Mendelsohn said that the NCI could assume a greater role in pulling together advocacy groups and reminding the American people that cancer is the most common cause of death in the United States for those under age 85. Dr. Abeloff pointed out that the accrual of minorities into clinical trials is one of the rigorous parameters set up for a center to become an NCI-designated Cancer Center or to retain its current Cancer Center status.

Dr. Chabner observed that two things will make a difference in terms of overcoming cancer: early detection with prevention, and treatment; but there is a serious national problem regarding the time that it takes for a protocol to be reviewed and activated in the Cancer Centers. Dr. Mendelsohn suggested that the agencies which impose the regulations should meet and discuss what each is doing. He noted that about every 6 months to 1 year, a major regulatory policy is adopted that disrupts everything that has been done in the past years; Medicare's reimbursement for patient care costs in clinical trials is a recent example. Dr. Chabner recommended that the NCI coordinate a common policy among the Cancer Centers, the clinical trials, and industry about how trials should be reviewed and activated. Dr. Doroshow said that the NCI has control over the Cancer Center Support Grant (CCSG) guidelines, but not other things. Regarding the time process, Dr. Doroshow mentioned that the NCI funded a review at Cancer and Leukemia Group B (CALGB), which revealed that it takes 384 steps from the inception of a trial concept for it to be approved by the CALGB; no patient is enrolled during those steps. These steps relate to

internal review boards (IRB) and a series of feedback review loops with individual reviewers. Dr. Chabner added that, in each of the Cancer Centers, there is a scientific review by an IRB that goes back over the whole process before the activation process. Dr. Barker noted that NCI's recent dialogues with the Food and Drug Administration (FDA) serve as examples of the type of engagement in risk benefit needed to encourage the American people to buy into cancer medications. Dr. Abeloff predicted that this will become the greatest impediment to young researchers, because young faculty members already are frustrated that they cannot work in a more efficient way.

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources, said that many of the recommendations mirror what the Translational Research Working Group (TRWG) is developing, and that the SPORE directors and the EDRN group are dealing with similar issues. He applauded the Cancer Centers for taking a leadership role in stimulating activity to support collaboration, coordination, and cooperation.

Dr. Everson asked about new approaches to developing an effective infrastructure to link Cancer Center's expertise with community hospitals, clinical oncologists, and primary care physicians. Dr. Abeloff answered that this need focuses on developing the infrastructure and the methodologies to determine why this has not happened and how to improve the situation. Dr. Mendelsohn offered that the word "collaboration" should be viewed in a new light; it is possible for a health care system to work where more is shared between physician practices, oncologists, the Cancer Centers, and other groups where a patient would receive the best value of care when a community of doctors becomes the "whole" doctor.

XIV. REPORT OF THE WORKSHOP TO REVIEW THE NCI'S RAPID ACCESS TO INTERVENTION DEVELOPMENT (RAID) PROGRAM—DRS. JOSEPH E. TOMASZEWSKI, JOHN MENDELSOHN, AND JAMES DOROSHOW

The NCI's Rapid Access to Intervention Development Program (RAID). Dr. Joseph E. Tomaszewski, Deputy Directory, DCTD, described the RAID program. The concept for this program was reported to the NCAB in December 1997 by Dr. Bob Wittes, who was then the Division Director, DCTD, and approved by the Board of Scientific Advisors (BSA) in February 1998. In March 2000, the BSA endorsed the continuation of the program. In July 2005, a workshop, chaired by Dr. Mendelsohn, was held to review the program, and participants included scientists from academia and the pharmaceutical drug industry. Dr. Tomaszewski explained that, following his introduction, Dr. Mendelsohn would present a report on the 2005 workshop, and Dr. Doroshow would follow with the NCI's response and the Division's action plan for implementing the report.

The RAID program was created to promote the development of anti-cancer agents from academic centers. It provided access to what primarily is a preclinical contract research program managed by NCI's institutions Developmental Therapeutics Program (DTP). This allowed studies to occur under the investigator or academic center sponsorship rather than under NCI's sponsorship through the Cancer Therapy Evaluation Program (CTEP). Examples of RAID tasks include the acquisition and formulation of bulk drugs, the production of a variety of biologicals, the testing of the efficacy of an agent in a variety of animal models, and the conduct of relevant pharmacology and toxicology studies in an attempt to bridge the gap between a lead discovery and a drug for investigation.

RAID's unique features include the partnering of NCI internal and contract research and development (R&D) resources with extramural academic scientists needs; it also allows facile access to NCI's in-house expertise. The output from the program is very tangible, in that it provides data and reports that are suitable for investigative new drug (IND) submissions, data for licensing to third parties,

and products for clinical trials. The goal has been to use between $10 and $15 million per year of existing contract research resources.

There are eligibility requirements for participation in RAID. The program was designed such that only academic or nonprofit investigators may apply; it is expected that most applicants for activities funded by RAID will have an appointment in an institution with an NIH-assured IRB, or have formal collaborations with a staff member of such an institution. Research collaborations between academic and any size corporate partner are acceptable, provided that the technology is not yet licensed. Additionally, technology can be licensed to a small business (SBIR).

