DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
134th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 7-8, 2005

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

NATIONAL CANCER ADVISORY BOARD
NATIONAL CANCER INSTITUTE

The National Cancer Advisory Board (NCAB) convened for its 134th regular meeting on Tuesday, June 7, 2005, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, June 7, 2005, from 8:30 a.m. to 4:30 p.m. and closed to the public from 4:30 p.m. to 5:30 p.m. On Wednesday, June 8, 2005, the meeting was open to the public from 8:30 a.m. until adjournment at noon. NCAB Chair Dr. John E. Niederhuber, Professor, Departments of Oncology and Surgery, University of Wisconsin-Madison, presided during both the open and closed sessions.

NCAB Members

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

President's Cancer Panel

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

Alternate *Ex Officio* NCAB Members

Dr. Michael Babich, CPSC
Dr. Allen Dearry, NIEHS
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. T.J. Patel, DVA (absent)
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD (absent)
Dr. R. Julian Preston, EPA (absent)
Dr. Anita Schill, NIOSH (absent)
Dr. Donald Wright, OSHA

MEMBERS, EXECUTIVE COMMITTEE, NATIONAL CANCER INSTITUTE, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Karen Antman, Deputy Director for Translational and Clinical Sciences
Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships
Dr. J. Carl Barrett, Director, Center for Cancer Research
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Mark Clanton, Deputy Director for Cancer Care and Delivery Systems
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. David Elizalde, Deputy Director for Management and Executive Officer, Office of the Director
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Harold P. Freeman, Director, Center to Reduce Cancer Health Disparities
Dr. Paulette Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Dinah Singer, Director, Division of Cancer Biology
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
Ms. Barbara K. LeStage, National Cancer Institute, Director's Liaison Group
Ms. Judy Lundgren, 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. INTRODUCTION, WELCOME, AND APPROVAL OF MINUTES—DR. JOHN NIEDERHUBER

Dr. Niederhuber called the 134th meeting of the NCAB to order and welcomed all of the Board members. He then asked that everyone pause for a moment of silence and recall the reasons for the meeting: the strong belief in the work the Board does to deliver care to patients who are suffering from cancer and their families.

He welcomed Dr. LaSalle Leffall, Jr., Chair of the President's Cancer Panel (PCP) and Charles R. Drew Professor of Surgery, Department of Surgery, Howard University College of Medicine, and extended a special welcome to *ex officio* members of the Board: Dr. Peter Kirchner, Department of Energy (DOE); Dr. Allen Dearry, National Institute of Environmental Health Sciences; Dr. John Potter, Department of Defense; and Dr. Michael Babich, U.S. Consumer Product Safety Commission. Dr. Niederhuber extended a special thanks to the National Cancer Institute (NCI) staff members who work with the NCAB and acknowledged the presence of and the support given to the Board by Dr. Paulette Gray, Director, Division of Extramural Activities (DEA), NCI, and Executive Secretary of the NCAB. He also recognized representatives of the liaison organizations and acknowledged members of the public attending the meeting. Members of the public were invited to submit to Dr. Niederhuber or Dr. Gray, in writing and in a timely manner, any comments regarding items discussed during the meeting.

Motion. A motion was made to approve the minutes of the February 16-17, 2005, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE MEETING DATES—DR. JOHN NIEDERHUBER

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda, which have been confirmed through 2007 and asked that members notify Dr. Gray of potential conflicts with any of the dates.

Dr. Niederhuber then reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

III. NCI DIRECTOR'S REPORT—DR. ANDREW VON ESCHENBACH

Dr. Andrew von Eschenbach, Director, NCI, extended greetings to all present and thanked the Board members for the time and the effort they put into supporting the NCAB. He noted that many issues, some of which had received significant media coverage, had arisen since the last Board meeting, and stated that he would like to have some of the issues serve as a focus for Board deliberations, conversations, and advisory input. Dr. von Eschenbach then shared two observations regarding the climate currently surrounding the cancer research community. Increasingly over the past 3 years, the NCI and the broader cancer community had begun to see evidence of reaching or being very close to some of the anticipated ends of the cumulative research efforts conducted over the past 30 years. That is, evidence that findings from cancer research could begin to impact on the disease in a way that would save peoples lives. In addition, he described a communal sense of anticipation coming from the realization that the NCI is on a new and different journey than the one started in 1971; a journey of discovery, development, and delivery that brings new opportunities and entirely new ways of preventing, detecting, and eliminating cancer. He cited the climate as an opportunity to focus on people and the wealth of talent within the National Cancer

Program (NCP) and specifically at the NCI. Turning to the issue of staffing, Dr. von Eschenbach announced the following three changes in staff:

- The appointment of Dr. Paulette Gray as Director of Extramural Activities;
- The appointment of Dr. Carolyn Compton as Director of National Biospecimen Research; and
- The appointment of Dr. Piotr Grodzinski as Program Director for Cancer Nanotechnology.

As the NCI pursues new and important strategic initiatives, it will focus on the nurturing and development of individuals. It also is important that the NCI continue to help define the architectural blueprint that will guide the staff in creating and building the Institute's future around a constant emphasis on the continuum of discovery, development, and delivery across the Nation and around the world. Much of NCI's work focuses on the delivery portion of the continuum. Regarding the delivery end of the continuum, the NCI has been engaged in a very comprehensive effort to view delivery as an important platform of discovery. Through the delivery of new and more effective interventions and combinations of drugs, biologics, and devices, delivery offers researchers an opportunity to examine fundamental mechanisms of human cancer that feed back into the discovery process.

Dr. von Eschenbach described NCI's efforts to re-engineer the clinical research infrastructure, which began in January 2004, with his charge to the Clinical Trials Working Group (CTWG) to fine-tune the systems of the past with consideration for the 2015 goal. Some of the infrastructure from the past needed to be replaced, and some needed modification or adaptation to serve future needs and fit into the new reality of clinical operations more effectively. He highlighted the fact that the Board would be asked to accept the CTWG Final Report outlining the new architectural blueprint for clinical research infrastructure, and in doing so, consider the report as part of an ongoing redesign effort that will continue to need the Board's advice, direction, and guidance. He also stated his firm commitment to implementation of the report's recommendations.

Returning to the continuum of discovery, development, and delivery, Dr. von Eschenbach noted that there are many parts of the NCI portfolio in the discovery and development phases of the continua that directly affect and inform the delivery process. Those parts can be defined broadly as translational research as opposed to clinical research. The NCI has major portfolio investments in translational research. For example, program project grants and contracts, the Rapid Access to Intervention Development (RAID) Program, and the intramural program represent significant investments, as does the significant commitment made to the Specialized Programs of Research Excellence (SPORE) programs, which has grown 694 percent since their inception in 1992. The Board was asked to consider ways to synergize, integrate, and coordinate current and emerging opportunities in a way that would fuse and nurture the delivery end of the continuum.

The focus on translational research has been and continues to be informed by the work carried out in closely related areas. Recently, the PCP initiated work to examine opportunities that exist in translational research. Similarly, the NIH has redirected some of its efforts to address the concept of a translational research initiative. It will use the infrastructure that is currently in place in many academic centers to help redefine the translational research programs in those institutions in ways that resemble what the NCI has done with the Cancer Centers Program. Another critically important activity in translational research is the effort to train and develop staff and create investigators who are uniquely adapted to emerging clinical realities and opportunities.

To further support and assist the NCAB, Dr. von Eschenbach requested the creation of a Translational Research Working Group that would function in an aggressive, transparent, open, and inclusive fashion, similar to that of the CTWG. Over the next year, the Translational Research Working Group will look at

the entire landscape of translational research and begin to define what would optimize the opportunities in translational research and create a context and a blueprint for much more effective management of resources to meet the opportunities presented. The group also will attempt to position part of NCI's portfolio to accelerate the discovery, development, and delivery continuum. Dr. Ernest Hawk, Director, Office of Centers, Training, and Resources (OCTR), Office of the Director (OD), was selected to lead this working group. Dr. Hawk will report to NCAB's Cancer Centers Subcommittee. Dr. von Eschenbach then asked Dr. Arthur Nienhuis, Chair of the Cancer Centers Subcommittee, to accept on behalf of the subcommittee, responsibility for this new working group.

In summation, Dr. von Eschenbach described the work before the Board as moving aggressively within the delivery construct to deliberate the outcomes of the Clinical Trials Working Group and to begin implementation of the planning task force and working group for translational research.

Questions and Answers

Mr. David Koch, Executive Vice President, Koch Industries, asked whether, given the expense of clinical trials, the new concept is designed to achieve more at a much lower cost. Dr. von Eschenbach explained that it would. Mr. Koch asked how this would be done. Dr. von Eschenbach suggested that the new technologies would allow questions to be answered using much smaller patient populations, create greater precision, and the insight gained would reveal the optimal intervention to take forward into larger clinical trials that would compare efficacy of the new intervention versus the standard therapy. The greatest cost efficiencies will come from the increase in quality and the elimination of waste. Mr. Koch asked if that meant that double-blind trials would no longer be the "gold standard," and whether there was another way of performing comparative trials more effectively. Dr. von Eschenbach replied that within the portfolio of clinical trials, some traditional strategies would be used, but other opportunities and options, such as "Phase Zero" mechanisms, would be explored. Specific mechanisms would be applied for specific reasons to obtain outputs or outcomes that move the agenda forward. Dr. Niederhuber asked Dr. Daniel Von Hoff, Director, Translational Genomics Research Institute, to add to this discussion. Dr. Von Hoff offered as an example the process recently used to test Herceptin under which the use of 468 Her2 neu positive patients, at a cost of $10 M, precipitated the drug's approval. If Her2 neu positive patients had not been selected, it would have taken 24,000 unselected patients, at a cost of $480 M, to achieve the same results. The 50-fold improvement achieved by selection not only decreased the number of people put at risk, but also it generated enormous savings that could, theoretically, release funds for 50 more studies with the selected patients. Dr. Koch inquired whether there was potential for applying that concept to other drug development processes. Dr. Von Hoff stated that it could. Dr. Carolyn Runowicz commented that she supported the concept, but questioned an inherent conflict of interest with science and the pharmaceutical companies. Dr. Von Hoff stated that he did not believe such a conflict existed. Dr. Niederhuber offered that both views were equally valid, and cited the progress of current long-term negotiations designed to mitigate pharmaceutical and biotech issues and develop ways to promote collaborative efforts. Dr. von Eschenbach added that opposite views on the subject pointed to an inherent systems problem that requires a systems solution.

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

Dr. Leffall reminded the Board that the PCP had completed a series of meetings on Translating Research to Reduce the Burden of Cancer that more fully explored the effectiveness of this component of the NCP. At the last Board meeting, he summarized some of the testimony heard by the Panel and the key issues that participants raised. A strong message was delivered to the Panel about the need to address gaps in translating cancer discoveries from laboratories to physicians and patients across all communities. Participants noted that delivering everything that currently is known in the scientific community to the

American people would have an immediate impact on cancer morbidity and mortality, but many communities do not have the benefit of that knowledge. One suggestion to narrow this gap was to target geographic areas of excess mortality. The Panel heard that there is a continuing and pressing need to engage community physicians, community-based organizations, and local advocates and to connect cancer centers and academic medical centers to local cancer care delivery, including disseminating information and providing access to care.

