DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
137th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 7, 2006

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 137th regular meeting on Tuesday, February 7, 2006, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, February 7, 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. NCAB Acting Chair Dr. Daniel D. Von Hoff, Senior Investigator and Director of Translational Research, Translational Genomics Research Institute (TGen), Phoenix AZ, presided during both the open and closed sessions.

NCAB Members

Dr. Daniel D. Von Hoff (Acting Chair)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Moon S. Chen, Jr.
Dr. Kenneth Cowan
Dr. Jean B. deKernion
Dr. Ralph S. Freedman
Dr. James H. French (absent)
Ms. Kathryn Giusti (absent)
Mr. David Koch (absent)
Dr. Eric S. Lander
Dr. Diana M. Lopez (absent)
Dr. Arthur Nienhuis (absent)
Ms. Marlys Popma (absent)
Dr. Franklyn G. Prendergast
Dr. Carolyn D. Runowicz
Ms. Lydia G. Ryan

President's Cancer Panel

Dr. LaSalle D. Leffall, Jr. (Chairperson)
Mr. Lance E. Armstrong (absent)
Dr. Margaret Kripke (absent)

Alternate *Ex Officio* NCAB Members

Dr. Michael Babich, CPSC
Dr. Louisa Chapman, OSTP (absent)
Dr. Allen Dearry, NIEHS
Ms. Raye-Anne Dorn, VHA
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
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 (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, 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
Mr. Thomas Hooven, Deputy Director for Management
Dr. John Niederhuber, Chief Operating Officer and Deputy Director for Translational and Clinical Sciences
Dr. Alan Rabson, Deputy Director, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Acting Associate Director, Center to Reduce Cancer Health Disparities
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

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

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I. CALL TO ORDER, OPENING REMARKS, AND APPROVAL OF MINUTES—DR. DANIEL VON HOFF

Dr. Daniel Von Hoff, Senior Investigator and Director for Translational Research, Translational Genomics Research Institute, called to order the 137th NCAB meeting. He welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, staff, and guests. He welcomed Dr. Margaret Foti, Executive Director, American Association for Cancer Research (AACR). 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. Von Hoff 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 December 6-7, 2005, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE MEETING DATES—DR. DANIEL VON HOFF

Dr. Von Hoff called Board members' attention to future meeting dates, which have been confirmed through 2007. He noted that alternative dates are being sought for the meeting scheduled for June 5-7 because of a conflict with the American Society for Clinical Oncology (ASCO) annual meeting. Members were asked to consider June 14-16 or June 19-20 as alternatives and register their preferences with Dr. Gray.

III. NCI DIRECTOR'S REPORT—DRS. ANDREW von ESCHENBACH AND JOHN NIEDERHUBER

Dr. Andrew von Eschenbach, Director, NCI, reminded members that this NCAB meeting marks the fourth anniversary of the beginning of his tenure as the NCI Director. As such, it is an opportunity not only to focus on future opportunities and challenges for the NCI but also to reflect on achievements and accomplishments during the past 4 years as the NCI has been embarking on a new trajectory. He thanked Board members and all present at the meeting for having made the past 4 years successful with regard to the NCI's agenda. As a result of the new trajectory, the NCI effort has been focused on a destination believed to be achievable and capable of being reached as early as 2015. Rationale for the trajectory was the belief that progress in cancer and biomedical research could be coordinated and integrated in such a way that the process of cancer and its outcome—suffering and death—could be preempted. During the past 4 years, the NCI has been managing its portfolio of investments in cancer research aggressively across the continuum of the cancer process, from understanding genetic mutations that are responsible for susceptibility to the disease to focusing on issues concerning survivorship and living with cancer. Dr. von Eschenbach recognized the support and help received from the NCAB and other advisory boards in their guidance and oversight capacity that have enabled the NCI to meet specific milestones across the agenda. He acknowledged that issues and concerns were raised after introduction of the 2015 goal as a way of focusing and mobilizing the NCI effort. After 4 years of focus on the specific steps and initiatives to be fostered and promoted to achieve the necessary progress toward the goal, it has become apparent that no one is questioning the ultimate outcome or the destination, although there may be a continuing struggle as to whether the goal can be accomplished in 2015 or 2014 or 2016. Dr. von Eschenbach pointed out that it can now be envisioned that the process of cancer can be preempted to prevent development of the disease or promote early detection with greater precision such that behavior of cancer can be modulated and controlled and people can live with it. He emphasized that this

destination is being adopted and supported both within and outside the cancer community. During the 35 years since the National Cancer Act has been in effect, cancer research has led the way and is now leading not only in understanding the genetic and molecular basis of the diseases known as cancer, but also in the more extensive transformation referred to as the "molecular era" or "molecular metamorphosis" in other diseases. Dr. von Eschenbach noted that the progress made in the past 4 years should be understood in the dual context of moving toward the goal of cancer preemption and leading the larger effort in the broader array of diseases. As testimony to this, he called attention to the Department of Health and Human Services (DHHS) budget roll out the previous day, when Secretary Mike Leavitt described the discretionary component of the budget as being focused on transformation of health, moving away from the model of treating advanced disease to the disease preemption model that has been at the core of the NCI strategy to achieve the 2015 goal.

Dr. von Eschenbach stated that the perspective of what is possible to accomplish and the NCI's leadership role gained from looking back over the past 4 years should be kept in mind in considering the current difficult times. He reminded members that the strategic plan developed 4 years ago was based on a business plan with increasing resources specifically directed to the NCI. However, in the President's budget for Fiscal Year (FY) 2007, increases in funds for discretionary spending are constrained. Maintaining the research momentum necessary for the current NCI trajectory will require continued hard work on the part of the NCI to ensure that its resources are being used most effectively and strategically. Dr. von Eschenbach noted that the NCI leadership is committed to making difficult choices between those programs that it will continue to grow and those that are believed to have met their desired outcomes and can be ended, enabling the transfer of their funds to other priorities. In making those fiscal decisions, scientific excellence will be the most important criterion, but the decisions also will be made in the context of strategic priority. Priorities include avoiding duplication and overlap, taking advantage of opportunities for synergy and complementarity, and ensuring a continued pipeline for the development of intellectual capital by investing in young scientists and new investigators across the basic to clinical research continuum. Dr. von Eschenbach stated that the NCI will work aggressively to leverage resources by finding opportunities for partnership and collaboration with other agencies, other NIH Institutes and Centers (ICs), and other components of the cancer program to ensure maximum momentum with regard to the investments that are being made.

In conclusion, Dr. von Eschenbach noted that the 35-year investment in the National Cancer Program has resulted in enormous growth and output. He cited, as testimony to that, the power and strength of 61 NCI-designated Cancer Centers nationwide, as well as the many other cancer centers that have developed as part of the process and have become important centers of excellence and opportunities for growth and increased impact on biomedical research. As another example of growth and output, he cited the recent NCI grants for nanotechnology initiatives, in which one cancer center's nanotechnology program led the way to a partnership with a state university and brought in significant gifts from two major corporations, a fourfold leveraging of NCI funds with regard to their ultimate impact. He concluded that the picture is one of tremendous progress being made through cancer research and with regard to NCI leadership in terms of a larger biomedical transformation that is impacting on health and the health care system. The transformation also is impacting on NCI's ability to bring other scientific ventures into the program, including the physical sciences. He vowed that the NCI will continue on its current trajectory and move closer to the goal, accomplishing that in the context of wise and effective use of available resources and leveraging those investments to bring other investors into the process. Going forward, the NCI can be expected to continue to achieve the record of success experienced in the past, which the NCAB helped to make possible through its effort, contributions, stewardship, oversight, and advice.

NCI FY 2007 Budget Update. Dr. John Niederhuber, Chief Operating Officer and Deputy Director for Translational and Clinical Sciences, Office of the Director (OD), resumed the Director's report with a review of the proposed FY 2007 NCI budget and NCI policy for FY 2007. The President's recommended FY 2007 budget, as presented to Congress the previous day, included an appropriation for the NCI in the amount of $4.75 B, a decrease of $39.75 M (-0.8 percent change) from FY 2006 budget of $4.79 B. The President's recommended budget of $28.6 B for the NIH remains the same as the FY 2006 budget, with $140 M earmarked for the NIH Director's office for the Roadmap Initiative, the start up of the Office of Portfolio Analysis and Strategic Initiatives (OPASI), and biodefense countermeasures. Current NIH working guidelines are: no change in the average cost of competing Research Projects Grants (RPGs); no inflationary increase for direct recurring costs in noncompeting continuation grants; and no change in the stipend level for National Research Service Awards (NRSA). Within the NIH FY 2007 budget, a $1.8 M investment in a new investigator program called Pathway to Independence will be allocated to the NCI to create a program similar to its Temin Award, which funds about 20 investigators per year. The Temin Award provides 2 years of support for fellowship years and 3 years of support as the new investigators transition into academic positions. The Pathway to Independence initiative in the NIH budget is targeted at $15 M to support about 150 investigators. The NCI will participate in the program with the other Institutes, but the name for the NCI awards will not change. Dr. Niederhuber called attention to a sum of $7.8 M that is included in the NCI budget as part of the NIH initiative on genes, environment, and health; an additional amount totaling almost $40 M in the NIH budget is slated for other Institutes, including the National Human Genome Research Institute (NHGRI).

Dr. Niederhuber then compared the NCI amounts for all budget mechanisms in the FY 2006 appropriation with those proposed for the NIH in the President's FY 2007 budget. For Total Research Grants, the proposed amounts represent a decrease for noncompeting and competing RPGs of 1.3 percent and 6.2 percent, respectively, and a change of -1.8 percent in the overall line item, which includes funds for Centers, Special Programs of Research Excellence (SPOREs), and Special Centers. The proposed amount for all other NCI budget mechanisms (including contracts, intramural research, research management and support, buildings, and facilities) represents an overall change of -1.1 percent. With a $57.3 M or 1.8 percent increase for NCI's participation in the Roadmap Initiative, the decrease for the Total NCI with Roadmap line item is -0.8 percent.

Priority Setting and the Strategic Planning Process. Dr. Niederhuber described the process for developing the NCI Strategic Plan. Each Division and Center worked to develop suggestions for strategic priorities and, after 15 months of deliberation, identified 200 possible strategic goals. From these the Executive Committee selected eight goals that comprise the current strategic plan for achieving the 2015 goal. Together with the entire NCI leadership, an agreement was reached to redeploy within the budgets of the Divisions approximately $25 M per year as an Enterprise Funding Pool for initiatives that span the NCI. Integration and Implementation Teams were formed, which have focused to date on three areas—advanced imaging, bioinformatics, and lung cancer—and have influenced the setting of strategic priorities for funding in the NCI's extra- and intramural programs. This has led to the selection of Requests for Applications (RFAs), Program Announcements (PAs), and contracts aimed at adjusting the portfolio to meet envisioned gaps or needs of the overall NCI program to reach those strategic goals.

Dr. Niederhuber reminded members of programs and initiatives that are implemented across the NCI Divisions and Centers: Bioinformatics; Nanotechnology, Cancer Genome Atlas, Clinical Trials Working Group (CTWG), Proteomics Initiative, Biorepositories and Biospecimens, and Translational Research Working Group (TRWG).

Retreats. Dr. Niederhuber presented highlights from the Joint Board Retreat, which was held on January 10 and the 11th Intramural Scientific Retreat held the following day. Attendance at the Joint

Board Retreat included members of the NCAB, Board of Scientific Advisors (BSA), Board of Scientific Counselors (BSC), the Chairs of the President's Cancer Panel, and Director's Consumer Liaison Group. Participants offered guidance on how NCI programs can continue their current trajectory, given fiscal limitations. Alternative budget scenarios for FY 2007 were modeled to give attendees an idea of how a change in one item (e.g., number of grant awards or payline) affects the overall budget. At the end, advisors agreed to aid an in-depth analysis of strategies, including how to better promote partnerships with industry and other outside groups, support training, and find new mechanisms to measure progress and evaluate programs. Asked to rank their preferences for funding considerations, retreat participants believed the highest priorities should be funding first-time investigators, maintaining the R01 payline, and maintaining the number of grants funded. Lower priorities were given to limiting the number of submissions by an investigator, dollars per grant, and number of grants an investigator may have.

Attendance at the 2006 Intramural Scientific Retreat included 560 participants from NCI's Center for Cancer Research (CCR) and Division of Cancer Epidemiology and Genetics (DCEG). Dr. Niederhuber noted that this retreat is welcomed by scientists of the intramural program as a time for discussion, interaction, and development of new collaborations. This retreat marked the first year for the NCI Director's Intramural Innovations Awards in recognition of the development of highly innovative approaches and technology aimed at significant cancer-related problems. Awards targeted to tenure track or newly tenured principal investigators (PIs) were made for 12 PI projects. Awards targeted to postdoctoral fellows, staff scientists and clinicians, and senior scientists were made for 22 career development projects. Other highlights of the retreat were the award lectures. This year's Rosaline E. Franklin Award Lecture for Women in Cancer Research was given by Dr. Joan A. Steitz in recognition of her studies in snRNPs. The Alfred G. Knudson Award Lecture in Cancer Genetics was given by Dr. Elizabeth Blackburn and was entitled "Interventions in Telomerase Action in Human Cancer Cells." Dr. Steven Rosenberg gave the Alan S. Rabson Award Lecture for Intramural Research on the topic "The Development of Human Cancer Immunotherapy."

Personnel Appointments. Dr. Niederhuber announced the following appointments made since the December NCAB meeting: Mr. Tom Hooven, Deputy Director for Management; Dr. Lawrence Samelson, Deputy Director, CCR; and Dr. Crystal Mackall, Acting Chief, Pediatric Oncology Branch, CCR.

Interagency Agreement: NCI and Food and Drug Administration (FDA). Dr. Niederhuber provided a brief update on initiatives being undertaken by the NCI/FDA Task Force. The NCI participates in the FDA's Critical Path Initiative, which has the goal of modernizing the drug development process. One outcome of this collaboration is the new guidance developed for Exploratory Investigational New Drug (IND) studies. INDs are issued to ensure compliance with current good manufacturing practice (CGMP) standards in the manufacture of the candidate drugs for early Phase trials. Exploratory INDs apply in trials involving administration of sub-therapeutic doses of candidate product over a limited period of time with no therapeutic intent. Objectives of the studies are to determine mechanism of action, develop pharmacokinetic data, select lead products from a group of candidates, and explore biodistribution using imaging technologies. This IND approach allows for small-scale or laboratory-scale production for exploratory studies and provides an opportunity for an incremental approach to manufacturing that is appropriate for the development stage of the agent.

Intramural Research. Dr. Niederhuber presented a progress report on the Trans-Institute Angiogenesis Research Program (TARP), which will be one of the agenda items at the upcoming NIH IC Directors' meeting. Dr. Judah Folkman, a national leader in the field of angiogenesis research, will be present for that meeting. Dr. Niederhuber noted that Dr. Steve Libutti, Surgery Branch, is one of the NCI point persons leading the TARP. He called attention to ongoing angiogenesis studies: (1) the

embryogenesis studies of NCI scientist Dr. David Solomon and his interest in working with other NIH investigators in this area; (2) cross-Institute interest angiogenesis as illustrated by ophthalmology colleagues in the National Eye Institute (NEI); (3) work related to the release of stimulating factors and formation of new blood vessels in the tumor process studies; (4) work related to the angiogenic switch and antiangiogenic therapy, which included the identification of activators and inhibitors; (5) the use of dynamic magnetic resonance imaging (MRI) to monitor response to anti-vascular endothelial growth factor (VEGF) antibody therapy; (6) work in Dr. Libutti's laboratory with an RGD-phage that selectively targets tumor vessels and application of this finding to show that RGD-phage expressing tumor necrosis factor (TNF) inhibits tumor growth and has therapeutic potential.