Dr. Tomaszewski next shared two examples of projects and their outcomes.

(1) Dr. Elizabeth Jaffe, Johns Hopkins, worked on an allogeneic pancreatic cancer vaccine. The background indicated that tumor cells that were genetically modified to secrete GM-CSF would generate a much more potent T cell response. It was not feasible, however, to accomplish this in an autologous fashion, as the cost and the amount of time involved, especially with pancreatic adenocarcinoma, was prohibitive. An allogeneic vaccine strategy, therefore, was adopted, and Dr. Jaffe requested production of two clinical grade GM-CSF secreting lines, which were designated as PANC 6.03 and 10.05, for treatment of pancreatic adenocarcinoma patients. Production conditions were established at the NCI FCRDC facilities by the Biopharmaceutical Development Program (BDP) to produce sterile lines suitable for human use. Approximately 240 vials of each cell line were produced. It took six production runs to produce one of the agents; the other one, which was a much more difficult process, took 12 runs to produce the materials. Additionally, a Drug Development Group (DDG) project was employed to produce sufficient material to conduct a Phase II trial in 60 patients. The preliminary analysis of these studies reveals that the 1- and 2-year survival rates are 88 and 76 percent, respectively.

(2) The work of Dr. Michael Sporn, Dartmouth, required the synthesis of some triterpenoids labeled as CDDO and CDDO methyl ester to allow *in vivo* preclinical testing. These particular triterpenoids bind to PPAR gamma, induce differentiation in several tumor types, and suppress the *de novo* synthesis of COX-2 and iNOS. The application was submitted in February 1999 and reviewed in April; in October, 25 grams of each compound were delivered to Dr. Sporn. He completed *in vivo* studies with both agents and returned to the NCI in April 2001 for further preclinical and clinical development through the DDG. NCI's IND was filed and approved earlier this year, and there are two Phase I trials open. To date 10 patients have been treated with this particular agent.

RAID has funded 16 cycles, in which 336 applications have been received and 119 of those have been approved. To date, 81 projects have been completed and 35 INDs have been filed and approved by the FDA. More than 1,600 patients have been treated with these agents and, through interactions with the program, 28 of these agents have been licensed. The cost for the entire program has been about $91 million.

Report of the Workshop To Review the NCI's RAID Program. Dr. Mendelsohn served as Chair of the workshop. He noted that Drs. Bill Hait and Lou Weiner chaired subcommittees on small molecules and biologics, respectively. There also was tremendous interest and participation by NCI staff representatives, as well as staff support. At the workshop, held on July 13, 2005, participants were asked to review the goals, operations, and track record of RAID, and to make recommendations.

Several major issues were identified during the workshop and are summarized in the workshop report. (1) The endpoint should be entry into Phase 0/I clinical trials. (2) Review and oversight should involve continuity rather than *ad hoc* evaluation; yearly checks on progress; and tougher enforcement to

ensure that investigators meet specific deadlines and milestones, or exit the project. (3) NCI staff should be delegated with greater authority over the process when investigators accept funds and then delay in meeting research targets, ignore recommendations, or lose interest. (4) NCI drug development staff should have authority to oversee contractors selected at FCRDC. (5) A two-tiered peer review system is proposed, such that the committee that provides the second (technical) review would be charged with oversight, including an annual review of progress. (6) NCI staff should exercise the authority to check the quality of compounds developed by investigators and contractors and to review data from their laboratories to make decisions. (7) Investigators should agree to accept (or formally address) advice and expertise provided by the NCI, in a joint and collaborative effort to move their discoveries into the clinic; investigators, however, would retain intellectual property rights.

Dr. Mendelsohn concluded with several comments about the workshop. (1) NCI staff who made presentations clearly understood the complexities of drug development. The participants felt that there are too few such individuals with the required experience and expertise to expeditiously move new drugs in the various NCI intramural and extramural programs into the clinic. Because of competition with big pharmaceutical and biotechnology companies, pay levels may have to be higher and authority may have to be increased. (2) The primary review process must be stringent in accessing the capability and commitment of the investigator and his/her institution to take a research discovery and perform the experiments required to move it into the clinic. Strict timelines should be established, with the opportunity for NCI experts to move into a strong mentoring position, or—if necessary—to take over the project (but not the intellectual property). (3) This program has major challenges: coordinating a research project involving an academic researcher, NCI staff and resources, and contractors performing specific stages in the process. (4) Throughout the process, the NCI should be friendly, supportive, but firm.

DCTD RAID Action Plan: Response to RAID Workshop Report and Recommendations. Dr. Doroshow focused on three points in describing the implementation of the recommendations to improve the RAID program: (1) improving the decision making process; (2) enhancing management support; and (3) increasing infrastructure support. He began with a graphic that illustrated the reorganization of RAID drug development. To maximize RAID's return on investment, it was perceived that better definition and communication in the areas of scientific priority focusing on disproportionate unmet needs—particularly rare cancers, pediatric cancer, classes of biologics, and natural products—was needed.

