DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
133rd NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 16–17, 2005

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

NATIONAL CANCER ADVISORY BOARD
NATIONAL CANCER INSTITUTE
BETHESDA, MARYLAND

Summary of Meeting
February 16-17, 2005

The National Cancer Advisory Board (NCAB) convened for its 133rd regular meeting on Wednesday, February 16, 2005, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Wednesday, February 16, 2005, from 8:30 a.m. to 4:48 p.m. The meeting was open to the public on Thursday, February 17, 2005, from 8:30 a.m. until 10:45 a.m. The meeting was closed to the public from 10:45 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
Dr. James O. Armitage
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 (absent)
Dr. David Koch (absent)
Dr. Eric S. Lander
Dr. Diana M. Lopez
Dr. Arthur W. Nienhuis
Ms. Marlys Popma
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

Alternate *Ex Officio* NCAB Members

Dr. Michael Babich, CPSC (absent)
Dr. Allen Dearry, NIEHS (absent)
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. T.J. Patel, DVA
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA
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, Acting 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
Mr. James Williams, National Cancer Institute, Director's Liaison Group
Dr. Monica Leibert, American Urologic Association
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

TABLE OF CONTENTS

WEDNESDAY, FEBRUARY 16, 2005

THURSDAY, FEBRUARY 17, 2005

WEDNESDAY, FEBRUARY 16, 2005

I. INTRODUCTION, WELCOME, AND APPROVAL OF MINUTES— DR. JOHN NIEDERHUBER

Dr. Niederhuber began by asking for a moment of silence to remember patients with cancer and those who have passed away from cancer. He welcomed members and *ex officio* members of the Board; representatives of liaison organizations; members of the President's Cancer Panel (PCP); Dr. Paulette Gray, Acting Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), and Executive Secretary, NCAB; other NCI staff; and members of the public. He extended a special welcome to PCP Member Dr. Margaret Kripke, Executive Vice President and Chief Academic Officer, The University of Texas MD Anderson Cancer Center; and *ex officio* members Dr. Allen Dearry, National Institute of Environmental Health Sciences; Dr. Peter Kirchner, Department of Energy (DOE); Dr. John Potter, Department of Defense; Dr. Michael Babich, U.S. Consumer Product Safety Commission; Dr. T.J. Patel, Department of Veterans Affairs; Dr. Richard Pazdur, Food and Drug Administration (FDA); and Dr. Donald Wright, Department of Labor. Members of the public were invited to submit to Dr. Gray, in writing and within 10 days, comments regarding items discussed during the meeting.

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

Motion. A motion was requested and made to approve the minutes of the November 30, 2004-December 1, 2004, NCAB meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

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 2006. He asked that members notify Dr. Gray of potential conflicts with the dates confirmed through 2007.

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

Dr. Andrew von Eschenbach, Director, NCI, extended greetings to all present and noted that his report would reflect on the accomplishments and achievements in understanding cancer etiology, detection, and treatment made collaboratively over the past years and on what is needed to move the National Cancer Program forward in coming years. He noted that the double-digit budget increases of the first years of his tenure when the NIH budget was doubling and the NCI budget was increasing by more than 79 percent made possible considerable growth and investment in a broad variety of initiatives. It became apparent that the rate of growth would slow significantly and that there would be an increasing need to reflect on the growth that had been achieved and focus on the issue of return on investment. To that end, the NCI portfolio was examined to address issues of differentiation and strategic priorities within the portfolio, with the realization that the opportunity to continue to grow in strategic areas would no longer be dependent on new dollars, but on redeployment of the dollars already there. One key element in being able to stage and initiate the necessary long-range management and leadership process was the crystallization and redefinition of the NCI mission and vision. The 2015 challenge goal was framed to focus and direct the NCI's intellectual and financial resources to the task of eliminating suffering and death due to cancer. Over the past 3 years, the NCI has worked to provide the infrastructure of strategies, tactics, and organization to achieve the 2015 goal. With the National Cancer Program placed on the 2015 challenge trajectory, the NCI now will focus on more proximate steps that will need to be accomplished

in the next 1-5 years, with appropriate milestones and measurable outcomes to evaluate progress in eliminating suffering and death due to cancer.

Dr. von Eschenbach informed members they would be considering major programs and initiatives that are intended to support the cancer enterprise across the entire domain of discovery, development, and delivery. NCI resources will be used to catalyze the process of providing essential tools and infrastructure to enable all who are engaged in cancer research to successfully contribute to the overall effort. The process will involve the nurturing of individual projects, but, more importantly, will drive the integration and coordination of that individual effort. Some examples are the integrative biology initiative and the Cancer Bioinformatics Grid (caBIG). Dr. von Eschenbach emphasized the importance of people to the success of all plans and initiatives, and gave assurance that the NCI will work aggressively in areas that involve the development of its human capital even as it deals with the realities and limitations of the current financial climate, especially with regard to the need to continue to train the scientists, investigators, and clinicians of the future.

Dr. von Eschenbach announced two pending changes in the NCI senior leadership team. He acknowledged their contributions to the National Cancer Program in their present positions and extended congratulations. Dr. J. Carl Barrett, Director, Center for Cancer Research (CCR), is leaving to become Global Head of Oncology Biomarkers at the Novartis Institute for Biomedical Research. Dr. Karen Antman, Deputy Director for Translational and Clinical Sciences, has accepted the dual position of Provost of the Medical Campus and Dean of the School of Medicine, Boston University. Dr. von Eschenbach then announced appointments that are being made to fill those vacancies. Dr. Robert Wiltrout, Director of Scientific Operations, NCI-Frederick Cancer Research and Development Center (FCRDC), has been appointed Director, CCR. Dr. Lee Helman will assume a newly created role as Acting Scientific Director for Clinical Research, CCR, in addition to his position as Chief, Pediatric Oncology Branch, CCR. His specific responsibility in the new position is to address, help promote, and direct emerging opportunities in the CCR. Dr. Craig Reynolds has been appointed the new Director of Scientific Operations for NCI-FCRDC.

Dr. von Eschenbach reported that his third All-Hands Meeting had been held the previous day. In addition to his State of the Institute Address, one highlight of the meeting was the presentation of the Director's Gold Star Award to recognize and honor the special and unique contributions made by five individuals in ways that typify the entire organization. The awards went to Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD); Dr. Gregory Downing, Director, Office of Technologies and Industrial Relations, NCI; Dr. Daniel Gallahan, Associate Director and Chief, Structural Biology and Molecular Applications Branch, Division of Cancer Biology (DCB); Dr. Jon Kerner, Assistant Director for Research Dissemination and Diffusion, Division of Cancer Control and Population Sciences (DCCPS); and Dr. Sanya Springfield, Chief, Comprehensive Minority Biomedical Branch, Office of the Deputy Director for Extramural Science.

Another discussion at the All-Hands Meeting focused on the challenges the NCI is facing even in a time of great scientific accomplishment and incredible opportunities. In particular, staffing in the Division of Extramural Activities (DEA) has been significantly impacted by the A76-mandated decrease in allowable full-time equivalents in the area of grants management support for the extramural research program. Dr. von Eschenbach noted that the DEA has been in the process of adapting to the mandate and has been able to maintain the level of service to NCI grantees. There do not appear to be any further implications for the NCI in 2005 with regard to A76 and the most efficient organization, but it is not known what the next series will be. Two other challenges relate to the posting on February 3 of a set of conflict-of-interest regulations and guidelines for NIH employees. The guidelines cover three broad areas: (1) outside

employment (whether compensated or uncompensated), (2) acceptance of awards, and (3) personal financial investments. These regulations were posted in the *Federal Register*. Dr. von Eschenbach briefly reviewed possible implications of these new regulations for NIH employees, including members of advisory boards. A 60-day period is underway, during which there is an opportunity for seeking answers to questions or responding to the regulations. For questions, clarifications, or concerns, the NCI community was directed to send an e-mail to conflictofinterest@of.nih.gov. With information received in the Office of General Counsel, the NIH will have an opportunity to propose modifications to the Department of Health and Human Services (DHHS) Ethics Office.

Dr. von Eschenbach next presented an update on circumstances regarding the clinical trial of colecoxib for prevention of adenoma. Administration of the drug was terminated in the trial as recommended by the trial's Data and Safety Monitoring Board (DSMB) in the course of its usual evaluation and review process after a finding of increased risk of cardiovascular deaths. The trial is ongoing because the duration of time left with drug administration was quite small and not expected to have any major impact with regard to altering efficacy outcomes, which are unknown at this point. Dr. von Eschenbach commented that the termination and notification process was well managed by Dr. Ernest Hawk, Chief, Gastrointestinal (GI) and Other Cancer Research Group, Division of Cancer Prevention (DCP), with the support of Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, Office of the Director (OD), NCI. Within 24 hours of the DSMB analysis and decision, the response process was laid out and all appropriate agencies, including the FDA, DHHS, and other NIH Institutes with ongoing clinical trials of COX-2 inhibitor, were engaged and responses made to inquiries from the press and other areas. A strategy for further management and analysis has been instituted and will be directed at the NIH level.

Members were reminded that Secretary Mike Leavitt has been appointed to lead the DHHS following the departure of Secretary Tommy Thompson. Dr. von Eschenbach commented that, like Secretary Thompson, Secretary Leavitt is committed to the work of the NCI and is particularly enthusiastic about NCI's involvement in the area of technology application to advance progress in cancer and committed to integrating the NCI effort in a way that coordinates with and complements many of the macroinitiatives in the cancer community. Secretary Leavitt also supports NCI relationships established with other DHHS agencies, for example the recently established joint FDA-NCI Task Force and the long-standing relationships with the Centers for Disease Control and Prevention (CDC), Agency for Health Research and Quality, and Health Resources and Support Administration.

Finally, Dr. von Eschenbach reviewed challenges presented by the President's proposed budget for fiscal year (FY) 2006, which provides a 0.7 percent increase for the NIH over FY 2005 and a 0.3 percent increase for the NCI. Implications of this essentially flat budget after years of double-digit increases were discussed at the Joint Board Retreat in January and at the previous evening's meeting of the NCAB Subcommittee on Planning and Budget. Significant changes can be expected with regard to NCI budget allocations and mechanisms. The redeployment strategy will be set up within the context of detailed and aggressive portfolio management to enable the NCI to move into new areas of investment when opportunities for major scientific breakthroughs present themselves.

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

Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel, and Charles R. Drew Professor of Surgery, Howard University College of Medicine, reported that the Panel concluded its 2004-2005 series of meetings on the translation of research to reduce the burden of cancer. The Panel convened the meetings in four regions of the country to examine barriers to progress in translating cancer research into

reductions in suffering and death due to cancer. The first three meetings were held on August 30, 2004, at the University of California–San Francisco Cancer Center in San Francisco, CA; on September 27 at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute in Columbus, OH; and on November 1 at The University of Texas MD Anderson Cancer Center in Houston, TX. Overviews of these first three meetings were presented at previous NCAB meetings and are available online at http://pcp.cancer.gov. Dr. Leffall presented key points emphasized by participants at the final meeting, which was held at Memorial Sloan-Kettering Cancer Center in New York City on January 24, 2005. 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 to connect cancer centers and academic medical centers to local cancer care delivery, including both disseminating knowledge and providing access to care.

