

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
135th NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
September 20-21, 2005**

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

**NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory board (NCAB) convened for its 135th regular meeting on Tuesday, September 20, 2005, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, June 7, 2005, from 8:30 a.m. to 4:15 p.m. The meeting was closed to the public from 4:30 p.m. until adjournment at 5:30 p.m. The meeting was open to the public on Wednesday, September 21, 2005, from 8:30 a.m. until adjournment at 11:45 a.m. NCAB Acting Chair Dr. Daniel D. Von Hoff, Director, Translational Genomics Research Institute (TGen), Phoenix AZ, presided during both the open and closed sessions.

NCAB Members

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

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

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

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Advance 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. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Harold P. Freeman, Senior Advisor to the Director, NCI
Dr. Paulette Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Mr. John Hartinger, Acting Deputy Director for Management and Executive Officer, Office of the Director
Dr. John Niederhuber, Special Advisor to the Director for Translational and Clinical Sciences
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. Roshunnd Drummond, American Society of Therapeutic Radiology and Oncology
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Monica Leibert, American Urologic Association
Mr. Doug Ulman, National Cancer Institute, Director's Liaison Group
Ms. Judy Lundgren, Oncology Nursing Society
Ms. Mary Mitchell, American Society of Therapeutic Radiology and Oncology
Dr. Clare O'Connor, National Science Foundation
Ms. Nancy O'Reilly, The American College of Obstetricians and Gynecologists
Ms. Barbara Stewart, Association of American Cancer Institutes
Ms. Julie Taylor, American Society of Clinical Oncology
Ms. Marie Zinninger, American College of Radiology

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DAY ONE: TUESDAY, SEPTEMBER 20, 2005**I. OPENING REMARKS, CALL TO ORDER, AWARD PRESENTATION, AND APPROVAL OF MINUTES—DRS. ANDREW von ESCHENBACH AND DANIEL VON HOFF**

Dr. Andrew von Eschenbach, Director, NCI, opened the meeting with the announcement that Dr. John Niederhuber, Professor, Departments of Oncology and Surgery, University of Wisconsin-Madison, has resigned as Chairman of the National Cancer Advisory Board and that he has accepted the position of Special Advisor to the Director, NCI, for Translational and Clinical Sciences. Dr. von Eschenbach announced further that Dr. Daniel Von Hoff, Director, Translational Genomics Research Institute, has agreed to serve on an interim basis as NCAB Chair. Dr. Von Hoff called to order the 135th NCAB meeting. He then joined Dr. von Eschenbach at the podium to assist in the presentation of the NCI Director's Service award to Dr. Niederhuber in recognition of outstanding stewardship as the Chair since 2002 and, before that, as a member of the NCAB. The Award recognized Dr. Niederhuber's scientific expertise and leadership that have helped guide the NCAB, NCI, and the National Program to new levels of sustained achievement. Following Dr. Niederhuber's words of acceptance, Dr. Von Hoff thanked Dr. Niederhuber for his service on the Board and for the briefing that he provided to prepare for today's meeting. He thanked Dr. Paulette Gray, Director, Division of Extramural Activities, and Executive Secretary, NCAB, for her guidance as he assumed the duties of the NCAB Chair.

Dr. Von Hoff welcomed members of the Board and Dr. LaSalle Leffall, Jr., Chair of the President's Cancer Panel (PCP or Panel) and Charles R. Drew Professor of Surgery, Department of Surgery, Howard University College of Medicine. A special welcome was extended to *ex officio* members of the Board: Dr. T. J. Patel, Department of Veterans Affairs (DVA); Dr. Peter Kirchner, Department of Energy (DOE); and Dr. John Potter, Department of Defense (DOD). Dr. Von Hoff recognized representatives of liaison organizations and welcomed members of the public in attendance. Members of the public were invited to submit to Dr. Gray, in writing and within 10 days of the meeting, any comments regarding items discussed during the meeting.

Motion. A motion was made to approve the minutes of the June 7-8, 2005, NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE MEETING DATES—DR. DANIEL VON HOFF

Dr. Von Hoff called Board members' attention to future meeting dates, which have been confirmed through 2007.

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

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

Dr. von Eschenbach thanked Dr. Von Hoff personally and on behalf of the NCI for his willingness to step into the role of NCAB Chair and, in that capacity, help to guide the NCAB in the important work to which it has been entrusted. He extended the thanks to the entire Board for its commitment and for the effort expended on behalf of the NCI and the National Cancer Program (NCP). He noted that the NCAB effort promises to be increasingly more important as the work of the NCI expands more broadly into what could be described as a network of networks. The role of the NCAB as set forth in the National Cancer Act of 1971 was not only to support and nurture the cancer research

enterprise through appropriate distribution of resources, for example, but also to lead the NCP. The NCP has expanded and will continue to become more expansive than just the cancer biomedical research community as systems solutions are sought to address cancer as the systems problem it is perceived to be. In that regard, Dr. von Eschenbach reminded members that: (1) opportunities for collaboration and integration within the broader community, nationally and internationally, are being pursued; (2) relationships with other Institutes within the NIH and with other agencies of the Department of Health and Human Services (DHHS) have been developed, for example, the joint task forces with the Food and Drug Administration (FDA) and the Center for Medicare and Medicaid Services (CMS) and the work with the Health Resources Services Administration (HRSA) in implementing the Patient Navigator Act passed recently by Congress; and (3) interactions and joint programs are being formulated and formalized with departments beyond the DHHS, for example, with the DOD at Fort Detrick and the DOE in a program exploiting the beam line potential for cancer research. Dr. von Eschenbach noted also spontaneous collaborations that have evolved such as that between the NCI-sponsored Cancer Center at Vanderbilt University and the Oak Ridge National Laboratory (ORNL) to apply high-end computing to biomarkers and mass spectrometry programs. He concluded that enormous opportunities for other synergies and interactions exist as the NCI continues to foster and drive these types of partnerships, and that the NCAB has an important role in providing advice and direction, not only in the management of the portfolio, but also in the management and amplification of these relationships. He expressed gratitude for the NCAB effort thus far and anticipated the continued NCAB support as the NCI faces the many challenges and significant barriers to its ability to carry out an ambitious agenda, challenges that will occur not only in the area of resource availability, but also in relation to NCI authorities and ability to implement these types of broader range activities.

Dr. von Eschenbach acknowledged that all plans and visions would be meaningless without participation by people attracted to the NCI mission and willing to contribute and be part of the organization. He expressed gratitude for the talented and committed individuals who make up the NCI, and he emphasized that the NCI is committed to an ongoing effort to nurture, recognize, and support them. In that regard, a recent survey across the entire Institute attempted to identify issues that were barriers to accomplishing tasks and to look for opportunities to eliminate them and improve on work force issues that would enhance both job satisfaction and performance. Dr. von Eschenbach indicated that work is continuing on career development programs, and that senior NCI leadership will be presenting an overall plan for work force development and nurturing at a future meeting with the Board.

Personnel Changes. Dr. von Eschenbach announced that Dr. Harold Freeman has moved from his former position as Associate Director, Center to Reduce Cancer Health Disparities (CRCHD), to assume the position of Special Advisor to the Director for addressing NCI's contribution and leadership in the larger arena of networking to eliminate cancer health disparities. In this role, Dr. Freeman will be the NCI liaison with HRSA as that agency develops strategies to implement the Patient Navigator Act. The experience gained in developing the patient navigator model within the cancer program and from the Request for Applications (RFA) released by the CRCHD will contribute to HRSA's larger effort and will ensure that cancer is an important part of the continuum of health care that is developed by HRSA. Dr. Freeman also will be working with the NCAB to foster and accelerate opportunities to address questions both within the DHHS and with other agencies. The goal is to drive not only the progress of the CRCHD and its activities, but also the entire NCI enterprise activity in fulfilling the commitment to eliminate health disparities, using cancer as a model. Dr. von Eschenbach expressed gratitude to Dr. Freeman for accepting the role as Senior Advisor for strategies to achieve the NCI 2015 goal in minority and underserved communities. Dr. von Eschenbach noted that the search for a full-time CRCHD Associate Director has begun and that Dr. Sanya Springfield, Chief, Comprehensive Minority Biomedical Branch, DEA, has accepted the position of Acting Associate Director, CRCHD.

In other management changes, Dr. von Eschenbach reported that Mr. Jack Campbell has resigned from his positions as Associate Director, Business Operations and Development (BOD), Office of Management (OM), and Chief, Research Contracts Branch (RCB), OM. Mr. Leo Buscher will serve as Acting Associate Director, BOD, OM, pending a permanent appointment, and Mr. Ted Cole has been appointed to succeed Mr. Campbell as Chief, RCB, OM. Mr. David Elizalde, who was serving as Deputy Director, OM, has resigned to accept an assignment in the Office of the Surgeon General, and Mr. John Hartinger has agreed to serve as Acting Associate Director for Management pending the selection and permanent appointment of an individual in that position. Dr. von Eschenbach pointed out that the NCI is fortunate in its wealth of talent and opportunities for people to come forward and serve in important interim roles, as well as in its ability to attract talent to the Institute both as full-time employees and on a part-time basis through the IPA mechanism. He indicated that the Institute is actively and aggressively exploring opportunities to use the IPA mechanism. This strategy enables extramural researchers to be brought in for a finite period and integrated such that they can contribute significantly to NCI activities in a variety of roles while maintaining connectivity with their parent organizations. This strategy accomplished the important goals of providing an opportunity for the NCI to help coordinate and integrate the development of networks and facilitating the flow of input from the community that could influence or alter decisionmaking or programmatic planning and enhance the NCI's ability to serve those communities. Dr. von Eschenbach indicated that Dr. Mark Clanton, Deputy Director for Cancer Care Delivery Systems, Office of the Director (OD), would be using the IPA mechanism to assemble implementation teams needed to put various programs in place and that it would become an important part of the NCI workforce enhancement and development effort.

NCI's Katrina Disaster Response. Dr. von Eschenbach described the response on the part of NCI personnel to the Katrina disaster, noting that it was an example of the impact of the NCI with respect to the whole theme of leadership. The immediate response on the part of NCI personnel was to assess and address the implications of the catastrophe with regard to interrupted care and separation from ongoing support for cancer patients throughout the region. Under the direction of Dr. Clanton, a network of Cancer Centers was mobilized; spontaneous and emergent activity was occurring in San Antonio and at the M.D. Anderson Cancer Center in Houston; and the University of Alabama-Birmingham and Moffitt Cancer Center in Tampa were contacted. The Cancer Centers Branch under the leadership of Ms. Linda Weiss created a network for communications with the Cancer Centers, and the Cancer Information Service (CIS) created an operation whereby the CIS could serve as a clearinghouse for information directing patients, their families, and health professionals to the Cancer Center resources that were being established. Simultaneously, the American Society of Clinical Oncology (ASCO) mobilized efforts to contact its community oncologists and integrate them into the network with the Cancer Centers. By means of a conference call during the first week, 60 Cancer Centers were able to define their resources and infrastructure and mobilize their capacity. The central communications capability served as a conduit into the community and back into the government's effort so that it was possible to coordinate and integrate the entire effort.

Dr. von Eschenbach noted that the Katrina effort is continuing work to ensure the cancer patients in that region are being served, and it remains an important commitment of the NCI. About 7,500 patients with cancer were identified who were on NCI protocols. With dispensation from the constraints of the Health Insurance Portability and Accountability Act (HIPAA), NCI's Cancer Therapy Evaluation Program (CTEP) has been providing data, guidance, and direction with regard to medication and therapy protocols for these individuals. By the second week, Dr. von Eschenbach noted, it was possible to reach the directors of the Cancer Center programs in the area who were beginning to identify investigator, faculty, and infrastructure needs beyond patient care. Through a second conference call, laboratories in the NCI network were able to identify opportunities that could address those needs, with the result that there is considerable support for researchers and infrastructures. Dr. von Eschenbach noted that the

intramural program has made significant contributions from the very beginning in the areas of both patient care and research/infrastructure resources. Dr. Lee Helman, Chief, Pediatric Oncology Branch (POB), Center for Cancer Research (CCR) quickly mobilized the intramural assets at CCR to clear beds for pediatric cancer patients from the disaster area. Dr. Robert Wiltrout, Director, CCR, arranged opportunities for investigators to be supported in the NCI for a period of time. Dr. von Eschenbach recognized that Louisiana State and Tulane Universities have been attempting to keep their communities together, rather than disbursed throughout the cancer community. He stated that the NCI intra- and extramural programs will continue to be a part of whatever balance can be found between what those universities can reconstitute locally and what must move to a different environment.

Dr. von Eschenbach explained that his detailed description of NCI's Katrina disaster response was intended to promote understanding of the principles and fundamentals underlying the NCI's ability to function in a coordinated and integrated fashion that brings leadership to a much larger agenda. He added that the mantra of collaboration and coordination across operational units will drive all initiatives.