The two-tiered evaluation process that Dr. Mendelsohn outlined will be implemented shortly. A new Evaluation and Oversight Committee will provide input on project recommendations and pipeline prioritization, and subcommittees will be established to address small molecules and biologicals. DTP staff will be involved in addition to *ad hoc* experts. This plan will begin with RAID's Cycle 18 review in the winter of 2007. Regarding the initiation of the projects, it is important for all involved parties to understand what the RAID program will and will not do, as well as how decisions about the projects will be managed, including "no-go" decision points. To improve the deployment of RAID resources, the principal investigator's organizational and intellectual property capabilities and ability to file an IND will be assessed. Moreover, comprehensive project plans will need to be developed and the feasibility of assisting with clinical trial planning will be examined. A DCTD project management office is being established to lead in the development and implementation of comprehensive drug development plans and reinforcement of milestones and deliverables. Two of four planned project managers have been recruited to lead trans-divisional teams. Dr. Doroshow displayed a chart that illustrated the project development plan and timeline from an NIH RAID cancer-related project.

Dr. Doroshow next described efforts to improve the infrastructure for investigators. To help investigators, a RAID principal investigator training program will be developed and implemented, and a policy and procedures manual will be created. Currently, a RAID Investigator 101 course is under development, incorporating FDA and NCI collaboration. Regulatory support services also will be made available to RAID principal investigators to assist in IND submission and avoid delays in trial initiation, facilitate subsequent interactions with the FDA, and improve planning for clinical trials. Because of the expense involved in Phase I trials, NCI Clinical Center resources are being made available to individuals who have RAID projects to open trials. Currently, three trials open at the Clinical Center include materials that were made by the RAID program to assist investigators either in speeding the accrual process or providing a different schedule for the application of a particular agent. This service will be reevaluated as new data become available and guidance will be posted on NCI's Web Site.

Program metrics will be developed by RAID program staff and widely communicated. Initially, the metrics focused on the number of completed projects and how many INDs were filed. There is now a shift toward clinical endpoints, such as the completion of early phase clinical trials and the number of patients treated. The development of prospective criteria by which to evaluate and discontinue projects has been discussed. In addition, RAID staff will review regular milestones for each project. Project discontinuation will be guided by a lack of productivity, a change in scientific rationale, and a change in portfolio focus.

Questions and Answers

Dr. Von Hoff noted that only 35 out of 81 INDs filed were approved and asked about the INDs that were not approved. He commented that Phase I trials are not enough to engage other players into working with a specific agent or IND, but rather hints of activity, such as a decrease in circulating tumor cells or functional imaging, are needed. Dr. Tomaszewski responded that in some instances, the projects failed to progress along the necessary milestones to reach the clinic; moreover, many agents were approved only for early activities and not for progression into clinical trials. Mr. Ingram observed that research and development chiefs of private companies are willing to engage in dialogue with the NCI and Cancer Centers to help improve outcomes, noting that everyone suffers in the zero-risk environment. Dr. Niederhuber supported Mr. Ingram's offer to serve as head of an NCAB subcommittee advisory group to work with the RAID program on drug development. Dr. Chabner reflected that a strategy is needed to take agents through Phase I and into Phase II, and it should work in tandem with Cancer Therapy Evaluation Program (CTEP) and the DDG. Dr. Doroshow responded that the RAID program was established to take compounds into Phase I, whereas other NCI mechanisms work with Phase II studies. Ms. Giusti stated that a number of organizations—such as the Juvenile Diabetes Research Foundation International, the Cystic Fibrosis Foundation, and the Michael J. Fox Foundation—have been successful in working grants through various levels of trials and may serve as models. Dr. Coffey raised the possibility of establishing a comprehensive cancer board, similar in scope to a War Board, to examine major societal issues related to cancer. Dr. Barker stated that there appears to be a cultural difference between what is accomplished by the RAID program and what occurs in the R01 investigator laboratories.

XV. PROGRESS REPORT: NCI INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGY (IMAT) PROGRAM—DRS. ANNA BARKER, GREGORY DOWNING, STEPHEN J. KRON, AND JAN E. SCHNITZER

Introduction—Dr. Anna Barker

Dr. Barker introduced the presentation on the Innovative Molecular Analysis Technologies (IMAT) program. The NCI recognized that technology grants do not fair well in peer review R01 study sections, and the assistance was needed to help investigators develop technologies for both first generation technologies in areas such as mass spectrometry, as well as for multiplexed technologies and very advanced technologies in drug delivery. The IMAT program has filled this gap for technology development, much of which can be commercialized. Dr. Barker introduced Drs. Gregory Downing, Director, Office of Technology and Industrial Relations; Stephen J. Kron, Associate Professor, Molecular Genetics and Cell Biology, University of Chicago; and Jan E. Schnitzer, Scientific Director, Sydney Kimmel Cancer Center, San Diego.