Dr. Leffall noted that the Panel considered this information, along with an abundance of other testimony and additional information gathered before and following the meetings, and prepared a comprehensive report to the President, Congress, and the Nation. This report was delivered to the White House on June 3, 2005. It was released publicly for the first time at the June 16, 2005, meeting entitled "Joint Translational Research Training Meeting: A Cancer Perspective," sponsored by the NCI and the Howard Hughes Medical Institute. The report addressed the emergent themes from the Panel's series of meetings, including team science and partnering, regulatory issues affecting translation, education and training, issues of public trust, technology and infrastructure, financing, and the importance of access to successful translation. Most importantly, it listed the Panel's recommendations for steps that should be taken by the health care system, policymakers, and the research community to improve the way the NCI and others discover, develop, and deliver scientific findings to all of those affected by cancer. The report also suggests stakeholders that have major responsibility for action.

Dr. Leffall explained that the PCP is in the process of planning its 2005/2006 series of meetings, which will bring together key stakeholders and decision-makers to address selected recommendations from the Panel's 2003/2004 report on survivorship, *Living Beyond Cancer: Finding a New Balance*, and this year's report, *Translating Research into Cancer Care: Delivering on the Promise*. Dr. Leffall noted that previously, each Panel member had selected a meeting topic for the annual series of four meetings. During a recent Panel meeting, however, the members thought it would be most appropriate to look at the key recommendations made in the past two Panel reports, identify the most significant ones, and bring together key people who could help implement change, rather than generate another report. This is an important step because the Panel cannot implement change. However, it can facilitate implementation, and the PCP has chosen to address its previous high-priority recommendations in greater depth in the coming year, rather than develop a new topic.

The first two meetings will be held August 25 and 26, 2005, in Washington, DC. The primary focus of the August 25 meeting will be development of a strategic plan to further activities in the areas of followup and treatment plans for cancer survivors, engagement of key players in this endeavor, and assessment of progress toward recommendations. Deliberations also will address unintended consequences of the Health Insurance Portability and Accountability Act (HIPAA) in relation to treatment and followup, a topic that was raised repeatedly during testimony delivered to the Panel, particularly during this past year. The meeting on August 26 will focus on adolescent and young adult cancer survivorship issues. The last two meetings of the 2005-2006 year are planned for October 24 and 25, 2005, in the Washington, DC area. These meetings will focus on key recommendations from the newly published report on translating research.

Questions and Answers

Dr. von Eschenbach asked when the PCP report on translational research would be available publicly. Dr. Leffall replied that it would be released on Monday, June 13, 2005. Dr. Neiderhuber asked Dr. Leffall to elaborate more on the plan for this coming year. Dr. Leffall noted that Dr. Margaret Kripke, Executive Vice President and Chief Academic Officer, The University of Texas MD Anderson Cancer Center and PCP member, had raised the issue initially and that he and Mr. Lance Armstrong, PCP

member, were in full agreement. Collectively, the Panel wanted to do something that would really make a difference, such as bringing together people with the power to make the kinds of changes that would bring to fruition some of the Panel's recommendations. Ms. Kathryn Giusti, President and Founder, Multiple Myeloma Research Foundation, Inc., asked if specific milestones or measurements developed would include determining whether the recommendations were being implemented. Dr. Leffall indicated that this was the case. Mr. Koch asked if there was an intended audience for the translational research report beyond the NCI, Food and Drug Administration (FDA), or other federal agencies. Dr. Leffall replied that the intended audience includes anyone with an interest in cancer, not just federal agencies. He added that during presentation of the report to the White House Office of Domestic Policy, it was suggested that the Panel have a similar meeting with Department of Health and Human Services Secretary Michael Leavitt and his staff. Dr. Peter Kirchner, Program Manager, Office of Biological and Environmental Research, Medical Sciences Division, U.S. Department of Energy, asked if there was any information on whether or not early telemedicine had made any impact on the distribution of high-quality health care to all segments of the population and whether telemedicine could be used to improve health care in areas where high concentrations of specialists are not available. Dr. Leffall stated that there is a firm belief that such would be the case, but there are no data to prove the assumption. Dr. Kirchner asked whether any attempts had been made to collect impact information. Dr. Leffall noted that the Panel had discussed the issue and was trying to determine the best way to gather that information.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response, OD, NCI, reported that the President's Budget gives the NIH $28.8 B and that the NCI would receive $4.8 B of that amount. The House Appropriations Subcommittee was expected to mark up the NCI appropriations bill during the week of June 9, but the Senate had not projected a mark up date at the time the report was given. Ms. Erickson presented information on the several congressional hearings that had taken place since the last NCAB meeting. In April, there was a House Appropriations Subcommittee hearing and a Senate Appropriations Subcommittee hearing. Dr. Elias Zerhouni, NIH Director, was the principal witness at both hearings; Dr. von Eschenbach, along with the other Institute and Center (IC) Directors, participated in those hearings. Later in April, there was a hearing entitled "Setting a Path for Reauthorization: Improving Portfolio Management at the NIH." Dr. Zerhouni again was the principal witness, and he presented information on the proposed "Office of Portfolio Analysis and Strategic Initiatives." In May, Dr. von Eschenbach testified for the NCI at the Senate Appropriations Committee hearing on gynecological cancers that highlighted a recently introduced bill called the Gynecological Cancer Education and Awareness Act, also known as Joanna's Law. At the end of May, there was a joint hearing by the House Committee on Resources and the House International Relations Subcommittee on Asia and the Pacific that addressed the effects of nuclear testing in the Marshall Islands. The NCI was one of three government agencies asked to testify about this issue. The witness for the NCI was Dr. André Bouville, Lead Radiation Dosimetrist, Chernobyl Research Unit, Division of Cancer Epidemiology and Genetics.

Ms. Erickson presented highlights of the following bills before Congress considered to be of interest to the NCAB: The Patient Navigator Outreach and Chronic Disease Prevention Act, the Stem Cell Research Enhancement Act, and the Stem Cell Therapeutic Research Act. The Patient Navigator Bill was introduced in April by Congressman Robert Menendez (D-NJ) and was reported by the Energy and Commerce Committee on May 4, 2005. The Senate Bill was introduced by Senator Kay Bailey Hutchison (R-TX) and reported by the Senate Health Committee at the end of April. The bill was not expected to go to the full House until July. This bill would amend the Public Health Service Act to authorize a demonstration grant program to be administered by the Health Resources and Service Administration (HRSA). The grant program would provide patient navigator services to reduce barriers and improve health care outcomes. The bill authorizes an appropriation of $25 M over 5 years for this

grant program. The Stem Cell Research Enhancement Act garnered some attention in the press. The bill was introduced by Congressman Mike Castle (R-DE) and cosponsored by Congresswoman Diana DeGette (D-CO). There also is a similar bill in the Senate introduced by Senator Arlen Specter (R-PA). The House passed this bill on May 24. It is designed to expand the lines of stem cells that are available for research. A second bill on stem cell research, focusing on umbilical cord blood stem cells, was introduced and also passed the same day.

Questions and Answers

Dr. Daniel D. Von Hoff, Director, Translational Genomics Research Institute, asked for additional information about the congressional hearing on improving portfolio management at the NIH. Dr. Niederhuber asked if the discussion was part of the authorization process. Ms. Erickson explained that discussion about portfolio management was part of the reauthorization process. The focus of Dr. Zerhouni's testimony was on the Office of Portfolio Management. Congressman Joe Barton (R-TX) discussed several goals that he had in reauthorizing the NIH. One of those was the concept of budget clusters, which was discussed at the hearing in a very general way; another was disease reporting, which would be addressed by the new office that Dr. Zerhouni proposed. Dr. Von Hoff inquired about the particulars of budget clusters and the disease reporting. Ms. Erickson replied that the budget cluster concept was outlined in a very general way, noting that 27 ICs at the NIH may constitute too many budget line items and perhaps there may be another way of organizing the budget that would reduce those numbers. Although there has been a great deal of discussion about a reauthorization bill, a hearing tentatively scheduled in May was cancelled, indicating that a large amount of discussion was still taking place. Current information shows that the bill has not been written, so there is not much information about what it may look like.

Dr. Jean deKernion, Professor and Chairman, Department of Urology, Senior Associate Dean for Clinical Operations, David Geffen School of Medicine at the University of California-Los Angeles, asked Ms. Erickson to discuss the implications of budget clustering. Ms Erickson indicated that it was not clear, particularly for cancer, what the concept of budget clustering would mean. Dr. Niederhuber commented that the Board is responsible for advising the NCI, and therefore, needs to understand the potential budgetary impact of this bill, especially as it relates to reallocation of funds. Dr. deKernion also voiced concern that there could be serious implications for the NCI and advised the Board to become as educated as possible to understand the impact of any changes that may arise from the process. Dr. Niederhuber added that both the NCAB and the Board of Scientific Advisors have a responsibility to stay in touch with such issues and to rally the appropriate groups to provide input into the process. Dr. Paulette Gray added that for clarification, her office would send Board members as much information as possible regarding the intent of either the Senate or Congress in dealing with budget clustering and portfolio analysis.

VI. FINAL REPORT: CLINICAL TRIALS WORKING GROUP—DR. JAMES DOROSHOW

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, opened his presentation by thanking Dr. Howard Fine, the CTWG Co-Chair, and all of the contributing subcommittee chairs and co-chairs for their assistance in preparing the CTWG Final Report. He reminded the Board that the CTWG began with a vision of the future direction of cancer clinical trials that encompassed enhancing the best components of the NCI-supported clinical trials system to develop a cooperative enterprise built on a strong scientific infrastructure and a broadly engaged coalition of critical stakeholders. The scientific rationale for changing the current clinical trials system addressed advances in cancer biology that provide the opportunity to move beyond cytotoxic treatments to more effective therapies and recognized the potential to improve the practice of clinical oncology. Dr. Doroshow

explained that successfully restructuring NCI's clinical trials enterprise to optimize patient outcome required the following: (1) the routine incorporation of the tools of cancer biology into cancer clinical trials; (2) the cooperative, interdisciplinary, efficient, and functionally integrated approach to clinical trials conduct; and (3) an implementation strategy that recognizes the high value of components of the current clinical trials system, and simultaneously challenges those components to work together in new ways. Key elements of the implementation strategy incorporate the values of Cancer Centers, SPOREs, Cooperative Groups, grant-supported clinical trials staff, the Community Clinical Oncology Program (CCOP), community oncologists, and patient advocates. In addition, successful implementation requires acknowledgment that progress means challenging each component of the current system to work together and securing the enhanced commitment of the extramural community to the increases in effort and responsibility required to more broadly assist the NCI in the governance of the entire cancer clinical trials enterprise. Most importantly, successful implementation of the proposed restructuring mechanisms requires the development of a formal system to evaluate and measure the impact of the restructuring initiatives.

The plan proposed by the CTWG is organized around the five common themes of: (1) coordination, (2) prioritization and scientific quality, (3) standardization, (4) operational efficiency, and (5) integrated management. Within those themes, 22 specific initiatives were developed. Full implementation of the restructuring plan is projected for completion in 4 to 5 years, with a majority of the initiatives scheduled for implementation by the end of Year 3. It is expected that all initiatives will be established as routine practice by the end of Year 7.