Digital Mammography Imaging Screening Trial (DMIST). Dr. von Eschenbach called Board members' attention to the recent announcement of preliminary results from DMIST, which showed that digital mammography is the equivalent of film mammography for detecting breast cancer in the general population of women studied. However, DMIST also showed that women with dense breasts, women younger than 50, and those who are perimenopausal may benefit from digital mammograms. Dr. von Eschenbach noted that DMIST was another example under the theme of leadership, collaboration, and coordination, and he briefly reviewed the history of the trial. In 1993, digital mammography was surfacing as a potential opportunity to enhance early detection of breast cancer, and that mission-specific opportunity drove the effort of the NCI to promote research to determine whether digital mammography was the equivalent of, better than, or inferior to film mammography, an appropriate responsibility of the Institute. However, the development of the trial spoke to the issue of leadership, in that five different companies making digital mammography equipment were persuaded to bring their technology to the study as part of the investigation. The result was that, at the end of the study, the question could be answered across the continuum of digital mammography. Dr. von Eschenbach commented that this leadership significantly enhanced the outcome of the study. The second part of the planning process was to bring in the FDA and CMS at the beginning of protocol development so that regulatory and reimbursement issues could be addressed from the beginning. Dr. von Eschenbach noted the importance of realizing that the study results established the opportunity for digital mammography to be used more effectively in the subset of patients in whom detection is enhanced. In addition, by demonstrating the equivalency of digital and film mammography, the study moves research and cancer detection more aggressively into the digital era of oncology. Dr. von Eschenbach noted that DMIST dovetails significantly with the effort ongoing through the Cancer Bioinformatics Grid (caBIG) in that it contributes a mammography-related, digitized module that can become part of caBIG.

Strategic Planning. In another topic under the leadership theme, Dr. von Eschenbach called attention to the implementation of the recommendations of the Clinical Trials Working Group (CTWG) being led by Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), in which the recruitment for key leadership of components is underway. The next step will be to identify the membership of the Translational Research Working Group (TRWG) under the leadership of Dr. Ernest Hawk, Director Office of Centers, Training and Resources (OCTR), NCI. Dr. von Eschenbach noted that the TRWG will have significant implications with regard to NCI's ability to formulate a longer range strategic plan for many of the programs that fall within the larger rubric of translational research, including the Special Programs of Research Excellence (SPOREs). In addition to these planning groups, the NCI is continuing to drive its overarching planning process that will result in the annual preparation of three documents: the Strategic Plan, Bypass Budget, and Progress Report. The Office of

Communication (OC) is managing the development of the three documents, but the input to the documents is from the various components of the Institute. Dr. von Eschenbach noted that current efforts are focusing on the Strategic Plan and 2007 Bypass Budget, and that the Institute looks to the NCAB for a response and guidance on the drafts that will be forthcoming. The Bypass Budget will emphasize particular strategic areas to: (1) expand the work and effectiveness of the Cancer Centers Program to support the DHHS Health Information Systems Initiative, which focuses on opportunities that emanate from caBIG; (2) establish linkages and bridges between advanced technologies and science; (3) integrate and streamline cancer clinical trials through the full implementation of CTWG recommendations; and (4) further the integration of interdisciplinary endeavors through the continuum of discovery, development, and delivery with equal focus on the tumor, the persons with the tumor, and the populations affected by the tumor.

Budget Update. Dr. von Eschenbach reported that the NCI is on target to appropriate fully the \$4.8B NCI budget for Fiscal Year (FY) 2005, which ends on September 30. Inasmuch as the FY 2006 budget process has not yet moved to conclusion, the prospect is that the NCI will operate for a time under a continuing resolution. Dr. von Eschenbach noted that the 0.3 percent increase over FY 2005 that is proposed in the President's FY 2006 budget means that the NCI could be operating in a deficit budget situation because of outyear grant commitments. The FY 2007 budget processes have already begun, and the proposed amounts are not known. Dr. von Eschenbach cautioned that it will be necessary to be prepared for a continued deceleration and to be able to address both a justification for increasing the budget and program planning for all budget eventualities.

Next, Dr. von Eschenbach addressed the issue of questions raised both locally and nationally with regard to the return on the investment that has been made in biomedical research and, by extension, in the NCI. He reminded members that the journey to conquer cancer began in 1971 when resources were committed to the National Cancer Program and to the leadership that the NCI would bring to that effort. He pointed out that cancer was not well understood at that time and that significant progress has been made over the past three decades. The progress can be measured by the continuous declines being seen in cancer mortality. Although the ultimate solution to the cancer problem has not been found, the NCI is committed to a solution to the outcome, the elimination of suffering and death due to cancer, and remains convinced that this goal can be achieved by 2015. Moreover, he contended, there is another part of the story to tell; namely, that the commitment made in 1971 empowered the NCI to lead what is almost certainly a biomedical revolution. Led by the NCI, the effort has resulted in the movement from a macroscopic and microscopic view of diseases like cancer to a molecular understanding, and the movement in perspective has brought about a metamorphosis that has changed the future of the disease. The rate of transformation has accelerated during the past 10 years, and, although the contributions made daily by researchers are partial and incremental, their summations tell the story of how the disease progresses, invades, disseminates, metastasizes, and ultimately kills, and thereby point to enormous opportunities for intervention. Dr. von Eschenbach expressed the view that the investment made in the National Cancer Program and the NCI, as well as the authorities given to the NCI in 1971, have driven and are leading this biomedical revolution and that leadership must continue. To support that view, he presented data on NCP contributions to medical research compiled from a National Library of Medicine (NLM) survey of PubMed, which showed that cancer, more than any other disease, is driving contributions to medical and scientific literature. Specific findings were: (1) the understanding of the relationship between genetics and disease is being driven primarily by contributions that have come from the study of cancer, which has become a model for that process; (2) contributions to the field of molecular biology as it relates to disease are being driven and continuously accelerated by what is emerging from the investment made in cancer research; and (3) literature on clinical trials and disease from 1980 to 2004 show that cancer is leading, driving, and significantly accelerating the clinical translation of knowledge on the relationships between genetics and disease and molecular biology and disease.

Dr. von Eschenbach concluded that the National Cancer Program as implemented under NCI leadership has achieved not only progress and improvement in cancer survival and quality of life throughout the past three decades, but also the creation of a pathway and trajectory to the future. Continued leadership of transition to the era of molecular medicine and molecular oncology will significantly eliminate the fear of suffering and death due to cancer that motivated the initial investment and commitment. Dr. von Eschenbach called on the NCAB in its advisory capacity, intramural NCI, and the entire extramural cancer community to sustain the effort and continue the trajectory, remembering that 2015 is a goal to be realized, not a certainty.

Questions and Answers

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, The University of Texas, pointed out that the Katrina event highlighted the vulnerability of underserved populations and a recent Agency for Healthcare Research and Quality (AHRQ) study identified an inordinately large number of barriers that exist to the accrual of those patients to clinical trials, including issues of awareness and opportunity. He asked whether the NCI would be addressing this problem on a broad basis, with a comprehensive program. Dr. von Eschenbach described the comprehensive view with which the NCI is addressing the problem, including the role that Dr. Freeman will play in expanding NCI impact and sphere, the work of the CRCHD, and the integration of programs that address disparities in other NCI components engaged in addressing disparities, such as Cancer Control PLANET (Plan, Link, Act, Network with Evidence-based Tools) in the Division of Cancer Control and Population Sciences (DCCPS). Moreover, the NCI is reaching out to enhance and contribute to programs that are occurring at the systems level. These include working with the White House on a broader domestic policy agenda and continuing the effort to drive full implementation of health disparities programs across the DHHS, such as those under the aegis of the Centers for Disease Control and Prevention (CDC) and HRSA. Outside the government, programs like C-Change have significant commitments to addressing the problem of health disparities, and the NCI is contributing to those. Dr. Freedman asked whether the current budget constraints would preclude addressing the disparity problem fully, and whether the NCI is working with state and city governments to address the problem, as the larger cities have high concentrations of the underrepresented. Dr. von Eschenbach replied that the NCI does work with state and city governments, and the leadership role works in two ways. He explained the two components of leadership by citing the example of Dr. Jon Kerner, Assistant Deputy Director for Research Dissemination and Diffusion, DCCPS. Dr. Kerner leads NCI's effort concerning Cancer Control PLANET and other DCCPS programs. Dr. Kerner plays another leadership role in collaborations with State Cancer Plans, the American Cancer Society (ACS), CDC, and C-Change.

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

On behalf of colleagues on the President's Cancer Panel, Dr. Leffall congratulated Dr. Niederhuber on the excellent job he did as Chair of the NCAB. He reported that the Panel's 2005-2006 series of meetings, which began in August, will differ in scope and purpose from those in the past but will remain consistent with the Panel's mission of monitoring the development and execution of the Nation's cancer program. Recommendations are made to the President for improving the national effort to address the burden of cancer for all citizens across all populations and communities. Typically, the Panel gathers information on a specific cancer-related topic in the course of its minimum of four meetings per year and presents its findings and recommendations in a report to the President and Congress. Dr. Leffall noted that in the current series of meetings, the Panel has chosen to address high-priority recommendations made previously to the President and Congress. The recommendations will be studied in depth, and strategies to help accelerate their implementation will be developed.

Dr. Leffall reported that the first two meetings in the series were held in Washington, DC, on August 25 and 26 and had the goal of identifying the actionable steps that can be taken from the Panel's recommendations from the 2003-2004 report entitled "Living Beyond Cancer: Finding a New Balance." This report identified and addressed critical challenges faced by cancer survivors across the life span. A roundtable with key stakeholders was convened on August 25 to identify and prioritize steps needed to develop adequate treatment records and follow-up care plans. Progress to date in these areas was reviewed, and the Panel heard of promising initiatives already underway to develop patient-oriented clinical summaries and disease-specific guidelines for long-term cancer survivors. The August 26 meeting focused on adolescent and young adult cancer survivorship and access to care issues. The first roundtable addressed research needs specific to adolescent and young adult cancers. Reaching this itinerant population for follow-up and surveillance has been a significant hurdle, impairing research efforts. It was suggested that better models be developed to go to the patients in settings in which they feel more comfortable. A second roundtable considered the Panel's recommendations relative to insurance coverage and access to care for cancer survivors of all ages. Education about the awareness of available resources could enhance access to care, as could patient navigation programs that guide cancer survivors through the complex medical care system. Studies demonstrating cost/benefit advantages of specific services also could increase coverage by insurers who have a stake in cost-effective, evidence-based care for patients. Involving corporate partners in insurance access issues also was proposed.

Dr. Leffall noted that efforts by stakeholders to pursue studies and develop policy platforms are underway in a number of these areas. Each of the roundtable groups remained optimistic that progress can be made to implement these recommendations within the next 2 years. Specific steps were identified for moving the Panel's recommendations forward, and follow-up commitments were made by those who were present. Dr. Leffall stated that these steps and commitments will be part of the Panel's report at the conclusion of the meeting series.

Dr. Leffall reported that the Panel will hold meetings on October 24 and 25, also in Washington DC, to discuss recommendations from its 2004-2005 report entitled "Translating Research into Cancer Care: Delivering on the Promise." On October 24, the Panel will focus on team science, clinical research, and infrastructure issues. Based on testimony provided during the 2004-2005 series, it was determined that the current culture and infrastructure of the cancer research enterprise are at the root of many of the impediments to translating basic science discoveries into improved cancer prevention and treatment interventions. The first roundtable will follow up on the Panel's recommendations for advancing team science, which has been identified as the new paradigm for achieving progress and translating basic science discoveries into useful interventions. Panel recommendations for improving team science include: modifying existing institutional reward systems; promoting collaborative science through new funding mechanisms; and examining peer review systems relative to basic and clinical research support. The second roundtable will address infrastructure issues relative to attracting and retaining young investigators to careers in translational and clinical research. Dr. Leffall noted that the Panel had specifically recommended more protected research time and mentoring, new or expanded student loan buy-back programs, and expanded efforts to recruit and retain young scientists, including those from underrepresented populations, to perform clinical and translational research.

Dr. Leffall reported that the Panel will shift its focus at the October 25 meeting to consider dissemination and community participation as they relate to translation of treatment advances into clinical practice. Inasmuch as approximately 80 percent of patients with cancer and survivors receive their care in the community, disseminating prompt, accurate information about cancer prevention or treatment advances to community health providers and the public in usable formats is a critical step in the translational process. Community participation in research design and implementation, as well as in

dissemination of research findings, is equally vital to the widespread adoption of cancer prevention and treatment advances. A single roundtable will address recommendations in these areas from the Panel's 2004-2005 report.

Questions and Answers

Ms. Kathryn Giusti, President and Founder, Multiple Myeloma Research Foundation, Inc., commented that, at the October meeting, it would be valuable if groups who are addressing major obstacles with some success could be brought in to share their experiences so that others could learn from them. Dr. Leffall thanked her and noted that he would pass her comments to his colleagues on the Panel.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response, began by reviewing the status of FY 2006 appropriations. The President's budget, which was announced on February 7, included appropriations of \$28.8B for the NIH and \$4.8B for the NCI. The House bill with appropriations of \$28.7B for NIH and \$4.8B for the NCI was passed in June and sent to the Senate. The Senate bill, with appropriations of \$29.65B for NIH and \$4.96B for the NCI, was reported in July, but the debate and vote in the Senate had not yet been scheduled at the time of the NCAB meeting.

Next, Ms. Erickson briefly reported on three Congressional hearings of interest to the Board. On July 19, the House Energy and Commerce Committee held a hearing on NIH Reauthorization, before which Dr. Elias Zerhouni, Director, NIH, was the only witness. On that same morning, the Senate Committee on Energy and Natural Resources held a hearing entitled Effects of Nuclear Testing in the Marshall Islands. Dr. Kiyohiko Mabuchi, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics (DCEG), testified. On September 7, Dr. Ted Trimble, Cancer Therapy Evaluation Program (CTEP), DCTD, was a witness before the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources hearing entitled "Women and Cancer: Where Are We in Prevention, Early Detection, and Treatment of Gynecologic Cancers?" Ms. Erickson noted that emphasis was placed on the Gynecological Cancer Awareness and Education Act (Johanna's Law), and NCI's testimony focused primarily on NCI education and outreach efforts in this area.