IMAT Program Overview—Dr. Gregory Downing

Dr. Downing explained that the IMAT's mission is to develop and apply new technologies that transform researchers' abilities to identify molecular changes that distinguish pre-cancerous and cancerous cells from normal cells. The program aims to focus innovative technology development on cancer, solicit highly innovative technology development projects from the scientific and medical communities, and accelerate the maturation of meritorious technologies from feasibility to development and/or commercialization. It was established in 1998 to encourage highly innovative cancer technology development projects that: address the complexity of cancer, including myriad molecular and cellular processes, and understand relevant genes and roles of nucleic acids, proteins, and other cellular factors and modifications; provide novel mechanisms, program, and review structures to support innovative cancer-relevant technology from inception, as well as the development of novel applications of those technologies that uniquely enable cancer biology research by R01 investigators; and ensure that resulting technologies are robust and appropriate for intended applications in basic, preclinical, and clinical settings. IMAT is a high-risk, high-impact project that emphasizes technology development and application. It is structured around milestones that address quantitative measures of specificity, sensitivity, speed, and other performance parameters, and that involves a staged process that requires quantitative evidence of progress before advancing to the next stage. Some IMAT funding opportunities are directed at small businesses under SBIR and STTR; since inception, approximately one-quarter of applications and one-third of awards are for small businesses.

Dr. Downing shared a schematic to illustrate the life cycle of an IMAT technology development project based on a grants mechanism. The ideas are presented in what is called Phase I or the R21 phase, which is an exploratory, proof-of-concept element of understanding molecular and genetic aspects in the cancer cell. Performance milestones are used to gauge whether a project is making sufficient progress to enter Phase II funding, also called the R33 component and the Phased Innovation Award (combined R21/R33). Three RFA solicitations are used: Innovations in Cancer Sample Preparations, Innovative Technologies for the Molecular Analysis of Cancer, and Application of Emerging Technologies for Cancer Research. The flow of these programs supports many other aspects of IMAT's mission; the programs feed into NCI biological and clinical research programs, public-private partnerships, and commercial industry, which all contribute to the discovery and use of technologies, approaches, and knowledge to understand, prevent, detect, diagnose, and treat cancer. The IMAT review process focuses on technology development vs. hypothesis-driven research, reviews milestones and recommends improvements, considers whether technology is an improvement over state-of-the-art, and reviews continuity by using previous IMAT panel members and IMAT grantees.

Dr. Downing briefly described six case studies that illustrate the IMAT program's influence in the field. (1) Dr. Jonathan Oliner, Affymetrix, presented some aspects that were important in the early stages of developing chip-based technologies. (2) Dr. Gary Latham, Ambion, worked on enzymatic tools such that researchers can store tissue samples without significant loss of RNA integrity. (3) Dr. John R.

Yates, University of Washington/Scripps, helped establish the multi-dimensional protein identification technology, MudPIT, that supports the transition from 2-D gel electrophoresis to 2-D liquid separation techniques. (4) Dr. Mark Chee, then with Illumina, made important contributions to the ultra-high-throughput Illumina bead platform to allow researchers to simultaneously assay more than 100,000 points for gene expression, alternative splice detection, and protein expression. (5) Dr. David Krizman, Expression Pathology, has developed new technology that permits effective, high-throughput discovery and analysis of protein biomarkers in formalin fixed paraffin embedded (FFPE) tissue. (6) Dr. Robert H. Daniels, Quantum Dot Corp. (Invitrogen), focused on quantum dots (semi-conductor nanocrystals) as photostable labels that emit extremely bright light in a range of colors enabling researchers to monitor complex interactions within living cells or *in situ* on tissue microarrays.

The IMAT program also is focusing on overcoming technical barriers to research productivity, with attention paid to nucleic acids (micro RNAs, RNAi, epigenomics, alternative splicing, genomic regulatory factors, and mutation detection) and proteins (localization, fractionation and quantitation, identification of low abundance and transient proteins, small molecule interactions, protein interactions, and structure/function modifications). Additionally, molecular interactions (pathways and networks, transient complexes, real-time macro molecular interactions, and metabolite detection/quantification) and molecular device/chemistry (nanotechnology, microfluidics, surface chemistries, sensors, and platform integration) are being examined. In addressing these barriers, IMAT has introduced a paradigm shift that includes: increased sensitivity, improved labeling tools, increased throughput, reduced cost, more quantitative focus, single molecule/cell approach, reduced sample size, rare entity isolation, and parallel processing.

Dr. Downing acknowledged the efforts of the IMAT program management team and referred the NCAB members to visit http://imat.cancer.gov for further information.

Developing Tests for Bcr-Abl and Gleevec® Resistance in CML Patients—Dr. Stephen J. Kron

Dr. Kron described the development of tests for Bcr-Abl activity and Gleevec® resistance in chronic myeloid leukemia (CML) patients. This project is an intersection of technology and translation and involves numerous collaborators from many disciplines. Dr. Janet Rowley, University of Chicago, provided the first molecular understanding of a cancer by identifying that chromosome 9/22 balanced translocation in almost every CML. From this, it was hypothesized that genetic changes were underlying other cancers, leading to cytogenetic testing that looked for the Philadelphia chromosome and the wild type 9 to perform molecular diagnosis for CML and monitor patients during therapy. Approximately 10 years later, Dr. Owen Witte, then a postdoctoral with David Baltimore, and colleagues identified the translocation and discovered that it was a characteristic breakpoint that clustered around the transposition between the Abl gene, named after a virus identified by Dr. Herbert Abelson at NIH, now at the University of Chicago, and the Bcr breakpoint cluster region gene on 22, and that created a new gene on the Philadelphia chromosome, BCR-ABL. This finding made it clear that the CML patients make a new gene product called Bcr-Abl that can be found as an RNA in their CML cells; Dr. Witte and others recognized that Bcr-Abl was encoding an activated kinase, an enzyme, that uses ATP to phosphorylate other proteins and therefore is a potential drug target.