Coordination initiatives are directed at enhancing information sharing, developing incentives for collaborative team science, and coordination of the regulatory process in the scientific enterprise. Prioritization and scientific quality initiatives are meant to establish new transparent processes for the design and prioritization of clinical trials and for facilitating the conduct of correlative science and other ancillary studies conducted during NCI-funded investigations. The prioritization initiative includes the creation in Year 1 of: (1) a combined Extramural/Intramural Investigational Drug Steering Committee that will provide strategic input into a variety of issues, including the NCI drug development pipeline, clinical development plans for new agents, and assistance in the strategic evaluation of letters of intent; and
(2) scientific steering committees composed of Cooperative Group disease committee chairs, clinical and translational investigators, CCOPs, SPOREs, P01s, Cancer Centers, and NCI intramural and extramural programs who are experts in the specific diseases, as well as patient advocates, community oncologists, and experts from early therapeutics, imaging, correlative science, quality of life, and industry communities as appropriate. These committees will conduct state-of-the-science meetings to develop priority areas for Phase III clinical trials development, and are responsible for evaluating and refining ideas for Phase III trials developed by the Cooperative Group disease committees or investigators. Because this initiative represents a significant restructuring of the current procedure for selecting Phase III trials, a formal evaluation will be conducted in Year 2 after it has been implemented to examine the success of the process in the initial disease categories that have been selected.

The standardization initiatives were designed to promote the development of defined clinical research tools and procedures that would minimize duplication and reduce the effort required to initiate and conduct clinical trials. The information technology infrastructure is an important target of the standardization initiative. Operational efficiency initiatives focus on improving patient accrual rates and cost effectiveness as well as speeding up the initiation and conduct of clinical trials. Integrated management initiatives address the need to restructure both extramural and intramural oversight of clinical trials. Two enterprise-wide initiatives that address the integrative management of NCI-funded clinical trials also have the greatest potential to change the current system. The first recommends creation

of a permanent Clinical Trials Oversight Subcommittee of the NCAB to continually advise the NCI Director regarding the conduct of clinical trials across the Institute. The second would integrate the overall management of clinical trials within the NCI by having senior NCI leadership develop recommendations for a more coordinated management and oversight structure for the full spectrum of clinical trials supported throughout the Institute.

Dr. Doroshow noted that the 22 initiatives proposed by the CTWG are interactive and interdependent. The coordination initiatives to develop a comprehensive clinical trials database and to realign funding guidelines are essential to a more transparent prioritization system. Better coordination of NCI's clinical trials system with the FDA and Centers for Medicare and Medicaid Services (CMS) will enhance the efficiency of developing new therapies and support more rapid rates of patient accrual. The increased involvement of community trials staff and patient advocates in the protocol prioritization process will increase patient accrual rates by developing clinical trials that are more attractive at the local level. Increased operational efficiencies that lead to enhanced clinical trials accrual rates will allow studies to be completed more rapidly, facilitating overall prioritization. A standardized interoperable clinical information technology structure will support all other areas by providing common electronic case report forms and by improving coordination, prioritization, and the efficiency of NCI-funded clinical trials. The entire system needs to be overseen by an integrated clinical trials management system that is advised by an expert panel of extramural clinical investigators. The estimated cost for Year 1 of the restructuring plan is $7.1 M, increasing to $20.6 M in Year 2. It reaches a steady state at approximately $29 M annually by Year 3. The largest portion of those projected expenses (75 percent) directly support extramural clinical trials.

The CTWG suggested mechanisms to evaluate the success of the implementation process. One of the expected difficulties in this area will be the absence of a common evaluation system outside of the grant review process. Thus, evaluation poses a challenge in terms of the establishment of a structured evaluation system. The group's suggestion was to engage experienced evaluation specialists to assist in the development of the appropriate tools with the critical baseline evaluation, which underlies NCI's ability to determine the impact of these initiatives.

The CTWG also indicated that any evaluation process should involve external clinical trial experts and the acquisition of new forms of empirical data, both subjective and objective. The focus of the evaluation should be on the management of the implementation program, defined management measures, documented changes in the performance of the clinical trials system produced by the measurable initiatives, and any improvements observed in overall clinical trials outcomes that could be related to the restructuring process directly. Dr. Doroshow noted that ultimately, the true value of the restructuring plan would depend on whether or not the initiatives measurably increased the number of clinical trials that improve medical practice either through the development of new therapies or diagnostic procedures, or through the development of better biomarkers that meaningfully enhance the specificity with which cancer treatments are delivered. Fifty years ago, the NCI had the foresight to initiate support for networks of investigators and institutions engaged in clinical trials that could speed the development of new cancer therapies. Over the next half century, with enhanced commitment from extramural investigators, physicians, patient advocates, and the new investment called for by restructuring, the CTWG expected that the NCI, in collaboration with the clinical trials community, would lead the process of translating extraordinary advances in cancer biology into clinical trials that materially improve the outcome of cancer patients everywhere.

Finally, Dr. Doroshow expressed his sincere appreciation to all of the members of the CTWG who had invested so much of their time and effort in developing the recommendations over the past 1.5 years. He then asked his co-chairs and subcommittee members to come forward to assist in answering questions.

Dr. Niederhuber suggested that Dr. Doroshow introduce each member. Dr. Doroshow then introduced the CTWG members who were present: Dr. Richard L. Schilsky, Professor of Medicine, Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago Pritzker School of Medicine; Dr. Mark J. Ratain, Leon O. Jacobson Professor of Medicine, Chairman, Committee on Clinical Pharmacology and Pharmacogenomics, Associate Director for Clinical Sciences, Cancer Research Center, The University of Chicago; Dr. Steven D. Averbuch, Executive Director, Merck Research Laboratories Clinical Research, Oncology/G.I.; Dr. Howard Fine, Chief, Neuro-Oncology Branch, Center for Cancer Research, NCI, NIH; Dr. Peter C. Adamson, Division Chief, Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia; Dr. David H. Johnson, Director, Division of Hematology/Oncology and Deputy Director, Vanderbilt Ingram Cancer Center, Vanderbilt University Medical School; and Dr. James L. Abbruzzese, Chairman and Professor of Medicine, Department of Gastrointestinal Oncology and Digestive Diseases, The University of Texas MD Anderson Cancer Center.

Questions and Answers

Ms. Giusti asked whether the evaluators would be responsible for evaluating 5 to 10 cancer centers in the first 2 years. Second, she commented that the focus appeared to be on Phase III trials, and asked whether starting at Phase I or Phase II would reduce the expense of using correlative science in a Phase III trial. Dr. Doroshow explained that there would be a small number of steering committees in the first 2 years, and an evaluation would determine whether a mid-course correction was necessary. He also noted that the CTWG plans to strike a balance between early and later phase studies.

Dr. Niederhuber asked Dr. Richard Pazdur, Division Director, Division of Oncology Drugs, FDA, to comment on the drug steering committee from the FDA's perspective and asked Dr. Schilsky to share his insight on how the process will work with the Cooperative Groups. Dr. Pazdur noted that the FDA was very involved with this process and would be interested in participating further. Dr. Schilsky indicated that he was pleased with the report's findings and anticipated a profound positive influence for the better in the way cancer clinical trials are conducted in this country. He mentioned that the Gastrointestinal (GI) Intergroup had recently reorganized along similar lines. Although some concern had been expressed among the Cooperative Groups about whether the prioritization process would make their internal prioritization process superfluous, it is important to have a national prioritization process.

Mr. Koch asked whether the CTWG had given any thought to collapsing Phase III into Phase II to save time and a significant amount of money while ensuring that what replaces Phase II and Phase II/III properly measures the effectiveness and safety of the therapy under development. Dr. Doroshow stated that the suggested procedural change was of great interest to many. The possibility of getting drugs to patients earlier, using smaller numbers of patients if the appropriate pharmacodynamic molecular tools are available, and conducting clinical trials with fewer patients represented an ideal that could be achieved through a revised prioritization process. Dr. von Eschenbach commented that those and other related issues would become more critical as researchers look to the FDA for earlier drug approvals and move from interventions that are more preventive than therapeutic in nature. Dr. Schilsky added that recent discussions have exemplified the importance of a very close working relationship between the NCI, FDA, and CMS. This kind of interaction between federal agencies is critical, and the fact that it has begun to occur will impact the cancer research community significantly.

Dr. Arthur Nienhuis, Member, Department of Hematology/Oncology, Division of Experimental Hematology, St. Jude Children's Research Hospital, asked how the CTWG envisioned the sequential review process through which prioritization would occur after a protocol is developed. Dr. Abbruzzese responded that the CTWG did not envision a sequential process, and that the disease committees that currently existed within the Cooperative Groups would be involved in the scientific steering committees

in a particular area. He added that the GI Intergroup used a similar process to prioritize and discuss Phase III concepts as they emerged. Dr. Fine added that it was important for the Board to know that the CTWG and the NCI do not intend to micromanage the committees; rather, the intent is for each disease committee to self organize based on its usual organizational methods.

Dr. Runowicz asked whether the Cooperative Groups had an opportunity to review the CTWG report, and if so, how much input they would have in changing or modifying it. Dr. Doroshow explained that most of the CTWG thought that releasing the report would be inappropriate before the NCAB had reviewed it, so the Cooperative Groups have not seen the report. Dr. Niederhuber noted that the CTWG compiled the report through a very open process over the course of 18 months, so anyone with an interest had the opportunity to provide input into the process.

Ms. Lydia Ryan, Service Line Clinical Director, Hematology-Oncology/Stem Cell, Children's Healthcare of Atlanta, AFLAC Cancer Center, asked Dr. Doroshow to comment on the possible approach for pediatrics. Dr. Doroshow commented that in most instances, pediatricians were ahead of adult oncologists. There has been much consolidation, organization, and cooperation with the Pediatric Oncology Branch, which will participate in the restructuring effort.

Dr. deKernion mentioned that within academic institutions, there is little reward for clinical investigators. He asked how this issue would be handled under the restructuring plan. He also asked whether any thought had been given to the savings inherent to the restructuring process. Dr. Doroshow responded that planned financial analyses would identify any savings or cost efficiencies. Incentives have been built into the budget for the restructuring process, the CTWG has considered means of allocating incentives, and a justification model has been developed.

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, asked to what extent the group has analyzed data to determine the extent of the barriers to minority recruitment and participation in clinical trials, and what was planned to address the issue. He also asked about county hospitals' access to clinical trials. Dr. Doroshow replied that the CTWG spent a fair amount of time considering both issues and agreed to identify what works and try to utilize and supplement those activities rather than invent a new program. Because a substantial amount of the minority accrual to NCI-funded trials comes from minority-based CCOPs, they would be the main conduits for identifying effective strategies.

Dr. Pazdur asked about the interface with industry within the proposed organizational structure. Dr. Averbuch noted that there would always be elements that remain in the private sector and those private interests are industry driven. The thrust of the CTWG report was identifying where private-public partnerships exist with an eye on making those processes more efficient with respect to setting up dialogues.

Mr. Koch stated that it was not clear to what extent the FDA was involved in the development of the plans and asked whether the FDA wholeheartedly supported the report's recommendations. Dr. Pazdur assured Mr. Koch that the FDA had significant involvement in developing the report, as referenced in the acknowledgments on page 2 of the report.

Dr. Anna Barker, Deputy Director, Advanced Technologies and Strategic Partnerships, NCI, asked whether there were any innovative ideas about prioritization. Dr. Ratain replied that currently, the success rate for oncology drugs, defined as FDA approval, was 8 percent. He also acknowledged the need to do a better job of prioritizing which drugs to take to Phase III trials so that the Phase III trials are successful and focus on critical issues in Phases I and II.

Ms. Ryan asked about the role of the Cancer Bioinformatics Grid (caBIG) in helping the standardization and data collection systems. Dr. Ken Buetow, Director, NCI Center for Bioinformatics, stated that in many ways, caBIG laid the foundation for creating systemic data standards through development of infrastructures and the coordination process. CaBIG will be used as leverage for expansion of standardization into the broader community.