In a more complete update on NIH Reauthorization legislation, Ms. Erickson reminded members that Representative Barton, as Chairman of the House Energy and Commerce Committee, began holding a series of hearings that are expected to continue during the next 4 years. The first draft of a bill was presented at the July 19 meeting, and the second draft was received by the NIH on August 22. The next step will be the introduction of the bill, but information is not available on when that would take place. Ms. Erickson reviewed key points in the bill. (1) Current Institutes and Centers (ICs) are divided into two categories, those with mission-specific responsibilities like the NCI and those with science-enabling responsibilities such as the National Human Genome Research Institute (NHGRI). The number of ICs in each category cannot increase. (2) The NIH Director's authority, as summarized by the Committee, is to ensure that scientifically based strategic planning is implemented in support of research as determined by the IC Directors, and to coordinate programs across ICs to ensure that the NIH research portfolio takes advantage of collaborative, crosscutting research. (3) A Division of Program Coordination, Planning and Strategic Initiatives is created in the statute and located within NIH/OD. It will identify scientific areas in need of research that involve the responsibility of more than one IC. The Division is to receive IC input and will require an advisory body review of its actions. (4) A common fund for trans-NIH research is established in the statute, to be funded by a percentage of the overall NIH budget. The money would be allocated to ICs to conduct the research activities, and the overall size of the set-aside will gradually increase during a 3-year period. (5) The statute allows for some demonstration projects. The first project,

Bridging the Science, would be conducted by the National Science Foundation (NSF) and DOE, and the research would be performed at the interface of biological, physical, chemical, mathematical, and computational sciences. The second project, High Risk/High Reward, would use grants, contracts, or other transactions for high-impact, cutting-edge research that fosters scientific creativity and increases fundamental biological understanding. (5) With regard to authorizations of appropriations, the statute eliminates separate authorization of appropriations for individual ICs and delineates three authorization of appropriations—NIH OD, mission-specific ICs, and research-enabling ICs.

Ms. Erickson reviewed cancer-specific provisions in the bill. With regard to Centers of Excellence, the first draft of the bill gave the Director, NIH, authority to establish Centers of Excellence but did not define the term. The second draft specifically excludes the National Cancer Research and Demonstration Centers, so the NCI will not be subject to the NIH Director's approval for creating cancer centers. In terms of reporting requirements, the first draft of the bill deleted the reporting requirement for the President's Cancer Panel, and the second draft restored it.

Ms. Erickson concluded by briefly summarizing other legislation of interest. The Patient Navigator Outreach and Chronic Disease Prevention Act was signed into law in June. The bill creates a demonstration grant program, to be implemented by HRSA. House Continuing Resolution 210, which supports the goal of eliminating suffering and death due to cancer by 2015, was introduced in July.

Questions and Answers

Dr. Carolyn Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, asked if training issues were covered in the hearing on women and cancer. Ms. Erickson noted that the issue was raised with the panel that included patient advocates but not with the panel of government witnesses, and the government's role in training was not addressed. Dr. Von Hoff expressed concern that the reauthorization legislation as currently written would not be helpful in accomplishing the 2015 goal. Dr. Kenneth Cowan, Director, Eppley Cancer Center, University of Nebraska Medical Center, asked whether further hearings were planned and whether a formal comment period will be opened for organizational comment on the proposed legislation. Ms. Erickson explained that comments had been submitted on both drafts, but the legislation, once it is introduced, will not be subject to comment from outside organizations. Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at UCLA, observed that, although organizations may not comment further, there will be time for public comment when the NIH Reauthorization bill is introduced, so it will be important to know when that happens. Ms. Erickson agreed to inform the Board if the bill is introduced or of any upcoming hearing.

VI. STATUS REPORT: TRANSLATIONAL RESEARCH WORKING GROUP (TRWG)— DR. ERNEST HAWK

Dr. Hawk prefaced his status report on the organization of the TRWG with a brief discussion of the background and rationale for its creation. He cited cancer medicine's emerging transformation from the 20th century paradigm based on a morphologic/histopathologic definition of disease to the 21st century paradigm based on a more dynamic cellular/molecular understanding of disease processes. Implications of the transformation are an increasing focus on disease prevention and health preservation. Those implications carry with them greater responsibility to realize the promise they hold. Dr. Hawk pointed out forces at play in the anticipated evolution in cancer interventions that retard progress, such as behavioral inertia, aging, resource limitations, and disorganization, as well as progress promoters such as molecular medicine, personalized medicine, and advances in imaging and communication. He then reviewed the many components of NCI's bench-to-bedside and back research infrastructure and the key

roles they play in facilitating translation from basic science to clinical trials. He called attention to components of the OCTR portfolio, in particular the Cancer Centers Program and SPORes; the roles they play in promoting translational research; and programmatic questions that arise concerning their organizational premises and effectiveness.

Against this background, the TRWG is in the process of being organized, based on the rationale that: (1) advances in cancer biology offer enormous opportunities to improve public education and clinical practice; (2) NCI programs with a translational focus have proliferated during the last decade; resources are limited, but the potential for translational research is unlimited and expectations are high; (3) opportunities exist for accelerating progress by identifying and reducing redundancies, identifying and addressing unmet needs, facilitating communication, and improving coordination. Dr. Hawk noted that the TRWG is intended to be a national initiative to evaluate the status of NCI's investment in translational research and develop a vision for its future in an inclusive, representative, and transparent manner. Anticipated steps for the TRWG will be to acknowledge and learn from the work of prior and concurrent efforts, define the scope of activity; evaluate existing programs; provide vision and recommendations, including near-term adjustments of existing program and long-term vision; and develop an implementation strategy. Dr. Hawk announced that Dr. Lynn Matrisian, Ingram Distinguished Professor and Chair of Cancer Biology, Vanderbilt University, and Dr. William Nelson, Professor of Oncology, Urology, Pharmacology, Medicine, and Pathology, Johns Hopkins University, have agreed to assume leadership positions on the TRWG.

Next, Dr. Hawk reported that a TRWG Strategic Plan has been developed with the help of input received from approximately 40 interested scientists, advocates, professional societies, and advocacy groups. Initial steps in the plan were the announcement to the NCAB at the June meeting and identification of senior leadership as noted above. Next steps are to develop membership rosters for both the TRWG and two planned roundtables; share foundational documents; design a Web-based communication platform; initiate a translational research outcomes evaluation; plan the first roundtable and receive public comment to address the questions of what an optimal translational research program would look like in 2015 and how the NCI could best facilitate that future; convene the first roundtable; develop the draft model and recommendations based on the first roundtable; publicize the draft and recommendations; receive public comment; convene the second roundtable to discuss the draft model, recommendations, and evaluation results and then develop a draft implementation plan; finalize the implementation plan; and present the final model, recommendations, and implementation plan to the NCAB.

Questions and Answers

Dr. deKernion recommended a linkage between the CTWG and TRWG to ensure that the best opportunities for clinical trials are chosen and the best use is made of NCI and industry resources to get better drugs to the bedside. Dr. Von Hoff suggested that a list be compiled of all drugs for which the Investigational Drug Branch, CTEP, has ever filed an Investigational New Drug (IND) application. The list could include the drug's intended target and status to help scientists find and consider them for application against new targets.

VII. UPDATE: HUMAN CANCER GENOME PROJECT—DR. ANNA BARKER

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, OD, began by thanking Dr. von Eschenbach and Dr. Francis Collins, Director, NHGRI, for their commitment to the Human Cancer Genome Project, which provided the impetus to begin to plan such an undertaking. She thanked Dr. Eric Lander, Chair, *Ad Hoc* Subcommittee on Biomedical Technology, NCAB, for

introducing the project to the NCAB and Board of Scientific Advisors (BSA), and she introduced and thanked colleagues on the NCI-NHGRI Project Management Team: from NHGRI—Mark Guyer, Jane Peterson, Peter Good, and Brett Osenberger; from the NCI—Jessica Malone, Danielle Gerhardt, Kenneth Buetow, Carolyn Compton, and Gregory Downing. Board members were reminded that the purpose of this effort, as proposed by the NCAB Subcommittee, was to create a database or “catalogue” of all the genomic alterations in cancer. The goal of this particular project is to initiate a 3-year pilot to address key questions, to determine the feasibility of a full-scale project that will ultimately facilitate development of a complete “catalogue” of all genetic alterations in cancer. Enabling factors that contribute to the rationale for doing the project now are the significant knowledge base resulting from NCI’s investment in understanding molecular biology and genetics of many cancers, rate of progress of genomics analysis technologies, and knowledge gained from NHGRI’s complementary high-throughput projects.

Dr. Barker described the Cancer Genome Project as a network of networks, in that synergies will be derived from many NCI and NHGRI programs. She reviewed the major milestones to date since the NCI-NHGRI Exploratory Workshop in 2004. To date in 2005, the following milestones were reached: the NCAB Subcommittee presented its report on the proposed project to the full Board; NCI and NHGRI announced their commitment to the pilot project; the Project Management Team initiated project planning; and a multi-sector workshop was held. Dr. Barker explained that the workshop, entitled “Toward a Comprehensive Genomic Analysis of Cancer,” was a broad community discussion to identify critical issues for consideration in the design and implementation of a pilot project that would lead to the ultimate identification of all genetic alterations in cancer. Participants numbered about 150 and came from public, academic, private, and survivor sectors. Workshop participants were challenged to consider a variety of issues that could become barriers unless they were dealt with beforehand. These included biospecimen collection, quality, and annotation; tumor heterogeneity; DNA quantity and quality; current sequencing technology limitations; detection of broad genetic changes; data collection and analysis; lack of standard definitions of cancer subtypes; and informed consent, data release, and intellectual property (IP).

Dr. Barker reported that the workshop identified that finding the right samples for the pilot project was seen as the major issue to be addressed. Based on information gained from participants, NCI staff has compiled a best-case scenario for obtaining the necessary quality of samples to be used. The second issue to emerge from the workshop was the decision of how many and which tumors to select for sequencing. Dr. Barker noted that, ultimately, qualification and selection of the tumors to be sequenced will be made by peer review. It was recommended that an in-depth genomic analysis be made of more than one tumor; two to three seemed a reasonable quantity. Another suggestion was made to explore several other tumors during the pilot project, but this would likely be cost-dependent. Workshop participants identified several practical and scientific considerations in making choices and recommended that tumor quality needs to be high and available to all participants.

Data management and access received considerable attention, and the consensus was that these data should be released rapidly, the quantity of information provided should be maximized, and access to all data for research purposes should be unrestricted, using data-release models that currently exist. Dr. Barker pointed out, however, that unrestricted access to cancer genome data, because of associated clinical annotations, will require solving the problem of how selected patient-associated data can be released under confidential and possible encrypted approaches. Dr. Barker noted that the NCI is interested that the pilot project be caBIG-driven in terms of the databases and be compatible with all of the databases. In addition, there should be multiple portals for access, and access should be available across all of the communities, including the private sector. Another issue that received considerable attention was how to leverage complementary cancer genome analysis capabilities without slowing down the intent of the project, recognizing that two different cultures are being merged. Dr. Barker noted that

the idea emerging from the advisory group is that the project will have two different kinds of centers, the NHGRI production centers to sequence the genes and cancer biology genomic centers to identify those genes and regions to sequence. The latter would leverage the NCI's considerable investment in cancer biology and genomics. Regarding the genome centers themselves, NHGRI and the NCI members of the team are working to optimize current genome sequencing capabilities for rapid progress by addressing issues of whole genomic amplification, defining ideal sample needs, and reducing signal noise. They will start with known cancer-associated genes and build from there, using current sequencing capacity while driving new technology development.

Dr. Barker noted that workshop consideration of informed consent as it relates to managing genome sequence data was long and difficult, and the proposed pilot project creates new issues for consent. The possibility of identifying individuals from the genome sequencing data means that a more direct consent will be needed. There will be a need for re-consent to use samples from existing biorepositories and a tiered consent for future research. Learning from the best practices evolving from other large sequencing initiatives will be necessary, as will the establishment of an encrypted, hacker-proof database for selected patient-associated data. A final issue emerging from the workshop was that this pilot project must drive technology development. The emphasis will be to attract R01 investigators to innovate, especially in the genome analysis technology area. Discussions focused on using available NCI and NHGRI programs, such as the NCI's Innovative Molecular Analysis Technology (IMAT) program, to drive technology development and on including technology development in all NCI-NHGRI centers, and incorporate all advances as quickly as they become available to increase efficiency and accuracy and reduce the cost of this project.

Concerning the timeline, Dr. Barker noted that plans for the pilot project are being finalized and will be brought to the BSA at the November meeting, with a report to the NCAB in December. The current plan is to issue the RFAs and Requests for Proposals (RFPs) in late 2005 or early 2006 and make the awards in 2006.

Questions and Answers

In response to Ms. Giusti's question about how the RFA process will work for selecting candidate tumor types, Dr. Barker explained that a two-part process is envisioned, the first part being a Request for Information (RFI) asking for candidate nominations to be considered, followed by a competitive procurement. Dr. deKernion expressed the view that it would be better to collect the specimens prospectively with the proper consents than retrospectively. He expressed concern at the proposed project's potential impact on funding for new investigators and senior investigators with innovative ideas, and asked about the projected budget. Dr. Barker stated that the estimated investment is \$50M from the NCI and NHGRI, but she called attention on the R01 science opportunities that evolved from the human genome sequencing project. Dr. Freedman suggested that the informed consent process could be facilitated if a very well-designed, well-worded material transfer agreement (MTA) is developed that incorporates IP aspects and privacy protection issues, such that they can be used as a reference and facilitate the process when these projects go through the Institutional Review Boards (IRBs).