About 10 to 15 years later, a drug was developed that provided a good prognosis for CML patients. That drug was named STI571, renamed Imatinib, and sold as Gleevec® by Novartis, thanks to the patients of Dr. Brian Drucker, now at Oregon Health Sciences. Dr. Kron shared graphics that showed how Abl embraces the Gleevec molecule to displace ATP and inactivate the kinase. There has been a fair amount of discussion since 2002 about Imatinib-resistant kinase mutations in Bcr-Abl patients. These patients, who initially may have benefited from Gleevec®, develop mutations that lower affinity for

Gleevec® yet allow the kinase to function; the Bcr-Abl can still have its oncogenic effect, and Gleevec® can no longer inhibit it. Mutations on the Abl kinase P loop, an important regulatory domain, are particularly significant. A second generation of Bcr-Abl inhibitor drugs to replace Gleevec in resistant patients is in development or approved, but there are no predictive assays underway to help in selecting which if any should be used. Clinical challenges include: the need for rapid testing for Imatinib resistance, the selection of second-line therapy, the identification of effective dosage, and determining the failure of STI therapy.

The measurement of Bcr-Abl activity poses a technology challenge, particularly in the desire to understand whether the kinase is on when Gleevec or the approved alternative, AMN or Dasatinib, are present. To do this, researchers need to be able to detect Bcr-Abl activity in a whole cell lysate directly from the patient's blood. The process needs to be rapid, robust, and simple, and amenable to the clinical laboratory or it will not be useful. It also must be adaptable to high throughput for it to be used in the screening for new drugs and to accelerate the process.

An approach that has been employed is to use small peptides that have been selected through library screening. Dr. Kron mentioned a short peptide called Abltide as being an Abl substrate that has a tyrosine that is phosphorylated by the Abl or Bcr-Abl kinase. The goal of a kinase assay is to detect ADP, the phosphotyrosine, or the phosphopeptide, and ignore the cell lysate, other kinases, and phosphatases. The project started with a proof-of-principle bead-based assay of Bcr-Abl in cell lysates. Dr. Kron exploited a molecular recognition trick to add a second peptide to the Abltide to make it stick better to the Bcr-Abl and Abl kinases. A super substrate that was very highly phosphorylated by Abl or Bcr-Abl resulted; when Imatinib was added, the phosphorylation went away. Dr. Kron showed a peripheral blood ficoll-paque extracted sample from an Imatinib-resistant patient compared to the wild type Bcr-Abl from a leukemia cell line, K562; the IC_{50} in this simple assay was about 10 μM for the K562 cells but there was no response to Imatinib in the patient sample.

Dr. Kron next described how a new technology called Luminex was adapted to a new purpose. This involved tiny plastic beads with glutathione on them which allows glutathione-S transferase protein fused to Abltide to be stuck onto the beads. The beads were reacted with cell extract, plus or minus Imatinib, and analyzed using anti-phosphotyrosine antibody and anti-IgG with phycoerythrin (fluorescent protein). The samples were run through a small bench-top machine, the Luminex reader, to sip each well of a 96 well plate and analyze the fluorescence. Dr. Kron showed work of an undergraduate at the University of Chicago who found that, in the absence of Imatinib, there are about 1,000 units of fluorescence while, with Imatinib, the activity is only 50 units, with an IC50 of about 20 μM. Additionally, Dr. Kron worked with Dr. Sean Palacek, a chemical engineer at the University of Wisconsin, Madison, to develop an acrylic super glue for proteins. A polyacrylamide hydrogel carries a Bcr-Abl substrate; when Bcr-Abl, plus or minus Imatinib, is added and detected, more added Imatinib results in less signal (IC_{50}) of about 20 μM. This simple technology can be used to screen for new inhibitors.

The next generation of technology uses matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF). In a vacuum, a laser desorbs proteins and peptides from the surface, which then enter the time-of-flight tube of a mass spectrometer where they are separated by mass over charge, yielding a tool to measure molecular weight. Phosphorylation causes a mass shift of 80 units and the two peaks both display impressive signal to noise. Thus a computer can analyze the amount of peptide and phosphopeptide present, and the ratio of these two reveals the amount of phosphorylation. Adding Imatinib affects this by up to 80 units, which is an amazing signal to noise. This technology has been adapted to chips as well. To move further toward an integrated assay system, the Cotter laboratory at Johns Hopkins University is making mini-MALDI-TOFs, where the time-of-flight tube is 4 cm rather

than a meter as in commercial spectrometers. Based on such a device, one could build a bench-top kinase evaluator that could yield a diagnosis or drug response profile within 1 hour after obtaining a blood specimen.