Dr. Niederhuber pointed out the number of Institutes in addition to the NEI that have investigators participating in the NCI-led TARP, including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Neurological Disorders and Stroke (NINDS); and the extramural Juvenile Diabetes Research Foundation (JDRF). Accomplishments to date include: (1) sponsorship of a workshop on opportunities for cross-discipline collaboration for vascular developmental biology research, (2) a Web site for the TARP; (3) new collaborative RFAs; (4) sponsorship of a Nature Insight on angiogenesis; (5) review of the angiogenesis grant portfolios for the five member ICs; and (6) the convening of a panel to review the current angiogenesis portfolio and offer opinions on new directions and opportunities. Dr. Niederhuber concluded by noting that TARP is another example of continuing NCI leadership in the NIH and the extramural community. The NCI will continue trying to make a difference with its allocated resources, planning carefully to move forward even in times of fiscal constraint. Dr. von Eschenbach added further emphasis to points made by Dr. Niederhuber, noting that the TARP presents a powerful opportunity for leveraging intramural NIH and extramural resources to address a critically important issue on the cancer research agenda. Regarding the NCI/FDA Task Force, joint initiatives in addition to the joint training program and exploratory IND are the pharmaceutical industry/FDA/NIH agreement that is being formulated under the auspices of the NIH Foundation to address the issue of biomarkers. The NCI will play an important lead in that initiative on behalf of the NIH. Additionally, a Memorandum of Understanding (MOU) was recently signed by the NCI, FDA, and Center for Medicare and Medicaid Services (CMS) to bring those groups together for collaborative efforts. Dr. von Eschenbach concluded by stating that the important work being done in the intramural program are efforts to drive the intramural program into an area of differentiation around innovation and technologies that defines the intramural program's uniqueness and value added to the greater extramural program in a way to maximize the intramural investment.

Questions and Answers

Dr. Von Hoff pointed out that during the past month NCAB members have received numerous e-mails about the current difficult fiscal situation. He noted that as the research community tries to make a case for increasing the budget, it would be helpful to have a clear idea of NCI priorities and a straightforward message to put out and rally behind. He suggested that the clear and concise priorities presented in the Director's report be communicated and made available to every investigator through some forum. Dr. von Eschenbach reminded members, first of all, that the NCI has changed over the past few years and puts a high premium on communication of the NCI story. A recent change occurred when a trilogy of expression was created from the traditional Bypass Budget document. The Strategic Plan communicates what is needed to accomplish the mission; the Business Plan sets forth the information from the traditional Bypass Budget as a more focused iteration of the initiatives and costs that are believed to be needed within that budget allocation; and the Progress Report provides accountability for previous investments. He noted that these more discreet and more specific documents will help the research community to understand NCI priorities. Dr. von Eschenbach made the second point that the

NCI tries to maintain a balanced portfolio across the discovery, development, and delivery continuum, so different aspects of that are being heard. He noted that the NCI does have priority areas on which it is focusing and principles that are being used to guide decisions, namely, putting science first, promoting young investigators, and maintaining intellectual capital. The NCI will continue to work with the Board in looking for ways to communicate those priorities and principles to the American taxpayers and the scientific and research community more effectively.

Dr. Carolyn Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Centers, University of Connecticut Health Center, asked about plans for implementing the agreement reached by the joint Boards at the retreat to aid in the NCI's in-depth analysis of strategies. Dr. Niederhuber explained that the Subcommittee on Planning and Budget had already begun that task at it meeting on the previous day and a report would be forthcoming from Chair, Dr. Franklyn Prendergast, later in the meeting. Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, asked for and received clarification on how the Enterprise Funding Pool of approximately $25 M would be redeployed among the Divisions. Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at University of California at Los Angeles (UCLA), called attention to the fact that a decrease in the NCI budget of 0.8 percent is in reality a decrease of 0.8 percent plus the increment it takes to maintain the current funding level, or really a 3.8 or 4.0 percent deficit.

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

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Howard University College of Medicine, reminded NCAB members that findings from the Panel's 2005-2006 series of meetings entitled "Assessing Progress, Advancing Change" had been presented at the December meeting. Those meetings addressed high-priority recommendations made previously to the President and Congress regarding cancer survivorship issues and translating research into cancer care. The Panel is currently preparing its Annual Report to the President and Congress from that meeting series, which will be released at the upcoming ASCO Annual Meeting in Atlanta, GA. The Panel will be holding a press conference to release and discuss the findings from its report on Friday, June 2, and will be hosting two educational sessions on June 3 to address further those findings. Dr. Leffall noted that he would be hosting the first session, which will address challenges in cancer survivorship. The second session to address challenges in translating research will be moderated by Panel member Dr. Margaret Kripke. A number of distinguished experts will participate with the Panel to discuss model programs aimed at addressing the Panel's recommendations.

Dr. Leffall reported that the Panel is also in the process of planning the 2006-2007 series of meetings entitled "Promoting Healthy Lifestyles To Reduce the Risk of Cancer." This series will focus on ways to reduce cancer incidence and mortality through the promotion of healthy lifestyles. Areas of particular interest are the impact of tobacco use, environmental tobacco smoke, obesity, physical activity, and nutrition on the risk of developing cancer. Two meetings will focus on the obesity topics and the other two on tobacco. Meeting dates and locations are: September 11, Minneapolis, MN; October 23, Lexington, KY; December 5, Portland, OR; and February 12, 2007, Jackson, MS. The meetings will be structured to address current scientific evidence and research for half of the day and focus on model programs relevant to healthy lifestyles and cancer risk reduction during the second half. Dr. Leffall noted that, inasmuch as the Panel is in early planning stages, comments and suggestions from the NCAB would be welcome. In particular, information on possible model programs that could be highlighted would be valuable in the Panel's planning process. Dr. Leffall called attention to a fact sheet about the Panel's 2006-2007 series that had been distributed and the contact information included therein.

V. LEGISLATIVE UPDATE—MR. DAVID PUGACH

Mr. David Pugach, Senior Program Analyst, Office of Policy, Analysis and Response (OPAR), OD, began with a review of activity related to FY 2006 and FY 2007 appropriations. The FY 2006 appropriations, which provided $28.6 B for the NIH and $4.8 B for the NCI, was signed into law by the President on December 30, 2005, after adoption of the Conference Report by the House on December 14 and by the Senate on December 21. Mr. Pugach pointed out, however, that the budget amounts as legislated were ultimately reduced because the FY 2006 Defense Appropriations Act provided for a 1.0 percent across-the-board rescission to all government appropriations except for the Veterans Administration (VA) and emergency spending. The appropriations process for FY 2007 has begun with the release of the President's Budget Request and its presentation to Congress. The House hearing has not been scheduled yet due primarily to a reorganization of staff on the majority side, but the first appropriations hearing for the Labor/HHS Committee in the Senate is scheduled for March 15. Mr. Pugach noted that Dr. Elias Zerhouni, Director, NIH, will serve as the key witness for the NIH and will be accompanied by the Institute Directors to assist in answering questions.

Congressional Activities. Mr. Pugach reported that Dr. Niederhuber met with Representative Rosa DeLauro on December 8 and Representative Tammy Baldwin on December 14; Representative Baldwin sits on the Energy and Commerce Subcommittee on Health, and Representative DeLauro sit on NCI's appropriations committee in the House. Dr. Greg Downing, Director, Office of Technology and Industrial Relations (OTIR), provided a briefing on the NCI's nanotechnology portfolio for staff from Senator George Allen's office. A follow-up briefing has been requested. Representative Michael Burgess, also a member of the Energy and Commerce Subcommittee on Health, visited the Clinical Center where he met with Dr. Steven Rosenberg, Chief, Surgery Branch, CCR; Dr. Niederhuber, and Dr. Edward Trimble, Head, Surgery Section, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD).

Legislation of Interest. Mr. Pugach reported that the Stem Cell Therapeutic Research Act of 2005 was signed into law on December 20, 2005. This bill authorizes the C.W. Bill Young Cell Transplantation Program, which provides for the collection and maintenance of human cord blood stem cells for the treatment of patients and for research. He noted that, among the other stem cell bills currently pending, the Stem Cell Enhancement Act has already passed the House and has a good chance of being one of the first bills to be put before the Senate during the current session. The bill would allow for federal funds to be used in research on embryonic stem cell lines derived from surplus embryos at *in vitro* fertilization clinics, provided the donors give their consent and are not paid for the embryos. Mr. Pugach noted that another piece of legislation being tracked by the NCI is the American Center for Cures Act of 2005, which was sponsored by Senator Joseph Lieberman (D-CT) and introduced by Senator Harry Reid (D-NV) late in the year. Co-sponsors are Senator Thad Cochran (R-MS), Chair, Senate Appropriations Committee, and Senator Kay Bailey-Hutchinson (R-TX), also on the Appropriations Committee. The bill would establish the American Center for Cures as a new NIH IC to promote more rapid translation of public and private research into therapies and to house the NIH's technology transfer activities. The Director would be presidentially appointed. The Center would support federally funded research and development centers similar to the program in existence at NCI-Frederick and would house a newly created Health Advance Research Projects Agency (HARPA). Mr. Pugach noted that the bill was referred to the Senate Committee on Health, Education, Labor, and Pensions, but there is no indication as to when the Subcommittee plans to act on it. Mr. Pugach concluded by noting that the OPAR is continuing to track a number of bills and Congressional priorities in addition to the budget reconciliation and stem cell legislation.

Questions and Answers

Dr. deKernion questioned whether the HARPA as proposed would duplicate or overlap what is already in place at the NIH, and he suggested the need for a more in-depth discussion at a future meeting on how all parts would work together. Mr. Pugach replied that not much is known because the committee has not yet held hearings on the bill, and no background material is available other than the bill summaries. Fundamental questions to be answered are how the bill would be implemented and where the necessary additional resources would be found. Dr. Eric Lander, Director, Broad Institute of Technology and Harvard Medical School, asked whether the legislation proposal came out of reports in the scientific or industrial communities that suggested the need for the Center. Mr. Pugach replied that it has been a longstanding and ongoing interest of Senator Lieberman and that staff from his office have met with members of the NIH community during the past 6 months. Dr. Barker added that the idea for an applied science center began long ago and AACR and many colleagues were requested for input at one time.

VI. ANNUAL REPORT: AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)—DR. PETER JONES

Dr. Peter Jones, President, AACR, presented to the NCAB the AACR annual report under the topic "Strategic Leadership To Hasten Progress in Cancer Research." The AACR mission is to prevent and cure cancer through research, communications, education, and collaborations. Dr. Jones noted that this international association of scientists, clinicians, and translational researchers, with its membership of 24,000 and mailing list of 70,000, is positioned to play a major role in making cancer a disease of the past. One goal is to become more of an authoritative source in the voice of cancer research worldwide. Several mechanisms through which the AACR drives its scientific agenda are think tanks, task forces, committees, working groups, annual meetings, special conferences, publications and Website, and workshops. In the past year, a Council of Scientific Advisors was created with the charge to review the status of cancer research and evaluate progress to date; identify scientific opportunities and challenges; consider ways to address national policy impediments; and propose new strategies for implementation. The Council will make recommendations to the AACR Officers and Directors, and the AACR Foundation Board of Trustees.

Dr. Jones noted the strong connection between the NCI and AACR in their shared vision to hasten progress in cancer research. One example of this is the human epigenome issue, on which Dr. Jones reported at a recent NCAB meeting. The NCI has organized two workshops in this research area and the AACR sponsored the Human Epigenome Workshop, co-chaired by Dr. Jones and Dr. Rob Martiennsen in June 2005, to develop a plan for a future human epigenome project. The AACR continues to foster progress by forming a Task Force to address this area internationally. NCAB members were reminded that epigenetic changes are common in human cancer, play a key developmental role, and have potential for diagnosis. Dr. Jones commended the inclusion of an epigenetic component in the Cancer Genome Atlas Project and called attention to the workshop report entitled "The Blueprint for a Human Epigenome Project" in *Cancer Research*. A second example of the shared vision is proximity of the AACR Cancer Stem Cells Workshop on February 1-4 and cancer stem cells as an agenda item at this NCAB meeting. Dr. Jones noted that the AACR hopes to be able to drive the issue of cancer stem cells to the forefront, representing as it does a major conceptual change in the way cancer is viewed. He emphasized the importance of identifying the role of cancer stem cells in the formation of human cancer and its treatment.

Dr. Jones called attention to the AACR's other scientific focus areas and the measures being undertaken to address them. Cancer prevention is being addressed through an international conference, position papers on early detection and a role in prevention, a Cancer Prevention Website, and the Cancer Prevention Task Force. Cancer Immunology is being addressed through a Cancer Immunology Task Force, a special conference, collaboration with the NCI on areas related to information on cancer, and a

joint Think Tank on inflammation and cancer that could lead to a larger meeting. In another area of focus, a Tumor Microenvironment Working Group is being formed, to be co-sponsored by the International Cancer Microenvironment Society and the Metastasis Research Society. Dr. Jones noted that the AACR would be working closely with the NCI in this area also. Strategies for a continued AACR focus on clinical and translational research include several major meetings that are international in scope in 2006 and 2007, planning for an award to recognize Outstanding Team Science, and collaboration with industry through the Industry Advisory Council and the AACR-Industry Roundtable. Scientific areas where AACR activity has been increasing include biomarkers, standardization in bioinformatics, and aging and cancer.

Dr. Jones called attention to upcoming meetings. The 97th AACR Annual Meeting will be held on April 1-5 in Washington DC, with Dr. Daniel Haber as Program Committee Chairperson. On November 14-18, the AACR-NCI-European Organization for Research on the Treatment of Cancer (EORTC) International Conference on Molecular Targets and Cancer Therapeutics will be held in Philadelphia. On September 12-15, a new medium-sized meeting on Molecular Diagnostics and Individualized Therapy will be held in Chicago. Dr. Jones noted that the AACR has sponsored 120 special conferences over the past 20 years promoting new directions in science and achieving much success in driving the various agendas. The next meeting in this series, entitled "Frontiers in Basic Science," will be held in 2008.

Dr. Jones reported on other recent AACR activities and accomplishments. A book publishing program was launched in 2006. AACR Educational Workshops have been of value, including those on Methods in Clinical Cancer Research, Molecular Biology in Clinical Oncology, and Pathobiology of Cancer, which were supported by NCI grants; several others are scheduled or in development. A new magazine called *CR (Collaboration—Results)*, to be published quarterly for advocates and survivors, will be released at the AACR annual meeting. Dr. Jones briefly reviewed the role AACR continues to play in science policy and legislative affairs, with the goal of ensuring that cancer remains a national priority. To that end, an office of government relations will be opened in Washington, DC, this year. He reminded members of the results of the AACR-Lance Armstrong Foundation (LAF) poll conducted a few years ago by the Gallup organization. Of the people who responded to the poll, 70 percent believed not enough was being done to fund cancer research and 80 percent strongly favored or somewhat favored increasing federal funding for cancer research. Dr. Jones expressed the view that the decrease in cancer research funding proposed in the President's FY 2007 budget should be communicated to the public and that the AACR should play a role in communicating this message. In another new program called Expedited Funding for Innovative Cancer Research, the AACR is becoming more involved in the direct funding of individuals. The program will leverage significant new funding from industry and individuals for critical scientific projects. Requests for Proposals (RFPs) will soon be issued for grants funded through the V Foundation-AACR Grants in Translational Cancer Research and the new AACR-Jeannik M. Littlefield Fund for Metastatic Colon Cancer Research.

In closing, Dr. Jones called attention to the fact that the AACR was established in 1907 as the first organization in the world dedicated to conquering cancer. The AACR Centennial to be celebrated in 2007 will mark milestones of the last 100 years in cancer research. Numerous national and international events are planned for scientists, the public, cancer centers, and legislators, to emphasize the mission of the AACR. Working with the NCI, the observance will spotlight the value of cancer research and its impact on the cancer patient or survivor. Dr. Jones pointed out that the AACR and NCI share a vision for progress that includes agreement that major opportunities exist for changing the face of cancer, recognition of the remarkable pace of scientific discovery, and belief that cancer researchers are now poised to engage in "breakthrough thinking" about the next wave of progress. He stated that the AACR values its partnership with the NCI and will work tirelessly to achieve the common goal of hastening the

prevention and cure of cancer. He acknowledged the work of Past President Dr. Margaret Foti and AACR staff in making sure that cancer is a national priority and cancer research is moving forward and translated as efficiently as possible.