Dr. Franklyn Prendergast, Director, Mayo Clinic Cancer Center, asked whether a specific set of questions would drive the proposed project or whether it would be a data-gathering exercise across all possible technologies. Dr. Barker expressed the view that the project would start out as a data-generating exercise but quickly orient toward finding targets. She projected that there would be much R01 investigation around potential targets that are identified when the data become available. Dr. Prendergast concurred with that direction; he then asked how the technology would be selected to avoid creating a fragmented or fragmentary dataset and what criteria would be used to define the dataset. Dr. Barker

expressed the view that the secret will be in integrating into meaningful answers on what the community already knows how to do, for example, in the areas of epigenomics and expression profiling, and she hoped that submitted proposals would do that in selecting genes and regions for sequencing. Dr. Prendergast commented that standards would be needed to define what constitutes integration and coherence.

Dr. von Eschenbach reiterated Dr. Barker's invitation for insights or comment from NHGRI colleagues. Dr. Peterson commended Dr. Barker's summation of the project and progress to date, and she looked forward to translating the NHGRI experience to medicine. Dr. von Eschenbach then addressed the issue of financing for cancer genome sequencing, noting that when the project was originally introduced, discussions in the larger community, including Congress, focused on both the scientific validity and potential impact of the ultimate project and its cost, but moved rapidly to a concern about cost alone. He emphasized that the estimated total cost in those discussions was a guess, and that neither the premises nor available technologies for that ultimate project are known at this time; there is great vision around what its ultimate implications could be in terms of the ability to manage a disease like cancer and set the stage for a variety of other diseases. He emphasized the importance for the entire community and the Board to focus only on the proposed pilot project, not an ultimate project somewhere in the future. He noted that the pilot represents the ability to begin to help the community come together in a coordinated, cohesive, and integrated way to explore, test, and define. The current proposal maintains only that the goals of the pilot can be accomplished in 3 years and that the cost associated with that is \$50M each from the NCI and NHGRI, some of which would be "in-kind" contributions using already existing resources and facilities. Dr. von Eschenbach commented further that the community would have to accept the tension that exists in always coming to a balanced portfolio. Referring to his earlier report, he noted that the NCI must be as explicit and transparent in its strategic plan concerning the scientific opportunities, the business plan needed to match those opportunities, and the progress achieved so that people understand the extent of the investment, its justification, and the expected return on the investment. He expressed the view that the return on investment in the cancer genome sequencing project would be great because of its potential to help define what is known and determine what is not known, and in the process, develop tools, insights, and relationships that will open up more hypothesis-driven research opportunities than otherwise.

VIII. UPDATE: CMS-NCI ONCOLOGY PILOT PROJECT—DR. MARK CLANTON

Dr. Clanton reminded Board members that the 1-year old CMS/NCI Working Group was established to determine how best to bridge the evidence-generating process as represented by the clinical trials and the health care delivery system as represented by the CMS for more effective translation of knowledge, tools, and techniques to have a public health impact on cancer. He began by reviewing provisions in the Social Security Act that currently govern reimbursement. Anticancer chemotherapeutic agents are eligible for CMS coverage: (1) when they are used in accordance with FDA-approved labeling; (2) for off-label use, when the drugs are listed in authoritative drug compendia; and (3) when a Medicare contractor determines an off-label use is medically accepted, based on guidance provided by the Secretary. Next, Dr. Clanton reviewed routine cost coverage in clinical trials according to current Medicare National Coverage Decisions (NCDs): not covered are the investigational item itself; items provided solely to satisfy data collection and analysis requirements in the protocol; and items and services usually provided by research sponsors free of charge. Covered items include conventional care; items and services required solely for provision of the investigational item and clinically appropriate monitoring or prevention of complications; and items needed for reasonable and necessary care arising from the provision of an item or service (e.g., complications).

Dr. Clanton reviewed issues that arise with current NCD clinical trials coverage: (1) there is

regional variability in the interpretation of routine costs by local contractors; (2) the cost of anticancer drugs for off-label indications is determined by local contractors; and (3) non-routine costs are not covered. Dr. Clanton noted that, at the inception of the pilot, the NCI and CMS entered into discussions to explore how the two agencies could align their resources and new agency-specific goals could accelerate development of evidence for emerging cancer treatment regimens. Through the discussions, a proposed approach was developed linking coverage to participants in specific trials. The goals of the CMS-NCI Pilot Project are to: (1) offer consistent national coverage for these specific trials; (2) ensure advancement in knowledge for these agents; (3) accelerate development of evidence for new and emerging cancer treatments; (4) ensure beneficiaries' rapid access to promising new uses of technologies under controlled clinical trial conditions; (5) serve as a potential model for additional coverage expansions in clinical trials for other anticancer agents by both CMS and other insurance carriers; and (6) encourage industry to invest in clinical studies that will expand the knowledge base.

Dr. Clanton indicated that the NCI was asked to identify trials for the pilot project that study off-label uses of four agents important in colorectal cancer (CRC) per the NCD for chemotherapy. The drugs—oxaliplatin, irinotecan, bevacizumab, and cetuximab—are of interest to the NCI from a therapeutic point of view and to CMS because of the need to cover them. The nine trials selected for inclusion in the pilot are a mix of Phases I, II, and III and include six for colorectal cancer, one for head and neck carcinoma, one for gastrointestinal stromal tumors, and one for pancreatic carcinoma. Dr. Clanton noted that the studies are in various stages of development, although several will begin enrollment soon, and he stated that they will address questions that are likely to lead to important changes in therapy. Coverage for the project will include all routine and nonroutine costs associated with these trials so long as a “benefit category” exists and the item is not prohibited by statute or a national non-coverage decision. Dr. Clanton noted that coverage has been made available through an NCD that has been communicated to CMS contractors. The intent is to decrease the variability by which local contractors and fiscal intermediaries act in these trials. Tests and evaluations for pretreatment and randomization tests to support eligibility will be covered, as will treatments, all ongoing tests and imaging evaluations during therapy and follow-up, and treatment complications.

Dr. Clanton pointed out that the CMS has engineered solutions to the problem of supporting these specific clinical trials within the framework of the coverage system. Special code modifiers will be used for processing claims. The billing algorithm has been simplified to assist providers in billing according to this process and CMS in tracking the process. A strategy has been worked out for reimbursing self-administered questionnaires, which are a routine part of data collection in the trials but fall under none of the benefit categories. Dr. Clanton noted, however, that co-pays cannot be waived within the structure of the law governing the CMS. Finally, Dr. Clanton described the comprehensive communication network that has been developed for the pilot, which includes separate CMS Web Sites for the public, contractor medical directors, Medicare providers, and billing offices. Monthly conference calls will be held with CMS contractor medical directors, and there will be national meetings with CMS regional contractors. General information sheets are being created for physicians, patients, and patient referral information, the latter to ensure that tests for referred patients are coded and billed appropriately. In addition, information has been disseminated to cooperative groups, and there has been an ongoing information exchange with ASCO and other organizations.

Questions and Answers

Dr. Runowicz asked if the usual per-patient reimbursement in NCI-sponsored clinical trials would be withheld in lieu of CMS reimbursement if a patient is enrolled in one of the specific pilot project trials. Dr. Clanton replied that the NCI trial reimbursement and mechanism by which it is paid would remain unchanged. CMS reimbursement in the pilot-specific trials would provide coverage for incremental or

additional costs. He pointed out that the pilot has the potential to make it possible to approve more people in Medicare to trials more quickly, and to facilitate the dissemination of information that the trials exist and show that combinations work through the evidence produced in the trials. Ms. Lydia Ryan, Service Line Clinical Director, Children's Healthcare of Atlanta, AFLAC Cancer Center, commended the secondary goals of establishing the mechanistic pieces that will be necessary at the local and state level, bridging language and culture differences, and beginning to establish trust. Dr. Prendergast asked whether the selection process for any subsequent CMS project would continue to go through NCI/CTEP or whether there could be some other peer review mechanism to identify what might constitute an outstanding clinical trial. Dr. Clanton replied that selection for the next set of drugs or cancer sites will depend on the outcome of the pilot and its success in establishing a mechanism whereby future trials can be considered. Dr. Von Hoff commented on the interest in the pilot and subsequent trials on the part of the Board and suggested that the Working Group should consider drawing up usage guidelines for the mechanism under development. Dr. James Armitage, Joe Shapiro Professor of Medicine, University of Nebraska College of Medicine, observed that the ultimate effect of enabling the CMS to support approved research more broadly would be to expand the number of people, especially older people, who would have access to clinical trials; the total number of trials would not change, however, unless more money is available to fund the clinical trials themselves. He asked if the pilot project might lead to expansion of the funding for research organizations. Dr. Clanton replied that the pilot project is intended to begin to solve the systems problem by expanding access and bringing the evidence closer to the NCD process. Challenges related to funding for additional trials will depend on FY 2006 and FY 2007 budgets.

Dr. James Rollins, CMS Medical Officer, CMS/NCI Oncology Working Group, conveyed his appreciation on behalf of the CMS for the opportunity to work with the NCI. Inasmuch as the CMS is statutorily unable to conduct research but can work collaboratively with other federal agencies, this linkage will provide CMS the opportunity to become more evidence-based and able to provide services to its members who can benefit from this type of research. To Dr. Freedman's question about goals for minority recruitment in the pilot project, Dr. Clanton replied that there are no explicit goals, but that this evolutionary process has the potential to improve minority and underserved participation in trials, given the demographics of the Medicare population. Ms. Ryan suggested as a future agenda item an update on this collaboration and the results not only in terms of clinical trial reimbursement, but also what the relationship between the CMS and the clinical research entity could look like in developing those linkages and minority data-gathering capabilities. Dr. von Eschenbach concluded the discussion by thanking Dr. Rollins and the CMS for their partnership and collaboration in this effort that has the goal of finding a systems solution to a systems problem and for their willingness to use cancer as a model to transform health care in the United States.

IX. FDA/NCI INTERAGENCY ONCOLOGY TASK FORCE (IOTF)—DR. ANNA BARKER

Dr. Barker reminded members that the IOTF was formed by an Interagency Agreement in May 2003 following a meeting between then-FDA Commissioner Mark McClelland and Dr. von Eschenbach to consider the use of cancer as a model for a demonstration project for collaboration on issues of mutual interest, particularly the development of drugs. Since inception, it has grown to involve more than 100 people in subcommittees devoted to interventions development process, surrogate endpoints, clinical development of biomarkers, imaging and imaging endpoints, advanced technologies, and prevention and training. Highlights of IOTF progress to date include: (1) Process Enhancement—exploratory INDs for small molecules and biologics and new Good Manufacturing Practice (GMP) regulations for experimental agents; (2) Markers of Clinical Benefit—imaging endpoints and biochemical markers for drug development; (3) New Common Bioinformatics Platforms—standards for clinical trials submissions, e-INDs, and CRIX; (4) Advanced Technologies—Critical Path initiatives related to nanotechnology and molecular diagnostics; and (5) Training and Joint Appointments—training programs for Ph.D.'s and

MD.'s.

Dr. Baker then presented an update on the work underway in the subcommittees. In the **Process Subcommittee**, steps in the process of drug development were reviewed to identify ways to make the review process more efficient. As a result, a guidance document on Exploratory IND Studies was drafted by the FDA, with broad NCI input, to permit studies of experimental drugs without the requirements for a full Phase I trial. The comment period has ended, and the guidance is now open for public review. A Senior Leadership Team (SLT) process is in place through which NCI investigators can receive help in the resolution of IND issues. The roll out of the SLT pilot and Web Site will be announced by the NCI. White Papers are being written in preparation for drafting a guidance document on toxicology issues, similar to that recently developed for GMP issues.

Through the **Imaging Biomarkers Subcommittee**, a mini-working group was formed to focus on key imaging science issues for development of volumetric imaging for oncology. The joint manuscript on fluorodeoxyglucose positron emission tomography (FDG PET) has been published in *Clinical Cancer Research*, and the Subcommittee is looking specifically at how FDG PET can be used more effectively to establish surrogacy endpoints for clinical benefit, an area of interest for possible CMS reimbursement. The White Paper and a manuscript on molecular probes have been completed and are the basis for efforts to move molecular probes through the process toward initiating the necessary clinical trials. A public-private partnership to involve the NCI, FDA, NIH Foundation, and the public sector is in discussion to develop imaging biomarkers. Drs. Barker and Clanton are working with the FDA and CMS to develop a Memo of Understanding (MOU) on the concept of biomarker pre-identification, clinical trial design with input from the community, and execution of the trials as a basis for the FDA's development of a guidance for surrogacy.