Dr. Niederhuber again expressed the gratitude of the Board for all of the effort that went into developing the report. Dr. von Eschenbach pointed out that one of the greatest strengths of the cancer program and the cancer community is their incredible diversity. An ability to come together as a diverse community and trust each other to work toward a common purpose has emerged. The CTWG's report will change the future of clinical research in this country. The NCI is committed to making those changes.

VII. WORKING LUNCH: UPDATE: FDA TASK FORCE—DR. ANNA BARKER

Dr. Barker began her presentation on the Interagency Oncology Task Force by citing its growth into a large enterprise, noting that Dr. Pazdur would direct the new Office of Oncology Products. She informed the Board that the Task Force was engaged in collapsing the drug trails' approval system. Two objectives of the Task Force are to lower the risk of investing in drug discovery and development and to engage the private sector further. Dr. Barker added that the extent to which biomarkers could be discovered and integrated would inform the process at all phases. The Interagency Oncology Task Force continues to inform and expedite the drug approval process. The collaborative process has provided evidence that post-genomics drug discovery and development will drive an entirely different process.

One of the issues being attacked is the process itself; from the Investigational New Drug (IND) stage through the New Drug Application (NDA) process. The desire for endpoints has driven the process—the need is to have new drugs be highly effective, very safe, and approved rapidly. The Task Force has been working on advanced technologies, means of evaluating them, and has implemented three training programs for Ph.D.s and M.D.s to assist them in traversing the regulatory path and understanding the regulatory process. In the area of advanced technologies, nanotechnology is of greatest concern. Along with the FDA, the NCI is has been jointly developing a strategic plan for nanotechnology over the past two years.

Imaging is another target of the Task Force's efforts to address surrogate endpoints. Dr. Janet Woodcock, Acting Deputy Commissioner for Operations, Director, FDA Center for Drug Evaluation and Research (CDER), has been interested in accelerating the extent to which imaging can be used in clinical trials and Drs. Gary Kelloff, Dan Sullivan, and George Mills from the FDA also have been working collaboratively to accelerate the use of imaging endpoints in clinical trials. One manuscript on the use of fluorine-18-labeled fluorodeoxyglucose positron emission tomography (FDG PET) in clinical trials is in press, and another is in preparation. An initiative on volumetric measurements for clinical trials is in development as well. Bioinformatics has been a topic of significant collaboration between NCI and the FDA, especially as it relates to many of the challenges that the FDA faces in harmonizing bioinformatics systems for all phases of clinical development. The IOTF has worked on integrating the caBIG infrastructure from its initiation by the NCI.

Another target of the Task Force is the development of an electronic IND (eIND), parts of which are in development currently. One of the components associated with this effort is the Cancer Investigator Exchange (CRIX), which will list investigators and all of the information about completed clinical trials. The NCI is working on eIND standards with the FDA, Health Level 7 (HL7), and other standards bodies.

This activity, which is of high interest to the private sector, is moving very quickly, and many private partners are anticipated.

A clinical biomarkers initiative, which will define more of the scientifically based endpoints to be addressed, is being developed. Meanwhile, some first-generation endpoints, like prostate-specific antigens, are under discussion and will remain on the agenda.

Dr. Barker asked Dr. Pazdur to comment on endpoints activity. Dr. Pazdur briefly discussed the workshops held with the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), and the American Society of Hematology (ASH). He also noted the change from an emphasis on survival as an endpoint to progression-free survival, or disease-free survival (DFS), or time to progression endpoint, stating that the shift was much more in keeping with the position of European researchers who use DFS and time to progression as an approval endpoint.

Dr. Gary Kelloff, Chief, Chemoprevention Branch, Division of Cancer Prevention (DCP), NCI, noted that the strategy in working with the NCI on imaging was to move to an earlier point in the process, identify the technologies that are close to being validated, define the state of the science, and suggest what incremental studies need to be done to achieve validation. Then, looking at the universe of possibilities specifically for imaging, FDG PET was selected because it comes close to a level of evidence that would allow its validation in prospectively designed trials. The second effort in imaging involved examining the group of imaging probes that are almost ready to be embedded in trials, which will be earlier than has been done previously. Collaboration on volumetric imaging is just beginning.

Dr. Barker recognized the work done by Drs. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program, NCI, and Janet Woodcock and invited Board members to visit the FDA Web Site for more information. She also advised the Board to look for the "Guidance for Industry Investigators and Reviewers: Exploratory IND Studies" report and take advantage of the opportunity to comment on it. Comments from members of the Board may contribute to fundamental changes in the way early clinical trials could be conducted.

Dr. Christian said that to assist investigators in understanding the FDA's drug approval process for exploratory INDs, two points of contact had been developed: (1) a regulatory affairs liaison, who helps investigators use existing channels effectively in resolving questions or disputes; and (2) a senior leadership team to resolve questions or disputes when a satisfactory resolution, using standard mechanisms, has not been achieved. The exploratory INDs are geared toward allowing early evaluation in limited numbers of patients. Making these processes simpler and clearer, and phasing in requirements for the earliest trials, should accelerate the development of new agents and reduce some of the risks, which would encourage investigators to bring more compounds forward.

Dr. Barker mentioned that the Task Force has started a new plan in chemoprevention, which she hopes to discuss at the next NCAB meeting.

Questions and Answers

Dr. Freedman asked whether the review process for the new exploratory IND could best be accomplished within major institutions, by companies, or under contracts. Dr. Kelloff replied that the exploratory IND was designed to get drugs to "first in man" studies faster than had been done previously. In response to a question from Dr. Freedman regarding the development of new imaging probes, Dr. Barker replied that the Task Force was hoping to bring the imaging companies to the table with the FDA and the NCI in a consortium that would allow conduct of some interesting but demanding trials.

VIII. OVERVIEW OF NCI INTRAMURAL CLINICAL RESEARCH ACTIVITIES— DRS. ROBERT WILTROUT, LEE HELMAN, AND JOSEPH FRAUMENI

The Center for Cancer Research (CCR)

Dr. Robert Wiltrout, Director, CCR, NCI, outlined the activities of the Center for Cancer Research (CCR). With a goal of adding value and uniquely contributing to the overall NCI challenge, the CCR supports a large basic discovery component that is linked to innovative technologies. Through its highly respected staff, it provides leadership and innovation in clinical trial development and performance. Within the intramural program, it provides training for basic scientists and scientists seeking translational and clinical experiences. The review and rewards structure, which focuses largely on retrospective analysis, provides an impetus and flexibility for individuals to conduct high-risk, potentially high-payoff basic and clinical research. The CCR also has the ability to recruit diverse cohorts of patients to perform purely science-driven trials; very few standard of care trials are conducted in the Clinical Center by the NCI.

The two largest areas of emphasis within the CCR are basic research and clinical research; however, there also is significant activity in translational research, including one of the largest programs in HIV and AIDS-related research in the United States. These are supported by a clinical infrastructure, a substantial effort in advanced technology development, and some aspects related to molecular oncology. The CCR has training programs that transcend all of these areas and provide researchers with interdisciplinary and team-oriented training experiences. The major intramural program areas are immunology, molecular targets, genetics, and genomics. Most of the scientists have administrative homes in laboratories or branches, but during a reengineering process similar to that proposed by the CTWG, the CCR turned its focus to a matrix-type structure that promotes work on crosscutting initiatives that link basic science to clinical science through the translational resources in some of the technology cores. There are four major areas of critical activity that comprise the CCR's Centers of Excellence: advanced biomedical technology, molecular epidemiology, immunology and immunotherapy, and molecular oncology and molecular targets.

Dr. Lee Helman, Acting Scientific Director for Clinical Sciences, CCR, discussed the clinical program's current projects, vision for the future, and path forward. Currently, the intramural clinical program is the largest cancer-focused clinical research center in the world, capable of performing patient-intensive clinical research focused on developing new approaches for prevention, diagnosis, and treatment. As a critical component of the Nation's overall cancer program, the intramural programs are patient-intensive rather than volume-intensive. Two-thirds of the work encompasses treatment studies, the vast majority of which are Phase I, Phase II, or pilot studies. The remaining work is comprised of surgical, psychosocial, screening, imaging studies, and specimen collection, fulfilling the mission to conduct early clinical studies that will be tested in the broader context if they are successful. In addition, clinical program investigators provide major clinical support to the overall clinical research enterprise within the Clinical Center, as part of the clinical infrastructure across Institutes. The CCR conducts several ongoing extramural partnerships, initiatives on glioma and health disparities, and a leukemia and lymphoma profiling project. Within the intramural program, the Center also is beginning to work on molecular imaging, leveraging this activity to collaborate extensively with the extramural community.

The vision for the CCR's future will focus on testing science-based hypotheses, examining diseases or disease processes, and maximizing understanding of how to intervene in the disease process by examining cancer networks using genetic, proteomic, and imaging tools. The path forward will embrace the phase zero target assessment and solidify a partnership with the DCTD. Tissue procurement is slated to be a major effort as is the incorporation of functional imaging. The overall goal is to provide the initial

rationale and guiding principles for further agent development, based on man rather than xenografts, using available technology to segue delivery into discovery.

In terms of development, the CCR plans to develop a tissue acquisition core for every patient that comes into the Clinical Center through the NCI. The entire proteomics portfolio is under review to determine how proteomics will impact the clinical molecular targets core. In addition, the CCR is in the midst of a number of staff recruitments.

Questions and Answers

In response to a question on health disparities from Dr. Moon Shao-Chuang Chen, Professor, Department of Public Health Sciences, Leader, Population Science, University of California Davis Cancer Center, Dr. Michelle Bennett, Associate Director for Science, Office of the Director, CCR, described two activities in the health disparities realm: (1) the initiation of outreach/clinical operations at the Cardozo/Shaw clinic to offer second opinions or consults to their existing cancer patients, and (2) the establishment of a Patient Navigator Academy to train a cadre of patient navigators. Dr. Chen asked about the stated goals of this initiative and the program's connection to the Center to Reduce Cancer Health Disparities (CRCHD). Dr. Bennett noted that the recent Patient Navigator Academy Workshop was held in combination with the CRCHD and DCTD. Dr. Helman commented that like other major cancer centers around the country, the CCR is attempting to understand and address the barriers that make minority populations feel less welcome as participants. Dr. Freedman asked whether the CCR plans to use its clinical molecular targets core to help with the standardization of assays for the clinical trials program. Dr. Doroshow indicated that it would be used to develop standard operating procedures for specific agents. Dr. Wiltrout added that the CCR also played an active role in tissue procurement and annotation. Dr. Nienhuis inquired about the methods used in conducting "first in man" studies and patient accrual to the Clinical Center. Dr. Helman stated that the problem was nonexistent because patient accrual had increased by about 25 percent. Regarding the metrics of "first in man" studies, Dr. Helman noted that an external advisory committee was being formed to routinely evaluate CCR and that some percentage of its studies would be developed enough to give the positive results needed to move beyond Phase I studies. Dr. Wiltrout noted that the entire intramural program was peer reviewed regularly by individual site visit teams that send their results to the Board of Scientific Counselors for a second review of the science and the clinical program.