Questions and Answers

Dr. von Eschenbach paid tribute to the record of accomplishments by the AACR and the leadership and spirit in which they were achieved. He acknowledged the value of the NCI-AACR partnership with regard to the enrichment of the scientific effort to understand and then to deal with cancer. Looking to the future and at the joint commitment to ensure the pipeline of intellectual talent into cancer research, Dr. von Eschenbach asked about the AACR's plans with regard to using its membership, leverage, and leadership to work with academic institutions to effect a cultural change around criteria for promotion and tenure that will help address the problem of intellectual talent. Dr. Jones replied that the Associate Members Council provides a forum in which new scientists can express their views on these kinds of problems. Dr. Foti added that a dialogue has taken place within the Clinical Translational Steering Committee to try to effect a change, and a decision has been made recently to form new Education and Workforce Committees to address the team science issue and work for change. Dr. von Eschenbach noted that the NCI would welcome partnership with the AACR if an opportunity arose to address the problem within any venue, for example, the American Association of Medical Colleges or the Council of Deans. Dr. von Eschenbach then referred to the AACR's emphasis on standardization of bioinformatics and asked whether this included plans to engage the private sector, which has developed and is using tools for data mining, such that the volume of information the AACR is assembling can be translated into knowledge more quickly and transparently. Dr. Foti responded that, on the basis of an idea that surfaced at the recent AACR-Industry Roundtable meeting, two separate URLs were immediately secured and a program is being developed to aggregate all cancer information assembled through AACR initiatives, mine it, and find ways for distribution to both scholars and the public. In addition, initiatives are underway internally to create separate Web sites for the many different subject areas such as prevention or the tumor microenvironment. Dr. Foti noted that the advice of individual scientists is needed as to how the information can best be put together and what the potential is for mining information in their areas.

Dr. Runowicz cited the results of the AACR-LAF survey and asked whether the AACR had plans to organize or lead the effort to increase public awareness of the proposed decrease in federal funding for cancer research. Dr. Jones agreed that the AACR is in a good position to act (e.g., opinion articles by Board members for the newspapers), and that making the public directly aware of the cut would be helpful. Dr. Barker noted that the AACR has been effective in the past in every instance when it has assumed a significant role in policy development and that there are almost as many problems in policy that also could hinder research. Dr. Lander noted that this is the time for aggressive action by the scientific community. Dr. Foti commented that the AACR plans to sponsor a new poll in the coming year and that the centennial observance provides an opportunity to act. She expressed the hope that the AACR can help make a difference.

Dr. von Eschenbach observed that cancer is a global issue and asked whether, in light of its extensive international collaborations, the AACR views these as an opportunity to provide leadership in creating partnerships so that others are joining the United States in making an investment in cancer research. Dr. Jones replied that the International Affairs Committee is specifically addressing those issues, that Africa and India are areas where the AACR could have some focus, and that the upcoming meetings in Asia will seek to increase possibilities for research and funding in the future. Dr. Foti added that she and Dr. Jones are traveling soon to Singapore and Hong Kong to explore how scientists in the

developed world can make a difference in the developing world. She pointed out that what is learned from the developing world also can enrich science in the United States.

VII. INTRAPERITONEAL CHEMOTHERAPY FOR WOMEN WITH OVARIAN CANCER—DR. EDWARD TRIMBLE

As background for his report on a recent NCI Clinical Announcement on Intraperitoneal Chemotherapy for Women with Ovarian Cancer, Dr. Trimble reviewed past and recent clinical studies of intraperitoneal (IP) therapy. He reminded members that the concept behind IP therapy is an old one. NCI studies by Dr. Robert Dedrick in 1978 proposed IP therapy for women based on the ability to deliver a high IP concentration of the drug, the prolonged IP drug half-life, and a prolonged systemic drug half-life. Lessons from early clinical trials were that IP therapy seemed to be ineffective for women with bulky intra-abdominal disease and that the pharmacokinetic (PK) advantages were notable for certain drugs comparing the IP concentration to systemic concentration. Based on these early trials, Phase III trials were undertaken beginning in 1988, primarily in the United States, but also in Europe and Taiwan. Six of the trials were for women with advanced stage ovarian cancer after primary surgery, and one was a consolidation trial of platin-based chemotherapy for women with no evidence of disease after primary surgery. Dr. Trimble reviewed the accrual and treatment data from the largest three trials, all of which were sponsored by the NCI. The first was led jointly by the Southwest Oncology Group (SWOG) and Gynecologic Oncology Group (GOG) and compared cisplatin administered intravenously (IV) and cyclophosphamide versus cisplatin IP and cyclophosphamide IV. The second, a followup study, was led by GOG with SWOG and the Eastern Cooperative Oncology Group (ECOG) and compared cisplatin IV and paclitaxel versus induction carboplatin plus cisplatin IP and paclitaxel IV. Results of both studies were positive. The most recent trial, a GOG study, opened in 1998 and compared cisplatin IV and paclitaxel versus cisplatin IV and paclitaxel IV+IP. Results were published in January 2006 in the *New England Journal of Medicine (NEJM).*

Dr. Trimble presented summaries of available data for treatment hazard and survival ratios from two groups of the studies comparing IP versus IV therapy. The combined data from the first group—a small Italian study, the two GOG trials, and an EORTC study—demonstrated a treatment hazard ratio for progression-free survival (PFS) at 0.79, favoring IP regimens across these four studies. The second group of six studies, which included the SWOG/GOG and a Taiwanese study, demonstrated a significant improvement in survival associated with IP therapy. Across all of the studies, the improvement in median PFS was 12 months. Dr. Trimble noted that, for the most recent GOG trial, the improvement in median survival was 16 months. He then reminded members of the guidelines for issuing NCI Clinical Announcements, which are made to bring new information of unusual importance to the attention of clinicians as rapidly as possible. They call for a review of data by an independent panel nominated by the investigators and the NCI, and the recommendations are forwarded to the Director, NCI. The guidelines specify that the Clinical Announcement should be timed with publication of the manuscript so that relevant data are available immediately to doctors and patients. Dr. Trimble pointed out that this mechanism is used infrequently; only 5 have been issued in the past 18 years. In the case of the IP studies, the GOG and SWOG investigators proposed that the NCI consider an announcement. An independent panel of experts nominated by the GOG, SWOG, EORTC, and NCI reviewed the data from the trials and voted to recommend that the NCI issue a Clinical Announcement. The proposal was reviewed by NCI's Senior Management Team and the Executive Committee, which also reviewed data from the Surveillance, Epidemiology, and Endpoints Research (SEER) database and a recent SEER/Medicare study. The data showed that less than 1.0 percent of women with Stage III ovarian cancer were receiving IP therapy, despite the two studies that have been published.

Dr. Trimble stated that, to explore the reasons why IP therapy was not being used, focus groups of doctors, advocates, and nurses were convened; the reasons they gave demonstrated the extent of the educational job ahead. A trans-NCI team was developed to write the text of the announcement, which was reviewed in the Office of the Director, NIH, and by the FDA, the independent panel that had been convened, and Bristol Myers-Squibb, co-sponsor of two of the trials. Dr. Trimble noted that the NCI worked with *NEJM* editors to time the Clinical Announcement with publication of the paper and an accompanying editorial, and with editors of *Gynecologic Oncology* for expedited review and simultaneous electronic release of the manuscript for the secondary endpoint of the trial related to IP catheter outcomes, together with an editorial by Dr. Trimble and Dr. Michaele Christian, Director, CTEP, DCTD. In addition, a review article is being prepared for publication in *Lancet.* The national release of the NCI Clinical Announcement was timed with the January 5 issue of *NEJM* and press releases by the NCI and gynecology and oncology professional organizations. Local press releases were issued by NCI Cancer Centers and research sites that had been active in the trials. The announcement received national television coverage on January 5 and 6, was picked up by the national wire services, and covered in both national and local newspapers and by the foreign press in France, Australia, the United Kingdom, and Canada. Dissemination of the announcement was extended to advocacy groups with the help of the NCI Office of Liaison Activities (OLA) and through the NCI Web Site with the help of the Cancer Information Service (CIS). Educational materials were developed collaboratively with the NCI Cancer Centers and Cooperative Groups and made available to doctors, nurses, and patients via a Web site hosted by the GOG. Dr. Trimble noted that the NCI has been working with various professional societies to disseminate the news and with the Cooperative Groups to set up local, regional, and national conferences. In addition, the NCI has been contacted by groups in Australia, Austria, Canada, and the United Kingdom for help in organizing educational conferences on IP chemotherapy.

Dr. Trimble noted that plans for evaluation of the Clinical Announcement and dissemination process are being developed with the help of staff from the Division of Cancer Control and Population Sciences (DCCPS). The NCCN and the NCI-sponsored Cancer Research Network (CRN), early adopters of the information, have been asked to submit proposals for the evaluation. Moreover, plans have been made for evaluation through the SEER 2006 Patterns of Care Study and through SEER/Medicare, and collaborations are being sought with the American College of Surgeons and the National Cancer Database. Dr. Trimble noted that the records of industry partners in the studies may not be helpful in tracking use of the catheter ports and agents for peritoneal applications for various reasons. He stated that the NCI is continuing to work to improve IP chemotherapy with studies designed to decrease the toxicity and increase efficacy.

Questions and Answers

Dr. Freedman congratulated the NCI for making this information public and supporting the various studies. He observed that they highlighted the main issues surrounding IP therapy, namely, that there is no financial incentive for many oncologists and industry, and the advocacy group is small. He asked how long the NCI would work to keep these results in the forefront. Dr. Trimble replied that professional organizations, such as AACR, ASCO, Society of Gynecologic Oncologists, and the Oncology Nursing Society, have been asked for help. All have expressed interest and have plans; moreover, a seminar on IP delivery at the GOG semiannual meeting in January was oversubscribed. Dr. Trimble noted that the NCI is attempting to build on current enthusiasm and ensure that the necessary information is available. Dr. Runowicz observed that, inasmuch as only 40 percent of the patients received six cycles, the question arises as to whether it is a matter of two or four cycles or an infusion rather than IP issue, suggesting that IV infusion might be as good as IP administration. She noted that the toxicity was impressive in that only 40 percent of patients completed therapy. She also observed that the median PFS of 12 months in the group of studies was lower than overall survival 15-16 months in the

latest GOG study, when the reverse should have been true. She raised the question as to what the first-line therapy did that led to the better response to second-line therapy and noted the need to resolve these questions. Dr. Trimble acknowledged that there is toxicity associated with the regimen, but pointed out that advances have been made in delivering the therapy and managing catheter complications since the latest GOG study was written. Moreover, the data suggest that the IP approach, which was studied in all three trials, produces better results. He noted that GOG plans include a randomized Phase II trial looking at different IP approaches to decrease toxicity and improve deliverability. In addition, a number of Cancer Centers now have adopted IP therapy as their standard of care of women with optimally debulked disease.

Dr. James Armitage, Joe Shapiro Professor of Medicine, University of Nebraska College of Medicine, observed that the clinical announcement mechanism cannot be used frequently at the risk of losing effectiveness, and he asked how the NCI decided when to use it to influence cancer care in a positive way. He pointed out that better application of adjuvant therapy in breast or colon cancer or better screening for colon cancer would save more lives than IP therapy for ovarian cancer. Dr. Trimble replied that the mechanism primarily has focused on treatment advances in the past and an important issue for investigators in cancer treatment trials is whether research findings are being translated into the general oncology community. He stated that the issues raised by Dr. Armitage were considered in the deliberative process preceding the Clinical Announcement, and the decision was made that the information was sufficiently important that it warranted dissemination to women with ovarian cancer and their doctors. Dr. Samir Abu-Ghazaleh, Director, Gynecology and Gynecologic Oncology, Avera McKennan Hospital and University Health Center, pointed out that many physicians other than gynecologic oncologists perform surgery on patients with ovarian cancer and, for physicians in rural areas, IV therapy is easier than IP to administer. He noted that until all patients with ovarian cancer are treated by appropriate people, widespread delivery of IP chemotherapy might not be possible even though there is no question that the outcome is better. Dr. Von Hoff related his experience at a survivors' conference when a woman indicated that she would never agree to IP therapy on the basis of a discussion in her support group. He suggested the need for the NCI to find a way to address this situation at that level of discussion. Dr. Trimble stated that meetings are held every 6 months with the various ovarian cancer groups. Dr. Kenneth Cowan, Director, University of Nebraska Medical Center (UNMC) Eppley Cancer Center, University of Nebraska Medical Center, recounted that he had trained at the NCI at the time when Dr. Dedrick first developed the concept for IP therapy. He noted that Dr. Dedrick was a pioneer in this field, who looked on the treatment of patients as a mission for himself and for intramural NCI. Dr. Cowan commended the issuance of the Clinical Announcement.

VIII. CANCER STEM CELLS—DRS. MAX WICHA AND JONATHAN VOGEL

Breast Cancer Stem Cells: Implications for Prevention and Therapy—Dr. Max Wicha

Dr. Max Wicha, Director, University of Michigan Comprehensive Cancer Center, presented the results of research in his laboratory on stem cells in breast cancer that may have clinical implications for other malignancies. Like IP chemotherapy, the concept of stem cells in cancer is very old, but progress in science has made it possible to validate the concept in experimental models. Members were reminded that although breast cancer mortality in the United States and United Kingdom has steadily decreased since 1990 because of better screening and early detection, the outlook for women with advanced disease has not changed. Dr. Wicha expressed the belief that both the advances in adjuvant therapy and limitations in advanced disease are due in large part to the fact that the wrong cells are being attacked and it is the cancer stem cells that are driving the cancer. As evidence, he cited the familiar scheme showing that breast cancer develops in a stepwise manner over many years and noted that only stem cells live that long. Dr. Wicha stated that the cancer stem cell hypothesis has two components: (1) cancers arise from

tissue stem or progenitor cells; and (2) cancers once they are developed are "driven" by cells with stem cell properties or tumor stem cells. The latter component is more important from a clinical perspective. Members were reminded that the two characteristics that define stem cells are their ability to self-renew and their propensity for multi-lineage differentiation. Another consideration is that there are tissue-specific stem cells within each organ that are able to differentiate into cell types in that organ that have a more limited repertoire (e.g., a breast stem cell does not differentiate into a liver cell). Dr. Wicha expressed the belief that stem cells or their immediate progeny are the targets for transformation during carcinogenesis, which would have important clinical implications. His laboratory is studying normal stem cells in the human breast, trying to isolate and characterize them, and then characterizing how these normal breast stem cells are changed as they become cancerous.

Dr. Wicha provided evidence in support of the first part of the hypothesis—that cancers arise from tissue stem or progenitor cells. He pointed out that properties that have been attributed to cancer cells are actually properties of normal stem cells that have become tuberous sclerosis complex (TSCs) through dysregulation. In TSCs the ability to self-renew leads to uncontrolled proliferation and tumorigenicity, a key property that is dysregulated during the earliest phases of tumorigenesis when there is an expansion of stem cells. The ability of tumor stem cells to differentiate is a contributing factor to tumor heterogeneity and aberrant organogenesis. The long life and immortality of TSCs increases the risk of accumulating mutations and can cause defects in DNA repair mechanisms as well as genomic instability. The ability of TSCs to resist damaging agents explains chemoresistance and has important implications for therapeutics. The TSC characteristic of anchorage-independent survival, as well as its ability to migrate, is related to metastasis. As further evidence, Dr. Wicha pointed out that the Notch, Hedgehog, Bmi-1, and Wnt pathways, which have been found to regulate the process of self-renewal in the normal stem cell, lead to cancers when perturbed. As an example, he reviewed a study in his laboratory, which showed that perturbing the Hedgehog pathway in a mouse model promotes ductal hyperplasia.