Dr. Leffall noted that, in discussing strategies to improve the current system of translational research, participants touched on issues common to other meetings. The need for team science and collaboration among a growing multitude of professional disciplines was emphasized. The role of the academic medical centers will become increasingly important as the complexity of research increases and disparate specialists are required to collaborate. As at previous meetings, participants raised the issue of reviewing the unintended consequences of regulatory policies such as the Health Insurance Portability and Accountability Act (HIPAA). Removing intellectual property and patent barriers to drug development, particularly for chemopreventives, also was cited as a significant concern. Presenters at the Memorial Sloan-Kettering meeting viewed education, training, and support for young, talented physician researchers as critical components in translating research to the community. Finding ways to sponsor and support new physician researchers for a minimum of 3-5 years was suggested, along with sufficient protected time to participate in research.

The importance of health information technology was another focus of considerable discussion. The Panel heard that abundant data exist that could yield critical information on patterns of care and cancer care outcomes, but they are not linked in a way that maximizes scientific discovery. It was further emphasized that a more systematic approach is essential to developing validated biomarkers that measure clinical efficacy of potential cancer therapies, as well as markers that can serve as diagnostic tools to identify patients who will most likely benefit from particular therapies. Integrating validated markers into clinical practice also must be undertaken. Dr. Leffall summarized a dialogue regarding individualization of cancer diagnosis and treatment that occurred at this meeting. It was advocated that, inasmuch as the technology to tailor diagnosis and treatment now exists, it should be adapted to chart genetic modifiers that could lead to identification of personal pathways of cancer development and individualized therapeutic targets. Such advances could increasingly result in cancer therapies being classified into small subsets and targeted groups of patients. In the future, cancer may become a group of orphan diseases with highly specific and individually based treatments. To address the issue of how costly new therapies will be developed for these smaller markets, it was suggested that protection be explored through either the Orphan Drug Act or another small-market drug plan.

Dr. Leffall stated that the Panel's current task is to consider all testimony received at the four meetings and all written statements from individuals who were not able to attend to prepare a report to the President, Congress, and the Nation. The report will address recurrent themes, including team science and partnering, education and training, technology and infrastructure, financing, access, and regulatory

issues. Most importantly, the report will detail the Panel's recommendations for short- and long-range steps that should be taken by the health care system, policy makers, and the research community to improve the discovery, development, and delivery of scientific findings to all of those affected by cancer.

In the 2005-2006 series of meetings, the Panel is planning to bring together key stakeholders and decisionmakers to address select recommendations from both its report on survivorship and the upcoming report on translating research. The goal will be to address these high-priority recommendations in more depth and develop strategies to accelerate their implementation. It is anticipated that all meetings in the new series will be held in Washington, DC. Proposed dates are: two consecutive meetings on August 25 and 26, 2005, another two on October 24 and 25, 2005, and, if needed, an additional two on January 23 and 24, 2006.

Questions and Answers

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, The University of Texas, asked whether strategies had been suggested for overcoming the challenges involved with integrating community hospitals into clinical trials. He noted that hospitals frequently lack Institutional Review Boards (IRBs) and must rely on Cancer Centers for proper monitoring oversight, which involves additional costs. Dr. Kripke replied that community models have been developed. Presentations by a number of individuals indicated that they have developed networks of community hospitals that are able to participate in clinical trials programs. Although there is considerable expense involved, some individuals, organizations, and states have decided that this is the wave of the future to translate advances in cancer treatment to the community. Dr. Kripke expressed the view that the planning for and funding of dissemination strategies should be an aggressive agenda item going forward. Dr. Niederhuber expressed the concern that the pressures on the clinical side to be productive and generate an income stream for the institution appear to be in direct conflict with the academic issues and scholarship. Dr. Carolyn Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, raised the issue of differences between protected time for surgeons versus nonsurgeons related to the need for maintaining skills and competence, inasmuch as 20 percent of the nonresearch time provided for in the clinician scientist awards must be divided between the clinic and operating room. She urged that the differences between the two communities be distinguished to promote surgeon clinician scientists. Dr. von Eschenbach commented that the issue of dissemination and embedding state-of-the-art care into the community is part of the agenda of the NCI/Center for Medicare and Medicaid Services (CMS) Task Force that has been established. A pilot project in that area is being considered, and discussions are underway with respect to moving forward with an electronic health initiative; progress in these initial projects will be reported to the Board.
Dr. Freedman emphasized the importance of ensuring that all populations get equivalent or equal access to the level of care provided by the Cancer Centers.

Dr. Leffall called for Drs. von Eschenbach and Kripke and Dr. Maureen Wilson, Executive Secretary, PCP, and Assistant Director, Ethics Office, OD, NCI, to join him at the podium. He then announced that, as of the January Panel meeting, Dr. Wilson was no longer serving as Executive Secretary of the Panel. On behalf of the Panel, Dr. Leffall thanked Dr. Wilson for her 13 years of service and commended her for her competence, ability, and unflagging enthusiasm for the work of the Panel. Dr. von Eschenbach joined the Panel in thanking Dr. Wilson for her service to both the PCP and to the entire NCI in her capacity as NCI Ethics Officer. It was announced that Dr. Abby Sandler, Acting Chief of the NCI Institute Review Office, is the new Executive Secretary of the Panel.

V. BIOETHICS AND THE FUTURE OF BIOREPOSITORIES—DRS. ANNA BARKER AND ARTHUR CAPLAN

Dr. Barker reminded members that for the past few years, the NCI has been assessing the issue of biospecimens and biorepositories to plan an approach that can be carried out in the short- and long-term. An analysis of resources within the NCI was conducted over the last 6 months, and a summary of the results was reported to the Board at its November meeting. The final report will be ready for distribution in the near future. Because it funds the largest number of biorepositories and because biospecimens are extremely critical in the new age of genomics and proteomics research, the NCI recognized the need to clarify issues surrounding biorepositories and establish standard operating procedures to address issues such as access and bioethics to empower investigators in all NCI communities. Members were informed of other NCI biospecimen and biorepository initiatives, including: (1) a pilot project with the Special Programs of Research Excellence (SPOREs) in prostate cancer to examine the state of the national effort in this area, and (2) an effort to bring foreign countries with biospecimen programs together to discuss the harmonization of this area. She introduced Dr. Arthur Caplan, Director, Center for Bioethics, University of Pennsylvania, to explore what needs to be considered in the area of bioethics as it relates to biorepositories.

Dr. Caplan expressed the view that ethical issues are crucial to the success of genomics and proteomics research to realize the goal of targeting and personalizing medicine, and that success will depend on getting biorepositories built and integrated both nationally and internationally. He contended that the ethics problems can be identified and that consensus on principles that should govern biobanking is achievable. Biobanking was defined as the storage of biological samples or data created from biological samples for diagnostic, therapeutic, or research purposes. To illustrate the challenges for the future of biobanking and biorepositories, he gave an indication of the number of nations and organizations, some for-profit and some nonprofit, already in the arena. Problems that can be expected in the future relate to identifying obligations all organizations—public or private, national or international—have to pool, organize, and exchange data. Dr. Caplan maintained that the overriding challenge will be to secure public trust that biobanking and the biorepositories that are established will meet the overarching goals of ensuring respect for individual autonomy and dignity, advancing public health, developing new treatments, advancing future research, protecting persons or groups from harm, and promoting efficiency. According to the Rand Report on Human Tissue Repositories, however, the challenge in securing trust is that "there are currently no national standards for tissue repositories that collect and store specimens for research use."

Dr. Caplan stated that ethical challenges to building trust to meet public concerns relate to: (1) individual discrimination and the loss of insurance or employment, (2) group discrimination such as that encountered by Ashkenazi Jewish women and those with *BRCA* 1 and 2 markers, (3) exploitation, and (4) fair access to data (including biosamples) and products derived from the data. He proposed three key areas in which public trust can be built and where consensus can be derived, namely: (1) collection of samples, (2) access and ownership, and (3) privacy and confidentiality. In the area of sample collection, ethical requirements that are going to be necessary to impose will have to recognize the different types of collectors, whether collection is dedicated or incidental, the range of subjects from whom biospecimens are collected, and whether collection is being done nationally or internationally because of the need to account for local custom. Dr. Caplan proposed that principles are needed to cover collection issues related to competition for biospecimens (priorities and access to approaching potential donors), payment (a reasonable standard for compensation for work and time), competency of the collectors (including standardized informed consent language), and control over incentives (equity, publication).

In the area of access and ownership, Dr. Caplan explained that the guiding principle is that donors should be made confident that fair access to the biospecimens will be guaranteed, consistent with maximizing the opportunity to find treatments and maximize public health. For-profit organizations also must be bound by the reality that they work in a gift-based world and have particular goals to achieve, such as public health improvement, treatments, and advancement of research. Dr. Caplan characterized privacy and confidentiality as the most crucial and pressing ethics problem in terms of protecting the privacy of individuals in biobanks. He pointed out, however, that there are no harmonized rules with respect to protecting privacy, and no standard or common language in the United States to describe the data and samples. The problem of instituting a common language increases when biobanking initiatives expand to include foreign nations and their variations in terminology and meanings. He expressed a preference for the concept of "anonymisation" as meaning human biological material plus information as to tumor type, treatment received, donor's age, etc., but stripped of all information that would permit the identification of the donor/patient.

Dr. Caplan recommended immediate action to arrive at an agreement on key moral terms and then to drive toward anonymisation as the principle of choice and secondarily toward delinking of patient information, with transparent and trustworthy third parties in control of identifying information. By comparison, European countries, with their national health system or other safety nets, rely more heavily on a strong consent process to preclude unapproved use. Dr. Caplan argued in favor of anonymisation or delinking as a primary focus, with the consent process carrying a lesser weight because of problems often associated with it. In summary, he recommended for the biorepository policy: (1) a national policy on anonymisation; (2) national priorities for access; (3) clarification of costs and profits as well as transparent adherence; (4) guaranteed access to researchers for research purposes only and at all times; (5) advocacy for patient access to products that result from biobanking; and (6) harmonization, not only of standards for specimen collection, but also of moral concepts.

Questions and Answers

Dr. Barker asked what the message should be for NCI communities in terms of how to move the field forward. Dr. Caplan recommended that NCI grantees be reminded to acknowledge that biobanking is grounded in altruism and act accordingly, anonymise first, interact transparently with groups and organizations that want to collect tissues, and remember that the goal is to protect individual dignity and privacy. Dr. Freedman asked whether totally unaffiliated review groups should be involved in biobank decisionmaking, and Dr. Caplan replied that public participation should be encouraged as past of the effort to maintain transparency. Dr. Arthur Nienhuis, Division of Hematology and Oncology, St. Jude Children's Research Hospital, asked why there is an aversion to individual discrimination in the context of biobanking, when it is accepted that insurance companies already use risk factors to determine liability on the part of the insurance industry. Dr. Caplan replied that in the context of the war on disease, altruistic gifts should not invoke a penalty. Dr. Kirchner asked whether there were differences in the ethical challenges that apply to tissue and blood biobanking versus medical image banking. Dr. Caplan noted that the same considerations of standardization, harmonization, stored images, data transfer, and anonymisation appear to be universal in the whole arena of imaging and suggested that it would be useful to initiate conversations between the two groups.

Dr. von Eschenbach asked Dr. Caplan to suggest how the field could be moved forward, and Dr. Caplan suggested that it is time for the community to lay out what it thinks the rules should be through meetings or working groups, grant and contract mechanisms, and collaborations with professional groups. Dr. Niederhuber asked how the NCAB could act to develop a dialogue from the investigator and patient perspective. Dr. Barker reminded members that, in addition to the recently completed survey of NCI-supported biorepositories, a committee has been formed within the NCI to

consider the issue of standard operating procedures, access, consent, and HIPAA. As a result of interfaces with the Board of Scientific Advisors (BSA), the NCI plans to hold a forum during the summer to develop a set of recommendations. The goal is to bring the recommendations to the September NCAB meeting for action relative to how the NCI should address its grantees and contractors with regard to policies in this regard. Dr. Barker recommended that the NCAB be represented on the BSA committee.