IMAT Facilitates Technology Exploration To Advance Clinical Translation—Dr. Jan Schnitzer

Dr. Schnitzer described the use of a large-scale systems biology approach to find new targets that are easily accessible to antibodies for immediate interaction with tumor blood vessels and for penetration into the tumors. Delivery is a key problem in cancer imaging and targeted therapy. Poor delivery can be limiting because of *in vivo* barriers as well as poor targeting and access to tumor cell surface target proteins. Small molecules present an opposite problem, in that access is easy throughout the whole body, and is not limited to tumors. Imaging provides a way to look noninvasively for biomarkers and determine what is happening with the delivery of therapeutic agents. The need is for accessible new targets and ways to target and penetrate solid tumors.

Many powerful genomic and proteomic technologies exist that can analyze more than 10,000 genes and gene products in a sample all at once. In defining which ones can be targeted, however, there is a dilemma around how to choose and validate the meaningful few accessible targets when there are thousands of candidates. The reduction of data complexity requires new analytical approaches that focus the technology on improving the rapidity of discovery and validation.

A hypothesis-driven analytical approach was used to reduce the complexity by asking key biological questions to focus on the power of global identification technologies. The goal is to identify new targets that are accessible to biological agents for tissue-specific imaging, delivery, and therapy *in vivo*. The question posed was which part of the tissue is inherently and fully accessible to agents (Abs) in the blood and the answer was the vascular endothelium. Based on this, the working hypothesis was that the tissue and disease microenvironment modulates EC phenotype and molecular expression. It was unclear whether EC proteins with sufficient tissue-specificity existed.

Dr. Schnitzer displayed a picture of an electron micrograph of a red blood cell in a micro vessel and directed attention to the endothelium, which can be isolated with caveolae from the remainder of the tissue through a nanotechnology coding procedure. This process has occurred in multiple species, multiple organs, and solid tumors through the IMAT Program. The first draft of the rat endothelial cell proteome is now complete with about 7,000 total proteins identified, and about 1,800 non-redundant proteins identified in the plasma membranes isolated from each of these tissues. Approximately 3 to 5 percent are unique to the tissue, and about 200 proteins were found to be concentrated in the caveolae. Incorporating a high level of QC analysis on the samples to eliminate false positives, membrane isolations were performed, and both new and known angiogenic marker proteins were discovered.

Dr. Schnitzer mentioned that annexin A1 was found to be expressed as a 34 kilo Dalton protein on the surface of the endothelium in the tumors but not found expressed in other tissues of the body by proteomics as well as by Western analysis. A series of antibodies were made that were specific only to annexin A1 and injected into a rat tail vein, along with very low doses of radioactivity; within 3 to 4 hours after the injection, it was seen through spectrometer imaging to accumulate in the tissues. In addition, 80 to 90 percent of the animals that were injected with the targeting antibody survived, whereas the control animals died within 5 days. This also was found to be expressed in the micro vessels of a variety of human tumors such as breast, lung, liver, gastrointestinal, prostate, brain, and ovary tumors.

Research conducted during the past 2 years, but not yet published, has focused on the caveolae as a means to target transcytosis by the caveolae to cross the normally restricted barrier and penetrate into

the tumor tissue. To target the caveolae specifically, nanoparticles were conjugated to existing antibodies that were identified for targets; these then were injected into the circulation to accumulate in the caveolae; this accumulation is not seen in normal tissue. An intravital microscopy was used to see, within seconds of the tail vein injection of the fluorescence antibodies, binding that occurs to the surface of the tumor vasculature and the tumor outline. Within about 1 to 2 hours of this process, the whole field turned completely green, and it was possible to penetrate, bind, transcytose and move the material into the tumors. The amount of fluorescence that is seen inside the micro vessel is always less than what is seen within the tissue; for this reason, active pumping is used. In some models, whole tumors can be turned green in 45 to 60 minutes after intravenous injections.

Dr. Schnitzer showed several images captured by SPECT imaging. One picture of a rat lung with multiple tumors that were SPECT imaged *in vivo* captured quantified radioactivity; the tumors showed 35 percent of the injected dose per gram, whereas normal organs showed little or no level of targeting. Another image was of a B16 melanoma model with the subcutaneous tumors. A colon cancer model in mice revealed the tumors and radioactivity as well. The Her-2-neu spontaneous tumor model has yielded a similar result. Dr. Schnitzer also shared a movie of an intravital microscopy of solid GFP-tumor eradication by radioimmunotherapy. He noted that the system works well with orthotropic tumors, but non-orthotropic tumors seem to have a significant problem with the expression of some antigens. Complete remissions can be induced with 30 μCi in 80 percent of the cases; in those cases in which fluorescence returns, a second injection is given, and 100 percent of the tumors disappear. This usually occurs 1 to 2 weeks after the first injection.