Dr. Wicha then reviewed work in support of the second component of the hypothesis—that cancers are "driven" by cells with stem cell properties. He compared the stochastic model for tumor development with a cancer stem cell model that he is developing in collaboration with Dr. Mike Clark, Stanford University. The classic model recognizes the heterogeneity of cancer cells but suggests that most cells can proliferate extensively and form new tumors through random mutations. The new cancer stem cell model demonstrates the hypothesis that although cancer cells are heterogeneous, only rare cancer stem cells have the ability to proliferate extensively and form new tumors. Dr. Wicha noted that, based on evidence in a Canadian study that such a hierarchy could exist in hematologic malignancies in leukemia, he and Dr. Clark began work to see whether a similar model could apply in solid tumors. He described mouse model studies, which demonstrated that only a subset of transplanted human breast cancer cells have the ability to form tumors—in these studies, those negative for the extracellular matrix receptor CD24. Both nontumorigenic cancer cells and cancer stem cells were found to have a malignant appearance, but only stem cells gave rise to new tumors. Because stem cells are defined by two properties—self-renewal and multilineage, further studies were conducted to show that breast cancer stem cells give rise to phenotypically diverse tumors after transplantation.

Dr. Wicha described additional studies that were undertaken to confirm the findings related to the role played by the activation of pathways like Hedgehog and the transcription factor Bmi-1 in tumor stem cell formation. He presented a diagram of what he and colleagues believe happens during carcinogenesis derived from these studies. As one example of the clinical implications, Dr. Wicha reviewed a study across 10 tumor types by Glinsky, et al., published recently in the *Journal of Clinical Oncology* entitled "Bmi-1 'Stem Cell' Signature and Patient Survival." Patients with the "stem cell" profile had markedly poorer survival compared with those without the profile. He noted that this finding across all 10 tumor

types suggests there is a commonality of stem cells in a variety of different cancers that carry this prognostic implication.

Dr. Wicha then discussed implications of the tumor stem cell model: (1) the cell of origin may determine the molecular profile; (2) molecular profiling studies tell what the stem cell of the tumor is and the differentiated progeny it produces but may miss important tumor stem cell genes; (3) tumor stem cells may have a significant role in metastasis; (4) identification of tumor stem cells and the mutated stem cells *in situ* may have diagnostic and prognostic value; (5) elimination or differentiation of the mutated stem/progenitor cells may be an important prevention strategy. He described work in his laboratory to develop models that identify the origin of the different molecular profiles of breast cancer. He pointed out that, from the substantial literature, the overall molecular profiles of breast cancer can be separated into basal, luminal A, and luminal B categories, then explained how the tumor stem cell model could provide for a better level of understanding. He noted that the success of adjuvant therapies also can be explained better with a stem cell model in that anti-estrogens such as tamoxifen or aromatase primarily benefit patients with luminal A profiles because they eliminate the stem cells and cure patients at early stages. Similarly, for metastases, the cancer stem model suggests that the presence of a cancer stem cell is necessary for tumorigenesis. Nontumorigenic cancer cells may produce micrometastasis but do not have the proliferative potential to produce a clinically relevant macrometastasis. Dr. Wicha noted, therefore, that looking for stem cells at metastatic sites will be important. He added that the dormancy of tumors can be explained in that the microenvironment to which a tumor stem cell metastasizes may not support the immediate proliferation of the cell but the dormant cells go back into the cycle many years later and form metastases.

Dr. Wicha discussed the important implications of human cancer stem cells for treatment. Chemotherapeutic drugs and some of the new targeted therapies are tested in animal models and Phase II clinical trials in which tumor regression is the main primary endpoint. The stem cell model suggests this is the wrong endpoint. Agents selected for their ability to shrink tumors might be largely killing the differentiated cells in a tumor that is heterogeneous with only a small portion of stem cells. Dr. Wicha suggested that this may account for tumor recurrence and explain why longevity or ultimate survival of a patient is not affected much by tumor shrinkage. He proposed that effective therapies should target tumor stem cell population while sparing normal cells, and noted that his and other laboratories are working on potential strategies to target that population. Dr. Wicha concluded that work in his laboratory during the past 1.5 years is producing substantial evidence for similar stem cell components in a variety of cancers. What is interesting is that some of the stem cell markers are shared across different cancers, suggesting that the agents that are developed to target stem cells in one tumor may have broad applicability.

Characterizing Keratinocyte Stem Cells—Dr. Jonathan Vogel

Dr. Jonathan Vogel, Senior Investigator, Dermatology Branch, CCR, reported on efforts in the CCR to characterize tissue stem cells and cancer stem cells (CaSCs). He prefaced his report by making several points: (1) CaSCs may represent a subset of cancer cells that have the stem cell properties of self-renewal and unlimited replicative potential that are necessary for long-term tissue repopulation; (2) these CaSCs may generate additional CaSCs in the process of self-renewal, differentiating to phenotypically diverse cancer cells with only a limited proliferative potential; (3) in some human cancers, cell surface markers have been identified that can distinguish CaSCs from other cancer cells with a more limited proliferative potential, raising the possibility that the CaSCs can actually be distinguished going forward; and (4) in terms of mechanisms, some mutations may target normal tissue stem or progenitor cells and expand those populations; this may be the first step in cancer formation. Dr. Vogel pointed out that CaSCs may represent novel therapeutic targets for treating epithelial carcinomas. Goals to be accomplished to better characterize CaSCs and demonstrate their existence in epithelial cancer are: (1)

identify unique panels of cell surface markers on them to provide a "handle" so that these cells can be manipulated; and (2) develop *in vivo* assays of human carcinomas that can determine if putative CaSCs are able to reconstitute the cancer and exhibit properties associated with stem cells (e.g., self-renewal and long-term repopulating ability). Dr. Vogel noted, however, that well-characterized and unique cell surface markers for either normal stem cells or CaSCs in epithelial tissues are not known and good *in vivo* assays for many human epithelial cancers do not currently exist.

Dr. Vogel stated that the study of tissue and CaSCs is an emerging area of interest in the CCR, and he briefly described the focus of several CCR investigators who are working to characterize tissue stem cells of liver, breast, and skin to promote a better understanding of the relationships between normal tissue stem cells and CaSCs. Dr. Snorri Thorgeirsson is comparing global gene expression patterns or signatures of genes of distinctive human hepatocellular phenotypes with variable prognoses. For many years, Dr. Gilbert Smith has studied mammary gland tumorigenesis in mammary epithelial stem cells based on the hypothesis that mammary carcinomas arise as clonal populations of transformed tissue-specific stem cells and their differentiating progeny. He has made a number of contributions to mammary gland biology, including the development of the mammary fat pad transplantation technique as an *in vivo* stem cell assay. In collaboration with Dr. Smith, Drs. Michael Gottesman and Barbara Vonderhaar have been establishing *in vivo* assays for human breast cancer based on the murine mammary fat pad assay to analyze human breast cancer more systematically. At NCI/Frederick, Dr. Michael Dean has been identifying and characterizing MDR genes of the ATP binding cassette or ABC family of transporters. The major focus of his laboratory in the Dermatology Branch, CCR, has been to develop an "infrastructure" to identify, isolate, and characterize keratinocyte stem cells (KSCs) and their progeny.

Dr. Vogel explained that his laboratory has been exploring the hypothesis that the knowledge and experimental approaches derived from these KSC studies will provide a roadmap for identifying and characterizing the role of CaSCs in nonmelanoma skin cancers such as squamous cell and basal cell carcinomas. He described ongoing work in his laboratory to show how these approaches can be applied to epithelial tissue stem cells. As background, he explained that KSCs can be identified as label-retaining cells (LRCs). In renewable tissues like the epidermis, KSCs are believed to divide infrequently, and these KSCs can be identified by their ability to retain a nucleotide (BrdU) label. Dr. Vogel demonstrated this with a kinetic example in the skin. In the setting of BrdU, the KSCs, which divide asymmetrically, will pick up the BrdU and give rise to transit amplifying cells that proliferate rapidly and give rise in the skin to super basal postmitotic cells, differentiating keratinocytes. At the end of this labeling period, all keratinocytes in the skin will be labeled with BrdU. When the BrdU label is removed and a prolonged washout period follows, the postmitotic differentiating cells in the skin and other epithelial tissues will be lost, and the transit amplifying population, which continues to proliferate, will dilute out the label. Dr. Vogel explained that in the skin, the LRCs are scattered throughout the intrafollicular epidermis in the basal layer and highly enriched in the hair follicle known as the bulge. It is believed that these LRCs represent KSCs; however, to be detected, the LRCs need to be fixed and made permeable to antibodies against the BrdU nucleotide label. Consequently, biological studies, including assays to assess their stem cell behavior, cannot be performed. To identify, isolate, and characterize living KSCs, a unique panel of cell surface markers on human LRCs would be needed.

Dr. Vogel stated that his laboratory has pursued two approaches to address this problem, both of them applicable to other epithelial tissues. The first, an RNA approach, consists of laser capture microdissection (LCMD) of LRC from the bulge area of human hair follicles, followed by microarray analysis. Dr. Vogel described studies to detect LRCs in epithelial tissues such as the skin using this approach after grafting human scalp onto an immunocompromised mouse model and labeling all keratinocytes with BrdU as shown by fluorescence-activated cell sorter (FACS) analysis. He summarized the findings from these studies: (1) LRCs may provide one starting point to identify unique markers in

stem cells and their progeny in epithelial tissues; (2) a panel of genes including membrane markers CD200 and FZD1 were specifically upregulated on LRC-enriched bulge keratinocytes; and (3) although the CD200+ cells selected from the mid-portion of human hair follicles had a proliferative advantage during *in vitro* culture, good *in vivo* assays in animal models are necessary to demonstrate stem cell behavior. The second or proteomic approach, in collaboration with investigators at NCI/Frederick, involves using high-throughput mass spectrometry (MS) to quantitatively analyze membrane proteins on FACS-sorted LRCs.

Dr. Vogel stated that the Dermatology Branch also has been working to develop *in vivo* assays to confirm the stem cell behaviors of self-renewal and long-term repopulating ability of candidate KSCs. An *in vivo* competitive repopulation assay was developed recently using a raft culture-grafting system that takes advantage of the laboratory's ability to grow skin and its access to endogenous HLA2 markers that avoid problems with gene silencing for marker genes. In the assay, a test population of cells that either contains pure putative CaSCs or is enriched for CaSCs is competed with a control population that does not contain KSCs. Dr. Vogel noted that this *in vivo* assay was used to determine whether alpha6-integrin-bright keratinocytes and side population (SP) keratinocytes possess self-renewal and long-term repopulating ability, to test the hypothesis that side population keratinocytes may represent very primitive KSCs. These results represent the first *in vivo* demonstration that human alpha6 integrin-bright keratinocytes are enriched for KSCs while the SP keratinocytes do not contain KSCs represents the first *in vivo* proof of the hypothesis.

Looking to the future, Dr. Vogel noted that his laboratory in the Dermatology Branch is continuing its focus on identifying and characterizing CaSCs. To characterize the biological behavior of CaSCs, *in vivo* mouse model assays are being developed for squamous and basal cell carcinomas that are able to assess the ability of putative CaSCs to recapitulate the cancer *in vivo*. Currently, three-dimensional raft cultures and nanofibrous scaffold supports are being used in this effort. After the model has been developed, the goal will be to determine whether CaSCs exist within squamous cell carcinoma and develop methods to identify and purify them. The first step in this effort will be to use the cell surface markers that will have been identified for KSCs and their progenitors. Dr. Vogel concluded that within the CCR there is a considerable amount of expertise and a growing interest in characterizing epithelial stem cells and using this knowledge to understand the role of CaSCs in the initiation and maintenance of epithelial carcinomas. Key goals are to: (1) identify cell surface markers that will serve as "handles" to isolate and manipulate CaSCs in a way that enables investigators to deal with these cells in tissue culture; and (2) develop *in vivo* models that can assess the ability of putative CaSCs to recapitulate human cancer.

Questions and Answers

Dr. Jones observed that the cancer stem cell discussions underscored the need for the cancer research community to understand them. He commented that one unexpected item of information from the recent think tank on this topic was that many of the pathways actually are inactivated by epigenetic mechanisms. For example, Bmi-1, which was discussed by Dr. Wicha, is a chromatin-remodeling protein. Dr. Wicha commented further that Bmi-1 is thought to regulate the switch by turning off p16 and that the epigenetic silencing of p16 has been shown in a number of tumors, as well as in early breast cancer. He expressed the view that the epigenetic changes that may lock these stem cells into a self-renewing configuration and expand them may be one of the earliest events in carcinogenesis. Dr. Armitage commented that the conclusions from stem cell research matches well with experience in treating hematologic malignancies in that acute myelocytic leukemia is presumably the most differentiated and the easiest to cure, whereas those malignancies thought to be injurious to primitive cells are not cured with drugs. He asked whether there are any circumstances where curing a patient with

drugs was not merely the result of finding a way to kill a sufficient number of stem cells to make the tumor die but also could be an alteration of tumor microenvironment. Dr. Wicha agreed that the tumor microenvironment with its stromal-epithelial interaction is an important component of treatment. He pointed out that it is actually an interaction between the microenvironment and the stem cell. The area known as the niche is the surrounding environment, and it is thought that metastases are determined largely by the stem cell-niche interaction; therefore, some therapies may be working on the niche rather than the stem cell. As an interesting sideline, Dr. Wicha noted that, even though almost all patients with chronic myelogenous leukemia go into remission with Gleevec therapy, almost no one is cured and the cancer progresses if the Gleevec treatment is stopped. The progression occurs with a kinetics that is predicted by the stem cell model. He expressed the view that this is an indication that targeted therapies may improve the patient's condition, but a way must be found to target the stem cell.

Dr. Niederhuber asked whether it is possible that the supporting microenvironment cells should be thought of as changes in tissue stem cells as well. Dr. Wicha replied that current information on the crosstalk between tumor and stroma is indicating that the stroma is actually activated. Studies of the wounding profile show that the same kinds of genes expressed in a wound are expressed around a tumor, leading to the hypothesis that stem cell pathways are similar to tissue regeneration after an extreme injury. He expressed the view that probably the most important emphasis in the area of cancer stem cell research is how stem cells are controlled by the microenvironment. Dr. Freedman asked whether it is now possible to establish rules for isolating cancer stem cells from other cells in a tumor. Dr. Wicha replied that this is being done by means of functional assays. Dr. Franklyn Prendergast, Director, Mayo Clinic Comprehensive Cancer Center, asked about the extent to which circulating tumor cells have the phenotypic characteristics of tumor stem cells. Dr. Wicha agreed that is an important question, and he cited studies in his institution looking at circulating breast cells as a possible marker of bad prognosis as well as studies by other groups to determine whether metastases are enriched for stem cells. He noted further that clinical literature in both breast and prostate cancer suggests that, at the time of diagnosis, about 30 percent of patients have micrometastases but only one-half of that number actually recur 10 years out. The hypothesis for those who recur is that either their cells are not stem cells or the microenvironment of their stem cells is insufficient to allow them to self-renew. Dr. Prendergast asked about sentinel node tumor cells. Dr. Wicha replied that it is important to know whether cells in the sentinel node are stem cells and not just shed cells, which highlights the need for good stem cell markers. Currently, it is necessary to use a battery of markers to identify stem cells, but the goal is to use gene-expression profiling to obtain good markers of stem cells that could be used for immunohistochemistry. It would then be possible to examine a variety of completed clinical trials retrospectively and ask whether the micrometastases stem cell markers carry important prognostic implications.

Dr. deKernion asked how solid the evidence is that the pathway to malignancy in an organ almost always depends on change in the stem cells of that organ. Drs. Wicha noted that the change is believed to occur in the cells that have self-renewing potential, which is a characteristic of the stem cell, therefore, all that is needed is deregulation of an existing process. He pointed out that other cancers appear to arise from progenitor cells that have the potential to differentiate into several cell types and that it is important to make the distinction between the two concepts of self-renewal and division. It was noted that Dr. Von Hoff was one of the pioneers in cancer stem cells, and that he and colleagues developed a functional test. The view was expressed that the underlying hypothesis of that test should be revisited and modern marker tests correlated with the ability of the putative stem cells to grow in agar.