VI. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response, OD, reported that the President's budget, which was announced on February 7, provided a $28.8 B budget for the NIH and $4.8 B for the NCI. Hearings are scheduled tentatively for April 6 in the Senate and for early March in the House. Unlike previous years when NIH hearings lasted 3 days and were centered around themes, a 1-day hearing is planned for all of NIH, with no format specified at this time. Ms. Erickson gave an overview of the makeup of the 109th Congress and reported on changes in Senate leadership and the status of appropriations and authorization Committee leadership in both the House and Senate. New Senate leadership includes Senator Harry Reid (NV) as Minority Leader and Senator Richard Durbin as Minority Whip (IL). New Chairs for the full Appropriations Committee in both chambers are Senator Thad Cochran (MS) in the Senate and Representative Jerry Lewis (CA) in the House. The overall subcommittee structure is uncertain, but no change is indicated for the Labor, HHS, Education Subcommittee, which has jurisdiction over the NIH appropriation, and Senator Arlen Specter (PA) is expected to remain as Labor, HHS, Education Subcommittee Chair in the Senate and Representative Ralph Regula (OH) is expected to do so in the House. The NIH authorization committee in the Senate is Health, Education, Labor and Pensions (HELP), with Senator Mike Enzi (WY) as the new Chair and Senator Ted Kennedy (MA) as the Ranking Minority Member. HELP has no specific subcommittee with jurisdiction for health issues. In the House, NIH's full authorization committee is Energy and Commerce, with Representative Joe Barton (TX) as Chair and Representative John Dingell (MI) as Ranking Minority Member. The Subcommittee on Health has specific jurisdiction over NIH authorization; the new Chair is Representative Nathan Deal (GA), and Representative Sherrod Brown (OH) remains as Ranking Minority Member. Finally, Ms. Erickson called attention to the final report on the 108th Congress included in the Board meeting books.

Questions and Answers

Dr. Niederhuber expressed the Board's interest in the resumption of hearings on NIH reauthorization in the 109th Congress and asked Ms. Erickson to distribute copies of any draft bill to members of the Board if there should be any action in that direction in the interim between NCAB meetings. Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, requested an update on the construction loan program legislated as part of the Medicare Reform Bill.
Ms. Erickson explained that the Secretary, DHHS, delegated authority to the CMS, and the NCI is working with CMS to implement the loan program.

VII. AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL REPORT—DR. LYNN MATRISIAN

Dr. Lynn Matrisian, President, American Association for Cancer Research (AACR), began by summarizing the conclusions reached by Dr. Margaret Foti, CEO of the AACR, at last year's annual presentation to the NCAB. After an overview of the breadth of activities occurring within the AACR, Dr. Foti concluded that the complexity and scale of the cancer problem mandate an urgent and energetic response, that the public demands an effort to conquer cancer at the earliest possible time, and that the partnership between the AACR and NCI will help lead the way to the prevention and cure of cancer. The

good news is that scientific discoveries are coming at an accelerated pace, with opportunities for translational studies at an all-time high. Moreover, the Gleevec experience demonstrated that targeted therapy is a viable approach to making a difference, and the public is well aware of these opportunities. Obstacles to achieving the ideal of targeted therapy are: (1) less than optimal communication between basic and clinical scientists, (2) "smaller markets" resulting from newer molecular therapies, (3) numerous barriers to clinical trials, (4) regulatory issues, and (5) lack of sufficient flexibility in the current system.

Dr. Matrisian recounted her experience as a basic scientist studying matrix metalloproteases (MMPs) in Phase III clinical trials. This early targeted therapy was tried in more than 12 clinical trials with four different compounds, but no clinical endpoints were reached and no MMP inhibitor has made it to the clinic in the fight against cancer. Dr. Matrisian noted that the reason for failure of the targeted therapies in some of these Phase III trials is not known because the investigators ran insufficient controls on these studies to determine the reason for failure and make corrections. The INTACT trials with Iressa, which involved more than 2,000 patients, were carried out without the benefit of subsequent knowledge of a subpopulation of patients with molecular alterations in the targeted pathway. Dr. Matrisian noted that this kind of information applied to trials can make a difference. Whereas current clinical trial design focuses on using a targeted therapy in a specific cancer and looking for survival endpoints, the hope for the future is individualized medicine in which individual patients and tumors that will respond to the targeted therapy can be identified using molecular diagnostic approaches. The eventual goal is a pathway approach to the chemotherapy aspects of cancer treatment that is independent of the organ site. Patients can be stratified and receive benefit from the targeted therapy, making significant inroads in reducing suffering and death from cancer. Dr. Matrisian proposed that the following are needed to arrive at a pathway approach: (1) increased efficiency by learning from every patient in the clinical trial; (2) high-caliber, well-designed, carefully executed clinical trials with appropriate correlative studies; and (3) attention to molecular heterogeneity. She suggested that more science can be applied to clinical trials by adding pharmacodynamic measurements to determine whether the investigational drug modulates the target as anticipated. In addition, the use of both a candidate and an unbiased approach to molecular diagnostics would provide information about the differences between the responders and nonresponders that could be taken forward in the future irrespective of the outcome of the trial. Dr. Matrisian concluded that smaller trials might be smarter and that a true academic, industry, and NCI partnership is needed for this effort, because the trials influence all of these constituencies.

Dr. Matrisian reported that the AACR is collaborating with the Association of American Cancer Institutes (AACI), and the American Society of Clinical Oncology (ASCO) in an initiative to promote clinical trials that incorporate more science, to be known as Translational Investigation by Experts at Research, or TIER 1 trials. TIER 1 trials will be partnerships among the NCI, industry, and academic centers to leverage the strengths of each entity, minimize the risks of missing an "effect," and increase cooperation. Progress to date includes a white paper that will result from the organizational retreat at Lansdowne in September 2004 and a demonstration project that is under development. The AACR has plans for an annual Molecular Diagnostics meeting to begin next summer, expansion of the AACR/ASCO Clinical Trials Workshops to provide training in ways to incorporate these types of laboratory correlates in clinical trials and extension of the workshops to locations in Switzerland and Australia, and pilot-testing at Vanderbilt University of the AACR Pathways Network featuring an interactive Web site to provide basic science expertise and information to very specific clinical trials. Thus, the AACR is acting as a catalyst for advances in the prevention and cure of cancer.

Dr. Matrisian noted that the AACR plays a critical role in education of the public to meet the increasing expectations in the areas of cancer prevention and care, quality health care/quality of life (QOL), and for current information on scientific and medical advances, clinical trials access, and science policy. Public

expectations also extend to progress and return on the investment in cancer research. To meet some of those expectations, the AACR has instituted a new Survivor and Patient Advocacy Department, to be directed by Ms. Gwen Darien, former Editor-in-Chief of the magazine *MAAM*. Goals of the Department in 2005 include a Web site portal for the survivor and patient advocacy community; expansion of the Scientist-Survivor Program; and publications for cancer survivors, patient advocates, family members, scientists and health care professionals.

Dr. Matrisian stated that the AACR believes strongly in the need for NIH reauthorization and the updating and strengthening of the 1971 provisions and authorities of the National Cancer Act. The AACR also strongly advocates for giving the NCI what it needs in funding, flexibility, and authorities to conquer cancer. Dr. Matrisian remarked that the AACR can play a vital role in collaboration with the NCI to meet the 2015 challenge goal by stimulating creativity and innovation in science, educating and training the next generation of cancer researchers, offering programs and publications that meet the needs of the cancer community, and engaging in partnerships with other sectors and organizations that will accelerate progress. She emphasized that the AACR is very interested in strengthening AACR-NCI partnerships and advocating for adequate funding for the future.

Questions and Answers

Dr. Runowicz referred to Dr. Matrisian's slide noting NCI pressure to include laboratory correlates for molecular diagnostics, pharmacodynamics, and pharmacogenomics and asked whether the FDA also should consider including these markers before a new drug is introduced. Dr. Pazdur agreed that all patients should have adequate tissue samples to examine molecular markers and somatic mutations retrospectively. He noted that discussions within the Agency are focusing on FDA's authority in this matter and how to avoid overly burdensome mandates yet ensure that adequate science is presented on which to base decisions. He commented that it is better if people do things because they want to do them, and, perhaps recent or future studies that show drugs can be resurrected by examining biomarkers and subpopulations of patients might serve as positive examples. Dr. Barker commented that the NCI and FDA are working through the Interagency Oncology Task Force (IOTF) to address these issues and that there is an opportunity through the FDA's Critical Path Initiative to begin to address gaps in the science. She raised the issue, however, that this is a science problem that should be addressed by scientists working together and moving down the Critical Path with the idea that they will be bringing diagnostics and drugs to the FDA for approval. Dr. James Doroshow, Director, DCTD, commented that a major recommendation of the Clinical Trials Working Group (CTWG) was the development of core research services for correlative studies for national trials.

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

Dr. Gray thanked all staff in the DCTD, DCCPS, Division of Cancer Prevention (DCP), and Office of Information Systems and Computer Services who brought the data together for this report. Board members were informed that the DEA will submit the report on behalf of the Director, NCI, after the NCAB review. Dr. Christian reminded members that the report flows from the NIH policy on inclusion of women and minorities in clinical research as mandated by Congress in 1993 in PL 103-43 and implemented through the NIH Revitalization Act of 1993. The Advisory Council of each Institute is required to prepare a biennial report describing the manner in which that Institute has complied. At the NIH level, the report is prepared centrally by the NIH Office of Research on Women's Health and includes a statement relevant to each Institute that its advisory board reviews. At the NCI, the inclusion policy is implemented by the Office of Grant Program Coordination, which provides Institute-wide coordination and communication through the Accrual Working Group made up of Division

representatives, as well as information, training, and problem-solving help. Dr. Christian described NCI procedures for implementation of the NIH policy in the areas of policy dissemination, pre- and postaward activities, and postaward monitoring. Because the NIH requires a format for reporting that aggregates all Phase II trials whether they are treatment, behavioral, or epidemiologic observation, the overall treatment trial data are well-balanced for gender, but individual clinical trials vary considerably because of dramatic variations in sizes. In addition, large population-based screening trials tend to dominate the aggregate. Another complication occurred when the NIH policy was updated to meet new Office of Management and Budget (OMB) standards based on 2000 census data, which created racial and ethnic standards for federal statistics and administrative reporting, effective January 2003. Data now are collected in the three categories of ethnicity, race, and sex/gender, and subset analyses by race, ethnicity, and gender are required for Phase III clinical trials beginning with initial funding after 1995. The current reporting cycle covers data reported in FYs 2003 and 2004, which represent subjects enrolled in FY 2002 and FY 2003.