Division of Cancer Epidemiology and Genetics

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), NCI, described three aspects of the DCEG that address clinical research: (1) randomized clinical trials, (2) leveraging clinical trials for epidemiologic research, and (3) molecular epidemiology. The Division's role in randomized trials includes three ongoing interventions: an HPV vaccine trial in Costa Rica, and two U.S.-China collaborations involving stomach cancer and pre-cancerous lesions (antibiotic eradication of H. pylori) in Shandong Province, and esophageal cancer and dysplasia (vitamin supplementation) in Henan Province. Efforts are also made to leverage these and other clinical trials for etiologic research. One focus has been on cancer therapy trials, examining the risk of second cancers that are related to therapy and/or underlying genetic susceptibility to both the primary and secondary cancers. In terms of diagnostic trials, the DCEG has collaborated with the Division of Cancer Prevention to develop etiologic and early marker studies based on the prostate, lung, colon, and ovarian (PLCO) cancer screening trial. In addition, chemoprevention trials have been converted to cohort studies, such as the alpha-tocopherol and ß-carotene (ATBC) trial in Finland. These studies and others comprise a major part of the portfolio of research in molecular epidemiology, which integrates clinical and basic science components into cohort and case-control studies designed to advance our

understanding of cancer causation and inform preventive, diagnostic, and therapeutic strategies. In particular, molecular epidemiology strives to: (1) identify the carcinogenic risks associated with susceptibility genes and endogenous and exogenous exposures and their interactions; (2) examine intermediate phenotypes or early outcomes as well as molecular subtypes of tumors; (3) detect causal pathways in cancer initiation and progression; and (4) formulate and evaluate strategies and targets for intervention. The many challenges in this area are being addressed through multidisciplinary collaborations such as the Consortium of Cohorts as well as case-control international consortia that are investigating less common tumors, including non-Hodgkin lymphoma (NHL), brain tumors, esophageal adenocarcinoma, bladder tumors, and pancreatic cancer. Dr. Fraumeni described a study of NHL that is being conducted with investigators in the Surveillance, Epidemiology, and End Results (SEER) Program, and that is now part of an international coalition of case-control studies that are investigating this tumor. He stressed how the consortium approach can eliminate false-positive or false-negative leads through replication and pooling strategies, thus saving a lot of time, effort, and expense. A third type of consortia involves family-based studies, as illustrated by collaborative studies of hereditary melanoma designed to identify susceptibility genes and environmental interactions.

Questions and Answers

Dr. Niederhuber asked about the direction of future endeavors. Dr. Fraumeni pointed to a further emphasis on large-scale intramural/extramural collaborations in concerted efforts through molecular epidemiology to accelerate progress in understanding and controlling cancer.

IX. UPDATE: BREAST AND PROSTATE CANCER COHORT CONSORTIUM— DRS. ROBERT CROYLE, EDWARD TRAPIDO, MICHAEL THUN, AND DAVID ALTSHULER

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), NCI, described an experiment in merging the work of scientists—genomicists, population geneticists, epidemiologists, and basic scientists—that had not been merged very well historically. The special project, comprised of four extramural grants funded by the NCI and supported by the American Cancer Society (ACS), the World Health Organization (WHO), and other organizations, formed a core Consortium of pooled resources and fostered collaboration across existing cohorts to focus on and answer critical questions about breast and prostate cancer. Each of the historic competitors involved leads a cohort. Dr. Edward Trapido, Associate Director, Epidemiology and Genetics Research Program, DCCPS, NCI, provided a brief introduction to the topic and the project; Dr. Michael Thun, Vice President, Epidemiology and Surveillance Research, ACS provided an overview of the Consortium; and Dr. David Altshuler, Assistant Professor of Genetics and Medicine, Department of Molecular Biology, Harvard Medical School and Massachusetts General Hospital, presented information about the Consortium's Population Genetics Working Group with Dr. Thun. Dr. Croyle also noted that because the project is an experiment on composing a Consortium, the NCAB's feedback on next steps will be important, as would that of the Board of Scientific Advisors (BSA), whose input will be sought as well.

Dr. Trapido introduced the Breast and Prostate Cancer Cohort Consortium (BPCCC), by explaining that the NCI-supported Cancer Genetics Working Group has suggested a coalition approach to address concerns about a high false positive rate observed in several unreplicated studies of gene and environmental interactions of pathways and their relationship to cancer. The Consortium of Cohorts was born out of this suggestion. The Consortium of Cohorts consists of a coalition of investigators from 23 population cohorts representing 1.2 million individuals. The cohorts jointly examine large numbers of multiple outcomes. To be included in the Consortium of Cohorts, a cohort study must address extensive risk factors, be longitudinal in nature, and collect biospecimens, including germ-line DNA at baseline.

The general approach is to perform nested case-control studies of specific cancers within these cohorts to identify causal mechanisms and molecular and biochemical biomarkers of susceptibility, exposures, and early stage disease. The Consortium initiated a first "proof of principle" study, to prove or disprove whether there could be a collaboration fostered among population geneticists, biostatisticians, and epidemiologists, and to demonstrate the feasibility of studying gene-environment interactions by systematically collecting and pooling data from existing cohort studies. Many prominent investigators are involved and within the NCI; both the DCCPS and DCEG have played major roles. The BPCCC Study involves the coordination, standardization, pooling of results, scientific hypotheses, scientific discussions, data, data analyses, and reporting, which takes advantage of the existing funding for the cooperative agreements of the underlying cohorts. Cohort funding organizations include the NIH, the WHO, International Agency for Research on Cancer (IARC), and the ACS. All investigators must maintain their independent and continued funding. In 2003, four awards were made as a cooperative agreement. At 18 months, an external working group was asked to assist the progress, determine whether the program was meeting the proof of principle issues, and where they were scientifically. There was tremendous collaboration and positive group dynamics, not only between the groups that had not necessarily collaborated before, but also with the NCI. There was a good combination of biologic, genomic, and population-based sciences. Quality control had been initiated, and data already had been posted on the Web. The benchmark by which other studies will make decisions also evolved.

Dr. Thun noted that before the Consortium existed, there was no mechanism for planned replication of findings and inadequate standardization of the genetic approaches in association studies. Therefore, it was difficult to account for the differences in findings among highly similar studies. Breast and prostate cancers were selected because they are the most common cancers in the respective sexes. The study focused on the steroid hormone and Insulin-like growth factor (IGF) pathways because they are relevant to both sites, and the high penetrance genes do not explain the familial association for breast and prostate cancer, leaving an unexplained component. Dr. Thun described some of the Consortium members, their studies, and several of the scientific findings within and across some of the 23 cohort studies comprising the Consortium. He also outlined the basic organizational structure of the Consortium, its working groups, and the flow of the genetic and environmental information. He commented that the progress to date included establishing the mechanism that performs the detailed and comprehensive characterization of candidate genes; conducts these highly standardized genetic analyses in very large-scale, prospective association studies that can systematically evaluate pathways (not single genes); and has the potential to validate promising findings from other approaches.

Dr. Altshuler described the work and progress of the Consortium's Population Genetics Working Group. The overall approach has three parts. The first is to discover potential causal variants; the second is to measure the frequencies of those variants in patients with and without disease; the third involves integrating that information with other types of information to try to identify associations. Goals in this working group are based on two underlying hypotheses: (1) there can be coding regions or rare variants, and (2) there are common variants that influence disease. After reviewing specific information on study methods, Dr. Altshuler summarized the results by explaining that the work carried out by the Consortium of Cohorts studied both the HapMap samples and samples from a multiethnic cohort study and other studies. It appears that it is possible to transfer the information from the haplotype map to capture information from an individual cohort study without loss of information. The Consortium is a good resource that will support future research of this kind.

Dr. Thun offered information on and examples of the ways that integration and management have worked, some initial results, and future plans. He also described some interim goals that were set by the NCI for the Consortium's 18-month review. The first set of goals addressed the collaborative infrastructure. The second set of goals addressed genetic sequencing, which was underway when the

study began, the characterization of haplotypes, and the sharing of data. Other goals developed as the Consortium attempted to merge questionnaire data and systems from multiple cohorts to be compatible for both pooled and parallel analyses. In terms of the scientific plans for the consortium, as cohorts are followed they accumulate a substantial number of additional cases of all types of cancer, which facilitates further replication. In addition, the possibility of adding additional cohorts exists, particularly as it pertains to enlarging the ethnic-specific samples. There is a great deal of discussion about the combination of genes and analysis by pathway as well as ongoing efforts to conduct genome scanning to generate new candidate genes in pathways for which the Consortium would be poised to have a replication function. In addition, the New Hypothesis Committee is intended to enhance its ability to replicate studies that are in the literature and make public access to the genotyping data more user-friendly.

Questions and Answers

Mr. Koch asked whether it was disappointing that a good correlation between cancer in parents and children had not been found. Dr. Thun commented that it was disappointing, and added that only six genes had been fully characterized and there was value in negative findings. Ultimately, the contributions of the Consortium of Cohorts will involve identifying associations that are important, closing out false positives, and validating findings that look promising and that require large sample size to validate them.

Mr. Koch asked how genes for examination were chosen and what could be done to identify more promising genes to study. Dr. Thun replied that the genes in the steroid hormone and IGF pathways were chosen based on a strong biological basis indicating that both pathways would be important to breast and prostate cancer. Dr. Altshuler added that staged designs screening the entire genome for the most promising genes would be used.

Ms. Giusti commented that the Consortium starts its efforts, but it will want additional researchers to contribute to the work and asked whether the Consortium was providing only the raw data or tools for researchers to work with and, if so, how quality control was accomplished. Dr. Thun pointed out that each of these cohorts had its own unusual attributes, so there was no intentional or unintentional misuse of the data. Because the cohorts are governed by very different rules, data-sharing issues are worked out with each cohort proposing a plan and then proposing and agreeing on a joint plan. Dr. Trapido stated that some of the statistical methods and quality control developments were being published, and it is the Consortium's intention to make as many of the methods as possible available to the entire research community. Dr. Croyle reminded the Board that the Consortium was an experiment in progress from which lessons were being learned, particularly in terms of coordination management.

Dr. Franklyn Prendergast, Edmond and Marion Guggenheim Professor of Biochemistry and Molecular Biology, Professor of Molecular Pharmacology, Experimental Therapeutics Director, Mayo Clinic Comprehensive Cancer Center, inquired about methods of quality control under such difficult circumstances. Dr. Stephen Channock, Head, Genomic Variation Section, Pediatric Oncology Branch, CCR, described the laboratory side of the issue explaining that a structure had been developed for sharing information and samples as well as monitoring genotyping error, sequencing error, and haplotype determination; however, some issues are still being addressed. Dr. Prendergast asked what the approach would be to managing 50-60 genes. Dr. Thun indicated that it would be done gene-by-gene. Dr. Altshuler added that because some researchers are conducting whole genome association studies, there are investigators who have resolved such problems.

Dr. von Eschenbach commented that when engaged in a research endeavor in which the technologies impacting the research are developing at a faster rate than the investigation, such as in biodefense, "spiral

project management" has been used. It requires one to be designing research, while anticipating the fact that the same tools will not be used throughout the research endeavor. In light of that, he asked whether the Consortium had reached out to other arenas, where similar problems were being faced, to incorporate lessons learned from such experiences. Dr. Altshuler responded that the haplotype map project was designed 3 years of age according to that principle. It was explicitly designed with multiple technologies in mind, a Technology Development Working Group, head-to-head comparisons, and dollars held back to bring in new technologies midstream. He also acknowledged the need to make technology adjustments an explicit research goal to assist the traditional investigator who is not accustomed to planning projects around this issue.