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

Dr. Gray asked for concurrence by the NCAB in two delegations of authority to the Director, NCI, which will enable the NCI to function within Federal Advisory Committee Act (FACA) regulations,

and a statement of understanding with the NCI on operating principles in extramural awards. She reviewed the delegations and the provisions in the statement of understanding. **Delegation A** specifies that the NCAB delegates to the Director, NCI, permission to obtain, as stated in Section 413(b)(5) of the Public Health Service Act and "in accordance with Section 3109 of title 5, United States Code, the services of not more than 151 special experts or consultants who have scientific or professional qualifications to assist in accomplishing the mission of the Institute." **Delegation B** specifies that the NCAB delegates to the Director, NCI, permission to exercise authority as stated in Section 413(b)(7) of the Public Health Service Act, to "appoint one or more advisory committees composed of such private citizens and officials of Federal, State, and local governments to advise the Director with respect to the Director's functions."

Dr. Gray reviewed the provisions in the **Statement of Understanding with NCI Staff on Operating Principles in Extramural Awards**, which also fall within the Delegations of Authority to the Director, NCI. **Concurrence of the NCAB with recommendations of initial review groups will be required except for:** (1) grants with direct costs not exceeding $50,000 annually without other concerns and for individual National Research Service Awards; (2) applications over the 50th percentile will not have summary statements presented to the NCAB in closed session; (3) for applications assigned raw scores that are not percentiled, the cutoff will be a priority score of 250 for all mechanisms except R41, 42, 43, and 44 awards; for the latter, all scored applications will be included. **Expedited Concurrence:** (1) for R01 and R21 applications with percentiled or raw scores that fall within the NCI paylines for that mechanism, a process of expedited concurrence will be used; (2) the Executive Secretary will alert Board members with responsibility for expedited concurrence when review outcomes for eligible applications are available on the Electronic Expedited Concurrence portion of the Electronic Council Book. **Administrative Adjustments:** (1) permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards; (2) administrative requests for increases in direct costs that are the result of marked expansion or significant change in scientific content of a program after formal peer review will be referred to the Board for advice and recommendation; (3) actions not requiring Board review or advice, such as change of institution or investigator, phase-out or interim support, or additional support need not be reported to the Board; (4) NCI staff may restore requested time and support that were deleted by the initial review group when justified by the principle investigator in an appeal letter or restoration is in the best interest of the NCI and the project is of high NCI programmatic relevance.

In discussion, the Board requested information on the origin of Delegation A, which limits to 151 the number of Advisors the NCI Director can obtain, and on the optimal number of advisors needed to assist in accomplishing the mission of the Institute.

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

X. REVIEW OF PROGRAM PROJECT GRANT APPLICATIONS: CLUSTER REVIEWS—MS. DIANE BRONZERT AND DR. OLIVIA BARTLETT

Dr. Gray introduced Ms. Diane Bronzert, Associate Director, DEA, and Dr. Olivia Bartlett, Chief, Research Programs Review Branch, DEA, to present the revised paradigm for conducting P01 reviews using the cluster review process. She noted that this paradigm had been presented to NCI's extramural division directors. Program staff have been heavily involved in developing the implementation plans.

The plans were presented to the NCAB as an informational item to explain how the NCI will proceed with P01 reviews during the next year.

Update on Review of Program Project Applications—Ms. Diane Bronzert

Ms. Bronzert began the presentation by observing that the program project grants constitute an important component of the NCI's grant portfolio. Through these grants, which are multidisciplinary work that involve a minimum of three projects as well as support cores, the NCI supports transdisciplinary integrative research. Grants range from prevention and cancer control to translational work and basic research. There are 176 P01s that were competing and noncompeting continuations in FY 2005, worth $338 M in total costs, including competitive supplements. This comprises approximately 16.7 percent of the recent project grant pool; this percentage has remained stable over the years, even when the budget doubled. In 2005, 129 P01s were reviewed and 39 competing awards were made for approximately $67 M total cost. Eighty percent of the awards were for amended applications. Of the 20 percent of awards made to first time applications, all of those were competing renewal (Type 2) awards.

Ms. Bronzert provided background information on the review of the P01s. In 1994, the NCI re-established chartered P01 parent committees to provide the final score for the applications reviewed by individual review panels. In 2003, an NCI P01 Working Group, which was comprised of review staff and representatives from all of the extramural program divisions, reviewed the P01 review process and made several recommendations: (1) implement a pilot of review of P01 applications in clusters of 2 to 4 applications instead of setting up individual review panels for each application; (2) eliminate site visits, (3) continue to have the P01 chartered "parent" committees provide final priority scores. The cluster review process began with applications received in February 2004 for the FY 2005 awards. DEA obtained feedback from extramural reviewers and program staff over the next year to evaluate the cluster review pilot. The NCI P01 Working Group was reconvened in the summer of 2005 to look at the data and make further recommendations. The evaluation of the P01 cluster review process revealed that the number of reviewers and number of meetings decreased significantly compared to the individual review panels. Specifically, the number of review meetings decreased 55 percent from 125 in FY 2004 to 56 in FY 2005. In addition, the number of reviewers decreased 31 percent from 1,398 in FY 2004 to 969 in FY 2005. Nevertheless, the number of reviewers assigned per application actually increased from 11 to 12. The spread of priority scores improved, and there were positive evaluations from cluster review panel members. Finally, a cost savings of $220,000 was realized in FY 2005.

Based on this data and a realization of the need to implement what is "practical" rather than what may be "ideal", the Working Group made the following recommendations in July 2005: (1) continue review of P01 applications in clusters; (2) triage poor applications; (3) eliminate applicant teleconferencing during the review meeting to have time to discuss the applications more completely (SRA will contact an applicant if a critical question must be addressed for the review to proceed); and (4) implement a 1-year pilot of a single-tier peer review of applications in larger clusters (4 – 10 applications) by Special Emphasis Panels (SEPs). This pilot will be implemented with the February 1, 2006 receipt date. Each SEP will cover broad research topic areas. The SEPs will discuss and score the projects and cores and also assign the overall priority score. These recommendations were discussed with NCI's Extramural Advisory Board, composed of extramural staff from all NCI Divisions in October 2005. In November 2005, NCI's Extramural Division Directors Committee approved the recommendations, which were then presented to the P01 charter committee members in December 2005. The recommendations also were shared with any investigator who submitted a letter of intent, which is required for all P01s, for the February 1, 2006, deadline.

Ms. Bronzert described the advantages of using the large-cluster, single-tier P01 review process. It will streamline the review process significantly by replacing 16 to 19 cluster meetings plus three parent committees per round with 5 large cluster meetings per round. Moreover, fewer reviewers will be needed overall. The current chartered committee members will need to participate in only one meeting each round rather than two or three. It will be possible to schedule review meetings and recruit reviewers (senior reviewers) farther in advance of the meetings, even in advance of submissions since the broad topic areas are known. The new review process will also facilitate the triage of applications. The calibration of scoring will be easier because there will be fewer review panels. Finally, cost savings are expected, which is important in this era of fiscal stringency.

The DEA implementation plan is suspend meetings of the three P01 chartered committees during the pilot, and to distribute the current chartered committee members among the SEPs. However, DEA will maintain the chartered committees at full membership and will replace members who rotate off. The expectation is that the SEPs will form the basis for new chartered committees after the evaluation of the pilot. Teleconference and mail reviewers will be used in the SEPs to ensure that all required expertise is present on the SEPs and to ensure continuity with the previous review for amended applications. Program and review staff met on January 9, 2006 to discuss potential topic areas for the SEPs under this new model. The NCI P01 Guidelines have been updated to reflect the new review process, and they were made available to potential applicants for the February 1 receipt deadline; the updated Guidelines have also been posted on the DEA web site.

Special Emphasis Panel Research Topic Areas—Dr. Olivia Bartlett

Dr. Bartlett described the process DEA used to develop the new SEP research topic areas which will be piloted during the next year. Program and review staff held a one day meeting in January, 2006, and used mock clustering exercises with the P01 applications submitted for the January 2005 and May 2005 NCAB rounds to establish boundaries for and descriptions of the new SEPs. The potential topic areas were then tested by clustering potential applications for the February 1, 2006 deadline based on the letters of intent and other information known about the applications. The result was agreement on five broad topic areas for SEPs.

The parameters for establishing the P01 SEP topic areas used during the joint program/review meeting included: (1) a maximum of four to six SEPs, since the number of program project grant applications has decreased to 31 over the past few rounds; (2) an even distribution of applications across clusters each round, with a minimum of four applications each round; (3) areas of overlap to allow assignment of an application to more than one cluster for management of workload and member conflicts; and (4) clusters should cross NCI Extramural Research Programs.

The current P01 chartered committees include: Committee C—Basic Sciences, Committee D—Clinical Sciences, and Committee E—Cancer Epidemiology, Prevention, and Control. Each committee covers a wide variety of topics. Committees C and D generally run between 15 and 20 applications per cycle. Committee E generally evaluates between 6 and 10 applications, but there have been rounds with up to 15 or more applications. Committee E also handles unsolicited R01 applications proposing multisite interventional studies, and, occasionally, cooperative agreement or resource applications.

Five P01 SEP topic areas were defined during the January meeting: molecular biology; cell and tissue biology; discovery and development; clinical studies; and prevention, control, and population sciences. The topic areas of molecular biology and cell and tissue biology represent essentially two halves of Committee C. The molecular biology SEP will include studies on various types of carcinogenesis, DNA replication damage and repair, basic studies of radiation effects and radiation

biology, molecular genetics, structural biology, cell cycle control and cell signaling pathways. The cell and tissue biology SEP will cover studies of tumor microenvironment and metastases, angiogenesis, cellular aspects of tumor biology, basic studies immune mechanisms, and studies of hematopoiesis and stem cell biology. Two SEPs will represent essentially the two halves of current Committee D activities: The discovery and development SEP will includes biomarker discovery and development through to Phase 0 clinical studies and technology development, including medical imaging. There will also be a SEP for clinical studies, including clinical trials in immunotherapy and transplantation, chemotherapy, molecularly targeted therapies, gene therapies, radiotherapy, and surgery. Finally, there will be a SEP to cover prevention, control, and population studies, including cancer prevention, cancer epidemiology, risk analysis, genetic and environmental factors, health services and outcomes research, surveillance, nutrition, diet and energy balance, cancer survivorship and quality of life studies, and behavioral interventions.

The pilot will be evaluated based on feedback from reviewers, program and review staff from NCI's extramural divisions, and the SRAs. Among other factors, total number of reviewers required and how they are cross assigned among the applications will be analyzed. The length of the review meetings and measures of scoring calibration also will be evaluated. Lastly, cost will be considered, although it is not a driving factor in implementing the pilot.

Questions and Answers

Dr. Ralph Freedman wondered whether the NCI P01 Working Group had considered any significant disadvantages in the large cluster model. Ms. Bronzert replied that this was discussed and will be evaluated. However, the Working Group noted more advantages than disadvantages. The large cluster paradigm allows senior people with broad expertise and experience to review a broader range of projects as well as including reviewers with directly relevant technical expertise. The size of the review meetings, their functioning, and the variation in each of the SEPs are additional considerations that will be evaluated during the pilot. Dr. Gray added that review staff will ensure that all required expertise will be included on the SEPs to assure that each application receives appropriate review. Dr. Von Hoff expressed the appreciation of the Board for this update. He expressed his wish for greater cost savings but recognized that Washington, DC, is an expensive city. Dr. Bartlett added that per diems and other costs have risen since 2003. Dr. Gray thanked the P01 review staff and the program staff for the collaborative interactions that occurred during this process.

XI. TOBACCO CONTROL RESEARCH—DR. ROBERT CROYLE

Dr. Robert Croyle, Director of the Division of Cancer Control and Population Sciences, provided an overview of NCI's work on tobacco control issues, policies, and research. He referred the Board members to three materials contained within their meeting binder: (1) a booklet that summarizes NCI's current extramural, intramural, and interagency collaborations in tobacco control research; (2) a newsletter from the NCI State Cancer Legislative Database Program and provider updates on the status of state-level policies covering tobacco control surveillance activities; and (3) an information sheet describing an upcoming NIH state-of-the-science conference on tobacco use to be held June 12-14, 2006. This is an NCI-sponsored but an NIH-wide event, open to the public, to develop the issues and agenda for the next generation of tobacco control research. This event is being managed by the NIH office that handles consensus conferences headed up by Barry Kramer, a former NCI colleague.

Dr. Croyle highlighted additional tobacco-related events, including the World Health Organization's Framework Convention. This is a treaty process that 121 countries—covering 75 percent of the world's population—have ratified. The United States is a signatory, but the treaty has not been submitted yet to the Senate for confirmation. For the U.S. Justice Department's litigation against the

tobacco industry, many NCI-funded investigators and scientists have assisted the Justice Department in this litigation. Several have testified as expert witnesses and devoted a tremendous amount of time in this effort. Some have put their careers on hold for up to 1 year to work on this case. The case went to the judge on June 9, 2005, and the ruling is pending. Later in the process, the judge agreed to allow six public interest groups, including the American Cancer Society, to testify and provide recommendations for remedies should she rule against the industry. An appeal is expected if there is a ruling against the tobacco industry, but the process could include settlement negotiations as well. Furthermore, an increasing number of U.S. cities and states, and nations— including Ireland, Northern Ireland, Italy, New Zealand, Norway, and Scotland—have adopted smoke-free policies. These include a number of countries that nobody would have predicted or expected a few years ago to pass comprehensive smoke-free policies in restaurants and public work places. There is a lot of momentum around this, as these policies do reduce tobacco use.

Dr. Croyle reminded the Board that one of five adults, and one of five high school students, are smokers. Annually, more than 430,000 deaths in the United States are attributed to tobacco use. More than 5 million deaths per year worldwide are due to tobacco use. The tobacco industry is a large powerful industry working deliberately against what the NCI does. The Center for Responsive Politics reports that, since 1990, the industry has contributed more than $55 M to federal elections alone. This total excludes contributions to state and local elections. In addition, Dr. Croyle pointed out that the product is a moving target. Candy-flavored cigarettes, for example, clearly are aimed to appeal to youth. Camel cigarettes come in many flavors: mandarin mint, Hawaii colada, midnight madness, and warm winter toffee. This relates to the Justice Department litigation, which includes allegations about marketing to youth.

Dr. Croyle next introduced three speakers to present different aspects of NCI's niche in tobacco control. Dr. Corinne Husten, who is the Acting Director of the Office on Smoking and Health at the Centers for Disease Control and Prevention (CDC) and was a cancer prevention fellow at the NCI many years ago, will provide examples of how the NCI and the CDC collaborate on tobacco control. Dr. James Sargent, who is professor of pediatrics at Dartmouth College and the director of the Cancer Control Research Program at the Norris Cotton Cancer Center, is a leader in understanding adolescent tobacco use and the effect of informational and media exposure as an influential source of information to youth. Finally, Dr. Caryn Lerman is the Mary W. Calkins professor in the Department of Psychiatry and in the Annenberg Public Policy Center in the University of Pennsylvania as well as the associate director of Cancer Control and Population Sciences at the Abramson Cancer Center. Dr. Lerman is the principal investigator at the University of Pennsylvania's Transdisciplinary Tobacco Use Research Center, which is co-funded by the National Institute on Drug Abuse (NIDA). She will highlight the basic biobehavioral area of research. Along with other organizations like the Robert Wood Johnson Foundation and American Legacy, NIDA has been the NCI's closest partner within the NIH on many scientific initiatives. Dr. Croyle also noted that several NCI staff were in attendance, including Dr. Cathy Backinger, the Acting Chief of NCI's Tobacco Control Research Branch, and Ms. Mary Anne Bright, the head of NCI's Cancer Information Service who has played a key role in the implementation of the national quitline.

CDC and NCI Collaboration in Tobacco Control—Dr. Corinne Husten

Dr. Corinne Husten, Acting Director, CDC Office on Smoking and Health, began with the observation that the NCI and the CDC share a long history of collaboration. The partnership has allowed both entities to perform larger initiatives that neither could do by themselves. Collaborative efforts have included research in surveillance, intervention development and implementation, and evaluation. Dr. Husten described three recent activities—the National Network of Tobacco Cessation Quitlines, the Youth Tobacco Cessation Collaborative, and Helping Young Smokers Quit—that illustrated this collaboration.