The **Bioinformatics Subcommittee** is working in collaboration with the CTWG to harmonize databases as part of the process to develop a clinical trials reporting system. Development of the Registry for Bioinformatics Research Data is progressing and will be reported soon to the NCAB. The Registry is a Web-based clinical investigation and financial reporting system with data that will be available to both the public and private sectors. The Subcommittee also is working with other standards bodies to develop standards for clinical trials data reporting to the FDA (for example, HL7 and adverse events) and is proceeding with the electronic common technical document for the e-IND. The **Nanotechnology Subcommittee** is collaborating with the National Institute of Standards and Technology (NIST) to develop the Nanotechnology Characterization Laboratory (NCL) at the Frederick Cancer Research and Development Center (FCRDC) and clinical trials protocols for characterizing nanoparticles, nanowires, and nanotubes. Other initiatives include the March workshop on the use of nanotechnology in drug development, a May meeting with NIST to set standards for clinical trials in the area of nanotechnology, launch of the FDA and NCI nanotechnology Web sites, development of the FDA's publicly available database for nanoparticles characterization based on NCL protocols, and the development of a MOU to guide NCI, FDA, and NIST collaboration on research activities. Concerning the recently launched Fellowship Programs, the **Joint Training Subcommittee** reported receipt of 15 applications in the first round. Six fellows are incoming to the Oncology Product Research/Review Fellowship Program, and one fellow has been approved by the Selection Committee for a Cancer Prevention Fellowship. In conclusion, Dr. Barker expressed enthusiasm for the productivity of the partnership that has been developing between the NCI and FDA since the first discussion between Drs. McClelland and von Eschenbach and to the commitment of the individuals who are implementing their vision.

Questions and Answers

Dr. Von Hoff expressed concern that the Exploratory IND as currently constituted provides for

only one course of treatment per patient, and Dr. Barker noted that the issue already has been raised with the FDA, with the hope for a quick resolution as the initiative progresses. Dr. Prendergast asked about the White Paper to address GMP issues, and Dr. Barker replied that the White Paper and guidance that is being developed is intended to simplify requirements of GMP preparation of materials for early and exploratory work and will apply across all types of therapeutic modalities. Dr. Prendergast pointed out that GMP requirements will have to be different for the different technologies. Because of the great expense involved in trying to build across platforms, he suggested the need to discuss possible solutions, for example, regional centers with GMP capability for the different technologies. Dr. Barker pointed out that the Rapid Access to Intervention Development (RAID) Program currently is being studied as a possible vehicle to solve that problem. Dr. Prendergast then expressed the view that, except for cost, FDG PET would be a more effective tool than volumetric imaging for looking at therapeutic effectiveness. Dr. Barker pointed out that the reimbursement pathways could be defined if the NCI/FDA/CMS partnership with the private sector were to be implemented. Dr. Freedman commented that the IOTF is an important venture because the institutions must comply with the law and there is often a need for changes to the law; he concurred with the suggestion to have centers produce IND-cGMP-quality materials, particularly for the study of nanotechnology and bioimaging products. Dr. Kirchner asked whether the Nanotechnology Subcommittee had discussed the availability of training sites in nanotechnology applications and development, inasmuch as the DOE is establishing five nanotechnology centers with training initiatives that could be used. Dr. Barker replied that discussions about the overlap of nanotechnology initiatives are ongoing and that the NCI/DOE task force being formed could address issues such as the training programs. She concluded with an invitation to NCAB members to submit issues that they feel would benefit from IOTF consideration.

X. HARMONIZING PROCESSES AND POLICIES FOR NCI-SUPPORTED BIOREPOSITORIES—DRS. ANNA BARKER, JIM VAUGHT, RIHAB YASSIN, JULIE SCHNEIDER, AND CAROLYN COMPTON

Dr. Barker began by introducing members of the Biorepository Coordinating Committee (BCC) and commending their contributions to this initiative throughout the past 3 years. She also introduced and thanked Drs. Mark Rubin and Art Caplan who chaired two BCC workshops. She reviewed factors that make biorepositories and biospecimens a high priority for the NCI, including: (1) sponsoring, through R01s, the largest contingent of investigators ever assembled to conquer a disease; (2) launching caBIG to provide the IT infrastructure for large-scale databases and inter-institutional studies; (3) developing a national proteomics-based program in biomarker discovery to provide common technologies and standards; (4) collaboratively developing a program to sequence the cancer genome; and (5) launching a nanotechnology initiative to provide advanced systems that can interact with and interrogate cells for diagnosis and treatment. These and many other initiatives required to conquer cancer and realize a future of personalized molecular medicine have human biospecimens as a common need. The catalyst for moving the initiative more rapidly was the issue of public trust and a Congressional inquiry about the lack of a uniform, centralized authority in the NIH that regulates the handling of human tissue samples. The NCI was driven to create a chain of trust because molecular medicine has heightened patient concerns about genetic privacy, making the protection of patient privacy and confidentiality a paramount issue. After the 3-year analysis of NCI's biospecimens and biorepositories, the conclusion and consensus reached was that biospecimens are key to the future of molecular or personalized medicine.

Dr. Barker reviewed highlights of the internal and external review process that followed the identification of biorepositories as an area of critical importance. They included initial NCI surveys and community forums; the publication of the RAND and National Biospecimen Network (NBN) Blueprint reports; plans for a prostate pilot project to be conducted through NCI's prostate SPORes; an internal NCI study of biorepositories and meetings with NCI staff; the finalization of the prostate pilot project; the

formation of the BCC; the completion of a series of White Papers; and two workshops, for which reports have been completed and will be distributed. Dr. Barker reported that the prostate pilot project, a study designed to pilot key aspects of an NBN-like concept, will be launched soon. The goal is to develop a common biospecimen coordination system and informatics infrastructure for collaborative SPORE projects in prostate cancer. She then reviewed the objectives of the inventory of NCI-supported biospecimen resources and inventory results. The findings were that the NCI and cancer research community can improve significantly the return on an investment estimated at \$50M for the major resources, and more if R01 investments are considered. Overall, NCI-supported programs lack common standard operating procedures (SOPs), standards, and management principles; common definitions; computerized and common access to information on specimens and cases; and systematic coordination and distribution. Dr. Barker noted that the NCI is now poised to establish the necessary common infrastructure indicated by the inventory and analysis. Following the prior biorepository report to the NCAB and subsequent presentation to the Executive Committee, the BCC was formed with representatives appointed by Division Directors. Its mission is to advise the NCI leadership on issues related to harmonization policies for NCI-supported biorepositories.

She introduced Dr. Jim Vaught, Special Assistant for Biological Resources, DCEG, and Dr. Rihab Yassin, Program Director, DCB, two BCC members who organized the workshops to obtain input from the participating experts on key issues, proposed solutions, and answers to questions posed in the White Papers distributed before the workshops.

Biospecimen Collection Workshop. Dr. Vaught reminded members that this workshop dealt with best practices for establishing and maintaining biorepositories that support cancer research. He pointed out that the White Papers distributed prior to the workshop had documented issues that have been resolved by other organizations so that workshop discussions could focus on unresolved issues, particularly those related to operation, infrastructure, bioinformatics, and quality assurance/quality control (QA/QC). Bioinformatics and QA/QC issues were considered crosscutting, and an attempt was made to discuss them in all workshop subgroups. Topics addressed by the subgroups were: (1) purpose and use of biorepositories; (2) analytical methods for biospecimen-based research; (3) best practices for biospecimen collection, processing, storage, retrieval, and dissemination; (4) establishing biorepository evaluation and monitoring criteria; (5) access to biospecimens; (6) designing repositories to support research with emerging technologies; and (7) priority setting for biorepositories. The latter topic was intended to guide the NCI in assessing which repositories are meeting their goals and should be supported in the long term.

Biospecimen Access and Ethical, Legal, and Policy (ELP) Issues Workshop. Dr. Yassin stated that the ELP Workshop was organized to develop ethical policy guidelines that harmonize processes across NCI-supported repositories. This was done to facilitate the collection and unencumbered future use of biospecimens and associated data while protecting human research participants and promoting better science, thereby maintaining public trust. The workshop attempted to define NCI-addressable issues and identify those areas calling for partnerships with other organizations. A final goal was to initiate a process that would include public comment and further engage the biomedical research community in developing ELP guidelines. Five sessions of the ELP Workshop addressed issues beginning with the patient's enrollment of research participants and ending with the dissemination of research findings to the larger scientific community. One of the most contentious of the five topics was informed consent and the importance of developing a consent form that facilitates the collection and use of biospecimens across NCI-supported repositories, yet accommodates the provisions of HIPAA and the Common Rule. The privacy, confidentiality and data security session addressed the importance of having a system that protected the health information of patients and explained how to establish such a system with NCI-supported resources. Other topics were IRBs and Governance; Ownership, Legal, and Policy Issues; and Access to Biospecimens and Data.

Review of Recommendations. Dr. Julie Schneider, Technology Program Manager, Office of Technology and Industrial Relations, OD, summarized BCC recommendations that cover issues that can be dealt with directly by the NCI. Recommendations included strategies and actions to: implement first-generation best practices; evaluate current biorepositories; address complex ethical, legal, and policy issues; and establish management structure to coordinate NCI's future efforts. Implementation of the recommendations would have the goals of: (1) optimizing valuable NCI-supported resources; (2) establishing and maintaining a "chain of trust" to ensure accountability in the protection of patient information and effective stewardship of federal resources; (3) promoting investigator access to the highest quality, privacy-protected specimens collected and maintained using common SOPs; and (4) improving the quality of resulting scientific data. Based on the years of research and analysis that preceded the report, recommendations in the report are organized into seven major categories. The first category focuses on optimizing repositories for cancer research by identifying best practices for future prospective collection efforts. The recommendation is to adopt "first generation" collection guidelines and provide them to investigators. Dr. Schneider reported that these will be developed in the coming weeks and will be available for public comment. They will be revised based on that input and updated periodically as technologies change. The second recommendation is to begin developing sets of "second generation" guidelines that are primarily data-driven and recognize the need for different guidelines for different specimen types and analysis methods for different types of research. The process would be initiated in collaboration with appropriate expert organizations. The third and fourth recommendations in this category would be to define a minimal clinical data set that accompanies each biospecimen and implement a standard validation methodology to ensure accuracy and consistency.

The second category relates to QA/QC and the recommendation is to implement a quality management system that, at a minimum, includes: an overall QA/QC policy document; SOPs; verification of staff training; documentation of biospecimen quality; QA/QC spot checking; and periodic compliance auditing. Implementing informatics systems is the third category, and the recommendation highlights the importance of having NCI-supported repositories work toward using a caBIG-driven informatics system that addresses functionality; integration and interoperability; development practices that follow accepted software-development standards; ethical and legal issues to ensure compliance with regulatory standards; and informatics system assessment and auditing. Categorizing and assessing biorepositories is the fourth category of recommendations and implementation would involve establishing guidelines for categorizing biorepositories and then evaluating them based on criteria, including: research mission; level of patient consent; extent of associated clinical data; and physical characteristics and quality of biospecimens. The fifth category of recommendations addresses ELP issues and includes seven recommendations that fall within the purview of the NCI to address. They are to: (1) develop and promote the use of a standard informed consent document; (2) work with caBIG to establish patient privacy protection guidelines; (3) help develop guidelines to clarify IP issues and the rights of institutions that house biorepositories; (4) provide a model Material Transfer Agreement (MTA) to facilitate biospecimen sharing across institutions; and (5) establish common access guidelines for NCI-supported repositories in collaboration with groups that have appropriate experience and make them consistent with ethical principles, laws, regulations, IP policies, and consent form language; (6) require the submission of plans for custodianship of biospecimens and data during and after an NCI grant or award; and (7) encourage user fees that fairly reflect the recovery of costs and help develop models and planning tools.

Dr. Carolyn Compton, Director, Biorepositories and Biospecimen Research, NCI, then reviewed the additional recommendations in the category of ELP issues that will require the collaboration of other institutes, organizations, or agencies for resolution. They are to: (1) develop a strategy to harmonize Common Rule, HIPAA, and FDA regulations as applicable to biorepositories; (2) develop a national policy to address biospecimen ownership and custodianship issues at the highest appropriate level within

DHHS; and (3) develop guidelines for disclosing research results to patients. The sixth category of recommendations related to the issue of establishing reporting mechanisms. Three recommendations in that category were to: (1) collect information on biorepositories to inform funding priorities and decisions; (2) develop a plan and budget to support qualifying existing biorepositories; and (3) publicize existing biorepositories to encourage use. Finally, Dr. Compton noted that the NCI has put forward an administrative solution to the biospecimen issues on a constitutive level with a vision and a goal. The goal is to eliminate, to the greatest degree possible, the garbage in/garbage out paradigm of science. The NCI Office of Biorepositories and Biospecimen Research (OBBR) is to be established to coordinate biorepositories across the NCI, develop the science of biospecimen investigation, and facilitate the development of guidance and guidelines to maintain the highest quality biorepositories through collaboration with appropriate authoritative professional bodies. The OBBR will address these problems on an ongoing basis to ensure that the issues are concordant with the needs of the science that is funded by the NCI. An external advisory board, composed of physicians, scientists, ethicists, and legal experts, will be established to guide the process and provide input, and the BCC will be established as a standing committee.

The vision for the future is to establish biospecimen science as a valid, unique, and critical area of investigation meriting its own funding; elevate biobanking to a new level of professionalism equivalent to that attained in clinical medicine, which the biobanks will serve; and drive technology development to serve biospecimen science, biorepository operations, and, ultimately, serve personalized medicine, which will depend on patient biosamples. Finally, the NCI vision is for the United States to become a leader in the field of biobanking, working with and learning from the global community. Dr. Compton noted the significant investments in biobanking made worldwide because of the widespread recognition of the importance of biospecimens as data sources and because personalized medicine will depend so heavily on biobanking. The position of the United States in big science also will depend on the quality of the analyte, and biospecimens as an analyte cannot be ordered from a catalog. Dr. Compton pointed out that conferring standardized quality on human biospecimens will require science with data-driven operating procedures to support a systematic accelerated discovery in science and valid data output. She concluded that big science, which is so important to improving medicine, has placed increased rigor and quality demands on human analytes, and the NCI plans to meet that challenge.