A variety of other targets are now available. Targets specific to the liver, kidney, lung, and heart are being pursued with the NHLBI as part of IMAT's proteomic initiative. In some instances, the expression of these proteins can be shared by different organs. There are a number of proteins, however, that are not specific, but rather are common to all endothelial cells. This makes clear that there is a fingerprint or a signature at the surface of the endothelium in each of the tissues, which opens to research different phenotype altering events, such as in the tissue microenvironment and tissue-specific endothelial expression. These data reveal that the caveolae represent a new strategy of delivery in terms of imaging and therapy, and that transcytotic pumping occurs even more rapidly; the caveolae provide a means to extend beyond classic vascular targeting to deliver agents into a specific tissue by crossing the normally restricted endothelial cell barrier and, thereby, increasing bioefficacy by reaching the intended target (i.e., the cells inside the tissue) of most therapies. This may be enabling for many types of drugs, biologics, gene vectors, nanoparticles, and imaging probes.

This discovery platform combines a significant number of technologies dealing with subcellular fractionation, proteomics, bioinformatics, and antibody generation, and combining with rapid validation through *in vivo* molecular imaging. Data complexity can be reduced *a priori* from innumerable possible protein targets to between 10 and 100 candidates. A subset of this for research could be the transvascular pumping space. Dr. Schnitzer referred to his summary of the vascular and caveolar targeting strategy (*New Engl J Med* 1998;339:472-4), and noted that the work that he described today was accomplished with IMAT grant support.

XVI. ANNUAL CANCER STATISTICS REPORT—DRS. ROBERT CROYLE AND BRENDA EDWARDS

Dr. Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), introduced the presentation on the Annual Cancer Statistics Report. He referred the NCAB members to a copy of the near-final press release that will appear shortly in *The Journal of Cancer*. Dr. Croyle also pointed out that their materials include information on GIS, which holds a tremendous promise for understanding health

disparities and related surveillance data to local cancer clusters and trends. The Annual Cancer Statistics Report is intended for the research community.

Dr. Brenda K. Edwards, Associate Director, Surveillance Research Program, DCCPS, works with surveillance, descriptive epidemiology, and interpreting statistics, as well as statistical modeling and methodologic developmental work in relation to the CISNET network. She announced that the report was released electronically in *Cancer* yesterday, and summarized its main point as cancer death rates continue to drop. The report focused on the Latino population, and acknowledged that a number of cancers have much lower prevalence rates within the Latino population. When diagnosed, however, many cancers are at later stages. Progress has been made in the availability of cancer incidence data for use in the surveillance research and public health communities. Dr. Edwards displayed maps of the United States that showed improvements from 1975 through 2003 in coverage for population-based cancer incidence. Notably, in 2003 cancer incidence data were available for more than 80 percent of the U.S. population.

The ACS published a report that estimated the U.S. cancer burden in 2006. It projects that more than 1.4 million people will be diagnosed with cancer, with more than one-half of the diagnoses occurring in cancers of the prostate, breast, lung, and colon/rectum. More than one-half million deaths from cancer are expected to occur, with the greatest number in these same sites. There are more cancer deaths for pancreatic cancer, however, than for prostate.

Dr. Edwards described trends in cancer incidence and mortality in general, and then honed in regarding trends of breast (female), prostate, lung, colon and rectum, and thyroid cancers. For women, all sites have continued to rise at a small but positive rate. Cancer incidence in the prostate, lung (female), kidney and renal, leukemia, melanoma, thyroid, and myeloma is increasing. Incidence is decreasing, however, for lung (male), colon and rectum, oral cavity and pharynx, stomach, uterine corpus, ovary, and cervix. Rates for breast (female), pancreas, and all other sites for males have remained at a stable level. In mortality trends, lung (female), esophagus (male), and liver cancers have increased. Mortality trends in a number of cancer sites have decreased, however, including: lung (male), colon and rectum, breast (female), pancreas (male), prostate, leukemia, and non-Hodgkin's lymphoma (NHL). Cancers of the ovary, pancreas (female), kidney and renal (male), and melanoma (male) have remained level in their mortality trends.

Regarding female breast cancer, the incidence rates are much higher in white women than in black women. In other racial ethnic groups, Asian Pacific Islanders, Hispanics, and the American Indian populations also have lower incidence rates. In mortality trends, on the other hand, the death rates for black women are higher than for white women. The death rates for other racial ethnic groups for breast cancer are below the rate for white women. The reported statistics include a recent stabilization (nonsignificant 4 % per year downturn) in breast cancer incidence trends for women for 2001-2003, adjusted for a delay in the data entering the cancer databases. Factors considered as possible explanations for the stabilization in breast cancer incidence rates include the impact of the reduction in hormone therapy post WHI trial results, as well as a leveling off of screening with mammography.

In prostate cancer, the incidence rates are much higher in black men than they are in white men. The rate for white men is increasing.

Lung cancer trends are separated by gender; rates of incidence and mortality mostly move in parallel. The incidence rate for men is substantially higher than for women, albeit it is decreasing. Continued increases in lung cancer incidence and death rates are being seen for women.

Colorectal cancer trends may be temporally affected by an increase in colorectal screening, as seen, for instance, when President Reagan had his colon cancer diagnosed. National figures appear to be influenced by the number of organizations that encourage and promote utilization of screening for colorectal cancer. Both the incidence and mortality rates in colorectal cancer have been dropping for men and women.