Dr. Christian then presented detailed enrollment data for: (1) extramural research by sex/gender, with and without gender-specific studies; (2) FY 2003 and FY 2004 enrollments in extramural research studies in both the old format (reporting race and sex/gender) and new format (reporting race, ethnicity, sex/gender); (3) ethnic categories in both formats; (4) FY 2003 and FY 2004 enrollments in extramural Phase III research studies; (5) FY 2003 and FY 2004 NCI enrollment in extramural Phase III research studies by sex/gender; (6) enrollment in intramural research studies and number of studies in FY 2003 by race, and sex/gender; (7) enrollment in intramural research studies and numbers of studies in FY 2004 by race, ethnicity, and sex/gender; and (8) FY 2003 and FY 2004 accrual by sex/gender in intramural research studies. Cumulative enrollment data for CTEP treatment trials over a 9-year period showed that 82 percent of accruals are White, about 8.5 percent Black; 3.7 percent Hispanic; less than 3 percent unknown; and
2 percent Asian. Gender accrual for that period was 60 percent female and 40 percent male for all trials, but 40 percent female and 59 percent male when gender-specific trials were excluded. Finally, Dr. Christian presented enrollment figures for CTEP treatment trials in FY 2003 and FY 2004, which showed, by ethnicity, that 90 percent were non-Hispanic, 4 percent were unknown, and 4.5 percent were Hispanic. By race, the proportions were about 85 percent White, 7 percent Black, 4 percent unknown, 2.2 percent Asian, 0.5 percent American Indian or Alaska Native, 0.4 percent Native Hawaiian Pacific Islander, and 0.1 percent more than one race.

Questions and Answers

Dr. Niederhuber observed that there has been no progress in increasing minority accrual to research studies despite concentrated efforts at the NCI and extramurally. In response to a question from Dr. Diana Lopez, Professor, University of Miami School of Medicine, about implementation of the Progress Review Group (PRG) report, Dr. von Eschenbach noted that he presented a copy to DHHS Secretary Leavitt during their initial meeting and that the NCI continues to support and promote taking implementation to the next steps. Dr. Moon S. Chen, Jr., Professor, Public Health Sciences, University of California, suggested that accrual figures for T1-funded international population studies should be partitioned from the domestic data. Dr. Cowan asked whether there are other populations in addition to women and minorities that should be focused on to achieve the goal of overcoming barriers to enrollment in clinical trials and state-of-the-art care. Dr. von Eschenbach asked Dr. Kerner to describe the work he has been doing with Cancer Control PLANET and state cancer plans to identify for communities their unique needs with regard to prevalence, incidence, and evidence-based programs for intervention. Dr. Kerner commented that a recent NCI-commissioned research literature review revealed virtually no documented research evidence of successful strategies for accruing minorities and other underserved populations in clinical trials. Therefore, the first step will be to study the phenomenon and build the resulting evidence into the clinical trials process. Dr. Kerner noted that this is the focus of NCI initiatives

in the DCTD and other Divisions. The second step is to study the problem of translating the benefits of research into clinical practice so people see the value of participating in research, which is the focus of

Cancer Control PLANET and AACR initiatives. Dr. Kerner noted that the two issues are intermingled and need to be linked.

Dr. Cowan observed that the Cancer Centers are making a great effort to accrue underserved populations, such as underrepresented socioeconomic groups and those in rural America where there are no regional hospitals. He suggested that the Centers' efforts to address that issue and support the costly infrastructure needed for that research should be recognized in grant review and reported. Dr. Pazdur commented that the elderly are another population subgroup for which enrollment is lacking in new drug application trials, and he further pointed out that internationally, much of the enrollment is occurring in Europe, especially in the emerging countries of Eastern Europe. The result is that African Americans and Latinos also are not represented. Referring to Dr. Cowan's suggestion, Dr. Franklyn Prendergast, Director, Mayo Clinic Cancer Center, agreed with the need for complete consistency with respect to reviewer attitudes and comments on the issue of Cancer Centers and clinical trials reporting. He proposed that addressing the economic issue and the lack of longitudinal follow-through is one factor that could make a difference in the success of clinical trials accrual. He noted that people are accrued to clinical trials, then forgotten in the treatment stream that needs to follow, which is a fiscal consideration for institutions because these trials tend to be expensive. He called for a tangible change in policy, application, or both.

Motion. A motion for approval of the NCI Biennial Report on the Inclusion of Women and Minorities in Clinical Research was seconded and unanimously approved.

IX. ANNUAL DELEGATIONS OF AUTHORITY—DR. PAULETTE GRAY

Dr. Gray briefly reviewed the delegations of authority being requested from the NCAB:
(1) Delegation A would delegate to the Director, NCI, permission to obtain, as stated in Section 413(b)(5) of the Public Health Service (PHS) Act and in accordance with section 3109 of title 5, United States Code, the services of not more than 151 special experts or consultants who have scientific or professional qualifications to assist in accomplishing the mission of the Institute; and (2) Delegation B would delegate to the Director, NCI, permission to exercise authority, as stated in Section 413(b)(7) of the PHS Act, to appoint one or more advisory committees composed of such private citizens and officials of Federal, State, and local governments to advise the Director with respect to the Director's functions.

Next, Dr. Gray reviewed the statement of understanding with NCI staff on operating principles in extramural awards: Operations of the NCAB will be conducted by the NCI in accordance with management and review procedures set forth in the NIH Manual Issuance 4513. Specifically:

- Concurrence of the NCAB with recommendations of initial review groups (IRGs) will be required except for scored domestic applications assigned to the NCI, with recommended direct costs not exceeding $50,000 annually, as well as individual National Research Service Awards; these may be awarded without presentation to the NCAB. Applications over the 50th percentile will not have summary statements presented to the NCAB unless an award is to be made as an exception. For applications assigned raw scores that are not percentiled, the cutoff will be a priority score of 250 for all mechanisms except R41, 42, 43, and 44 awards. For the latter awards, all scored applications will be included.

- Expedited concurrence—for R01 and R21 applications (excluding those from foreign organizations) with percentiled or raw scores that fall within the NCI payline for that mechanism and have no

concerns noted that would be an administrative bar, a process of expedited concurrence will be used. Board members with responsibility for expedited review will be alerted when review outcomes for these are available on the Electronic Expedited Concurrence portion of the Electronic Council Book.

- Administrative adjustments—permission is delegated to the Director, NCI, to allow staff to negotiate appropriate adjustments in dollars or other terms and conditions of grant and cooperative agreement awards recommended by the Board. Administrative requests for increases in direct costs, which are the result of marked expansion or significant change in scientific content of a program after formal peer review, will be referred to the Board for advice and recommendation. Actions not requiring Board review or advice need not be reported to the Board. NCI staff may restore requested time and support that were deleted by the IRG when justified by the Principal Investigator (PI) in an appeal letter, the restoration is in the best interest of the NCI, and the project is of high NCI programmatic relevance.

Motion. A motion to grant Delegations A and B to the Director, NCI, and to concur in the statement of understanding with NCI staff on operating principles in extramural awards was seconded and approved unanimously.

X. UPDATE: INTEGRATIVE CANCER BIOLOGY PROGRAM—DRS. DINAH SINGER AND DANIEL GALLAHAN

Dr. Dinah Singer, Director, DCB, called attention to the report entitled "Think Tanks in Cancer Biology," which was distributed to the Board and summarizes the proceedings and recommendations of a series of DCB-sponsored meetings over the past 1.5 years. The goal of the meetings was to engage the research community in helping to identify gaps and opportunities in the broad spectrum of cancer biology. Dr. Singer highlighted two of the themes that emerged from the meetings: (1) continued support is needed for basic research in the entire spectrum of cancer biology, particularly in such areas as molecular immunology, tumor stem cells, tumor microenvironment, and cancer susceptibility; and (2) the classical reductionist approach to expanding knowledge of these processes must be complemented by an approach that permits the synthesis of knowledge. She noted that integrative cancer biology (ICB) is the name being given to the emerging field, which will require the collaborative efforts of cancer biologists, mathematicians, physicists, and systems engineers. She then introduced Dr. Dan Gallahan, Associate Director, DCB, to provide an update on the Integrated Cancer Biology Program (ICBP), which is DCB's first effort to respond to the Think Tank report's recommendations to facilitate this new field of integrative or systems biology. Members were asked to comment to Drs. Singer or Gallahan.

Dr. Gallahan described the systems or integrated biology approach as an iterative process of using the vast amount of information on the biology of cancer to generate mathematical or computational models that then are validated through clinical experimentation. He explained that computational models complete the cancer modeling spectrum of *in vitro*, cell-line, mammalian, and primate model systems by capturing the molecular and cellular processes in mathematical formulae that can reflect or mimic what is seen in the biological model systems. The power of computational models is that they afford flexibility, accessibility, and the possibility of endless refinement to more closely approximate the human condition and give new insights into cancer biology. Dr. Gallahan described the ICBP as an NCI consortium designed to develop a systems approach to cancer biology built on the three pillars of biology, modeling, and education. The ICBP will generate experimental systems and data for the development and testing of models, develop mathematical and computational predictive models that drive the biology, and develop and implement a training and outreach program to make a broader impact on this emerging field. Organizationally, the ICBP comprises nine funded centers—six full (P50) centers and three planning (P20) centers. Dr. Gallahan noted that the centers chosen by the DEA from the large number of applications cover the broad scope of tumor progression from cancer cell to metastasis.

Expectations for the ICBP are that it will be a cooperative interaction among the centers to develop and implement integrative cancer biology, create an organizational and scientific focus for the broader ICB community, serve a leadership role for this research community, and establish training programs. To highlight the basic approaches that will be used by all nine centers, Dr. Gallahan briefly described the specific focus and experimental designs of three of the programs: (1) Multiscale Mathematical Modeling of Cancer Invasion, Dr. Vito Quaranta, PI, Vanderbilt University Medical Center; (2) Integration of Oncogenic Networks in Cancer Phenotypes, Dr. Joseph Nevins, PI, Duke University Medical Center; and (3) Development of a Virtual Tumor, Dr. Thomas Deisboeck, PI, Massachusetts General Hospital. Updates on the work of the other centers are planned for future NCAB meetings.

Next, Dr. Gallahan discussed the structure and integration of ICBP. Within ICBP, the Coordinating Committee, co-chaired by Drs. Quaranta and Joe Gray, Lawrence Berkeley National Laboratory, provides oversight among the centers and information exchange with NCI program bioinformatics staff. Because of its dependence on bioinformatics and computing, the ICBP was developed in close collaboration with the NCI Center for Bioinformatics (NCICB), and caBIG has allocated a workspace for data exchange and the movement of ICBP models within the ICBP and to the cancer research community. Validation and refinement will occur within the centers and will continue when the models are disseminated to the greater community. Another interaction with the research community will be through the outreach and education component. The ICBP also will interact with clinical and technology programs and knowledge bases within the NCI. For example, ICBP will use patient data and information from investigators in the Cancer Centers and SPOREs, information from knowledge bases such as the Cancer Genome Anatomy Project (CGAP) and the Clinical Proteomics Program, and technology that has been developed in programs such as Innovative Molecular Analysis Technologies and the nanotechnology initiatives. The ICBP also interacts with the CISNET community and will be validating mouse models in close collaboration with the Mouse Models of Human Cancer Consortium. ICBP interactions beyond the NCI include those with the NIH Roadmap activities and other NIH Centers and programs; government agencies such as the National Science Foundation, National Institute of Standards and Technology, and the DOE; and national laboratories. There is interest in developing public/private partnerships in addition to the software development collaboration underway with IBM. Finally, ICBP has an international outreach through integrative assistance biology efforts currently underway in Europe and Japan.

Looking to the future of the ICBP, Dr. Gallahan reiterated that the major charge is to develop and validate predictive cancer models and establish an educational curriculum to help the field emerge. Collaborative activities will be proposed within the ICBP, and recommendations for NCI initiatives and infrastructure will be developed. With the ICBP, a new approach to cancer biology and biology in general is being generated whereby questions can be answered and, more importantly, new questions can be posed.