Dr. Barker invited Dr. Rubin, Chair, Biospecimen Collection Workshop, to comment. Dr. Rubin noted that Dr. Compton's comments recognized the importance of this undertaking and its impact on the ability to conduct the research described in the cancer genome project. He expressed the view that this is the basis for many of the studies to understand whether one is dealing with high-quality research or looking at an artifact; he emphasized the importance of focusing on biorepositories as a research endeavor and thanked the NCI for inviting him to participate.

Dr. Barker stated that the NCI is adding a day to the IBM biobanking meeting in the fall to bring international leaders in the field together to discuss the potential harmonization of their databases on a global basis. She then briefly discussed plans for beginning to implement the recommendations, pointing out that the degree of difficulty will vary and that some will require that Dr. von Eschenbach play a leadership role on behalf of the NCI to take some issues to a higher level within the NIH and DHHS. Immediate action items include formalizing the administrative structure and developing the "first generation" biorepository guidelines, requesting voluntary commitment from NCI communities to implement them. The goal is to move toward more substantive, data-driven guidelines and an appropriate structure for control over the next few years, in collaboration with the NCI community and professional organizations.

Questions and Answers

Ms. Giusti asked what the motivation would be for all repositories to comply with the guidelines and what would be considered metrics of success at one year. Dr. Barker replied that the sense garnered from the community is that people would appreciate some level of guidelines and that asking for voluntary compliance is a good thing to do in the early stages. She listed as measures of success understanding what specimens exist within the cancer research enterprise, having a communal network where specimens could be exchanged, and succeeding in having the research community sign onto the guidelines that have been proposed. Dr. Compton noted the importance also of having investigators understand what is available, increasing access to the biospecimens, and providing the information and quality level of specimen that is needed for the types of analysis being performed. Dr. von Eschenbach outlined the steps to implement this initiative, beginning with providing a validated, quality product that has value in fulfilling a need and obligation. Once such credible evidence exists, the second step is to extend adherence to those standards as a criterion for funding or resources. The third level would occur when a critical mass is reached that then becomes a motivator for independent participation in the initiative or risk losing something of value. He challenged the Board to deliberate and provide input on the idea of setting standards and then branding a concept of leadership that moves the NCI into a slightly different position.

Dr. Patel commended the steps being taken by the NCI to deal with tissue banking in a centralized fashion, and noted that the Veterans Administration, with its registry of 350,000 cancer cases collected during the last 8 years, would be following the lead. He asked about the projected NCI budget for this initiative. Dr. Barker replied that the budget will be driven by the science, as there are no good cost models at this point to guide future implementation. Dr. Armitage cautioned against getting completely lost in the process of collection, making sure that the biospecimens do not sit in repositories, unused because nobody has an experiment important enough to justify the effort it took to collect them. Dr. Barker replied that the NCI goal should be to strive for broad access to the very best specimens. She acknowledged that the method for understanding the platinum-level specimens and defining how to provide access is a hard problem but one that the NCI will have to take leadership in solving. Dr. Freedman asked about the issue of civil rights and the effect of HIPAA on this initiative. Dr. Compton replied that IT colleagues on this project have given assurance that all HIPAA issues can be addressed adequately with information technology and appropriate protections. Dr. Freedman noted the probability that specimens from abroad will be incorporated, and he asked about their oversight. Dr. Barker noted that working with other countries on their plans and gaining familiarity has shown them to be quite robust, rigorous, and successful. Moreover, those systems are looking to the United States for guidance in terms of defining the overarching issues.

Dr. Samir Abu-Ghazaleh, Director, Gynecology and Gynecologic Oncology, Avera McKennan Hospital and University Health Center and Avera Cancer Institute, asked who would make decisions and what mechanism will be in place to access the specimens in the future, and he asked for confirmation that he is right in advising his patients that no gain will be realized from their donation of tissue except for the generations of patients who follow. Dr. Barker emphasized that, ethically, the NCI believes that access to biospecimens should be open and eventually data from these repositories should be open. Concerning access decisions, Dr. Barker noted that currently decisionmaking remains at the level of those to whom the biospecimens belong. As the larger projects, such as sequencing the cancer genome, materialize that produce enormous amounts of data, prioritization will be almost a moral imperative, and the peer review approach probably will be adopted for the foreseeable future in terms of how the specimens get used.

Dr. Potter described the experience of the U.S. Military Cancer Institute in establishing a tissue bank. Motivation came from the fact that high-quality tissue could be assured by establishing SOPs in military operating rooms and by the opportunity presented to characterize the tissue with the extensive

DOD databases. The databases contain longitudinal data in almost all cases, as well as extensive ethnic and epidemiologic data. Dr. Potter noted that, after 3 years spent establishing the tissue bank, the Institute is almost ready to start collecting tissue. He thanked Dr. Joseph Fraumeni, Director, DCEG, Dr. Compton, and Dr. Schneider for serving on their scientific advisory board, and he expressed interest in partnering with the NCI effort.

Dr. Prendergast commented on the challenges to implementing this project, including those related to IRBs and institutional oversight committees dealing with HIPAA compliance, developing an operational plan, the cost for both the NCI and individual institutions, managing the annotation, and metrics for monitoring compliance to the SOPs. He observed that NCI leadership in the area of standardization would be very valuable and asked how compliance would be defined. Dr. Barker acknowledged that those barriers had been defined and discussed early on but noted that, across the community and with the processes that were undertaken, the belief is that progress is possible. Each of the barriers was considered, and the attempt was made to develop workable short-term and long-term solutions for each of them. With regard to compliance, Dr. Barker noted that the definition would evolve over time, but the advice from the workshops was to proceed, changing the community one step at a time and informing the changes with science. In further discussion, the consensus was that the project should proceed as proposed, with extensive professional society consultations and progress reports to the Board.

Motion. A motion to accept the report entitled “Harmonizing Processes and Policies for NCI-Supported Biorepositories” was seconded and unanimously approved.

XI. CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 552(b)(c)(6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Members were instructed to exit the room if they deemed their participation in the deliberation of any matter before the Board to be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

The en bloc vote for concurrence with IRG recommendations was _____. During the closed session of the meeting, a total of _____ applications were reviewed requesting support of \$ _____. The subcommittee meeting adjourned at 5: _____ p.m.

DAY TWO: WEDNESDAY, SEPTEMBER 21, 2005**XII. TRANSLATING RESEARCH INTO IMPROVED OUTCOMES (TRIO): THE CANCER CONTROL PLANET—DRS. ROBERT CROYLE AND JON KERNER**

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), introduced Dr. Kerner to present an update on Cancer Control PLANET, explaining that this is a Web portal that promotes reliance by public health program directors on evidence rather than anecdote or intuition in developing their programs. It was developed and is maintained and operated in collaboration with several other agencies. As a preface to his update on TRIO and Cancer Control PLANET, Dr. Kerner presented a few definitions and challenges related to research translation. The challenge is to help practitioners and the public understand what information from the huge amount of new science pouring from discovery and development aspects of the continuum is useful now versus 5 years from now. Translational research differs from research translation in that the former exists in the context of academia and industry, and the latter is carried out in the contexts of public health, primary care, and oncology specialty practices and each context differs from the others. He also made the point that research translation involves dissemination and implementation within those contexts as opposed to communication to the public. In addition, it is important to understand that getting evidence-based cancer control interventions into practice requires solving the dilemma of integrating the push of science with an understanding of what practitioners need to be successful in building the capacity of relevant intervention delivery systems and improving population health and well being. Translation can be defined as the transfer of evidence-based knowledge into routine or representative practice or, in another model, as the informed combination of evidence-based knowledge and local contextual knowledge into community applications.

Against that background and those understandings, Dr. Kerner explained that the TRIO program was initiated as a collaboration with the ACS, AHRQ, CDC, CMS, and HRSA to: (1) use and communicate cancer and behavioral surveillance data to identify needs, track progress, and motivate action; (2) develop tools to access and promote the adoption of evidence-based cancer control interventions; and (3) support regional and local partnerships to develop models that identify infrastructure barriers, expand capacity, and integrate science into comprehensive cancer control planning and implementation. Cancer Control PLANET (PLANET) is one tool developed under TRIO.

Dr. Kerner described PLANET as a Web portal that links critical information from all sponsors. The opening page displays five steps that can be followed to develop a comprehensive cancer control plan, with links as appropriate to the different sponsors where the specific resources can be found and downloaded. The five steps are to: (1) assess program priorities; (2) identify potential partners; (3) research reviews of different evidence-based intervention approaches; (4) find research-tested intervention programs and products; and (5) plan and evaluate the program. The same information can be accessed by cancer control topic. A link at the bottom of each page creates an e-mail to allow the user to send feedback on the portal. Dr. Kerner then demonstrated in detail the specific resources that are available for users to carry out each step in their own cancer control program planning processes. He showed how each tool can be customized to the particular location of the program, the targeted population, and the cancer care or prevention problem. For example, under step one, the State Cancer Profiles, a partnership between the CDC and NCI, provides statistics for prioritizing cancer control. Profiles can be generated by nation, state, or county on each cancer of interest and in map or graph format. All tools are developed with a user-centric design. In other steps where the effort is to link researchers and practitioners, names, contact information, and areas of expertise are included. For example, contact information for trained senior leadership teams is available to help the program planner identify potential partners under step two. Under step three, the Guide to Community Preventive

Services, a CDC-sponsored effort, synthesizes the science for multiple published studies in different topic areas, including those that relate to cancer prevention and control. Step three also leads to the AHRQ Web Site and U.S. Preventive Services Task Force information. Step four accesses information on Research-Tested Intervention Programs (RTIPs) organized by the NCI in collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA). Organization is by program topic area, and new programs are highlighted as they are added. Eligibility requirements for programs to be included in RTIPs are evaluation in a peer-reviewed research grant, publication in a peer-reviewed journal, and adaptability and usefulness of program and products in community or clinical settings.

Dr. Kerner then presented PLANET/RTIPs Web usage statistics. Since the program's launch in April 2003, more than 1,000 public health practitioners have been trained to use PLANET. The average number of visitors per month is 3,925 for PLANET and 892 for RTIPs, which currently has 53 programs posted. Since its initiation, 552 RTIP program CDs have been ordered and 5,159 products downloaded. Researchers who provide the programs are contacted monthly to verify contact information and present a report on usage of their programs or products. Dr. Kerner stated that a new evaluation effort is underway to determine how the programs are actually being used. In addition, the research community is being encouraged to use PLANET and test its dissemination capability, and R01 and R25 applications are beginning to come in that evaluate research dissemination.

Next, Dr. Kerner discussed the new Program Resource for Implementation, Management and Evaluation (PRIME) that is being developed as a partnership between the NCI and philanthropic organizations interested in funding evidence-based cancer control services. The first partner to be signed to PRIME is the Lance Armstrong Foundation, and conversations are underway with the Susan B. Komen Foundation and Legacy, as well as other cancer-related foundations. PRIME will be added to PLANET to further strengthen step five as an implementation resource. Another new program being developed in a partnership with the AHRQ and ACS is a Web site called Clinicians Linking Information to Patients (CLIPS), which adapts information from PLANET for handouts for patients, guidelines to physicians, and referral resources. A final initiative under development is PLANET for Health, a Web portal that will add content to translate the PLANET information management model to other diseases and risk factors. Dr. Kerner reported that the National Institute of Canada has agreed to put all Canadian content for cancer on PLANET for Health, and that operation is expected to be completed by the World Health Organization (WHO) meeting next summer. Discussions are underway with other potential partners for PLANET for Health, including the National Institute for Mental Health, National Institute for Alcohol Abuse and Alcoholism, National Institute for Drug Abuse, and CDC's Division of Nutrition and Physical Activity. Partners would pay a marginal cost to put their content on the PLANET engine. Dr. Kerner noted that he has been asked to lead NCI's effort on international cancer control activities and that he will be meeting with personnel from WHO, its International Agency for Research on Cancer (IARC), and the International Union Against Cancer (UICC) in coming months to discuss PLANET as a model.

Questions and Answers

Ms. Giusti asked how R01 research could be based on PLANET. Dr. Kerner explained that more substantive information is needed in addition to Web statistics to determine whether PLANET is influencing practice. The NCI is initiating its own evaluative study using a program from the Office of Management and Budget to sample users. In another example, the CIS, ACS, CDC, and the U.S. Department of Agriculture are collaborating on a project called Team Up. Team Up is training cooperative extension agents to collaborate with the CIS, ACS, and the Department of State health departments to reach women for cervical cancer screening using evidence-based approaches from PLANET. Return on investment is an important focus for evaluating the access PLANET provides to evidence-based programs on RTIP and data in an easy-to-use format that can be integrated into public

health practice. Dr. Von Hoff asked how PLANET can be made more available and useful in oncology practices, given oncologists' time constraints. Dr. Kerner replied that CLIPS is targeted at that dilemma in primary care practices, and efforts are underway to obtain similar data in a format for busy oncologists. Dr. Runowicz suggested the Oncology Nursing Society as a point of dissemination because nurses can speak with patients and their families.