The National Network of Tobacco Cessation Quitlines is a model of effective and successful interagency collaboration. In February 2004, former HHS Secretary Thompson announced plans for a national network of tobacco cessation quitlines so that all smokers in the United States could have access to cessation services. With that announcement, the NCI and the CDC, along with the state quitlines and partner organizations, established the network. Through this collaboration, the NCI provided a national telephone number or a portal number through which smokers could reach their state quitline, and the CDC provided funding for quitlines to states that did not have one. To ensure that smokers had immediate access to these services, however, the NCI provided, and continues to provide, interim counseling services for smokers in states that still do not have an operational quitline. In addition, the CDC provided some enhancement money to states that already had quitlines so that they could expand their services or expand their promotion efforts. In November 2004, the NCI launched the 1-800-QUITNOW number as the national portal to the quitlines in the United States. This partnership has been a resounding success. There are now quitlines in 45 states and four jurisdictions, and it is expected that, by the end of 2006, all states within the United States will have a quitline and that smokers will have access to those quitlines through the 1-800-QUITNOW number. Since November 2004, the 1-800-QUITNOW number has received more than 213,000 calls, primarily from referrals by health providers and some state promotions. There has not been an active promotion of the number otherwise; a concerted marketing effort is expected to yield even greater results. In addition, the NCI and the CDC are working together to evaluate the quitline initiative formally to monitor the implementation and to assess the public health impact. An external evaluation contract has been awarded to conduct a process evaluation concerning the services implemented, people's awareness and use of the services, and plan the outcome evaluation. The evaluation should be completed by the end of 2006.

The NCI and the CDC have partnered since 1998 on the Youth Tobacco Cessation Collaborative. This collaboration examines gaps in cessation services for adolescents and young adults. Members include major organizations that fund research, program, and policy initiatives around reducing youth tobacco use. One of the accomplishments was the development of the "National Blueprint for Action," a guide to youth and young adult tobacco use cessation to encourage research and implementation initiatives and to set goals and objectives to mark progress. This blueprint included 2-, 5-, and 10-year objectives, as well as funding strategies for research, implementation, and ways to increase the demand for cessation services by youth. The goal was to ensure that every tobacco user aged 12 to 24 had access to appropriate and effective interventions by the year 2010. The collaborative achieved its 2-year objectives, including the following: (1) established communication networks and databases, (2) established common definitions and standards for the research and intervention projects, (3) identified gaps in the scientific knowledge, (4) developed a coordinated research plan, and (5) advocated funding for youth tobacco-use cessation research. It recently updated its 2-year objectives for 2005 to 2007. One of the greatest successes was the collaborative's ability to draw more attention and resources to youth cessation efforts. For example, in 2003 the *American Journal of Health Behavior* (*Am J Health Behav*) published a supplemental issue devoted to youth tobacco cessation, and many of the articles included NCI and CDC staff who were part of the collaborative, as well as their partner organizations. The CDC published "Youth Tobacco Cessation: A Guide to Making Informed Decisions," a manual for the state tobacco control programs addressing the development, establishment, and evaluation of youth cessation programs.

Dr. Husten then described the Helping Young Smokers Quit initiative, which grew out of the Youth Tobacco Cessation Collaborative. The project is co-funded by the Robert Wood Johnson Foundation, the NCI, and the CDC. The impetus for this project was that little was known about the many youth cessation programs that existed in communities. Gaps in knowledge included their prevalence, location, services, target populations, and effectiveness. This partnership was designed to

evaluate the existing youth cessation programs through two phases. Phase 1, which has been completed, identified the existing cessation programs for youth in a representative sample of 408 counties within the United States. The programs were screened through specific criteria; they had to: (1) exist at least 6 months before the survey, (2) provide direct cessation services, (3) provide services to youth aged 12 to 24, and (4) not be part of an existing research initiative. The evaluation found that 62 percent of participating counties had one or more youth cessation programs. Urban counties were more likely to have programs than rural counties. Programs were less likely to be found in the lower socioeconomic status counties. The presence of programs was not related to a high level of smoking youth in the state or the county, nor was it related to a state or local government's tobacco control expenditures. Of the programs, 56 percent were voluntary, 35 percent had a mix of mandatory attendance and voluntary attendance, and 9 percent were mandatory only (i.e., students were required to attend because they violated a school tobacco policy). More than 80 percent of the programs were designed specifically for youth participants, and most had a formal structure. Eighty-eight percent had trained counselors, and 89 percent had a written facilitation guide or manual; 95 percent reported that they adhered closely to the program specifications. In terms of program content, 84 percent covered at least four of the six cognitive behavioral strategies that were assessed. Specifically, 76 percent included self-monitoring; 90 percent included contingency control, general health and lifestyle, and social support; 92 percent included interventions that disrupt smoking patterns; and 99 percent included coping skills training. In general, the programs were not costly. Seventy percent of them cost less than $10,000 per year, and the majority of the funding came from the states. Most of the programs felt that they were very stable and more than 70 percent of them thought they would be operating the following year. Phase II, which is starting, involves a longitudinal evaluation of high school-aged youth who are participating in more than 40 smoking cessation programs across the United States. The assessment will consist of four parts: (1) participant surveys, (2) program/provider surveys, (3) organization surveys, and (4) community surveys.

Dr. Husten concluded with the thought that the collaboration between the NCI and the CDC has been instrumental in research, development, and implementation of programs, as well as evaluation of some major tobacco control initiatives, including the National Network of Quitlines, the Youth Tobacco Cessation Collaborative, and Helping Young Smokers Quit, among others. The collaborative efforts link research with public health practice and encourage a stronger inter-agency working relationship.

Questions and Answers

Ms. Ryan asked whether any relationship existed between the numbers and types of cessation programs with tobacco funding in the state or even with tobacco use itself. Dr. Husten replied that the impetus comes most directly from school policies about smoke-free campuses; these programs offer an alternative to suspension. Dissuading the youth from starting to smoke or persuading them to quit when young yields the greatest impact in terms of reducing tobacco use, morbidity, and mortality. Ms. Ryan recommended that the community surveys for Phase II consider the elementary school curriculum attached to the high schools and the regional curricula to the individual high schools. Dr. Husten agreed to bring this idea to the Phase II group.

Dr. Armitage queried whether anyone has estimated the relative impacts of taxes making it difficult to smoke, laws that make it so there is no public place to smoke, and education, as well as determining which of these three deterrents is the most effective. Dr. Husten was unaware of a head-to-head comparison, but remarked that comprehensive programs work, reducing both consumption and use prevalence. The CDC is preparing a forthcoming paper concerning adult prevalence in terms of the amount of money being spent on comprehensive programs. In addition, the effectiveness of some specific interventions is known. For example, the CDC published the "Guide to Community Preventive Services," which examines the impact of tax, media campaigns, clean indoor air laws, provider reminder

systems, insurance coverage, and quitlines. The CDC encourages the state programs to work, at least a little bit, in all of the areas, despite possible limitations in funding. For example, the state should try to do earned media even if it cannot do paid media; likewise, if a state cannot enact a smoke-free law, there should be attempts to enact community smoke-free laws.

Dr. Moon Chen wondered whether the quitlines will be able to track the number of people involved in the youth cessation program, and whether the youth are accessing the quitlines to obtain more information. Dr. Husten answered that, in the states with quitlines, a proportion of the callers are adolescents or young adults. The NCI has funded studies concerning the effectiveness of quitlines with adolescents, but many of the randomized control trials for all interventions with adolescents are not showing robust positive effects. The quitlines have a tailored protocol for adolescents. Differential impacts by age and similar criteria are being considered in this evaluation and the assessments. The suspicion is, however, that the interventions are probably less effective for adolescents. Dr. Croyle noted that this collaboration is motivated to fill in the evidence gap around youth quitting.

Media Influences on Adolescent Smoking Behavior—Dr. James Sargent

Dr. James Sargent, Director, Cancer Prevention Research, Norris Cotton Cancer Center, thanked Drs. Croyle and Backinger for inviting him to discuss youth prevention and media influences on initiation of smoking among adolescents. He began by presenting a simple communication model that has been used since the 1940s, involving a source, a receiver, and a desired effect: a message proceeds from the source through a medium to the receiver to create an impact. Using this basic model, Dr. Sargent described a study of media influences—using movies as the medium—on adolescent smoking behavior. The study aims to: (1) describe smoking in popular contemporary movies, (2) assess exposure to movie smoking among adolescents, and (3) determine whether smoking exposure is linked with adolescent smoking.

The initial 2 years of the study were devoted to figuring out how to count tobacco in popular contemporary movies. The study used a work station-based counting system in which smoking, drug use, genre, and themes in movies can be coded. The counting system was hooked into the DVD time link to time the amount of smoking in the movies. Alcohol use and the amount of sexual exposure in the movies also were timed. To date, more than 1,000 movies have been coded for these data. Dr. Sargent showed a diagram that plotted the number of smoking exposures in 532 contemporary box office hits, sorted by the rating of the Motion Picture Association of America (MPAA). Few G-rated and PG-rated movies included smoking episodes. In the PG-13 titles, violence, sex, profanity, and the amount of smoking all increased to 76 percent. It reached 87 percent with R-rated movies. In the vast majority of movies—about 75 percent of them—there was less than 2 minutes of screen time devoted to smoking. This means that smoking could be removed from movies without altering the content of 98 percent of a movie.

The study next focused on how to link smoking in movies with adolescent smoking. Dr. Sargent mentioned several studies and papers that published study results. These include a cross-sectional study, published in the *British Medical Journal* (*Br Med J*) in 2001, that involved 5,000 northern New England adolescents; it revealed a strong relationship between the smoking that was witnessed in the movies and initiation of smoking by junior high school adolescents. A cohort followup study of 2,400 of those adolescents 1 year later showed that there was a longitudinal relationship—that is, the baseline exposure to movie smoking predicted smoking in the future among the nonsmokers.

A third study dealt with the issue of generalizing these findings, and those results were published in November 2005 in the journal *Pediatrics*. The study was designed as a random digit dial survey using telephone protocol to identify households with adolescents 10 to 14 years of age. It was a major

undertaking, starting with about 400,000 phone numbers, from which 6,522 adolescents were identified. The survey started with the 532 popular box office hits, based on the top 100 movies each year for 5 years prior to the survey. The movies were viewed, and all the tobacco use occurrences in each one were counted. The counting system randomly selected 50 movies, which are stratified by rating, from this pool for each adolescent. The adolescent was asked whether he or she had seen those 50 movies. Based on the movies that they watched and the amount of smoking in each, a score was developed for the number of tobacco use occurrences seen, which yielded the exposure variable. This exposure variable was divided into quartiles and by race/ethnicity, and charted according to the prevalence of smoking initiation. The overall prevalence was 10.1 percent of the population. The low exposure quartile of smoking was at a rate of about 2 percent. The high exposure quartile of smoking had a rate more than 10 times greater, at almost 25 percent. The study controlled for covariates that might be related to movie exposure and might be related to kids smoking, including sociodemographics (grades in school, gender, and parent education), social influences (parents, siblings, or friends smoking), personality characteristics (self esteem, sensation seeking, rebelliousness), and parenting (maternal responsiveness and supervision, parental disapproval of smoking).

Dr. Sargent next presented a multivariate analysis for all three studies. The adjusted odds ratios for the higher quartiles in movie smoking exposure compared to the reference were statistically significantly higher than the reference. The adolescents in the higher quartiles were between two and almost three times at greater risk for trying smoking, when other factors were considered. It is expected that the results from the longitudinal part of this national sample eventually will be published. Dr. Sargent noted that the study was cited in a 2003 letter sent from 28 state attorneys general to Mr. Jack Valenti, who was then president of MPAA. The letter cited the study and requested assistance with the problem. It prompted the first public response from the movie industry about smoking in the movies and led to meetings between Dr. Sargent and his colleague, Madeline Dalton, with the attorneys general, Mr. Valenti, the Director's Guild, and the Actor's Guild, during which the results of the studies were provided in further detail.

Dr. Sargent shared trends in movie smoking from the top 100 box office hits each year from 1996 to 2003. There is a markedly downward trend in smoking and R-rated movies, especially since 2001, from 32 percent to 18 percent. There also is some downward trend in PG-13 and PG movies. These decreases are important because a downward trend in adolescent smoking and movies parallels the downward trend that is seen in smoking among U.S. adolescents.

Dr. Sargent next described "reach"—a term that the advertising industry uses to indicate how many impressions an advertisement gained, or how many eyes saw an advertisement—in terms of U.S. adolescents. As noted earlier, the study randomly assigned movies to adolescent in the survey so that a representative sample of about 550 adolescents responded to each movie, and a percentage of those adolescents had seen each movie. From these movies, U.S. adolescents (aged 10 to 14) saw 13.8 billion lifetime smoking impressions. (An impression is each time an adolescent witnessed a smoking scene.) This is why mass media is important. The study also sorted the number of smoking impressions that were delivered by a movie. The top of the list was "A Perfect Storm," which delivered more than 350 million smoking impressions.

In addition to gross impressions, the study is examining contextualized smoking. The movie industry has responded by saying that it will try to eliminate smoking from G- and PG-rated movies. If smoking is divided by movie rating to determine the effect on adolescent behavior, what results is three curves that show very little smoking exposure in G- and PG-rated movies. Eliminating that exposure will not affect adolescent behavior much; eliminating PG-13 smoking and reducing R-rated smoking, however, could yield an enormous impact on adolescent smoking. Finally, the study examined smoking

characters and found that a bad character smoking has a greater effect on adolescents than a good character smoking. The message to the directors is eliminate the bad characters' smoking.

Questions and Answers

Dr. Chen asked whether any data were available on the prevalence of minority actors and actresses smoking in movies. Dr. Sargent replied that the study has begun looking at this issue. There are very few Hispanic actors, but the proportion of African American actors is parallel to the population: 11 percent. Of the 11 percent of African American characters, 16 percent smoke. The study eventually will plot the curves to show the exposure to African American actor smoking versus other actors smoking, and will relate that to the smoking patterns in minority adolescents.

Dr. Jim Armitage asked whether the analysis separated smoking as part of an historical portrayal, such as in "Good Night and Good Luck," versus smoking included simply because a director decided that it would be a good thing. Dr. Sargent replied that this distinction had not been made. He noted that actor John Travolta uses smoking extensively to depict different character traits. Most of the time, however, smoking is one dimensional; the bad characters often are identified by their smoking. In early movies, the tobacco industry paid the movie industry to include tobacco. Movie stars often started their careers in tobacco advertisements. For example, the old Chesterfield advertisements included Rita Hayworth and other actors. In short, tobacco has been part of moviemaking for a long time, and it takes a lot of work to persuade people to change their pattern of behavior when they make a movie. Dr. Sargent noted that only about 2 percent of movies involving tobacco use shows the health effects of tobacco use. Dr. Runowicz commented that she attended the Academy Awards once and was amazed at the number of actors who chewed nicotine gum because they were addicted to smoking and were not allowed to leave the building to smoke outside.

Improving Pharmacotherapy for Nicotine Dependence: From Mouse to Man—Dr. Caryn Lerman

Dr. Caryn Lerman, Associate Director for Cancer Control and Population Sciences, Abramson Cancer Center, expressed her appreciation for the opportunity to speak before the Board and thanked Drs. Croyle and Backinger for their leadership in population science and tobacco control. She described research from the University of Pennsylvania's Transdisciplinary Tobacco Use Research Center to illustrate both the transdisciplinary and translational aspect of the Center's work to develop medications for nicotine dependence. Despite the progress that has been made on tobacco control research, approximately one quarter of Americans continue to smoke. Currently, there are only two FDA-approved medications for nicotine dependence. One is a group of approaches for nicotine replacement therapies, such as nicotine gum, and the other is bupropion or wellbutrin, a successful antidepressant. Although these treatments increase or double in most cases the odds of quitting smoking compared to placebo, as many as 70 to 80 percent of individuals who are treated will relapse in the long term. Newer treatment models are needed for the clinical setting to improve the effectiveness of treatment.