X. OVERVIEW: THE NATIONAL ADVANCED TECHNOLOGY INITIATIVE (NATIc)— DR. ANNA BARKER

Dr. Barker began by noting that technologies are moving so fast that it is very difficult for the research community to move at the same rate. Based on NCI's 2015 goals, the NATIc is attempting to leverage the Institute's vast portfolio of resources to develop the networks needed to create a model that can take advantage of the science and the advanced technologies simultaneously. Because barriers to accelerating cancer research progress are increasingly technology-based, the cancer research community needs to develop a "network of networks" to advance biomedicine. In the last few years, the fundamental digital code of the cancer genome has resulted in many changes and will continue to do so. Dr. Barker emphasized the fact that cancer researchers can no longer work in a vacuum. Work must be conducted across and with other sectors; academics, government, the public, survivor groups, and internationally. Over the last 30 plus years, an enormous resource base in translational research and basic research has been formed through the research programs supported by the NCI. Overall, the investment in cancer is vast and much of it has been in the area of advanced technologies. To begin creating the required network of networks, the NCI mapped the locations of technology centers, finding some interesting overlapping capabilities. One of the ideas that emerged very early was the creation of a national network to leverage existing and emerging advanced technology development resources. Potential focus areas included bioinformatics and advanced computing, advanced imaging, drug discovery and high-throughput screening, proteomics, biomarkers and diagnostics platforms, molecular diagnostics, computational and systems biology, nanotechnology, biopharmaceutical development and scale up, biosensors and model systems engineering, and prototype engineering. Planning and implementation to date have produced recommendations for two major enterprise initiatives: (1) the Cancer Genome Initiative, and (2) the Proteome Initiative or a larger Biomarker Initiative. CaBIG is the bioinformatics platform through which the infrastructure for standards and data exchange was developed will provide the connectivity for the NATIc. CaBIG is the largest undertaking in biomedical informatics to date, and is receiving a great deal of attention. Common language and common software and systems are the hallmarks of CaBIG that are expected to empower and connect individuals. The pilot is underway in about 50 cancer centers. This has become a private-public partnership very quickly, and IBM is a potential packaging and distribution partner for the system's software.

The cancer genome project focuses on sequencing cancer genes and is a major undertaking with significant challenges. It will be implemented in phases; a pilot project will identify the issues and inform the development of a full-scale project. A known issue is the magnitude of the resequencing required, which will represent the equivalent of a number of human genome projects. In fact, the proposed program will be the largest and most important paradigm-shifting genomics analysis initiative in cancer to date. . It will drive new sequencing technology. Data collection, analysis, and data release constitute major issues. The National Human Genome Research Institute (NHGRI) and the NCI have created a management group to design the pilot study and manage the program.

Dr. Barker discussed NCI's nanotechnology programs noting its 6-year history in this area through the Unconventional Innovation Program. The NCI is a leader in nanotechnology and has programs that are moving the field forward in areas such as drug delivery capabilities, cancer cell targeting capabilities, and therapeutics. Many of the advances in genomics and proteomics are expected to come through nanotechnology, so the issues of bioinformatics and data will become more critical, especially in areas such as systems biology. Sixty-one nanotechnology-based drugs and 91 devices and diagnostics are in development. The NCI has created a nanotechnology characterization laboratory in its intramural program, which will help investigators characterize their projects, products, and technologies before they are submitted to the FDA.

The other area that NATIc is expending time and effort on is biomarkers, which reflect the state of the disease or the result of an intervention. Biomarkers have the potential to inform and enable every part of the drug development continuum. Significant efforts are needed in this area - especially in the area of molecular diagnostics. In summary, Dr. Barker suggested that over the past 1.5 years, the NATIc has put in place some of the infrastructure and underpinnings of the advanced technologies that will allow the NCI to move forward in the future and will proceed to implement the overall NATIc strategy in the next two years.

Questions and Answers

Mr. Koch asked whether the strategy behind the cancer genome project was to sequence a cancer and then compare the DNA sequence in that cancer to the sequence in a normal cell, determine what the differences are, and then try to understand which of those differences are causing the cancer. Dr. Barker indicated that this was the case and commented that doing so would be an awesome undertaking, given the plethora of unknowns associated with the sequencing process.

Dr. Niederhuber thanked Dr. Barker and adjourned the open session at 4:30 p.m.

XI. CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 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 recommendations was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,632 applications were reviewed requesting support of $761,186,501. The subcommittee meeting adjourned at 5:45 p.m.

WEDNESDAY, JUNE 8, 2005

XII. CENTER FOR CANCER RESEARCH CLINICAL ADVANCES—DRS. ROBERT WILTROUT, LEE HELMAN, AND STEVEN ROSENBERG

Dr. Wiltrout introduced Dr. Helman and Dr. Steven Rosenberg, Chief of Surgery, CCR, to present in-depth examples of ongoing CCR research as a followup to the overview of NCI intramural clinical research activities presented earlier in the meeting.

Proteomic Profiling Identifies Prognostic Subsets in Rhabdomyosarcoma (RMS)

Dr. Helman reviewed data from CCR studies treating patients with RMS, which show progress for survival since the 1960s, from less than 30 percent four decades ago to 70 percent for all patients currently. However, impact of the therapy has been remarkable for patients with localized tumors but almost nil in patients with disseminated disease. Dr. Helman stated that a focus of his laboratory over the past several years has been on understanding why therapy for RMS has had significant impact on survival for patients with localized tumors, which presumably included treatment of micrometastatic disease, but almost none on patients with gross metastatic disease. A decision was made to focus on patients with Stage III disease, for which cure rates are about 60 percent, and for which few good markers are available.

Building on previous research in the Pediatric Oncology Branch (POB) and other laboratories, which identified activated IGF-2 and mammalian target of rapamycin (mTOR) signaling in RMS, the decision was made to screen for activation of these pathways by applying the newly developed reverse-phase protein arrays. The research question to be answered was whether activation of these pathways would identify prognostic groups in Stage III patients. Laser capture microdissection (LCMD), which was developed at the NCI, was the chosen approach to looking at protein activation, particularly for examining only isolated tumor tissue. Reverse-phase protein microarrays were developed from 34 RMS biopsy samples obtained from POB/CCR patients to establish the state of the tumor before treatment. The value of this sample population was that therapy for the patients in the RMS studies was uniform, and outcome data were available to correlate with the protein activation findings. The samples were randomized by histology on the array so that the alveolar, embryonal, and botryoid histologies were distributed equally around the slides. Each slide was probed with a single antibody, and the signal was amplified using a peroxidase. Examination of the slides by eye and with the help of a heat lamp showed a segregation of tumors into clusters based on high or low level of expression of the proteins being studied. The clustering was determined to be based on survival rather than histology.

In clustering by protein expression of the 34 samples, 17 of 24 patient samples had high levels of the protein 4E-BP1, which correlates with decreased mTOR signaling, and the patients had good disease-free survival. Whereas, of the 10 samples that had low 4E-BP1 expression levels, only two of the patients were long-term, disease-free survivors. Furthermore, by looking at a few more proteins, it was possible to tightly cluster and predict with good accuracy, retrospectively, those patients who did well when treated on the same study, compared with those who did poorly. Dr. Helman explained that the significance of this finding is that a number of commercially available drugs inhibit mTOR signaling, including rapamycin, which has been used primarily as an immunosuppressive molecule in transplant surgery. Rapamycin compounds are in active clinical development for this application by Wyeth, Ariad, and Novartis. Dr. Helman briefly reviewed what is known about the mTOR pathway, concluding that the pathway is well enough understood to make it possible to predict who might benefit from the POB/CCR approach.

In summary, Dr. Helman concluded that: (1) reverse-phase protein array analysis of 34 Stage III RMS samples identified two distinct subsets of patients that clustered by survival and not by histology; and (2) activation of the mTOR pathway appears to predict for poor outcome in the group of patients with low 4E-BP1 and high phospo eIF4E. These findings are currently being confirmed in a separate, blinded sample set. The question to address is whether the suppression of mTOR with rapamycin improves response to current therapy, thereby improving survival. Dr. Helman noted that this question is being addressed currently in models in his laboratory. Preliminary *in vitro* testing data suggest that the mTOR pathway can be shut off in resistant tumors that have activation, and the tumors can be made more sensitive to standard cytotoxic therapy.

Questions and Answers

Dr. Von Hoff asked whether survivin molecules were present in the study samples and whether their presence had a possible correlation with patient outcome. Dr. Helman replied that suvivin was found in Ewing sarcoma and rhabdo, and that it correlated with an unfavorable outcome. Dr. Nienhuis asked about the status of drug trials for the mTOR inhibitors that are in clinical development by the pharmaceutical companies at present. Dr. Helman noted that Ariad Pharmaceuticals had seen responses in a number of sarcomas in a Phase I study, but none of the companies involved in drug trials had examined combinations. Dr. deKernion asked whether there is a need in future studies to select patients most likely to benefit from mTOR inhibition to make the cytotoxic therapy more effective. Dr. Helman indicated that patient selection would be beneficial to future studies.

Progress in the Development of Cell Transfer Immunotherapy for Patients With Cancer

Dr. Rosenberg reminded members that he and his colleagues have been working for many years to develop effective immune-based treatments for patients with cancer. This research has demonstrated that cell transfer immunotherapy can mediate the regression of advanced bulky cancers in more than 50 percent of patients who have advanced metastatic melanoma, as first reported in *Science* in 2002. The April 2005 issue of the *Journal of Clinical Oncology* reported three times as many patients with the same results. Dr. Rosenberg indicated that recent research results have provided a means to apply this treatment to patients with common epithelial cancers.

To put this research in the context of overall efforts to further the development of cancer immunotherapy, Dr. Rosenberg briefly reviewed the three main approaches used and the results achieved in various studies: (1) nonspecific stimulation of immune reactions, most notably with Interleukin-2 (IL-2); (2) active immunization through the use of cancer vaccines to enhance antitumor reactions; and (3) passive transfer of activated immune cells with antitumor activity (adoptive immunotherapy). In the first approach, 33 out of 409 patients with metastatic cancer, accrued between 1985 and 1996 and treated using high-dose bolus IL-2, experienced complete and lasting responses at a median followup of 14.3 years. This approach demonstrated that melanoma and renal cell cancer are systemic cancers that can be cured by a systemic treatment that stimulates T-cells to cause the regression of established cancers. However, the number of cures has been small. The second, or antigen-specific, approach to stimulating immune responses is an active area of investigation, but researchers have not succeeded in determining how to use cancer vaccines to mediate cancer regression. Only 43 out of 1,306 patients in 58 trials were objective responders as reported in 2004. Of the three approaches, only adoptive immunotherapy has worked effectively in melanoma. Currently there is potential for extending that success to other cancers. The advantages of cell transfer therapy are threefold. It is possible to: (1) administer large numbers of highly selected cells with high avidity for tumor antigens; (2) administer cells activated *ex vivo* to exhibit

antitumor effector function; and (3) manipulate the host prior to cell transfer to provide an altered environment for transferred cells.