XIII. EVIDENCE REPORT ON RECRUITMENT OF UNDERREPRESENTED POPULATIONS TO CANCER CLINICAL TRIALS—DRS. ROBERT CROYLE, ERIC BASS, JEAN FORD, AND MOLLIE HOWERTON

Dr. Croyle began the presentation by noting that DCCPS staff act as the NCI liaison to the AHRQ and collaborate with that Agency on its Evidence-based Practice Centers (EPC) program. He explained that the EPC is funded by AHRQ to conduct formal evidence syntheses in a number of different areas, and the NCI has used the program by funding some projects that AHRQ has done. One NCI-funded evidence review focused on recruitment to clinical trials. It was advertised as a task order, and the Johns Hopkins University EPC was selected as the project lead for this review. Dr. Croyle welcomed and introduced Dr. Eric Bass, Professor of Medicine, Johns Hopkins University School of Medicine; Dr. Jean Ford, Associate Professor of Epidemiology, The Sidney Kimmel Comprehensive Cancer Center; and Dr. Mollie Howerton, Instructor in Oncology, Johns Hopkins University School of Medicine.

Background. Dr. Bass stated that objectives of the presentation were to describe results of the EPC's systematic review of recruitment evidence in these populations and then present recommendations based on report findings. As background, he reminded members that the 1993 NIH Revitalization Act called for the inclusion of women and minorities in all human subjects research. Although the NCI budget nearly doubled in the 5 ensuing years and trial accrual increased, it was unclear whether all populations benefited. Numerous barriers to recruitment of underrepresented populations are known, and there has been increased attention to promoters of recruitment; yet questions remain about the effectiveness of strategies to increase the participation by these groups in clinical trials. Dr. Bass explained that the Johns Hopkins project sought to review and synthesize all of the published evidence on this topic by focusing on five key areas: barriers and promoters, effects of health care providers on recruitment, efficacy of specific recruitment strategies, measures of recruitment success, and methods that have been used to study recruitment strategies.

Conceptual Framework; Search Strategy; Study Characteristics. Dr. Ford noted that one of the first steps of this systematic review was to build on the conceptual framework of colleagues that the steps toward participation are awareness, informed acceptance/entering, and retention with multiple factors in each step that influence the individual. In the search for materials, 4,436 potential abstracts were retrieved from a variety of electronic databases. Further review of abstracts and articles, as the search strategy was refined, yielded 67 eligible articles to answer the study's key questions and, ultimately, 45 to address barriers to and promoters of enrollment. Of the 45, only 10 were published before 1996; the study designs were a mix of observational/experimental, descriptive (registry reviews, surveys), and qualitative (focus groups, semi-structured interviews); and settings in which the studies were conducted were primarily hospital and the community, with a few in other recruitment settings, including cooperative groups. The target populations for the studies focused most on patients or participants themselves, some on physicians, and a few on researchers. The majority of eligible studies focused on accrual to cancer therapeutic trials and fewer on prevention trials. Some studies focused on actual accrual to a trial as the outcome, but a significant number focused on behavioral intention rather than actual accrual. The largest number of available studies focused on African Americans and the elderly, with few on other underrepresented populations. Most studies were U.S.-based in regard to barriers and promoters.

Findings. A summary of barriers and promoters at the patient, provider, and health care system levels showed that a larger number of barriers was reported than promoters at every level. The most frequently reported barrier was mistrust of the research system, researchers, and the medical system. Other commonly reported barriers were perceived harms, the lack of education about trials, and logistics like transportation availability and the required time commitment. In synthesizing the reported barriers according to the study's conceptual framework, the lack of education regarding clinical trials was most frequently cited barrier to **awareness**, followed by the lack of dissemination of trial opportunities, the lack of cancer knowledge, and physicians' lack of awareness about cancer-related trials. Barriers to **opportunity** to participate in trials, in order of frequency, were logistics, demographic factors (e.g., age and race), co-morbid conditions, costs, provider relationship, and communication about available opportunities. Barriers to **acceptance of participation** were perceived harm; an aggregation of culturally relevant factors such as beliefs, patients' relationships with their providers, family considerations, physical and logistical discomfort, and attitudes towards research; and costs, including lack of health insurance. The most frequently reported promoters were perceived benefits of trial participation, patient incentives, altruism, culturally relevant education about clinical trials, and provider incentives. Other key findings included: (1) available evidence is mostly about accrual to therapeutic trials; (2) barriers to opportunity were frequently reported for both prevention and treatment trials; (3) limited data existed on Latinos/Hispanics, Asian/Pacific Islanders, American Indians/Alaskan Natives, older adults, and adolescents; and (4) barriers differed across populations. In a summary of the relation of barriers and promoters to the study's conceptual framework, Dr. Ford noted that **awareness** had 8 barriers and 6 promoters, **opportunity to participate** had 81 barriers and 29 promoters, and **acceptance or refusal of participation** had 25 barriers and 25 promoters.

Health care Provider Effects. Dr. Howerton reported on key findings from 10 studies of the effects that providers have on recruitment. Health care professional barriers include a variety of factors that relate to the opportunity to participate in clinical trials. Opportunity factors at the provider level include provider attitudes about clinical trials or their patient's ability to participate, the potential for noncompliance, and the provider's method of communication about trials. Other opportunity factors involve issues of eligibility such as patient age, disease stage, or comorbidity. At the level of study design, barriers were related mostly to eligibility and, to a lesser extent, to protocol complexity and length of study or visit structure. Dr. Howerton noted that two studies reported health care system barriers that played a role in decreased patient accrual to clinical trials, and the barriers operated at a variety of levels. At the interpersonal level, there was a lack of cultural competence among providers and staff and few minority investigators or personnel. At a professional level, providers did not necessarily know about available trials and protocols or have access to institutions conducting trials.

Efficacy of Recruitment Strategies. Dr. Howerton reported that five studies were located that tested various recruitment strategies for treatment or prevention trials and had some sort of comparison group. Of the five, only one was a treatment trial. Recruitment strategies or interventions varied from study to study, the target populations was very diverse, and most of the studies used recruitment letters, fliers, and telephone calls. After a brief review of each study, Dr. Howerton noted that three of the five studies showed an intervention effect. Limitations of the studies related to the efficacy of recruitment interventions were that very few evaluated the effectiveness of recruitment strategies, generalizations were limited, and the quality of study methods varied. Only one study recruited into a treatment trial, and that ability is a major metric of comprehensive cancer centers.

Measures of Recruitment Success. Dr. Howerton noted that 23 studies reported a degree of recruitment success. Recruitment equaled actual participation in all of these studies. Only two reported *a priori* recruitment goals: one with a goal of recruiting at least 22 percent of its rural study population met its goal; the other, a prostate cancer prevention trial, fell short of its goal of having eligible African

Americans constitute at least 8 percent of the study population. Challenges in defining *a priori* recruitment goals were the increased study costs and the need to balance competing priorities. The latter included disease-specific requirements, participant retention concerns, IRB requirements, and timeline requirements.

Methods to Study Recruitment. Dr. Howerton reported that 13 studies were eligible to answer the final key question and their study designs varied. Most were descriptive or randomized controlled trials but there also were a quasi-experimental, a case series, and a qualitative design that used focus groups.

Overall Summary. Dr. Bass summarized the findings, noting that more barriers to the opportunity to participate in a trial were found than to awareness or acceptance of trials. More evidence was found on barriers than on promoters, and mistrust was a common theme. Provider barriers were found to exist at the levels of professionals, study design, and health care system. There was sparse evidence on the efficacy of recruitment strategies. Recruitment goals were rarely reported *a priori*. A variety of methods was used to study recruitment strategies, but most were relatively weak designs. Dr. Bass noted that the evidence report had several limitations, most notably, the difficulty of synthesizing information because of the heterogeneity in both study design and data quality. The relation between and among barriers and promoters generally was not addressed in the studies, and they generally did not differentiate the overlap between underrepresented populations. A greater amount of evidence was found on the recruitment to therapeutic trials than prevention trials. Studies other than cancer clinical trials were excluded so that the focus could be specifically on the recruitment to control trials of cancer treatment and prevention. Finally, Dr. Bass acknowledged that many investigators have experience in recruiting underrepresented populations, but much of that has not been reported. Despite these limitations, he stated, enough evidence exists to recommend a greater emphasis on reporting *a priori* recruitment goals and results, consideration of a conceptual framework similar to that used by the EPC when designing and evaluating recruitment strategies, and training for investigators to enable them to identify and address barriers. Also recommended is the evaluation of the role of underrepresented health care professionals and community health workers, the cost-effectiveness of interventions, and tailored and targeted recruitment interventions.

Questions and Answers

Dr. Chen asked whether the Johns Hopkins study uncovered terminology being used to convey the idea of clinical trials, and whether the translation of that concept could be conveying some cultural meaning that creates a barrier to participation. Dr. Bass replied that to the extent it arose, it was probably classified under the category of cultural competency and understanding of terminologies. He noted that language implications probably have not been explored very well because of the small amount of work focusing on recruitment of non-English speaking patients. Dr. Patel asked how the education of oncologists could be carried out. Dr. Bass noted that the published evidence does not answer that question, although it does suggest that participating investigators need help in identifying and addressing the barriers. Dr. Ford added that, with regard to the education of providers and their linkage to the clinical trials enterprise, the disparities within the population must be considered. These include demographic differences as well as differences in training levels and connectedness to state-of-the-art activities. Dr. Patel asked whether Medicare and Medicaid patients are enrolled in trials or prevented from doing so because of additional cost and time to the oncologist. Dr. Bass pointed out the scarcity of published evidence and the fact that a systems-level problem may be harder for an individual trial to solve. Dr. Freedman observed that investigators are required to state their goals for minority recruitment as part of the grant application process, and he wondered how closely those goals were being monitored for cancer centers as well as individual investigators. Dr. Bass noted that his EPC team was concerned that the goals investigators set in their grants were not showing up in their ensuing publications or reports.

A recommendation to make that a standard and ensure that information about efficacious strategies is reported could help get underrepresented groups into trials and advance the field.

Dr. Freedman asked what could be done to facilitate the transfer of knowledge between centers of research and county hospitals in those major population areas with large concentrations of underserved patients. Dr. Bass pointed out that the CTWG has emphasized the importance of minority-based community clinical oncology programs. Dr. Armitage observed that the previous committee to improve clinical research that he chaired heard from the HIV lobby that the U.S. method for obtaining informed consent was a barrier, and from leading African American physicians that they did not feel involved or wanted, and that they had mistrust. Dr. Ford noted that the evidence consistently refers to trust as a critical variable and what is missing is how to develop new evidence to address some of those barriers. Dr. Freedman suggested that, as one possible step, clinical trial grant applications could require *a priori* recruitment goals, possible strategies to achieve them, and a realistic estimate of the resources needed. Dr. von Eschenbach thanked the EPC team for their report and presentation, noting that the evidence has been brought forward that focuses on a question that can be addressed. He proposed that the NCI immediately bring Drs. Doroshov, Springfield, and Croyle together under the leadership of Dr. Clanton to devise an effective implementation strategy for discovering and implementing solutions to the problem. The results of this collaborative effort would be reported to the Board.

XIV. EPIGENETIC CONCEPTS IN CANCER—DRS. DINAH SINGER, GARY FELSENFELD, ANDREW FEINBERG, AND PETER JONES

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), noted that much progress has been made in understanding the role that mutations in oncogenes and tumor suppressor genes play in the etiology of cancer by causing permanent changes in tumor cell growth and cell death. In addition to these genetic mutations, major contributors to cancer development include interactions between the tumor and its microenvironment and epigenetics. Epigenetics indicates a change in the genome that is heritable but does not alter the underlying DNA sequence. Epigenetic changes are clearly associated with cancer; therefore, understanding epigenetics and epigenetic phenomena is critical to understand the basis of cancer more clearly. She introduced Dr. Gary Felsenfeld, Chief, Laboratory of Molecular Biology, NIDDK; Dr. Andrew Feinberg, King Fahd Professor of Medicine, Johns Hopkins University; and Dr. Peter Jones, Director, USC/Norris Comprehensive Cancer Center, to present reports on the field of epigenetics and its association with cancer.

Epigenetics Overview—Dr. Felsenfeld

Dr. Felsenfeld explained that epigenetic information is not encoded in the DNA sequence but is transmissible during cell division by mechanisms that involve chemical modifications of DNA bases or the proteins with which the DNA is packaged. These modifications control patterns of gene expression, cell division, and other cellular functions. Defects in epigenetic mechanisms, much like mutations, can have profound effects on cells and organisms. Epigenetic modifications also can result, through the inactivation of different regions of DNA, in differentiation of similar precursor cells to mature cells with distinct phenotypes.

Epigenetic modifications that affect gene activity include DNA methylation, which usually occurs at cytosine residues found next to guanine residues (CpG islands). The enzyme that methylates the initial cytosine base is called a *de novo* methylase; other enzymes methylate the cytosine on the complementary strand. When the DNA strands are separated and new copies are made during DNA replication, the methyl group that was on the old strand is copied onto the new strand, thus propagating this epigenetic mark. In the nucleus, eukaryotic DNA is compacted into chromatin, which is comprised of repeating subunits called nucleosomes that contain a central core made of proteins called histones, around which the

DNA is wrapped. Nucleosomes contain two each of four kinds of histones, H2A, H2B, H3, and H4, all of which are subject to epigenetic modifications. Histone variants—which are encoded by separate genes, have different amino acid sequences, and have highly specialized functions—also exist. Accessible sites on the histones can be chemically modified, usually after they are incorporated into nucleosomes. Modifications include histone acetylation, phosphorylation, and ubiquitination, and specific enzymes exist to add and remove these chemical moieties.