To address this important cancer problem, the Center is working to translate discoveries in basic neuroscience, pharmacology, and genetics to improve pharmacotherapy for nicotine dependence. Neurobiological pathways believed relevant to nicotine dependence and smoking cessation outcomes are being studied. Treatments are sought that address specific molecular targets, which appear to be important in genetic susceptibility to dependence, and intermediate markers (or endophenotypes) are examined to help explain the biobehavioral basis of genotype by treatment interactions in smoking cessation. Dr. Lerman focused her presentation on one area of the Center's research: the interactions between opioid system genetic variation, naltrexone (an opioid antagonist medication), and nicotine abstinence. The opioid pathway is targeted because basic science research has shown that nicotine results

in an increase in opioid peptides in the brain, which bind to mu opioid receptors that are located on GABA-ergic neurons. These neurons are important because they modulate dopamine release. Increased dopamine release in the ventral tegmental area and the nucleus accumbens in the brain is an important part of the rewarding effects of nicotine as well as some other addictive drugs.

Dr. Lerman described the work of Dr. Julie Blendy, who conducts work on drug self-administration and drug reward and is now focusing her work on nicotine dependence. Dr. Blendy used a conditioned place preference paradigm. On the first day of the paradigm, mice were contained within a two-sided chamber; a door separated the two sides, and each side looked very different. On the first day, the mice were allowed to roam freely throughout the chamber to ensure that there was no bias in the beginning at baseline in terms of preference for a particular side of the chamber. A series of conditioning days followed, during which the mice learned to associate nicotine with one side and saline with the other side. On the test day, the mice roamed freely throughout the chamber and, depending on which side of the chamber they spent more time on, they exhibited a behavioral expression of a preference for nicotine or saline. Dr. Blendy's work, which was published recently in the journal *Neuron*, found that the mice that received saline on both sides of the chamber during the pairing days exhibited no preference to either chamber side. Mice that received 1 milligram per kilogram of nicotine spent significantly more time on the nicotine-paired side than the unpaired side. Interestingly, mice that received 2 milligrams per kilogram of nicotine on the paired side spent less time in the nicotine chamber. Naloxone, a drug that is a mu opioid receptor antagonist that blocks the mu opioid receptor, eliminated the nicotine conditioned place preference. When mice were pretreated with naloxone on the test day, the behavioral expression of nicotine reward was not seen. Naloxone also blocks nicotine's effects on creb phosphorylation, which is believed to be an important aspect of nicotine reward.

Based on Dr. Blendy's data, the Center decided to test the effects of naltrexone through a nicotine choice paradigm. It compares self-administration or behavioral expression of choice for a nicotine cigarette versus a de-nicotinized cigarette that is the same in every other way. The de-nicotinized cigarette serves as a control for some of the associations to smoking other than the nicotine, such as the sight and the smell. In this paradigm, smokers come into the laboratory and smoke their own brand of cigarette to standardize exposure. There is a 2-hour delay to cause a little bit of deprivation but not serious withdrawal symptoms. There is a double-blinded exposure to each of the research cigarettes—the nicotine and de-nicotinized cigarettes—and the subjective effects are assessed. After this, they have the opportunity to deliver four puffs during a 2- to 3-hour time period. They can take a total of four puffs from the cigarettes—all four puffs from one cigarette, or some mixture of four puffs from among the various cigarettes—every half hour, and they can choose which cigarettes. The outcome variable in this assessment is the number of nicotine puffs out of the total number of puffs that they could have taken, providing a behavioral expression of preference for nicotine. In another subject human behavioral pharmacology study, participants received placebo or naltrexone. Each time that the subjects participated in the nicotine choice paradigm, naltrexone reduced the number of nicotine puffs, similar to the mice that were pretreated with naloxone, which spent less time in the nicotine-paired side. It is a small but statistically significant effect.

Based on the results in rodents and humans that blocking the mu opioid receptor was associated with decreased nicotine reward, the Center decided to look into genetic variation in the gene for the mu opioid receptor known as OPRM1. This gene has a functional variant, A118G. It is a mis-sense single nucleotide polymorphism (SNP), and work shows that the minor allele, the G allele, is associated with reduced mRNA expression and protein levels. This variant is present in 25 to 30 percent of individuals of European descent. It is relevant, therefore, in terms of having some important behavioral effect at least in that group. The hypothesis is that smokers who carried the low activity G allele of OPRM1 would have a lower liability to relapse. This was tested in an open-label randomized clinical trial comparing two forms

of nicotine replacement therapy: nicotine patch versus nicotine nasal spray. All participants provided DNA for genotyping; this was part of the consent as the study was designed as a pharmacogenetic study. They received either transdermal nicotine or nicotine nasal spray for 8 weeks plus seven sessions of behavioral counseling. There was a 95 percent retention rate and followups were conducted during which abstinence was confirmed biochemically. The odds were twice as great that the group with the G allele would be abstinent at the end of treatment compared to individuals who are homozygous for the wild type allele. This was particularly pronounced in individuals who are treated with the nicotine patch. At the 6-month followup, the trend remained but, consistent with the pharmacogenetic effect, these people were off the drug and the effect was weakened at the 6-month followup. The study also considered intermediate measures that focused on negative mood and weight gain. Many of the smokers reported increases in negative mood, which prompts relapse. Individuals who had the G allele showed a more significant reduction in negative mood than those with the A alleles during the initial 2 weeks following the target quit date. The individuals with the G allele had less weight gain; they gained about 1.5 pounds between baseline and the 8 weeks of treatment compared to those with the wild type alleles who gained more than 5 pounds. Weight gain is an important determinant of relapse in smoking treatment. These studies found that pharmacologic blockade of the mu opioid receptor is associated with a reduction in nicotine reward in both a rodent model and a human laboratory model. In addition, a randomized clinical trial showed that the low activity G allele for the mu opioid receptor is associated with a greater ability to quit smoking, consistent with the preclinical data. This suggests that the mu opioid receptor as well as the interacting proteins, which control receptor desensitization and internalization, might be important targets for medication development and might provide information for tailored treatment based on genotype.

Dr. Lerman acknowledged study collaborators and closed the presentation by noting three objectives: (1) to identify novel targets for the development of nicotine dependence treatments, (2) to improve the delivery of nicotine dependence treatment by targeting therapy to smokers based on biological profiles, and (3) to facilitate effective and ethical diffusion of new models of treatment delivery to the clinic and to the public.

Questions and Answers

Dr. Freedman queried about research on secondhand smoke. Dr. Husten replied that a Surgeon General's report on secondhand smoke would be released later in 2006, possibly May or June. The report will provide a comprehensive review of the evidence across a variety of disease impacts on secondhand smoking. Previous studies have shown that secondhand smoke causes lung cancer, heart disease, SIDS, both pneumonia and bronchitis in children, and exacerbates asthma in children. Dr. Freedman asked if this would help legislators with regulation. Dr. Husten responded that while science plays a very important role in public health, politics often brings in other considerations. From a scientific point of view, she agreed that everybody needs to not be exposed to secondhand smoke. It causes disease in adults and disease in children. Politics, however, does not consider just the science.

Dr. Ken Cowan found the data in the genotyping interesting; he wondered whether it held true for the initiation of smoking, and if so, whether it would be better to focus attention on those who are more likely to become addicted or those who may need more stimuli to become addicted. Dr. Lerman noted that Dr. Neal Caparoso is addressing this question in his large case control studies. She added that statistical genetic studies have suggested that there are probably different genes that play a role in smoking initiation than those that play a role in nicotine dependence and smoking cessation. Regarding the use of genetic information to target smoking prevention, Dr. Lerman perceived genetics research as helping to tailor treatment for people who are already nicotine dependent. Dr. Prendergast asked whether there was any genetic information on the people who are strongly addicted, and whether there were particular SNPs involved. Dr. Lerman defined "strongly addicted" as those who fail multiple types of

treatment and confirmed that these individuals appear to have particular genetic variants for key receptors in the dopamine and opioid pathway. Further research at the University of Pennsylvania is examining the association of genes throughout the dopamine and opioid pathways with smoking relapse and treatment response.

XII. UPDATE: IMPLEMENTATION OF CLINICAL TRIALS WORKING GROUP RECOMMENDATIONS—DR. JAMES DOROSHOW

Dr. James Doroshow updated the Board members regarding the progress of the Clinical Trials Working Group (CTWG) on restructuring the NCI clinical trials enterprise. He began by listing the common themes of the restructuring plan, which 22 initiatives had focused on during the past 6 months: (1) prioritization/scientific quality—to involve all stakeholders in the design and prioritization of clinical trials that address the most important questions, using the tools of modern cancer biology; (2) standardization—to standardize information and technology (IT) infrastructure and clinical research tools; (3) coordination—to coordinate clinical trials research through data sharing and providing incentives for collaboration; (4) operational efficiency—to use resources most efficiently through improved cost-effectiveness and accrual rates, and more rapid trial initiation; and (5) integrated management—to restructure extramural and intramural oversight of NCI clinical trials. Dr. Doroshow next identified the goals for 2006, provided the current status of work, and described the implementation activities for 2006 for each of the above themes.

The implementation goals for prioritization and scientific quality are to establish an investigational drug steering committee to help prioritize early phase trials, establish a disease-oriented scientific steering committee for Phase III investigations, and develop criteria for correlative science and quality-of-life studies. Standardization goals aim to increase clinical representation on caBIG clinical trials work space, initiate case report form (CRF) work groups, and begin development of a credentialing system. In the area of coordination, the CTWG will work to develop a comprehensive database, expand the cancer trials support unit (CTSU) to enhance the ability of cancer centers and SPORE trials to interact with cooperative groups, and enhance NCI, FDA, and Pharma interactions. With respect to operational efficiency, the intent is to conduct management analysis of barriers to timely trial initiation, implement funding for expanded minority outreach, and initiate interactions with patient advocates and clinical trialists to improve awareness. Integrated management goals are to establish an extramural clinical trials advisory committee, integrate clinical trials operations within the NCI, and design an evaluation system and implement a baseline assessment.

The implementation activities to date and for 2006 are as follows. For prioritization and scientific quality, a formal mechanism for the investigational drug steering committee was established with the mandate to provide strategic input for the Investigational Drug Branch, review the CTEP clinical drug development plans, and perform a strategic evaluation of unsolicited letters of intent for new agent studies. At the committee's first meeting in September 2005, co-chairs were elected, a coordinating committee was formed, and policies and procedures began to be developed. Work also was begun to promote the Phase III investigations; specifically, a mechanism was established for disease steering committees that involved SPORES, cancer centers, P01s, community physicians, advocates, and NCI staff. Focusing initially on gastrointestinal, gynecological, and health and nutrition diseases, the committees will hold state-of the-science meetings, assist with trial development and prioritization, and help to develop correlative studies.

Regarding standardization, Dr. Doroshow announced that, with a tremendous amount of work, particularly working with caBIG and Dr. Kenneth Buetow, a detailed implementation plan has been completed for four new IT projects to enhance the clinical trials work space and electronic CRFs. One of

the next steps is to seek nominations from the cooperative group chairs, cancer centers, and SPORE PIs for these working groups, including one for the clinical trials database.

Dr. Doroshow informed the NCAB that, to expedite coordination, the executive committee of the GOG is working with the gynecologic (GYN) SPOREs to try to put up trials on the CTSU so that there would be a way, for the first time, for SPOREs and cancer centers to share credit and get funding for trials that might be performed on a national basis. Dr. Doroshow credited CTEP for improvements with issues related to the FDA. CTEP has worked hard during the past year to enhance SOPs for special protocol assessments to facilitate agreements among industry, cooperative groups, and the FDA regarding trial parameters.

With respect to operational efficiency, Dr. Doroshow noted that a management team from the Vanderbilt School of Management presented a barriers analysis of the Cancer and Leukemia Group B (CALGB) Operations Office to CALGB leadership last week. Another item of interest is that additional funding for minority outreach programs will begin with budget allocation. Finally, interactions will increase between advocacy groups participating on the disease scientific steering committees and NCI's Office of Communications and Office of Education and Special Initiatives.

Dr. Doroshow next turned to issues related to prioritization, scientific quality, and the overarching initiatives related to the CTWG recommendations. A major issue in the area of prioritization was to create an investigational drug steering committee to provide extramural input into the early phase studies for trials that the NCI, specifically through Dr. Gray's assistance, helped the IND to accomplish. A formal mechanism for this was developed in the context of U01s. The responsibilities for the investigational drug steering committee and a more detailed implementation plan were drawn up, and the first meeting of this group occurred in September 2005. The co-chairs have been elected. The coordinating committee has been formed, and policies and procedures are under development. This group will help CTEP review its clinical drug development plans for all new Phase I and II agents and provide additional strategic input into CTEP. This initiative is well on its way to becoming formalized.

With respect to the creation of a network of scientific steering committees for the design and prioritization of Phase III trials, Dr. Doroshow acknowledged Dr. Gray's assistance in helping to develop a mechanism to allow the steering committees to exist. There is a detailed implementation plan in place, focusing primarily on gastrointestinal, gynecological, and head and neck cancers. The responsibilities of the state-of-the-science steering committees will be to hold meetings to formalize the priorities around particular disease areas. They will be involved, from the earliest stage, in the development of trials, disease trial prioritization, and correlative studies ranging from quality of life to basic science laboratory translational studies. About 10 days ago, Dr. Abrams and Dr. Mooney from CTEP and Dr. Doroshow attended the gastrointestinal ASCO meeting and met with the gastrointestinal intergroup to discuss a detailed plan to formalize a gastrointestinal steering committee. This built on work that the gastrointestinal intergroup had embarked on more than 1 year ago and likely will lead to a process in which many separate communities—SPORE investigators, cancer center investigators, advocates, and community oncologists—are brought together into the process of developing large Phase III trials. The intergroup and scientific steering committee are interested in working on Phase II and III development processes. More than 2 weeks ago, the group met with the GYN GOG executive committee with the GYN SPOREs and a plan to develop that steering committee under the guidance of Dr. Trimble is underway. In early December, there was a previously planned meeting of the head and neck intergroup to which the four principal investigators from the head and neck SPOREs were invited. Dr. Doroshow talked with the intergroup about some of these plans, and they decided unanimously to form a scientific steering committee. Because there likely will be three scientific steering committees this year, work could be completed ahead of schedule. The NCI's support and facilitation—both from the appropriate

new infrastructure at the NCI as well as the efforts of members of all of the divisions throughout the institute—made this work possible.

The creation of an external clinical trials oversight committee to advise the NCI Director is the first of the overarching initiatives from the CTWG plan to be implemented. With the help of Dr. Gray and her staff, the first new NCI advisory committee in more than a decade has been approved by the DHHS and the NIH. The Clinical Trials and Advisory Committee will oversee the implementation of the CTWG initiatives and will have combined membership from the NCAB, the BSA, the BSC, and the Director's Consumer Liaison Group, with a majority membership appointed from new extramural clinical trials investigators and the clinical trials community. It will help to carry forward the implementation plan and also assist with issues as they arise. Several other issues affect the clinical trials around the country. The charter will be published soon in *The Federal Register*, followed by an inaugural meeting in June 2006.

The development of a coordinated organizational structure within the NCI to help manage clinical trials across the institute has proceeded with the help of Dr. Niederhuber and the Executive Committee. An important step has been to formulate and form a clinical trials operations committee that is populated by members of all the divisions, centers, and offices that perform clinical trials at the NCI. This matrix organization is charged with reviewing and prioritizing programs to evaluate the organizational infrastructures, identify duplicating efforts between divisions, look at all RFAs and PAs that involve clinical trials, approve those before they are presented to the executive committee, and provide guidance and comments on how to conduct clinical trials at a very high level and set the tone to be able to prioritize throughout the NCI.