Questions and Answers

Dr. Eric Lander, Director, Broad Institute of MIT and Harvard, recommended that it would be helpful as part of the overall program to enunciate the ICBP's broadly inclusive philosophy in regard to models, noting that a statement about the range of possible models would be important in future Requests For Applications (RFAs). Dr. Freedman commended the ICBP focus on validating animal models and recommended that they be validated for both efficacy and toxicity. He suggested that biologists who develop the models should discuss with clinicians what the criteria for validation should be for each application. Dr. Daniel Von Hoff, Director, Translational Genomics Research Institute, commented that the best model for man is probably man, yet the ICBP appears not to be using to advantage the huge databases of biospecimens that exist. Dr. Singer explained that although an effort was made to include as much of the continuum of the science as possible, the more clinical applications did not fulfill the criteria

of the RFA. However, the NCI is hoping that those groups will be brought in through the program called Activities to Promote Research Collaborations, which specifically identifies ICB as one of the target areas. Dr. Prendergast commented that much work in the past has focused on models of tumor growth and expansion, and he expressed interest in the possibility that elegant mathematical models of the liquid tumors (such as chronic myelogenous myeloma and multiple myeloma) could be built through the ICBP. He recommended strong encouragement of that activity by having appropriate grant mechanisms to support it.

XI. ADVANCED BIOMEDICAL TECHNOLOGY WORKING GROUP REPORT— DR. ERIC LANDER

Dr. Lander presented an overview of the report of the Working Group on Biomedical Technology. The Working Group was convened by Dr. von Eschenbach with the charge to identify specific technology-based projects and initiatives that would have broad transforming impact across the entire field of cancer research, with the ultimate goal of eliminating death and suffering due to cancer. On behalf of himself and Co-Chair Leland Hartwell, Dr. Lander thanked all members of the Working Group and the many others with clinical, industrial, basic science, and organizational experience for their contributions to this effort. To begin the study process, the Working Group gained an understanding of NCI's ongoing technology initiatives, including the technology-related programs, cancer biology think tanks, and the Clinical Trials Working Group (CTWG). Five focus groups were formed on the following topics: (1) characterization of cancer in the cell; (2) characterization of cancer in the organism; (3) public health; (4) cancer therapeutics and clinical tools; and (5) technology access, development, and dissemination.

Two strong themes emerged from the focus groups. In the first, enormous opportunities were perceived that would propel progress in cancer research by harnessing the power of technology to address key cancer challenges in the areas of: (1) genomic basis of cancer, (2) detection of cancer, (3) functional characterization of cancer, and (4) cancer models. The second theme related to exploiting the full power of technology by addressing systemic needs that affect cancer research broadly. These needs include improved systems to collect, maintain, and distribute patient samples; improved information systems for sample management, data collection, and data analysis; mechanisms to support multidisciplinary teams and team science; redesign of NCI clinical trials for greater efficiency in all aspects by taking maximal advantage of technology; and ensuring the broad dissemination of technology platforms.

Dr. Lander presented the Working Group's four recommendations based on input from the focus groups and its own discussions, and included in the report:

- The NCI should constitute a standing Cancer Technology Working Group with an ongoing charge to identify opportunities for technology-based programs to address key cancer challenges; evaluate whether the opportunities are ripe for solution; prioritize the opportunities based on importance and feasibility; and develop concrete recommendations for appropriate projects and initiatives to meet the challenges. The Cancer Technology Working Group also should periodically evaluate the systemic needs related to cancer technology and identify potential solutions.

- A cancer molecular diagnostics initiative should be established to coordinate and expand research on functional imaging of cancer *in vivo* and biomarker identification and detection in patient samples. Specifically, the Working Group recommends the creation of a standing Biomarker Discovery Working Group to coordinate work across the Institute on discovery and validation of endogenous biomarkers of cancer in patient samples and the creation and testing of imaging and other agents for *in vivo* monitoring of cancers and cancer therapeutics. The Biomarker Discovery Working Group should report annually to both the NCI Director and the BSA.

- A human cancer genome project should be initiated with the aim of obtaining a comprehensive understanding of the genomic alterations that underlie all major cancers. This recommendation was proposed as a specific project.

- A Phase I/II consortium should be established to accelerate the translation of technological advances and scientifically validated targets into clinical trials.

Dr. Lander then elaborated on the Working Group's recommendation for a human cancer genome project. He reviewed the scientific basis for the project, the implications of knowing the full genetic basis of cancers, the current status of knowledge in this area, and technologies and approaches that make this research possible at this time. The Working Group decided to take on the challenge of getting a comprehensive description of the genetic basis of all major types of cancer. Dr. Lander briefly reviewed what would be involved, including acquiring a collection of clinically annotated tumors from all major types of cancer, then characterizing them with respect to all the regions of genomic loss and amplification, promoters, chromosomal rearrangement, and aberrant methylation. In considering how to organize such a project, the Working Group came to the unanimous conclusion that the NCI would want to organize, in a competitive fashion through grant or appropriate contract competition, a network of cancer sample acquisition centers and cancer genome analysis centers. In addition, smaller technology development grants would be needed.

The Working Group also considered organizational constructs to address ethical, educational, medical, and regulatory issues and the need for free and immediate data release. In regard to management, the Working Group concluded that the cancer and genomics expertise within the NIH should be utilized, and recommended that the project go forward as an equal partnership between the NCI and the National Human Genome Research Institute (NHGRI). Also recommended was the creation of an International Coordinating Commission. Dr. Lander presented the Working Group's estimated costs and timeline for the proposed project at $150 M per year for a project period of 10 years or less. He emphasized that the proposed project should not be in competition with existing programs and, therefore, would need a source of new money. Next steps would be the establishment of a Joint NCI/NHGRI Working Group and a Science Advisory Committee and the launching of a pilot project focusing on three to five cancers at an estimated cost of $50 M. Dr. Lander noted that the Directors of both the NCI and NHGRI have expressed interest in implementing this recommendation.

Dr. von Eschenbach credited Dr. Barker and Dr. Daniela Gerhard, Director, Office of Cancer Genomics, with creating the liaisons and relationships needed to embed this initiative within the NCI organization. He then introduced Dr. Francis Collins, Director, NHGRI, to speak on the proposed Human Cancer Genome Project from the NHGRI perspective. Dr. Collins expressed enthusiasm about the proposal, the science that it will rest on, and the science it will encourage in a way that will catalyze the science on cancer in laboratories around the world. From the NHGRI perspective, Dr. Collins observed, the project is an opportunity to take the capabilities that have been developed as a consequence of the Genome Project and push the frontiers of medicine. He stated that the NHGRI has the capabilities in terms of a genome analysis component that could be turned in the direction of cancer quite quickly. He added that the Genome Institute is interested in the aspect of the project that would stimulate technology development and aims to be a partner in terms not only of ideas, but also in dollars.

Questions and Answers

Dr. Jean deKernion, Professor and Chairman, David Geffen School of Medicine at the University of California, Los Angeles, asked how much of the genomic analysis could be done intramurally.
Dr. Lander expressed the view that the whole strength of the cancer community should be brought to bear

on the problem through competition involving the intra- and extramural communities, companies, and academia. Dr. Nienhuis asked how the proposed human cancer genome project and CGAP differed in intent. Dr. Gerhard pointed out that CGAP constantly is evolving and will not be stopped; however, data from CGAP probably would be integrated to provide synergism with the data generated by the human cancer genome project. Dr. Barker expressed the view that the proposed project is a natural evolution of CGAP, and she noted that the cost of CGAP already has been reduced in line with the prospect that the proposed pilot might be undertaken. In response to a question from Dr. James Armitage, Joe Shapiro Professor of Medicine, University of Nebraska, about funding for the proposed project, Dr. von Eschenbach replied that the NCI is taking a comprehensive view of these major new bold initiatives and will employ a variety of strategies to fund them, including partnerships, leveraging other funds, modifying the scale of programs, cost capturing, and fiscal discipline. Dr. Cowan asked that a future agenda include an update on CGAP and how its future directions might complement the cancer genome project.

Motion. A motion to accept the report of the Working Group on Biomedical Technology entitled "A Strategic Plan for Improving Biomarkers for Cancer" was seconded and approved unanimously.

XII. INTERAGENCY ONCOLOGY TASK FORCE: MEDICAL AND POSTDOCTORAL FELLOWSHIP TRAINING PROGRAM—DRS. ANDREW von ESCHENBACH, LESTER CRAWFORD, JONATHAN WIEST, AND RAJ PURI

As background, Dr. von Eschenbach reminded members that the IOTF was created as a strategic partnership between the NCI and FDA to identify opportunities in which all partners would achieve individual missions and, at the same time, collaborate to transform the future of a disease like cancer and thereby transform health care in general. He alluded to the number of accomplishments by the IOTF in its 2 years of existence and introduced Dr. Lester Crawford, Commissioner-Designate, FDA, to present the background and an overview of the IOTF-sponsored Research and Regulatory Review Fellowship Program, the latest initiative to be undertaken by the partnership.

Dr. Crawford reminded members that NCI's mission is one of basic and clinical research to foster discovery of new medical products. FDA's mission is to assure the safety, efficacy, and quality of manufacturing of new medical products prior to marketing. It is part of the FDA's responsibility to ensure that basic discoveries turn into new and better medical treatments and to make the effort to create better tools for developing medical technologies. Dr. Crawford noted that the close collaboration with the NCI through the IOTF is an important step in joining the mission of the two agencies to produce a seamless process for speeding new technologies to cancer patients, toward the common goal of improving public health. One of the most important tools is a knowledge base that is built not just on ideas from biomedical research, but also on reliable insights into the pathway to marketed products for use in patients. During clinical testing, FDA scientists conduct ongoing reviews of emerging data on safety, efficacy, and product quality, witnessing the complete spectrum of successes, best practices, and failures. Thus the FDA is uniquely positioned to identify challenges to development and is working with the largest scientific community to develop solutions. Dr. Crawford stated that the implementation of a research and regulatory review fellowship program as part of the collaboration between the NCI and FDA is a critical first step in developing the all-important knowledge base. Clinicians and scientists who are selected for these fellowships will learn about the problems inherent in developing innovative products by participating actively in the review process. They will spend from 1 to 3 years at the FDA working with and being mentored by experienced reviewers and researchers. They will learn to recognize the characteristics of successful product development and be able to take this knowledge to their home institutions and incorporate it into their research on new cancer treatments from its earliest stages, thus enhancing the likelihood of success. Dr. Crawford introduced Dr. Raj Puri, Director, Division of Cellular

and Gene

Therapies, FDA Center for Biologics Evaluation and Research, who is Co-Chair, IOTF Training Subcommittee, to discuss the Research and Regulatory Review Fellowship Program in more detail.

Dr. Puri invited Dr. Jonathan Wiest, Center for Clinical Research, NCI, and Co-Chair, IOTF Training Subcommittee, to join him at the podium for the discussion of details of the Program. Through this program, the NCI and FDA are offering fellowship training in cancer-related scientific research and research-related regulatory review. The objectives are to: (1) train a cadre of scientists such that they develop a skill set bridging the product development and review processes; (2) build awareness of regulatory requirements into early stages of the product development processes; (3) improve planning throughout research and regulatory review to facilitate the movement of novel approaches from the bench to the community; and (4) facilitate the movement of drugs, biologics, and devices from basic bench science to commercialization. Dr. Puri noted that graduates of the Program will develop skills of value to academia, the pharmaceutical industry, and government agencies.