Histone modifications can affect transcription by activating or inhibiting gene activity. Upstream of the transcription start site are regulatory elements called enhancers, which stimulate transcription by binding regulatory factors that can interact directly with the polymerase complex bound to the transcription start site. Many of these factors can bind proteins that directly or indirectly recruit the enzymes that modify the chromatin template. In addition, this mechanism recruits ATP-dependent chromatin remodeling factors; these are distinct from histone modifying factors and help to open the chromatin structure, thereby rendering the promoter region more accessible to transcription factors, which is critical to gene expression.

Epigenetic marks communicate with one another and have hierarchical relationships, with certain modifications potentiating others; modified histones also can recruit other molecules that remodel chromatin to either activate or inactivate transcription. For example, methylation of lysine 9 on histone H3 allows binding of the heterochromatin protein HP1, which assists in chromatin compaction and silencing. Methylation of other histones can result in the recruitment of a nucleosome remodeling complex, which helps activate chromatin. Moreover, methylated CpG sites can recruit histone deacetylases, which inactivate nucleosomes by removing acetyl groups from the histones.

Chromatin silencing signals can be propagated. When DNA replicates, the old nucleosomes are randomly distributed on either side of the replication fork with their methyl groups. New histones will be synthesized and fill in the gaps and are thus likely to be positioned next to an old, methylated nucleosome, which recruits proteins that methylate the new nucleosomes, thus propagating the silencing methylation signal. To create silent chromatin initially, an area of DNA with a large number of repeated sequences is transcribed into double-stranded RNA, which can then be cut into small base pair fragments by a complex containing the enzyme Dicer. These fragments are separated and captured by a protein complex, RITS, and transported back to the original site of transcription, resulting in the recruitment of the enzyme that methylates lysine 9 on histone H3, creating silent chromatin.

DNA methylation also plays a major regulatory role in imprinting; the insulin-like growth factor 2 (IGF2) locus is a well-known example of this sort of regulation. Normally, the maternally transmitted IGF2 allele is inactive, while the paternally transmitted allele is active. The IGF2 regulatory region is not methylated on the maternal allele, but is on the paternal allele, at CpG sites. The control region contains binding sites for the CCCTC-binding factor (CTCF); when bound, CTCF can block the distal enhancers that are responsible for activating IGF2, thus blocking the transcription of the gene. On the paternal allele, methylation of the CTCF binding sites prevents CTCF binding and allows the upstream enhancers to activate IGF2 gene transcription.

Epigenetics and Human Disease—Dr. Feinberg

Dr. Feinberg discussed epigenetics' role in cancer and other human diseases. The epigenome consists of all epigenetic information, including modifications such as methylation and chromatin structure, across the entire genome. Except for exceptions like immunoglobulin gene rearrangement, the DNA sequence does not change throughout a person's life, but the epigenome does change, affecting differentiation and development. For example, a brain cell and a heart cell contain the same DNA

sequence; epigenetic changes to silence or activate specific genetic programs contribute to the very large phenotypic differences between these cell types. Epigenetic changes, rather than changes in DNA sequence, also appear to be important in distinguishing an aged cell from a young cell; research has demonstrated that DNA sequence does not change as people age.

In the development of cancer, genetic mutations appear to be the primary mechanism for gatekeeper mutations. These include mutations such as the adenomatous polyposis coli (APC) mutation, which causes a rare polyposis syndrome and is mutated in essentially all colon cancers. The genetic bases for many of the rare family cancer syndromes have been identified, and many of the genes involved in these rare syndromes are involved in tumors that are more common. Unfortunately, mutations are rarely found in normal cells, even in cancers with a strong genetic component. Cancer is believed to be approximately 30 percent hereditary, yet far less than 30 percent of the population has predisposing mutations in genes known to be involved in cancer. Even for colon cancer, which is the best understood genetic model for cancer, at most 3 percent of patients have a detectable, predisposing mutation. This low detection rate hinders the development of tests for common cancer risk.

Dr. Feinberg described the role of epigenetic changes in cancer. The first change found systematically in tumors was hypomethylation; every tumor that has been systematically examined shows dramatic changes in methylation levels, which can contribute to carcinogenesis in several ways. First, loss of methylation causes chromosome instability through the decondensation of the chromatin that helps stabilize centromeres, leading to chromosome rearrangements that are very significant in cancer; the most common genetic change in cancer is a change in chromosome numbers. Second, a number of genes are directly affected by loss of methylation, leading to their activation. These genes include oncogenes such as HPV16; hypomethylation and subsequent activation of HPV16 is a major cause of cervical cancer. Third, tumor suppressor genes, such as RB, p16, and APC also are silenced epigenetically, which is associated with hypermethylation, leading to tumor growth. Currently, some groups are developing blood tests for epigenetic changes that might enable testing for precancerous changes. In addition to methylation, global changes in other epigenetic marks, such as increases in variant histones and changes in acetylation and lysine methylation of histones, are seen in some cancers. Moreover, epigenetic changes are, by definition, reversible, thus leading to the hope that chemotherapies, or even chemoprevention strategies, can be developed based on the manipulation of epigenetic processes.

IGF2 is an autocrine growth factor that has a role in cancer and is overexpressed in many tumors. It is an imprinted gene, normally active only on the paternal allele and silent on the maternal allele. Loss of methylation on the maternal allele is often found in tumors and results in activation of the maternal IGF2 allele, leading to a double dose of IGF2, which creates a growth imbalance and leads to tumor growth. This mechanism was first discovered in Wilm's tumor of the kidney, and in the cancer predisposition disorder as part of Beckwith-Weideman Syndrome. It has subsequently been determined that loss of imprinting is a very common change in tumors. Loss of imprinting is commonly seen in colorectal tumors and can be observed in approximately 9 percent of the population and appears to be associated with a modest threefold to fourfold increase in risk. However, because the prevalence is high (9 percent), the population attributable risk would be significant and loss of imprinting could account for a significant fraction of colorectal cancer risk in the general population.

One question arising from this work is whether loss of imprinting preceded or followed tumorigenesis. An experiment to test this involved the creation of mouse models for colorectal cancer with loss of imprinting, mutations in the APC gene, or both. The mouse with only loss of imprinting did not develop colorectal tumors. The mouse with the APC mutation developed tumors, and the mouse with both the mutation and loss of imprinting developed a greater number of tumors. Loss of imprinting appears to be a modifier of risk that enhances the probability of developing cancer when a genetic change

occurs. Microscopic examination of the intestines of mice with loss of imprinting showed an increase in the number of progenitor cells; there is evidence that this occurs in humans as well, both in the colon, and in independent work showing methylation changes in human breast stromal cells of cancer patients. Epigenetic changes thus may affect how progenitor cells differentiate; other epigenetic changes can impinge on growth factors, such as IGF2, leading to a change in the progenitor cell compartment and imbalances between differentiated and undifferentiated cells. Interestingly, many of the most malignant and difficult to treat types of cancer have properties of the progenitor cell that initially gave rise to the tumor.

Dr. Feinberg explained that epigenetic mechanisms may have a role in diseases other than cancer. Most common diseases are adult-onset, with risk and severity increasing with age, and, presumably, accumulation of genetic and epigenetic changes. In addition to genetic variations and environmental factors that cause disease, epigenetic changes that may modify DNA and alter cancer risk by perturbing gene expression must be considered. To begin to address this, experiments have been performed in which a methylation site-specific restriction enzyme is used to fractionate methylated and unmethylated DNA and then hybridize the DNA to a gene chip, creating an overview of the methylation state of the entire genome. Methylation sites have been mapped onto the genome, and comparisons of methylation status can be made at specific sites.

Epigenetics and Cancer—Dr. Jones

Dr. Jones described the relationship between epigenetics and cancer. The profound differences in structure conferred by epigenetics can be seen when considering different tissue types; each tissue has the same genome but very different structures and functions. Many of these phenotypic differences occur because of differential gene expression that is regulated in part by epigenetic mechanisms, for example, by gene silencing via histone modification, DNA methylation, and other mechanisms.

DNA methylation can contribute causally to the formation of human cancer. In the cancer, retinoblastoma, the wild type retinoblastoma allele was always lost in tumors, leading to scientific proof of the existence of tumor suppressor genes. Similarly, in gastric cancers, the wild type allele of the cadherin gene is always methylated, or silenced, and in some colon cancers both alleles of the MNH1 gene may be silenced by methylation rather than mutation. This loss of heterozygosity, whether by mutation or gene silencing via methylation, can contribute to the development of cancer. Moreover, methylation changes can occur within regulatory regions, also leading to gene silencing. Methylation defects have been found in components of the six Weinberg pathways that contribute to carcinogenesis in ductal carcinoma *in situ* (such as evasion of apoptosis, sustained angiogenesis, and tissue invasion and metastasis).

Dr. Jones informed the NCAB that plans are underway to include epigenome analysis in the Human Cancer Genome Project and an AACR workshop on the human epigenome was held in June to discuss this topic. At this workshop, participants asked whether the technology was ready for high throughput sequencing of epigenomes. Some tools are available, such as a technique called MethyLight, which allows visualization of hundreds of markers simultaneously. Because epigenetic changes probably outnumber genetic changes in cancer, workshop participants decided that a reference epigenome was needed. Human fibroblasts were suggested as the source of the reference epigenome because they are easily obtainable and cultured. The reference epigenome would be sequenced at one base pair level of resolution; subsequent epigenomes would be sequenced at a lower level of resolution. This project will have major implications for cancer research and other disease states, including diseases of aging, which affect many people.

Questions and Answers

Dr. Nienhuis asked if Dr. Jones' talk implied that there is no clear reference epigenome because each tissue type will have a different pattern of methylation and histone modification. In tumors, it would seem necessary to compare tumor cells to normal cells within the same tissue. Dr. Jones answered that the goal would be to develop a large body of information concerning the epigenome of one tissue type. Thorough examination of this reference epigenome could lead to ideas for future investigations, once "hot spots" or particular regulatory areas are located. Dr. Feinberg commented that a starting point could be to analyze lymphocytes, fibroblasts, or both, as many samples of these tissue types are available. The next step would be to analyze a larger subset of tissues, including cancer tissues, and study them in slightly less detail, focusing on cost-effective experiments. For example, it would cost approximately \$10,000 to search the entire epigenome for methylation marks in certain regions.

Dr. Nienhuis commented on the dual and potentially opposing effects of demethylating agents, which could beneficially activate silenced tumor suppressor genes but simultaneously alter the imprinting pattern, which could be detrimental. He asked how the relative importance of these two possible outcomes could be assessed. Dr. Jones answered that until the epigenome is fully understood, it is not possible to answer this question. Dr. Feinberg added that it might be possible to target pathways through a rational drug design without necessarily trying to reverse the epigenetic change directly. Dr. Felsenfeld suggested that basic research on how imprinting signals are established is needed to define a "baseline epigenome."

When asked to rank the importance of a cancer genome study versus an epigenome study, Dr. Jones responded that both efforts are needed, particularly to generate information about the structure of the human chromosome at the molecular level. He noted that investigators currently are studying the epigenome, but as with early efforts in the field of genomics, a more comprehensive and collaborative approach is needed. Dr. Feinberg added that an epigenome project would be of great interest to all of the NIH Institutes because of the potential impact of epigenetics on diseases other than cancer. Dr. Felsenfeld commented that DNA sequence alone is not sufficient to understand normal versus abnormal cell growth. Additional information is needed concerning the recruitment of proteins to regulatory regions and the location of those regions, conditions under which genes are activated or silenced, and how activation or silencing is accomplished in various cell types.

Dr. von Eschenbach thanked the presenters and acknowledged Dr. Singer for her ongoing efforts on this project and in communicating its progress to the NCI, and Dr. Marge Foti, the CEO of the American Association for Cancer Research, which has been a partner in this effort. He observed that the presentations focused on chemical modifications but that the impact of physical and structural alterations also must be addressed to understand the epigenome fully. Dr. Feinberg agreed, stating that chemical modifications currently are the easiest changes to investigate, but further study is needed to understand how the DNA is physically arranged—for example, how genes and regulatory elements are brought into proximity with one another in a physical structure. Dr. Felsenfeld added that researchers are beginning to develop methods to examine the three-dimensional organization of DNA within the nucleus and the epigenetic modifications that lead to rearrangements that bring important regulatory elements close together. Improved high-resolution microscopic methods are needed to better understand the physical impact of epigenetic modifications. Dr. von Eschenbach suggested pursuing relationships with the National Laboratories, which is developing the sort of sophisticated technologies needed for this work. Nonetheless, any epigenomic project must address at the outset the gap between chemical modifications of the DNA sequence and the physical DNA structure in a systematic way.

Dr. Barker remarked that the presentations captured the importance of the relationship between

the genome and the epigenome. Classical genomicists and sequencers currently are struggling with the complexity of the genome, and further progress in epigenomics will aid in clarifying this complexity. Sequencing cancer genes is a huge undertaking; however, sequencing in isolation is not optimal. The fact that technology currently is available for epigenetic studies is encouraging, and an integrated effort to develop a cancer epigenome should be a priority.

XV. AGENDA ITEMS AND ADJOURNMENT—DR. DANIEL VON HOFF

Dr. Von Hoff requested that Subcommittee reports be postponed until the December meeting, and he asked that suggestions as to future agenda items be sent to himself or Dr. Gray.

There being no further business, the 135th regular meeting of the NCAB was adjourned at 11:43 a.m. on ~~Wednesday, September 21, 2005.~~ _____