Dr. Doroshow next introduced NCI's project management team: Dr. Deborah Jaffe (DEA); Dr. Raymond Petryshyn (OD), who reviewed cancer center support grants for 5 years; and Dr. LeeAnn Jensen (OD), who comes from CTEP and oversaw the Phase I and Phase II program. They are among the five doctoral-level scientists who have been helping to develop these scientific steering committees and are charged with the management of all of these initiatives. They will be working intimately with the extramural community, divisions, and centers to help coordinate and integrate NCI's clinical trials portfolio. Their responsibilities will include coordinating state-of-the-science meetings, as well as the interaction between CTEP and NCI's extramural investigators, and developing policies for these committees. In addition, they will help to ensure that the timelines for the development of new Phase II trials and extensive trials are met so that clinical trials are completed quickly.

A structured evaluation system has been established for these initiatives, starting with a series of baseline evaluations. The implementation review, the development of questionnaires, and a data gathering plan across the initiatives have been completed. By the end of FY 2006, qualitative and quantitative measures will be developed and a baseline will be established to measure, and modify as needed, the activities underway. This ambitious undertaking of 22 different initiatives will take 4 to 5 years to complete, and mid-course corrections will occur when the baseline data indicate that changes are needed. The management team will keep the NCAB apprised of the activities and successes, and likely will request input regarding the external clinical trials advisory committee and other committees.

Questions and Answers

Dr. Niederhuber observed that organizing the CTWG into an operational state, facilitating collaboration within the community to develop the plan, and following through with implementation has been a tremendous amount of work. Dr. Freedman referred to an article from DHHS' Agency for Healthcare Research and Quality that listed more than 90 barriers to the recruitment of minorities in

clinical trials and wondered to what extent that information was being incorporated into the CTWG program. Dr. Doroshow agreed that including such information is important and noted that a baseline is needed to determine whether those items accomplished actually made a difference. The current ideas to improve minority accrual by cancer centers are to increase the number of minority-based Community Clinical Oncology Programs (CCOPs) and to enhance the various plans that have been submitted and are being funded. Dr. Prendergast asked about the role of the centralized IRB in the whole process. Dr. Doroshow replied that one of the initiatives examines the barriers to adopting a centralized institutional review board. Dr. Prendergast wondered how the CTWG will figure into the upcoming reviews of cooperative groups. Dr. Doroshow explained that this will be a multi-year process and, because it is SPOREs, will involve more than cooperative groups, including clinical P01s.

Dr. Prendergast expressed his desire to discuss, sometime in the future, how realistic clinical trials are within the context of SPOREs. He queried whether a plan existed for a pilot within the CTWG to show the effectiveness of the process as a part of the implementation plan, what the timeframe would be, and how the deliverables would be stated. Dr. Doroshow answered that the disease steering committees are considered pilots, and that a formal evaluation likely would be conducted after 2 or 3 years following a committee's inception. This would allow enough time to see how the committee is functioning and determine whether changes are needed.

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

Dr. Anna Barker updated the Board on the activities of The Cancer Genome Atlas Pilot Project, opening with a brief recollection of the project's inception. About 4 years ago, the NCI considered how to harness all of the technologies that were advancing quickly in terms of genome analysis and genome sequencing to move more decisively and strategically toward targeted diagnostics and therapies. A meeting was held with the NHGRI, and Dr. von Eschenbach appointed a group from the NCAB, co-chaired by Drs. Eric Lander and by Lee Hartwell, to look at advanced technologies. One of the projects that came out of that initiative was this pilot project.

The mission of The Cancer Genome Atlas Project is to test the feasibility of a full-scale effort to explore the entire spectrum of genome changes involved in human cancer systematically and thereby achieve meaningful clinical impact in a few rationally selected cancer types. The goal of this pilot is to further develop and apply current analysis technologies systematically to identify genes and regions of potential importance to cancer and to tie this capability to NHGRI's existing genome sequencing infrastructure for the resequencing of these candidate genes. Dr. Barker echoed a comment from Dr. Croyle that the NCI is one of many players. NCI's partnership with the NHGRI represents an opportunity to leverage expertise from both entities, as the NHGRI knows how to use what the NCI's investigators have accomplished over the years.

Among the project's enabling factors is that there is a known human reference or sequence. The gene families and pathways that NCI investigators have been working on for 30 years include the kinases, the phosphotases, the transcription factors, and the hormone responsiveness factors. These are important for driving this project forward. The technologies themselves for copy number changes, platforms, expression profiling, and epigenomics are progressing. Epigenomics will be included in this project if the peer reviewers are convinced about their inclusion. There was an extensive discussion with the BSA regarding the Sanger experience, dealing with sequence known genes, especially the kinases and the druggable targets. The data have not been released into the public domain yet. There are a number of early indications that somatic mutations will be important potential targets.

The Cancer Genome Atlas Pilot Project has several clear components to it. Biospecimens are required to drive the project, and the source of qualified biospecimens has been an interesting topic of discussion. A central processing approach will be used for all the biomolecules to procure that will serve as a notable resource for the NCI and for genomics in general. There are two kinds of centers: NHGRI's high-throughput Sequencing Centers and NCI's cancer Genome Characterization Centers. A percentage of the sequencing capacity will focus on medical sequencing, and The Cancer Genome Atlas will be a set-aside as a part of this project. There will be a team within the NHGRI dedicated to this project. The characterization centers will focus on creating a pipeline of candidate targets to be sequenced. It is projected that between 10 and 50 samples will be analyzed each week for their genome and epigenome characteristics. Bioinformatics will be the key here to collect the information into an open source database that is set up and governed by rules similar to the Human Genome Project. A meeting about the database rules is planned for spring 2006. Tools for data mining also will be developed through caBIG, which will be the common platform. Overarching all of this is an NCI-NHGRI technology development effort that will be co-funded by both ICs, with additional funding from SBIR and R21 monies, and supported by a management structure. This center will be occupied by a complex management team composed of these participants along with the winners of the procurements.

Dr. Barker described the development of the project. The NCAB previously discussed whether this was the right project and the right time for it. The BSA asked a multitude of hard questions, and so the NCI put together a subcommittee to work through them. The BSA approved the project unanimously, and the community had an opportunity to discuss it in-depth. One of NCI's clinicians said, "I can't imagine us not doing this project."

Dr. Barker next addressed the issue of tumor selection for The Cancer Genome Atlas. Although there has been no decision made about this yet, criteria developed with the input from the extramural community include technical, ethical, legal, policy, practical, and temporal requirements. Dr. Barker shared some of the discussions that the NCI has had across the community about what an ideal tumor or collection would look like, such as: (1) tumor samples consist of at least 500 mg of tissue from previously untreated tumor; (2) tumor samples are frozen in OCT (glycerol-based medium); (3) at least 500 individual samples from unique cancer cases are available; (4) samples are properly consented for use in this project; (5) all tumors have matched normal samples; (6) samples represent a single histopathologic type of tumor and/or derived from a single cancer site; (7) individual tumor samples contain at least 80 tumor cells; (8) the tumor samples are derived from patients entered in a clinical trial with uniform entry criteria, consistent treatment, and clinical data that have undergone regular audits; and (9) tumors are from a primary tumor site. In terms of the tumor specimens and their distribution, this core resource will be an important resource for the entire process of collection and verifying the pathology and the authenticity of the pathologist reports, the central processing, standard operating procedures, the quality control, and the distribution of these biomolecules. There will need to be standard sets of samples for technology comparison across laboratories, which is a difficult issue. The distribution also will pose a challenge.

The Genome Characterization Centers will focus on expression profiling, copy number, and changes in epigenomics. There are many platforms for those. Those are the ones that probably are closest to being able to qualify for high throughput. In addition, the centers will work to improve these technologies, particularly for epigenomics. There will need to be real-time data release into a public database, although "real time" remains to be defined. The U54 (cooperative agreement) mechanism means that the centers will be managed as a group; approximately $11-12 M will be invested during the first year in these centers. It will be about $36 M overall. The Genome Sequencing Centers are dedicating about $50 M to this project through a U54 mechanism, and they will be dedicated to sequencing a large number of targets from two or more tumor types—at least two tumor types will be

sequenced in-depth, and it could be possible to look at many more tumors in a more cursory way. As the technology develops, these centers also will integrate and improve it. Finally, the bioinformatics core will be built around the caBIG platform and standards. It also will involve data management, database development, and specific analytic and data mining tools. It will take advantage of caBIG's participation in standards development across the community and participate in the interprogram communications.

Opportunities for technology development are being sought, including for genomic rearrangement, epigenomics, highly parallel single molecule assays, methods for selecting and enriching defined regions of the genome, and the magnitude of improvement in cost and throughput accuracy and precision. This will be funded under small business innovation research (SBIR), small business technology transfer (STTR), and R21, and the NCI will be investing about $2 M per year—$1 M from the SBIR/STTR program and $1 M from the R21 pool. The Genome Institute will participate through its SBIR program.

The most recent event was a public launch on December 13, 2005, at a news conference that was attended by Drs. Zerhouni, Collins, and von Eschenbach, as well as Ron de Pino and Bruce Johnson. Following the press conference, there was broad media response. Dr. Barker complimented Ms. Nelvis Castro and the Office of Communications for managing the launch. Dr. Barker shared a comment from a reporter on the McNeil-Lehrer Report: "This project, more than anything that has been done in medicine that I can recall, really brings the public into science.... It's creating a new excitement about research because people can understand this. They understand that if you can sequence the cancer genes, you can actually find out what's causing my cancer and maybe we can get to this personalized medicine that we're all talking about."

Factors that will be considered in evaluating the pilot project include: (1) robust genomic analysis of two tumors and identification of significant number of candidate genes for re-sequencing; (2) genome characterization and analysis performed with sufficient power (>500 samples/tumor) to provide a "pipeline" for re-sequencing important (occur at >5-10 percent frequency) cancer genes/regions; (3) ability to find genomic changes (e.g., loss of heterozygosity, deletions, amplifications, translocation, and epigenetic modifications) and re-sequence selected of these aberrations; (4) ability to differentiate tumor subtypes based on genomic alterations, which will be important for the development of new therapies and diagnostics; (5) establishment of a public database of sequences, characterization results, and clinical data; and (6) the possible discovery of new cancer genes from the tumors studied. The milestones for FY 2006 have been identified as: Quarter 1—NHGRI issuance of RFAs; Quarter 2—NCI issuance of RFA and RFPs and selection of tumor sets; Quarter 3—NHGRI funding of high-throughput sequencing centers; and Quarter 4—issuance of NCI awards.

Dr. Barker concluded with a reminder that the genome community has identified more than 2,000 genes that are believed to be associated with cancer. The Genome Characterization Centers already have many genes to begin sequencing. The Centers' identification of new genes and regions of interest, however, likely will drive the project and ultimately set the stage for creating that atlas and catalogue that would be a turning point in the war on cancer.

Questions and Answers

Dr. Prendergast asked about cancer stem cells in relation to the project. Dr. Barker replied that The Cancer Genome Atlas Project would present an opportunity to characterize cancer stem cells in a specific way, and they could be included in the proposals for the Genome Characterization Centers. Dr. Lander agreed with the idea of a pipeline, pointing out that if one thing can be characterized, then anything can be characterized, and added that the answer might be in the flow sort of stem cells, once

they are identified, or in the descendants of the stem cells that will bear any genetic mutations. He noted that the strength of larger characterization projects is their capability to shift focus to any problem. Dr. Prendergast agreed and expressed that the pilot project will provide time to work through the question of characterization much better and possibly make it more attractive to work with the cancer stem cells. He commented that traversing the reverse engineering route might be difficult, as cancer might progress through means other than stem cells. He advocated the development of a multidimensional approach to perform genomic analysis. Dr. Barker remarked that she had undervalued two things about this project: (1) the extent to which it would ignite new interest in research, and cancer research specifically; and (2) the extent to which it would allow institutions to leverage what they are doing. For example, at a recent launch of a nanotechnology alliance center, Dr. Barker heard a presentation about the use of nanotechnology platform genomic changes in the vasculature roughly 10 months before any indications of malignancy in a mouse model. She encouraged the NCI to take advantage of how quickly the technology is moving forward and to facilitate its use.

XIV. SUBCOMMITTEE REPORT: PLANNING AND BUDGET—DR. FRANKLYN PRENDERGAST

Dr. Prendergast presented a summary of the recent Planning and Budget Committee meetings to discuss the NCI budget. In January, the Committee held a joint meeting between the BSA and the Planning and Budget Subcommittee of the NCAB. Drs. Prendergast and Robert Young, Chair of the BSA, co-chaired the meeting. Dr. Prendergast highlighted the presented emerging concepts from the meeting.

One of the key ideas that emerged was to protect the young investigator to the greatest extent possible, by as many means as possible, such as offering preferential pay lines to young investigators. Dr. Prendergast noted that he has received 90 e-mails since January from investigators who heard that the most important issue discussed at the meeting was that the NCI budget is seriously compromised and will affect young investigators in the long term. There was wholesale agreement that there should be preferential pay lines. In addition, academic institutions will needed to be convinced of the value of team science as the scientific community and the NCI move toward more team constructs and away from the R01 construct.

A second issue was "parity and pain"—that is, all NCI programs, including those recently initiated, must share the overall burden of rescission. By "parity" is meant that the measure of rescission in funding needs to occur as a consequence of the rescission of funding to the NCI as a whole. All mechanisms need to be examined, and all NCI programs—those established and those recently initiated—must share the overall burden of rescission. The NCI must be seen to be moving ahead, but, in a time of reduced budgets, it is probably imprudent to make the assumption that it is feasible to constantly initiate new programs and accomplish more with less.

A third discussion revolved around the need to reexamine and justify the existence of and the funding allocations to all large-scale NCI programs. Program reductions and "sunsetting" of some programs seem inevitable with reallocation to other funding mechanisms.

The fourth key point was that pay lines for R01 grants at the 10th percentile are not tenable in the long term. Suggestions on how to ameliorate this included: (1) increase the number of grants by reducing the budgets awarded, (2) reduce the number of total grants held by any one senior investigator, and (3) pursue additional joint-funding mechanisms with non-NIH partners.

The fifth idea was to insure the balance of research among NCI's basic, translational, clinical, and population science portfolios. Dr. Prendergast indicated that "insure" means to protect. Basic research is the bulwark and basic research, in fact, sustains the entire enterprise. Dr. Prendergast observed that the infrastructure is weak for actual translation.

The sixth point cautioned that, in light of the current fiscal exigencies, mandatory allocations such as NIH Road Map initiatives need to be prudently tempered, especially in terms of planned expansions for years 2007-2009. Dr. Prendergast recognized that, although this is not under the control of the NCI, the issue needs to be broached assertively.

The seventh issue raised was that the NCI leadership must collaborate with members of the research community to develop more effective communications with Congress and the public at large. Dr. Prendergast pointed out that the NCAB had heard from Dr. Lander previously on this topic as well as had discussed this issue earlier during this meeting.

The eighth idea was that the cancer research community and the public should be engaged in defining what constitutes "return on investment." Dr. Prendergast mentioned the difficulty of calculating the return on investment for basic research in a sensible and intelligent manner; no one in the early 1970s, for example, would have forecasted the full consequences of recombinant DNA technology. Fundamental discovery research yields its rewards tangibly through time, but initially such returns often are not obvious. There is a need to engage the scientific community as to how best they think a return on investment should be defined and to help the NCI adjudicate how it allocates resources.

XV. FUTURE AGENDA ITEMS—DR. DANIEL VON HOFF

Dr. Von Hoff announced that the next NCAB meeting will occur June 14-15 (Wednesday and Thursday). He invited Board members to share future agenda items. Dr. Lander suggested that the NCAB consider what programs ought to be reduced or "sunsetted." Dr. Runowicz noted that the P2 file should be released this spring and might be able to present. Dr. Lander offered drug development as a topic.

(Whereupon, at ____p.m., the open session of the National Cancer Advisory Board was concluded.)

XVI. CLOSED SESSION—DR. DANIEL VON HOFF

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 2130 applications were reviewed requesting support of $600,831,749. The subcommittee adjourned at 5:15 p.m.

XVII. ADJOURNMENT—DR. DANIEL VON HOFF

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

There being no further business, the 137th regular meeting of the NCAB was adjourned at 5:30 p.m. on Tuesday, February 7, 2006.