Dr. Weist described the four fellowships that have been developed. The first fellowship, entitled "The Clinical Oncology Product Research/Review for Oncology Fellows," will train physicians in clinical trials methodology, analysis, epidemiology, and medical product development and regulation. Trainees will receive formal training in federal statutes, regulations, and principles and practices of medical product and clinical review. They will have an opportunity to participate in product development research projects at both agencies and be monitored by senior review staff. Eligibility requirements for the 3-year fellowships are an M.D. or M.D./Ph.D. and U.S. citizenship or permanent residency. In the second fellowship, "Clinical Oncology Product Research/Review for Board-Certified Oncologist," individuals will be trained in aspects of drug, biologic, or device development as well as standards for assessing those products for safety and efficacy. They also will receive training in federal statutes and regulations and be mentored by senior scientific review staff. This is a 1-year program for up to three fellows per year. Eligibility for Program 3, entitled "Oncology Product Research/Review for Fellows," is a Ph.D., M.D., or M.D./Ph.D. degree and a minimum of 3 years of postdoctoral training in a cancer-related topic. Individuals will be trained in the aspects of research and review of the medical product development process to facilitate the movement of drugs, biologics, and devices. Their federal statutes training will include issues related to manufacturing processes, characterization, testing, quality control, and quality assurance, and fellows also will participate in medical product development research. This program is for up to 2 years for up to six fellows per year. Fellows in Program 4, entitled "Cancer Prevention Fellows," will be trained in the drug, biologic, or device development and approval processes and their application to study populations (including healthy subjects for chemoprevention studies). Individuals with a Ph.D., M.D., or equivalent degree are eligible, and they will pursue an M.S. or M.P.H. in Clinical Investigation in the first year. This program is for up to 4 years for up to two fellows per year.

Dr. Weist announced that the program recruitment and rollout was beginning with this meeting and would be advertised to the research community through banner links from the Web sites www.cancer.gov, www.fda.gov, and www.nih.gov; advertisements in national publications and professional journals; and at national meetings. An FDA and NCI review committee has been established and will have the dual responsibility of screening and selecting qualified candidates and evaluating the program's effectiveness. Application deadlines are in place for each of the programs. Program outcomes will be determined through an ongoing evaluation process for both mentor and trainee, a biannual training plan update, tracking of graduates, and exit interviews for trainees. Benchmarks will be measured along the path of each trainee in coursework completion and the development of a minimum skill set, the latter to be determined by tests at the FDA and the review of investigational new drug or device exemptions.

Questions and Answers

In response to Dr. Freedman's question about utilization of the program graduates if they come from institutions without CGMP facilities, Dr. von Eschenbach explained that the vision for the program is that graduates will play major catalytic roles and network effectively in larger platforms to accelerate the process of discovery and regulatory approval. The goal is to get ideas from the laboratory to the point where they impact and affect the patients' lives. Dr. Barker added that the program addresses a major barrier identified by the IOTF in that oncology investigators often know little about the drug development process. These trained investigators will represent a leadership cadre for the future of targeted agents. Dr. Crawford added that graduates will be in great demand as purveyors of FDA's critical path approach that is being implemented to move products from the laboratory to the bedside as expeditiously and carefully as possible. Dr. Prendergast expressed the view that the need for people with regulatory expertise in the academic centers is a critical barrier to translation for diagnostics as well as therapeutics, and that principles of diagnostic clinical trials should be developed.

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

Dr. Prendergast, Subcommittee Chair, presented the report of the Subcommittee on Planning and Budget meeting held on the previous evening. He briefly summarized the discussion by Mr. John Hartinger, Associate Director for Financial Management, NCI, of the implications for the NCI of the budget for FY 2006 that currently is moving through Congress and the potential prospects for FY 2007. He noted the implicit consensus of the Subcommittee that it must find a way to help NCI leadership seize on emerging scientific opportunities, even in the face of budgetary constraints. Four issues to be addressed in coming months include: (1) assisting NCI leadership in determining how best to conduct portfolio review and management from the perspective of the community as a whole, (2) defining convincing and persuading arguments, (3) communicating the message more effectively, and (4) helping to decide how future Bypass Budgets should be constructed in an era without double-digit budget increases.

Motion. A motion to accept the report of the NCAB Subcommittee on Planning and Budget was seconded and approved.

THURSDAY, FEBRUARY 17, 2005

XIV. UPDATE: CLINICAL TRIALS WORKING GROUP—DR. JAMES DOROSHOW

Dr. Doroshow thanked Dr. Howard Fine, Chief, Neuro-Oncology Branch, CCR, NCI, for supporting the CTWG process. He noted that any success that might be experienced in going forward with the group's recommendations would stem from the tremendous efforts and abilities of the entire national extramural clinical trials community. Dr. Doroshow reviewed the rationale for the Working Group's process. Advances in molecular medicine offer incredible potential to improve clinical practice, but successfully addressing this opportunity requires a coordinated approach to enhancing interdisciplinary, scientifically driven clinical trials. To that end, an urgent need exists to integrate the very successful but functionally diverse elements of NCI's current clinical trials system. Doing so will enhance the timeliness and efficiency of clinical trials accrual by improving the scientific and bioinformatics infrastructure for clinical trials. Dr. Doroshow reminded the group of the charge issued to the clinical trials extramural community by Dr. von Eschenbach: to advise the NCAB on the development, conduct, infrastructure, support and coordination for clinical trials across the entire Institute.

Through a review of the Armitage and Implementation Committee reports and a detailed poll, the CTWG attempted to isolate and prioritize the most important issues in clinical trials research. The CTWG developed a subcommittee for each of the issues identified: patient accrual, regulatory affairs, core research services, standardization and infrastructure, coordination, and prioritization. Since the last report, the subcommittees have developed a series of proposed recommendations that have been revised through several rounds of review, discussion, and comment and accepted by the CTWG. Each subcommittee obtained input from the extramural clinical trials community about major concerns regarding cancer clinical trials. The recommendations leverage the unique components and capabilities of NCI's current clinical trials endeavors in an effort to enhance the interactivity of the existing system and focus on improving the scientific basis for cancer clinical trials research.

Dr. Doroshow shared the methods used to obtain input from the extramural community, acknowledging significant assistance received from Dr. Ken Buetow and colleagues. The Working Group developed a Web-based forum that was open from late November 2004 through mid-January 2005. The Working Group e-mailed information about the forum to more than 13,000 individuals in the broad clinical trials community, and more than 2,200 responses were generated. In real time, the subcommittees used the responses to augment, clarify, and inform the draft recommendations. Dr. Doroshow deferred reviewing the responses in detail, indicating that they would be posted on the CTWG Web Site along with the recommendations resulting from the day's meeting.

Subcommittee Reports

Patient Accrual Subcommittee—Dr. Richard Schilsky

Dr. Richard Schilsky, Professor of Medicine and Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago Pritzker School of Medicine, noted that the Patient Accrual Subcommittee's recommendations were designed to accomplish two goals: (1) increase the rate of patient accrual to cancer clinical trials, and (2) increase the accrual of underrepresented segments of the population to clinical trials. He presented the following draft recommendations developed by the Subcommittee:

- Provide standardized materials and other resources to help sites plan, staff, implement, and manage clinical trials. This would be accomplished by ensuring minimum funding for required site personnel, funding for community outreach to recruit a diverse patient population, the development of a variety of Web-based trial initiation tools, and the provision of educational materials for patients.

- Increase public visibility of NCI programs with the goal of expanding the rate of patient accrual to NCI-sponsored clinical trials. Implementation would include developing promotional and marketing programs for high-priority studies; partnering with community groups, consumer media, and physicians to communicate the patient benefits of trial participation; and creating tailored programs and community partnerships to engage minorities and special populations.

- Provide incentives that encourage patients and community oncologists to participate in clinical trials. One suggestion for implementing this recommendation involves developing an NCI certification program for clinical oncologists and educating patients about the unique qualifications of an NCI-certified clinician, prompting them to seek those individuals in practice. Ensuring adequate reimbursement for clinical care costs for patients who participate in clinical trials also is an important consideration and implementation issue in providing patient participation incentives. Reimbursed services should include counseling, patient education, and the complex system of patient management across clinical trials services. Communication of clinical trials results to the patients who have

participated in those trials, and recognition of their important contribution to the care of future patients, would encourage participation as well.

- Improve access to clinical trials for community oncologists and patients. Among the suggestions for implementing this recommendation are:
  - Developing CCOP mentoring programs with interested community oncologists, especially those serving minority populations.
  - Expanding the use of community-based, regional IRBs to decrease the lead time of protocol initiation and to conserve resources.
  - Improving the awareness, functionality, and utilization of the Cancer Trials Support Unit.
  - Creating multiple, user-friendly channels, including comprehensive Web sites, where patients and physicians can find information on cancer clinical trials.

Regulatory Issues Subcommittee—Dr. Steven D. Averbuch

Dr. Steven D. Averbuch, Executive Director, Merck Research Laboratories, Clinical Research, Oncology/G.I., reviewed the overall goal pursued by the Regulatory Issues Subcommittee, which was to enhance cooperation between federal agencies, industry, and other key stakeholders to reduce the regulatory burdens and to accelerate drug and device development. Specifically, the Subcommittee was charged with developing detailed approaches for increasing involvement in and enhancing the dialogue between all parties engaged in the NCI cancer clinical trials enterprise. Dr. Averbuch reported the Subcommittee's draft recommendations as follows:

- Develop specific guidelines and procedures for joint participation of the FDA and NCI in meetings, including those with industry, concerning new agents and diagnostics and devices, to coordinate and accelerate drug and device development. The ultimate goal is to achieve a more strategic and cohesive focus among the stakeholders.

- Reduce the auditing, monitoring, and regulatory burden on clinical trials sites by coordinating requirements of the NCI, FDA, and OHRP to identify specific changes that can eliminate redundancy and reduce costs. This is related to a common theme centered around identification of qualified and certified sites conducting clinical trials in the future.

- Increase the use of the NCI-FDA expedited concept protocol approval process and, in particular, increase awareness and utilization of the FDA special protocol assessment procedure for NCI-sponsored trials that are intended to impact on product labeling.

- Collaborate with the CMS and other payers and stakeholders to establish a robust and transparent process for identifying clinical studies that would warrant reimbursement of appropriate clinical trials and investigational costs. These studies would address critical questions about cancer practice that today are faced by patients, clinicians, and other decisionmakers.

- In collaboration with the FDA, ASCO, AACR, and other interested organizations, including patient advocacy groups, support training programs designed to increase the number of cancer investigators who are qualified to guide new agents and devices through the development and regulatory process.

Core Research Services Subcommittee—Dr. Frederick Appelbaum

Dr. Frederick R. Appelbaum, Director, Clinical Research Division, Fred Hutchinson Cancer Research

Center, presented recommendations on behalf of the Core Research Services Subcommittee. In developing its recommendations, the goals of this Subcommittee were to: (1) enhance access to the scientific infrastructure necessary to facilitate the conduct of high-priority correlative science studies to translate new discoveries into clinical practice, and (2) integrate strong scientific review of correlative studies with development and review of clinical protocols in an efficient and timely manner.