Dr. Rosenberg reviewed the development history of current treatments, beginning with the identification a decade earlier of a cell called a tumor-infiltrating lymphocyte (TIL) that could recognize cancer, be grown from tumor resections, and then be re-administered to mediate a low incidence of antitumor effects. Subsequent research to improve this treatment resulted in the development of techniques to clone TILs so that populations of individual cells with high degrees of tumor reactivity could be developed. In an early clinical protocol, 13 patients with metastatic melanoma were treated using cloned lymphocytes plus IL-2 with no responses of any degree. The problem was that the very large number of transferred cells with antitumor activity did not survive in the patient beyond 1or 2 days. This led to the hypothesis that eliminating the patient's immune cells would make space for the large number of cells with antitumor activity, which then could be subjected to the homeostatic cytokines that regulate lymphocyte numbers and repopulate the patient. In the Phase I study to test this hypothesis, 15 patients with metastatic melanoma were treated with infusions of cloned lymphocytes following administration of a nonmyeloablative but lymphocyte-depleting regimen. IL-2 was administered simultaneously with the lymphocytes. None of these patients responded, and again the reason was that the cloned lymphocytes did not survive beyond 1 week after treatment.

Based on recent information in immunologic literature indicating that CD8 cells were dependent on helper CD4 cells for their survival, a new technique has been developed for creating populations of lymphocytes that recognize the heterogeneous body of tumor antigens and contain CD4 and CD8 cells that recognize tumors. The earlier clinical protocol then was amended to call for infusion of up to 10 heterogeneous TILs (containing both CD4 and CD8 cells) selected for high avidity for tumor recognition, instead of cloned antitumor lymphocytes. The initial results from the Phase I study, treating 13 patients with this amended cell transfer therapy following lymphodepleting chemotherapy, were reported in *Science* in 2002: (1) 6 out of 13 patients with metastatic melanoma experienced objective cancer regression; (2) 4 patients had mixed or minor responses; (3) all had previously been refractory to IL-2 administration; and (4) 8 had prior chemotherapy. The persistence of antitumor cells was found to be critical to the mediation of antitumor effects. Updated results of this cell transfer protocol in patients with metastatic melanoma were reported in the *Journal of Clinical Oncology* in 2005. Of the 35 patients on the protocol, 18 had objective responses, 8 had minor or mixed responses, and 9 had no response. Dr. Rosenberg presented examples from among this study population to illustrate that there is no correlation between the bulk of disease and the likelihood of having a response. Moreover, mediation of regression of even bulky cancers has been shown to be reproducible. Extensive studies to analyze the cells and tumors that respond show a correlation between telomere length of persistent clonotypes and number of persistent T cells in blood at around 1 month.

Dr. Rosenberg then described three approaches that are being pursued in his laboratory to improve cell transfer therapy and extend the results beyond melanoma patients. The first approach is based on the finding that nonmyeloablative treatment works and the hypothesis that more ablation would increase efficacy of the therapy. Permission has been received to add 200 rads of whole-body irradiation to the preparative lymphodepletion. Four out of five patients treated with this increased depletion regimen have shown objective responses, but it is too early to know definitively whether this represents an improvement over the regimen without radiation. The second approach builds on the finding that persistence of the T cells in the blood is critical for getting antitumor effects. Genes encoding IL-2 or IL-15 have been transduced into antitumor lymphocytes used for therapy, thereby releasing the transferred cells from the need for persistent administration of cytokine IL-2, which has toxic side effects after a few days. Approval has been received to perform a gene therapy study using IL-2 gene-transduced cells.

Dr. Rosenberg noted that the third approach has potential for application to more common epithelial cancers: genes encoding highly avid, antitumor T-cell receptors (TcR) are transduced into the peripheral blood lymphocytes (PBLs) used for therapy. He demonstrated how this approach has been applied to treat melanoma patients during the past 6 months. The treatment involves stimulating PBLs with OKT-3, transducing the PBLs with MART-1 TCR retroviral vector and culturing them in IL-2, then infusing the transduced cells following lymphodepletion of the host, and administering IL-2 simultaneously. Regressions of melanoma seen in patients treated with this approach have led to the preliminary conclusion that normal human resting PBLs can be converted into cells capable of recognizing tumor antigens *in vitro* and capable of mediating cancer regression *in vivo*. Dr. Rosenberg concluded by describing studies to extend this approach to other common epithelial cancers. Of great interest is putting in TcRs that recognize the p53 or the ESO antigen so that patients with cancers other than melanoma can be treated.

Questions and Answers

Dr. Niederhuber asked whether patients are ever re-treated or receive re-infusions of cells. Dr. Rosenberg replied that most patients receive only a single treatment and those who have stabilized may be treated a second time. Dr. Niederhuber inquired about the significance of telomere length. Dr. Rosenberg noted that telomere length is quite important.

Dr. Diana Lopez, Professor, Department of Microbiology and Immunology, University of Miami School of Medicine, asked whether the population of CD4s added to patients in the present treatment are depleted or whole. Dr. Rosenberg indicated that CD4s are given whole. Dr. Lopez asked whether TcRs go into both CD8s and CD4s or preferentially the CD8s. Dr. Rosenberg explained that in his study, patients were given the effector CD8 killer cells and CD4 helper cells that also recognize antigen.

Dr. Nienhuis asked whether telomere length is lost during the *in vitro* expansions or whether it is variable from patient to patient. Dr. Rosenberg responded that the cells are grown in multiple cultures from which the culture with the greatest *in vitro* activity is selected for administration. This presents the option to test telomere length using flow assays and specifically select those populations that have longer telomeres.

Dr. Cowan asked whether immunosuppressive therapy obliterates other immune responses that might be generated *in vivo*. Dr. Rosenberg indicated that was the case.

Dr. Freedman asked whether patients receiving IL-2 transfected cells make high concentrations of IL-2 in the circulation. Dr. Rosenberg stated they did not. Dr. Freedman asked whether cloning and sequencing the TcRs in patients would produce data on a commonality that could be useful in creating cloned T-cell populations for therapy. Dr. Rosenberg replied that it did and his laboratory had done so extensively.

In closing, Dr. Rosenberg expressed the view that more widespread exploration of this kind of cell transfer approach is needed in spite of the labor-intensive nature of the research and the requirements for a unique combination of laboratory facilities and ability to administer experimental treatments. Dr. von Eschenbach commented that these presentations on research advances exemplify an important message that should be conveyed to the larger community and all stakeholders who are committed to the cancer program. In addition to its advisory and stewardship roles in making certain that the NCI investments are being managed wisely, the NCAB also can play an important advocacy role and be a voice to the rest of the community on behalf of the NCI and the NCP.

XIII. OVERVIEW: NCI-SUPPORTED HEALTH CARE DELIVERY RESEARCH AND RESOURCES—DRS. ROBERT CROYLE, RACHEL BALLARD-BARBASH,

DEBORAH SCHRAG, AND EDWARD WAGNER

Dr. Croyle pointed out that a steady dialogue has been maintained with the BSA about NCI's research efforts and the infrastructures and methodology development related to quality of cancer care and outcomes measurement, including the kinds of research questions that can best be addressed within the context of community health care delivery. Because primary care is a key element in the health care delivery system, to reduce cancer incidence and mortality, the NCI has engaged the Agency for Healthcare Research and Quality (AHRQ), HRSA, and others to conduct research on how cancer screening is delivered, how it can be detected, and how best to intervene to reduce behavioral risk factors for cancer. Key to these efforts is the patient's perspective as consumers of health care. Dr. Croyle noted that the task at hand is to provide a scientific foundation for delivering what is known about health care, as it exists today and for shaping the health care system of the future. The systems of care and the different contexts within which care is delivered are key independent variables to understand how to reduce cancer mortality and improve quality of care. Another key is the need for good population data on health care delivery and outcomes. Dr. Croyle explained that the goal of the overview is to engage the NCAB today in preparation for a broader conversation at future meetings when the Board will be able to act in its advisory capacity to help prioritize NCI's future directions in health care delivery research.

Progress Report: Building Resources for Cancer Quality of Care (QOC) Research

Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS, NCI, reminded members of the 2002 report by the Institute of Medicine (IOM) entitled *Enhancing Data Systems to Improve the Quality of Cancer Care*, which included recommendations about efforts needed to move forward to both monitor and better understand what is happening in health care delivery across the country. The issues in the IOM report also have been debated at a number of meetings. For example, key points emerging from the 2004 C-Change Cancer Surveillance and Information Summit were the need for data standards for all aspects of cancer surveillance from data collecting to reporting, the need for a modern and expanded scope and vision for cancer surveillance, and the need to work with the Office of the National Coordinator for Health Information Technology (ONCHIT) to make it a pivotal factor in improving both evaluation and quality of cancer care in the United States. In addition, the new framework for cancer surveillance from prevention through to end-of-life care, which was created by the National Coordinating Council for Cancer Surveillance, identifies many crosscutting information needs across the cancer continuum. Finally, all NCI Bypass Budgets since 2002 have designated "Improving the Quality of Cancer Care" as a priority area. Dr. Ballard-Barbash concluded that the goal of NCI investment and efforts is to improve the quality of cancer care by strengthening the scientific basis in both public and private decision-making in the areas of care delivery, coverage, purchasing, regulation, and standards setting.

Dr. Ballard-Barbash briefly reviewed DHHS and NCI activities in medical informatics in light of the recent announcement by DHHS Secretary Leavitt of the need for major movement forward in health informatics. The DHHS Office of the National Coordinator for Health Information has been working with the NCI to explore the potential for a number of NCI's cancer care delivery efforts, including the Cancer Research Network (CRN), to demonstrate progress that might be relevant for a larger forum in the country. Within the NCI, caBIG recently announced a DCCPS Special Interest Group to address the issue of creating electronic medical records (EMRs) that can be used both for research and to improve cancer care. Within the DCCPS, an Informatics Steering Committee is actively addressing the issue of using information technology to support research within health care delivery systems.

Next, Dr. Ballard-Barbash discussed innovations in medical informatics that are part of NCI research initiatives.

- The Virtual Data Warehouse within the CRN uses standardized analytic programs to capture information from all member research groups. The CRN also is developing the MediClass System based on natural language programming. The system will be used to classify EMR data automatically for tobacco cessation interventions.
- The Small Business Innovation Research (SBIR) grant is being considered as a mechanism to move medical informatics initiatives forward. One SBIR-funded effort under development is the standardized computerized mammography data system for the Breast Cancer Surveillance Consortium; another is focusing on integrating patient-reported outcomes in clinical oncology practices.

- The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) has developed an automated tool for abstracting care indicators from medical records.

- Web-based item banks and tools for patient-reported outcomes are being developed within the Patient-Reported Outcomes Measurement Information System (PROMIS), the NIH Roadmap Initiative.

Highlights of an NCI Research Resource: The SEER-Medicare Linked Database

Dr. Deborah Schrag, Memorial Sloan-Kettering Cancer Center, and Chair, ASCO Health Services Research Committee, provided highlights of the SEER-Medicare linked database, which is an NCI-sponsored research resource for understanding patterns of cancer care delivery. She presented data from the 2002 U.S. Census and from CMS sources to put the value of this resource into context. According to Census data, persons 65 years of age and older constitute 12 percent of the total U.S. population but 63 percent of the cancer population. Because an estimated 34 million of the 35 million persons in this age group obtain their health care coverage from the Medicare program, accessing what is happening vis-a-vis cancer care from Medicare data provides a comprehensive picture of the situation across the country. Through the SEER-Medicare linked database, the NCI supports grants-based funding mechanisms for SEER-Medicare studies by extramural researchers. The NCI and CMS also provide technical assistance for use of this resource through a technical assistance Web page, conferences, workshops, and journal supplements. They also support the ResDAC Center, a clearinghouse at the University of Minnesota for advice for researchers engaged in analyses of Medicare data.