Regarding thyroid cancer, there has been a long-term increase in incidence since 1980 for most groups. Some researchers suggest that this possibly is a diagnostic artifact of small papillary tumors based on the use of ultrasound and fine needle aspirates. Moreover, diagnostic scrutiny is associated with more prevalent thyroid disease in women. Finally, environmental factors, such as radiation exposures from nuclear weapons testing and accidents, radiotherapy, and diagnostic exposures, may be additional causes.

For Latinos, cancer incidence trends (1999-2003) are lower than non-Hispanic whites for most cancers; reveal that Latinos are less likely to be diagnosed with localized stage for cancers of the lung, colon and rectum, prostate, female breast, and cervix; and have higher incidence rates for myeloma (female) and cancers of the stomach, liver, and cervix than non-Latino white populations. Among minority populations, Asian Pacific Islanders show the highest incidence and mortality for liver cancer, whereas the black population has the highest mortality for stomach cancer. In addition, the incidence and mortality trends for kidney and renal cancers are on the rise for most populations. The black population has the highest incidence and mortality rate for pancreatic cancer.

Dr. Edwards next explained the rank ordering of cancer sites among the Latino population, compared with the non-Latino white population. Many of the top 10 cancer sites for Latino men, for instance, are the same as non-Latino white men, except that stomach and liver are included in Latino men, and melanoma of skin is included in the top cancers for non-Latino white men (and women). Additionally, although the cancer sites for both populations may be similar, the overall age-adjusted incidence rates are typically lower in the Latino population. Similar patterns are seen in women. Cervical cancer, which also is high among black women, is in the top 10 list of cancers for Latinas. Mortality for cervical cancer is highest, however, among the African American women.

The report also describes incidence rate by county-level poverty measurement for Latino and non-Latino white men and women. Dr. Edwards showed charts reflecting the attempt to evaluate social and economic factors that might be associated with differences in cancer rates. Groups were created based on the general poverty or affluence levels of resident counties, such as less than 10 percent or more than 20 percent of that population is in poverty; the most affluent would be less than 10 percent, and the least affluent would be more than 20 percent. For men, there is a small relationship for prostate cancer, with higher rates among men who may live in more affluent populations, whereas for lung and bronchus the non-Latino white population living in the more affluent populations have the lowest lung cancer rates and the least affluent having higher rates. There is not much gradient seen among the Latino male population. Latina women who reside in more affluent areas have a greater gradient for lung cancer. For breast cancer, both Latina and non-Latina white women from more affluent areas have higher breast cancer rates. Cervical cancer, however, is more prevalent among women from less affluent areas for Latina and non-Latina white women.

In conclusion, research findings regarding the Latino population, in which more than 90 percent of that population in the United States are covered, point to lower cancer rates, including lung, colorectal, breast, and prostate. A number of sites, however, such as myeloma in women, are higher. Dr. Edwards explained that efforts will continue to be focused on interpreting health disparities; the NCI currently is

working on the 2007 Annual Report, which will feature data on American Indians and Alaska Natives. For further information, the NCAB members were invited to visit several Web sites: www.interscience.wiley.com/cancer/report2006; http://www.cancer.gov; http://www.seer.cancer.gov/; and http://www.naaccr.org.

Questions and Answers

Dr. Runowicz queried whether the decline in incidence and mortality related to colorectal cancer that occurred in the mid 1980s was related to diet. Dr. Edwards responded that good data on risk factors for colorectal cancer are unavailable, but agreed that cooking methods may be related. Dr. Coffey noted that treatment of one disease or condition might increase the incidence of another; examples include *Helicobacter pylori* and flora in the esophagus, which is defensive against Barrett's esophageal lesions. Additionally, the decreased use of hormone replacement might reduce the incidence of breast cancer but increase the occurrence of colorectal cancer.

Dr. Chabner commented that information about stage migration within some of the categories of tumors that are decreasing in incidence would help determine whether early detection or improved therapy is the cause. Dr. Edwards mentioned that the SEER Program collects information on stage, particularly with breast cancer, but quantitative data to clarify stage migratory factors in detail are limited or not available.

Dr. Chen queried about the challenges that had to be overcome to be able to measure Hispanics as an entity, and the obstacles to address other populations, such as the American Indians, Alaska Natives, Asian Americans, and Native Hawaiians, to obtain similar data. Dr. Edwards explained that, because cancer information from the registries funded by the NCI and the CDC include race and ethnicity data, the registry community has adopted a strategy to compare cancer patient names with the 1990 Census information, and run a probability algorithm to determine the likelihood of a person with unknown ethnicity being attributed to the Hispanic population. The NCI used this approach in Louisiana, where they have some of the names from the Cajun populations, and they felt they had too many Hispanics. For the American Indian population, the work has included a linkage with the Indian Health Service (IHS) medical delivery system, requiring a three-way agreement. To accommodate sensitivities from that population, the cancer registries send their information to the IHS under secure condition, which maintains the list of names and determines whether that person has received care in the IHS system. If cancer patients are identified as receiving care from the IHS information, registry records with missing information can be corrected and thereby improve the identification of American Indians and Alaska Natives diagnosed with cancer. A names-list approach is being proposed for use with the Asian Pacific Island population as well.

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 139th regular meeting of the NCAB was adjourned at 11:44 a.m. on Thursday, September 7, 2006.