Dr. Appelbaum indicated that in considering potential recommendations, the Subcommittee addressed whether the clinical research enterprise in the United States suffers from a lack of adequate access to or support for core resources—laboratory, imaging, biostatistical, or other skilled ancillary services—that can enhance the impact of clinical trials to conduct ancillary science. He noted that similar to the CTWG, the Subcommittee had developed and mailed a detailed questionnaire and a personal letter from the Chair to each Cancer Center Director, SPORE PI, intergroup Chair, and cooperative group Chair to request their thoughts. Responses received from this process cited the need for a means to support correlative sciences that could enhance Phase II and in particular, Phase III clinical trials. Such studies might include, but are not limited to, pathologic or molecular analysis to determine treatment eligibility or stratification, pharmacokinetics or pharmacogenomic ancillary studies, molecular or imaging analyses for early response criteria, or economic or quality-of-life studies to better understand treatment outcomes. Respondents also mentioned difficulties in supporting the administrative and statistical burden of clinical trials. From the responses to its survey, the Subcommittee developed the following draft recommendation:

- Establish annual budgets for studies ancillary to clinical trials, including correlative science, health economics, and quality-of-life investigations that are accessible on a protocol-by-protocol basis. Dr. Appelbaum further explained that related to this recommendation are issues involving development of a means of certifying core services as adequate and a means of developing a review process to determine how such funds would disseminated.

Standardization and Infrastructure Subcommittee—Dr. David R. Parkinson

Dr. David R. Parkinson, Vice President and Head, Clinical Oncology Therapeutic Area for Amgen, Inc., offered information on the goals of the recommendations developed by the Standardization and Infrastructure Subcommittee, which were to: (1) improve efficiency, reduce duplication of effort, and achieve cost savings; (2) facilitate innovation and promote integration across trials; (3) facilitate data interpretation and data comparison across trials; and (4) allow for closer integration of biological measurements and clinical trials findings. In accordance with these goals, Dr. Parkinson emphasized that the complicated nature of clinical trials requires significant time and resources, so the opportunities for introducing higher standards of performance and greater efficiencies are proportional to those complications. Removing some of the technical, infrastructure, logistic, and mechanical burdens of conducting clinical trials will make it easier to ask and answer questions. He presented the Subcommittee's draft recommendations as follows:

- With concurrence from the FDA, establish standards for the essential data to be collected in clinical trials and the format in which it is collected. This effort will include defining core data elements and standardized case report forms, developing the caBIG standard infrastructure necessary to support clinical trials and interfacing caBIG with other databases utilizing standard elements, and consolidating redundant systems where possible as caBIG is implemented. Dr. Parkinson clarified this recommendation by emphasizing that the way in which data are presented in regulatory submissions needs to be globally focused, rather than just American-focused, because answering formal therapeutic questions and obtaining a regulatory basis for the eventual distribution of drugs is carried out on a global level. He also recognized Dr. Buetow's contribution to work in developing a

common technical infrastructure across trials and the need to continue that activity.

- Establish a process for official credentialing of research personnel and sites and create a national central database of credentialed investigators and sites. Although implementation of this recommendation seems to identify investigators only, staff such as data managers, research nurses, pharmacists, and other informatics personnel should be included. In implementing this recommendation, opportunities exist to track all personnel and to continue to educate them as the clinical trials process continues to evolve. The opportunity also exists to standardize the language of interaction between sites and sponsors. In addition, the field needs a more efficient way of keeping people apprised of new developments in standardization.

- In collaboration with clinical research sites and industry sponsors, establish a set of standard clauses for clinical research contracts that address complex issues such as intellectual property and publication rights. Implementation of this recommendation will eliminate delays in initiating clinical trials related to coming to agreement on intellectual property, certain issues related to publication, and some of the commercial and financial aspects of conducting of clinical trials.

- Establish a process for developing biomarker standards; set an expectation that correlative science studies will be performed according to standard protocols in credentialed reference laboratories.

Dr. Parkinson closed his presentation by noting that standardization is the area in which the achievements in efficiency and resource usage could be the greatest.

Coordination Subcommittee—Dr. David Alberts

Dr. David Alberts, Director, Cancer Prevention and Control, University of Arizona, Arizona Cancer Center, spoke first about the goals the Coordination Subcommittee set for developing its recommendations, which include: (1) promote and reward team science and collaborative clinical trials participation, (2) facilitate information exchange and collaboration among clinical investigators, (3) enhance the design and planning of new clinical trials by providing investigators with access to comprehensive up-to-date information about ongoing and completed studies, and (4) enable patients and community oncologists to make better decisions about cancer care by providing access to comprehensive up-to-date clinical trials information. Dr. Alberts presented the Subcommittee's two draft recommendations:

- Establish a comprehensive database containing regularly updated descriptive information such as protocol eligibility criteria, sites, accrual, etc. on all federally funded cancer trials, including CTEP, Cancer Centers, SPOREs, P01s, and R01s, which would be linked to all publicly available information on each trial. Data on adverse events, toxicity, and efficacy would be available to the extramural community as soon as they are approved for public release. To implement this recommendation, the NCI would need to create a Web-based interface to provide investigators with easy access to information for research planning, prioritization, and resource allocation. Implementation also would require the NCI to create additional Web-based interfaces to enable other interested parties, such as patients, to access the information easily.

- Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trials to effectively address the most compelling opportunities in cancer research today. Issues affecting implementation of this recommendation are the problems many investigators experience in gaining academic recognition for their work on clinical trials and institutional requirements to justify time expended on clinical trials at several institutional levels.

Prioritization Subcommittee—Dr. James Abbruzzese

Dr. James L. Abbruzzese, Chairman and Professor of Medicine, Department of Gastrointestinal Oncology and Digestive Diseases, The University of Texas MD Anderson Cancer Center, noted that the Prioritization Subcommittee initially asked one important question as its point of focus: Can we more effectively and efficiently prioritize clinical trials to ensure more rapid progress in oncologic care for the American public? In answering this question, the Subcommittee used three overarching goals: (1) provide more broad-based scientific and clinical advice to ensure the development and design of the most clinically important and scientifically informative clinical trials, (2) increase efficient use of resources through an open and collaborative process for setting national clinical trials priorities and reducing duplication and overlap in the conduct and implementation of these studies, and (3) increase the involvement of patients as well as community oncologists in the clinical prioritization process. From these goals, the following three broad recommendations were developed:

- Establish an external Investigational Drug Working Group to collaborate with NCI staff on strategy, design, and prioritization of drug-specific development focused on early clinical trials (Phase I/Phase II trials, targeted on specific novel therapeutic agents), and develop plans in conjunction with the NCI for early clinical trials in which the NCI holds an IND.

- Develop a formal working group mechanism for development and prioritization of disease-oriented Phase III trials that leverages the Disease Intergroup structure (which currently consists of collaborations between the existing cooperative groups), involves the broad oncology community, and facilitates open communication about all relevant studies that may lead to a Phase III initiative.

- Enhance involvement of community oncologists and patient advocates in the cancer clinical trials prioritization process through representation on working groups and creation of advisory committees and focus groups.

Working Group-Wide Recommendations—Dr. James Doroshow

Dr. Doroshow offered the following Working Group-wide recommendations:

- Establish a permanent clinical trials subcommittee with broad representation from the extramural clinical investigators, community oncologists, regulatory agencies, industry, and patient advocacy groups to continue to advise the NCI Director on the conduct, oversight, and implementation of clinical trials across the Institute. Implementing this recommendation is critically important, not only to oversee the implementation of each subcommittee's recommendations, but also to establish an ongoing means of handling the new issues in clinical trials research that those involved cannot anticipate.

- Develop the necessary organizational structure within the NCI to coordinate the entire clinical trials enterprise supported by the Institute. That this recommendation may be the most important of all because it will be impossible to organize clinical trials nationally until the NCI is able to coordinate these activities from within as well as externally.

Dr. Doroshow also spoke about the four common themes that permeated the draft recommendations: (1) proactive involvement of all stakeholders in the design, conduct, and prioritization of clinical trials; (2) standardization of clinical research tools from case report forms to contracts and credentialing; (3) coordinating clinical research through data sharing and providing incentives for

collaboration; and (4) efficient use of resources by avoiding duplication of effort and supporting the best-designed trials that address the most important questions.

Finally, the long-term goal for the CTWG is to combine the best components of the NCI-supported clinical trials system to develop a cooperative enterprise built on a stronger scientific infrastructure and to have a broadly developed and engaged coalition of critical stakeholders who are essential to the viability of a collaborative national clinical trials research endeavor.

Questions and Answers

Dr. deKernion noted the additional importance that all of the issues would take if the NCI goes forward with the human cancer genome project discussed earlier by Dr. Lander. He raised the issue of eventually developing an overarching IRB, stating that although it will take multiple agencies to agree on parameters, reaching consensus on the subject is vital to the clinical trials process. Dr. deKernion also raised the issue of inadequate minority recruitment, suggesting that a dedicated plan to include more underserved populations in clinical trials should be a major focus.

Dr. Nienhuis commented on the additional funds that the NCI would need to implement many of the recommendations and asked whether there were efficiencies that could be achieved within the current system that would free enough monies to allow implementation of some of the recommendations. Dr. Doroshow responded that approval of the recommendations would initiate development of an implementation budget. He also mentioned ongoing efforts to improve fiscal efficiency and the cost savings that could be realized when current paper-intensive data systems are replaced by electronic data. A meeting with Drs. Averbuch and Pazdur and a group of industry representatives had concluded that uniform electronic case reporting may be the single most important thing that the NCI could do to make the clinical trials process more effective.

On the topic of patient accrual, Dr. Freedman spoke about the importance of community and county hospital outreach as major sources that provide patients to clinical trials and about the possibility of having cancer centers play a role in assuming the responsibility as the IRB of record for trials based in facilities that do not have IRBs. With monitoring and regulatory support, such an arrangement would ensure a good standard of care for patients at these institutions. Dr. von Hoff followed up on this topic, suggesting that speed and accuracy would attract the high-quality organizational agents that would facilitate patient accrual and a clearinghouse for targets to be utilized by patients and doctors.

Dr. Runowicz mentioned that traditional minority recruitment is based on population, rather than on the percentage of persons with a disease or the mortality rate for minorities with a disease. She asked whether the group had considered changing definitions to alter patterns of minority recruitment. Regarding standardized case report forms for clinical trials, Dr. Runowicz highlighted the vast differences between the case report forms used by pharmaceutical companies, suggesting that the FDA be approached about standardizing its forms. Dr. Doroshow noted that the differences between types of clinical trials would not allow for 100 percent standardization of case report forms, but might allow as much as 80 percent of the data to be collected uniformly. Dr. Averbuch referenced the unanimous agreement he had received from industry peers regarding FDA's potential provision of guidelines on the subject. Dr. Pazdur agreed and added that a core case report form and a supplement to it might be an ideal combination because no regulations address the issue. Dr. Barker added that Dr. Buetow and colleagues at the FDA have been working diligently on this problem.

Dr. Barker also mentioned the idea of a centralized public database of biomarkers and asked how private-

sector resistance might be overcome without losing access to biomarkers used in unsuccessful INDs. She also noted that currently, FDA staff members are the only people who actually know the status of biomarker research. Dr. Parkinson replied that making participation either necessary or beneficial to the private sector would garner cooperation. Dr. Pazdur clarified that the FDA knows only what companies submit about biomarkers after being encouraged to do so by the FDA. Dr. Schilsky added that there is difficulty finding standard reference laboratories for large studies, so a mechanism to develop and certify standard reference laboratories for different biomarkers is needed, along with minimum standards for marketplace deployment of biomarkers.

In closing, Dr. von Eschenbach summarized CTWG's accomplishments, noting that the work identified in the recommendations showed the need to remodel, change many parts of the system, and remove only a few. There are parts of the system that the group must build upon, enhance, and enrich, and others that need to be coordinated and integrated in a more efficient and effective way.