The value of linking the databases is that SEER registries collect detailed clinical, demographic, and cause of death information for persons with cancer early on; whereas, Medicare data are longitudinal, extracted from claims for all covered health services from eligibility to death. Dr. Schrag noted that requests for use of this resource have increased dramatically since its inception in 1993, and the number of papers in published medical literature is now more than 200. The data can be used for a variety of analyses that span the course of cancer control activities, from screening and detection to terminal care.

Dr. Schrag described studies that used the SEER-Medicare database as a research resource. One example was a study published in the *New England Journal of Medicine (NEJM*), that documented disparities in the rates of surgery between blacks and whites, the actual survival difference, and the smaller survival difference that would have been possible if treatment were equal. The second study, published in the *Journal of the NCI (JNCI*), spanned the cancer care continuum from diagnosis and treatment to survivorship, examining utilization of chemotherapy following resection for patients with Stage III colon cancer. Data on this cohort of persons 65 years of age and older at each 5-year interval showed the percentage that received appropriate adjuvant therapy, the percentage hospitalized for toxicity, and 3-year survival rates. This analysis revealed that there is a sharp decline in treatment with age and that

there is a racial disparity with 45% of blacks versus 57% of white receiving adjuvant colon cancer treatment. Dr. Schrag explained that SEER-Medicare studies such as this often provide aerial snapshots of cancer treatment delivery, which emphasize the need for more detailed analyses of reasons FOR THE underlying patterns. Although SEER-Medicare data are not useful for explaining reasons underlying observed patterns of care, they help identify areas of variation and controversy and this information helps target and prioritize research. For example, the NCI-sponsored CanCORS study is able to explore in greater detail and seek out explanations for the patterns of care observed in SEER-Medicare studies. The CanCORS study covers the spectrum of cancer care for persons with lung and colorectal cancer to identify reasons care deviates from the ideal as a prelude to developing intervention strategies to improve cancer care delivery.

The third example from published studies illustrated the value of the SEER-Medicare database for evaluating emerging trends in utilization of new technologies. The study, which was published in the *NEJM*, looked at the use of androgen deprivation among men diagnosed with prostate cancer, described the rapid increase in use of this therapy, and associated that finding with an emergent increasing incidence in bone disease. Specifically, the bone disease manifested itself in fractures related not to the prostate cancer, but to the androgen deprivation. The fourth example, which was published in the *Journal of Surgical Oncology*, was a study of the roles of both the surgeon and the hospital volume in outcomes following colon resection. Dr. Schrag noted that this type of study has been carried out for a range of cancers, and absolute differences in survival outcomes in high-volume versus low-volume hospitals have led to recommendations that regionalization should be considered for high-risk, complex surgeries such as resection of esophageal and pancreatic cancers. As a final example, the 2005 Cost-of-Illness Report, which was based on SEER-Medicare data, illustrated the value of the database for studying how health care dollars are being spent with respect to the burden of cancer, specific chemotherapy drugs and procedures, and how the economics relate to specific phases of care and illness.

In summary, Dr. Schrag emphasized that the SEER-Medicare Linked Database can be used to identify potential disparities in the receipt of cancer treatment; document emerging trends in cancer treatment; identify areas for additional clinical outcome studies; indicate divergence between patterns of community care and evidence-based clinical guidelines; and inform policy decisions about centralization and regionalization of cancer care. Limitations of SEER-Medicare data also were acknowledged, such as the lack of information on: (1) care provided in HMOs; (2) patients in under age 65 who are not disabled or have end-stage renal disease; (3) non-covered services such as prescription drugs, long-term care, and free screenings; and (4) reasons for and results of tests. Dr. Schrag noted that another limitation is the length of time required to obtain data from CMS for the linkage, which delays the release of timely informatics; however, she added, this issue is being addressed. In conclusion, Dr. Schrag stated that this research has prompted ideas for expansion of this resource by developing new linkages, including: (1) SEER and Medicaid; (2) SEER and the Medicare Health Outcomes Studies (MHOs) that are being administered by CMS to Medicare managed care beneficiaries; and (3) SEER, Medicare, MHOs, and CAPHS.

In discussion, members emphasized the importance of striving for standardization of data reported, as well as all of the elements within the annotation, including reasonably common formats. Also emphasized was the need to promote consistency of core funding for registries at the state level where the initial collection of data occurs.

Highlights of an NCI Research Resource: The Cancer Research Network (CRN)

Dr. Edward Wagner, Center for Health Studies, Group Health Cooperative, reminded members that the CRN is a group of Health Maintenance Organizations (HMOs) that responded to an NCI Request for

Applications (RFA) to study a variety of questions related to the effectiveness of cancer care. Membership in the CRN, which has been funded since 1999 and was competitively renewed in 2003, includes 11 integrated prepaid group practice plans and an affiliated member, and currently has 27 projects in its portfolio. Dr. Wagner pointed out that the CRN complements the SEER-Medicare linked database in that it includes HMO patients and patients under age 65, can survey patients and health care providers with high response rates, and can access clinical records. The overall goal of the CRN is to conduct and enhance research on cancer prevention, detection, treatment, long-term care, and surveillance in the context of health care delivery systems. Specific aims relate to standardization of data collection, management, and analysis, increasing collaboration among CRN sites and with NCI investigators and academic centers; and augmenting the CRN's ability to respond to NCI priority questions related to the diffusion of innovations in cancer care into practice. CRN membership consists of six regions of Kaiser Permanente from Hawaii to Georgia and five non-Kaiser HMOs, with enrollment totaling more than 10 million including nearly 1 million African Americans and a similar number of Hispanic enrollees.

One core CRN project in the original submission, called HMOs Investigating Tobacco (HIT), was a study of the impact of programs and policies to help individuals stop smoking cigarettes. A second project in the original submission was Detecting Early Tumors Eases Cancer Therapy (DETECT), which was an effort to understand why, in systems with organized cervical, breast, and colorectal cancer screening programs, there was still a high prevalence of late-stage invasive cancer. The study examined problems in the delivery and receipt of screening services that might account for the missed opportunities that result in late-stage cancer. The third of the original projects was the Program Testing Early Cancer Treatment and Screening (PROTECTS), which looked at different approaches to reducing breast cancer risk or the risk of recurrence in women at very high risk. CRN projects under the renewal application have moved toward implementing intervention strategies: (1) Clinical and Pathologic Predictors of Ductal Carcinoma *in situ* (DCIS); (2) HIT 2, which focuses on improving adherence to tobacco treatment guidelines in primary care practice; and (3) Making Effective Nutritional Choices for Cancer Prevention (MENU).

Dr. Wagner noted that CRN projects are beginning to exploit data opportunities available in the integrated system. In HIT2, intervention is carried on through the use of EMRs, the informed patient, and feedback to health care providers to increase the effective delivery of high-quality smoking cessation guidelines. Other projects are making use of newly developed Web-based patient portals where enrollees can interact with their clinical care team and, in some instances, with their EMR. The health care and research potential for the latter is being exploited in studies to change behaviors related to dietary practices in patients at high risk of cancers with dietary relationships, as well as in a study to rationalize the use of tamoxifen both preventively and in breast cancer management. Other CRN projects include 6 projects in response to NCI priorities and 11 affiliated projects. In greater detail, Dr. Wagner demonstrated how the DETECT investigators were able to identify all of the patients in 7 HMOs with late-stage breast and cervical cancer and control groups for comparison, then use automated data capabilities, written medical records, and linkages with SEER and related population registries for additional data to document care delivery and screening experiences. Conclusions reached upon analysis of DETECT data have been presented to the prevention committees of the participating HMOs. Most of them are beginning to consider interventions that will help them contact and engage the hard to reach to reduce the absence of screening that seems to be deleterious to their membership. Major findings of this study have been published in the *JNCI*.

Regarding future directions, Dr. Wagner reported that the CRN has an Academic Liaison Committee, which is helping to develop Co-Investigator relationships with a variety of NCI Cancer Centers and academic institutions across the country. The goal is to develop formal affiliation arrangements. In addition, CRN collaborates with other HMO-related research projects such as those with CanCORS and the Center for Education and Research in Therapeutics, a project funded by the AHRQ to study drugs and

their effects. In closing, Dr. Wagner described the CRN vision for development of the CRN Health Information Resource not only to increase the quality and efficiency of CRN research, but also to make the CRN a national resource. The virtual data warehouse is a standardized aggregation of available automated data that includes the SEER data and HMO enrollment, utilization diagnoses, and demographics data organized in a common framework that would allow an investigator at a single site to write a program across the 11 HMOs that would be comparable to one from a single program. Explorations with caBIG are underway to incorporate the potential of that resource. Two innovations of the resource are the use of EMRs and the patient portal interactive Web sites. Because of time considerations, the overview by Dr. Ballard-Barbash of other examples of NCI quality-of-care initiatives was postponed until another meeting.

Questions and Answers

Dr. Chen asked whether the CRN study had documented any interventions to reach the people who have not taken advantage of the screening opportunities available through the HMOs. Dr. Stephen Taplin, Principal Investigator, DETECT, explained that the results of DETECT are being analyzed to determine strategies for reaching those populations. There is some ongoing qualitative work, particularly with ethnic minorities, as well as a randomized trial featuring telephone outreach. Attempts are being made to understand and address attitudes in low-income populations that make them less likely to come in for screening, and to make interventions more successful. He pointed out that the HMO structure presents an interesting opportunity in that people who do not come in for screening can be identified.

XIV. SUBCOMMITTEE REPORTS—DR. JOHN NIEDERHUBER

Subcommittee on Planning and Budget

Dr. Prendergast presented the report of the Subcommittee on Planning and Budget for discussion by the full NCAB. Major issues addressed at the meeting were: (1) metrics for research outcome and impact in light of the increasing emphasis on return for investment; and (2) communication. Discussion of the first issue focused on how to define return on investment for a specific research program or project and for different types of research programs or projects. Dr. Prendergast noted that, because the planned spring meeting on the metrics issue did not materialize, Subcommittee teleconferences are planned during both July and August to try to develop a template with quantifiable potential for outcome. The results of these deliberations will be disseminated to the full NCAB and addressed at a later meeting. The issue of communication of scientific research and the value of the science also elicited many suggestions and ideas at the Subcommittee meeting. These will need to be organized into an implementable plan. Dr. Prendergast expressed the view that the full NCAB should be engaged in a discussion on this issue, and that Cancer Centers should play a greater role in the communication effort.

In the discussion following presentation of the Subcommittee report, it was suggested that: (1) a future NCAB meeting agenda include a presentation on the science of communication as a foundation and structure to inform communication strategies; (2) there be increased NCAB liaison with the BSA on the issue of large-scale projects that are presented for concept approval, particularly as related to budgets, timelines, and evaluation metrics; and (3) the NCAB should consider some type of communication to the public of its advisory role on behalf of the public.

Ad Hoc Subcommittee on Communication

Ms. Ryan reported that the Ad Hoc Subcommittee on Communication is in the process of reorganization and formulating its agenda for the coming few years in collaboration with the NCI Office of

Communication (OC). During the summer, the Subcommittee will be conferring on the agenda, taking into account OC focus areas, and will report to the NCAB at the September meeting.

In discussion following the presentation, it was decided that the NCAB should submit occasional columns for publication in the *Cancer Bulletin* as one means of highlighting Board discussions and actions.

XV. ADJOURNMENT—DR. JOHN NIEDERHUBER

There being no further business, the 134th meeting of the NCAB was adjourned at 11:21 a.m. on Wednesday, June 8, 2005.

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Date John E. Niederhuber, M.D., Chair

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