Motion. A motion to approve the CTWG interim report was seconded and approved unanimously.

XV. STATUS REPORT: PROGRESS REVIEW GROUP REVIEW—MS. CHERIE NICHOLS

Ms. Cherie Nichols, Director, Office of Science Planning and Assessment, NCI, explained that the Progress Review Group (PRG) process involves three phases: (1) Phase I, Recommendation; (2) Phase II, Integration; and (3) Phase III, Reporting. Approximately 7 years ago, the NCI began identifying disease-specific priorities in cancer. In conjunction with the cancer community, the NCI led 11 PRGs covering
17 cancer sites. There also was one DHHS-sponsored PRG. Copies of the Breast and Prostate Cancer PRG reports were made available to Board members. With the completion of these two reports, the NCI has proceeded through Phase III. Reports for other cancer sites are being planned.

Phase I resulted in 12 individual reports that outline summary findings for the PRGs and detail priorities for specific areas of importance in cancer. The 12 PRG reports produced to date cover Prostate Cancer (1998); Breast Cancer (1998); Colorectal Cancer (2000); Brain Tumor (2000); Pancreatic Cancer (2000); Leukemia, Lymphoma, and Myeloma (2001); Lung Cancer (2001), Gynecologic Cancers (2001); Kidney/Bladder Cancers (2002); Stomach/Esophageal Cancers (2002); Sarcoma (2004); and DHHS Cancer Health Disparities (2004).

Each PRG is made up of 25-30 scientists, clinicians, and advocates with relevant, disease-specific expertise who come together—along with a larger group of roundtable participants—to develop a national research agenda on a particular cancer or group of related cancers. PRGs are charged with assessing the nature and magnitude of the problem, identifying important gaps and unmet needs, highlighting critical barriers and emerging opportunities, identifying priorities, preparing a written report, and advising on implementation of recommendations. The NCI maps report recommendations to its current portfolio, identifies major priorities, and reports back to the PRGs. The model has proven successful both for the NCI and for the community and facilitates priority setting across a large, complex landscape. Although led by NCI, the PRGs actually have included few NCI staffers as PRG or roundtable members. PRG Chairs select their leadership and PRG members select roundtable participants. To date, more than 300 individuals have participated as PRG members, and approximately 1,000 individuals have served on PRG roundtables in all nine regions of the United States. PRG membership has been international and has included more than 130 advocates and more than 40 industry representatives. Seventeen major cancer sites have been covered; of the top 10 cancer death sites, only liver and bile duct have not been represented to date.

The recent Prostate Cancer PRG and Breast Cancer PRG reports (Phase III) represented the first assessments of progress in addressing research recommendations that were identified for these areas in 1998. With regard to prostate cancer, the report identified a tripling of NCI funding between 1998 and 2002, an approximate doubling of the number of relevant projects, expansion of ongoing and initiation of new programs to sustain and advance both basic and clinical prostate cancer research, expansion of the SPORE network from 3 to 11 sites, and more than doubling of relevant individual training and career development awards. With regard to breast cancer, the report showed that funding increased by nearly 60 percent between 1998 and 2003, the number of relevant projects also increased by 60 percent, expansion of ongoing programs and initiation of new programs to sustain both basic and clinical breast cancer research, and expansion of the SPORE network from 4 to 10 sites.

One of the first PRGs addressed pancreatic cancer and recommended increasing the number of investigators in the field. The number of investigators working in this field has nearly doubled since the PRG report was issued in 2000. The NCI, in conjunction with the Pancreatic Cancer Action Network, is developing a Pancreatic Cancer Research Map to link investigators and track projects. The Brain Tumor PRG was conducted in 2000 jointly with the National Institute of Neurological Disorders and Stroke (NINDS). In response to the PRG's recommendations, the NCI and NINDS issued a Program Announcement (PA) using set-aside funding for research on understanding and preventing brain tumor dispersal. Under the Academic-Public-Private Partnership (AP4) Program, the NCI will leverage resources with pharmaceutical, biotech, nonprofit, and other entities to facilitate intervention development. The Lung Cancer PRG in 2001 recommended increasing the numbers of biospecimens collected to increase the utility of the ongoing National Lung Cancer Screening Trial. A lung cancer integration/implementation team has been formed, and a PA will stimulate multidisciplinary research on potential reduced-exposure tobacco products.

To date, impacts of the PRG process have included shaping research directions and outcomes for the NCI and the community; providing a resource for advocates, researchers, and professional societies; encouraging collaborative activities; promoting development of the common coding scheme, the Common Scientific Outline, and other new tools; and fostering greater understanding of common issues within and across disease sites. The Common Scientific Outline has been adopted by other organizations and has fostered international communications and sharing of results. Other developments that have been based on the work of PRGs include creation of the Multiple Myeloma Research Consortium and Prostate Cancer Funders Group.

A PRG evaluation was conducted to ascertain how well PRGs had met their charge to assess the nature and magnitude of the problem, identify gaps, highlight critical barriers and emerging opportunities, identify priorities, prepare a report, and advise on the implementation of recommendations. Thirty leaders, 32 members, 66 roundtable participants, and 6 NCI staff members were interviewed by telephone for this evaluation process. PRG leaders characterized the PRG process as having been an effective, coordinated, and organized method of gaining input from the extramural community that has broadened the focus of the NCI; having provided the "only way to identify the areas of basic and clinical science that are most likely to be fruitful in a given specific disease setting"; and having fostered greater understand of common issues across disease sites, especially within multisite PRGs. Other results included that PRGs provide a more global perspective of the research environment and a better understanding of how interaction between the academic and private sectors, advocates and industry representatives, and researchers and NCI could promote action.

Ms. Nichols cited the following lessons learned from the PRG process:

- The NCI responds better to fewer, more specific recommendations than to many recommendations.

- Early PRGs were hampered by a lack of tools and resources for analyzing NCI's huge awards and initiatives. This led to the development of better analytic tools.

- The NCI was overly optimistic about its ability to implement the full range of disease-specific recommendations.

- It is difficult to prioritize scientific objectives within and among disease sites.

- A diversity of participants increases the number of intersecting ideas.

- PRGs have fostered continuing collaborative activities and interdisciplinary interactions.

Questions and Answers

Ms. Nichols then asked participants for their advice and asked them to respond to the following four questions: (1) Is there still a role for the PRG process in priority setting? (2) Are there ways PRG reports can inform NCI investments? (3) What mechanisms can the NCI use to encourage and assist other organizations to play a leading role in implementing PRG priority recommendations? (4) PRGs help shape research direction and outcomes for disease-specific cancer research—what are the best ways to continue to seek advice from all fronts?

Dr. Niederhuber stated that PRGs have been useful and have fostered advances in disease-specific areas. Dr. Chen asked for some discussion of the status of the PRGs that currently are in Phase II. Ms. Nichols noted that a consortium model is being developed for understudied and lethal cancers and will be sent to the Executive Committee for review. Colorectal cancer will be the subject of the next PRG progress report. The current flat budget necessitates making choices regarding what the Institute can support. With regard to the DHHS PRG, Dr. Mark Clanton, Deputy Director for Cancer Care Delivery Systems, NCI, stated that two meetings of the Council on Health Disparities have occurred since the report was delivered to the Secretary. In the second meeting, the agencies involved were requested to review the components of the report that were specific to their agency and develop further recommendations. The CMS and CDC have performed this review and further detailed the report's recommendations. In addition, the NCI has been asked to participate in a conference call that has been scheduled in the near future, so efforts are underway to move this report forward. The NCI will submit its input to the Council on Health Disparities through NIH.

Dr. deKernion asked whether the membership of the PRGs is refreshed periodically. Ms. Nichols replied that each PRG has its own set of members with expertise in a particular area. The groups do not meet again with the NCI once they have offered their recommendations and have participated in a response meeting. Dr. deKernion asked who would identify opportunities and prioritize if PRGs did not. Dr. Niederhuber asked whether a transition is occurring in the way priorities are set—from a disease basis to a biology-of-cancer basis. He asked whether it is relevant to continue looking specifically at single cancer sites and whether that approach represents the best use of NCI resources. Perhaps PRGs as an ongoing process have reached their limit at this time. Dr. Clanton stated that the NCI has several ways of addressing priorities. A strategic planning process resulted in seven strategic priorities for which business plans are now being constructed. The Bypass Budget is another integrated planning process that is being used to help set priorities. PRGs are not designed to produce a singular set of priorities, but to inform, on a disease-site-specific basis, what priorities might be set.

Dr. Nienhuis stated that the PRGs have been extremely useful. In the future, however, it may be helpful to think about cancer in a more global and genetically based manner. Perhaps PRGs should be employed selectively in the future, but the overall trend should be toward strategic planning that focuses more globally on cancer as a genetic disorder. Similarly, Dr. Cowan commented that the PRGs have been enormously helpful in bringing together the community of scientists, advocacy groups, and industry to focus on a particular disease. This had not been done before and was very useful. Perhaps the process could be continued in the future on an *ad hoc* basis.

Dr. Lopez noted that the trans-HHS PRG was important because its focus extended beyond a single site. Dr. Freedman endorsed the idea of viewing cancer from a more global perspective and noted that biomarkers are seen across disciplines. The PRGs were helpful in getting the SPOREs going but do not encourage a cross-disciplinary approach. Dr. Runowicz concurred that the practice of establishing PRGs by organ site probably should be retired. She suggested hormone-related cancers as the subject for a more innovative type of PRG. Dr. Clanton remarked that PRGs actually are a tool as well as a way of exploring cancer sites. As a tool, the PRG process is applicable to more baseline scientific questions that affect multiple diseases.

Dr. von Eschenbach noted that the destination is the elimination of suffering and death due to cancer. The investment in prostate cancer should be directed toward that end. The question then becomes: what one would invest in to eliminate the suffering and death due to cancer and, subsequently, what are the critical elements that have resulted in that death? The answers may differ by site, but the investment needed to achieve the answer could be applied to other cancers as well. NCI's strategic planning process is an iterative and constantly redefining process. Investments that have been chosen on a strategic and tactical basis will be applicable to a variety of cancer sites, biorepositories, etc. A portfolio is in place. Now, tools are needed to inform the portfolio and to assist in managing, monitoring, and understanding the portfolio.

XVI. FUTURE AGENDA ITEMS—DR. JOHN NIEDERHUBER

Dr. Niederhuber announced that he would send members an e-mail in the next few days to request their input regarding thoughts, concerns, questions, and ideas. He will then work with Drs. von Eschenbach and Gray to plan the agenda for the June NCAB meeting. He noted that there are plans to work toward enhancing the Planning and Budget Subcommittee by bringing in members of NCI's two other advisory committees. Again, Dr. Niederhuber will work with Drs. von Eschenbach and Gray to do this. Selected committee members may be asked to contribute to this process before June.

With regard to clinical trials working group issues that had been raised that morning, Dr. Niederhuber noted that he and Drs. von Eschenbach, Doroshow, and Gray will explore how to address some of those items through a committee structure. Members of other advisory groups may be asked to help in this effort, along with individuals from the outside community.

Dr. Niederhuber then adjourned the open portion of the session. Participants were to take a 10-minute break and then return for the closed session.

XVII. 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 all other IRG recommendations was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,377 applications were reviewed requesting support of $721,326,550.

XVIII. ADJOURNMENT—DR. JOHN NIEDERHUBER

There being no further business, Dr. Niederhuber thanked Board members for attending and participating in the meeting. The 133rd meeting of the National Cancer Advisory Board was adjourned at noon on Thursday, February 17, 2005.