DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
136th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 6-7, 2005

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
December 6-7, 2005

The National Cancer Advisory Board (NCAB) convened for its 136th regular meeting on Tuesday, December 6, 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, December 6, 2005, from 8:30 a.m. to 4:45 p.m. The meeting was closed to the public from 4:45 p.m. until adjournment at 5:30 p.m. The meeting was open to the public on Wednesday, December 7, 2005, from 8:30 a.m. until adjournment at 11:30 a.m. NCAB Acting Chair Dr. Daniel D. Von Hoff, Senior Investigator and Director of Translational Research, Translational Genomics Research Institute (TGen), Phoenix AZ, presided during both the open and closed sessions.

NCAB Members

Dr. Daniel D. Von Hoff (Acting Chair)
Dr. Samir Abu-Ghazaleh (absent)
Dr. James O. Armitage
Dr. Moon S. Chen, Jr.
Dr. Kenneth Cowan
Dr. Jean B. deKernion (absent)
Dr. Ralph S. Freedman
Dr. James H. French (absent)
Ms. Kathryn Giusti (absent)
Dr. David Koch
Dr. Eric S. Lander (absent)
Dr. Diana M. Lopez
Dr. Arthur Nienhuis (absent)
Ms. Marlys Popma (absent)
Dr. Franklyn G. Prendergast (absent)
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. Louisa Chapman, OST
Dr. Allen Dearry, NIEHS
Ms. Raye Ann Dorn, VHA
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD (absent)
Dr. R. Julian Preston, EPA (absent)
Dr. Anita Schill, NIOSH (absent)
Dr. Donald Wright, OSHA (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Ms. Nelvis Castro, Acting Director, Office of Communications
Dr. Mark Clanton, Deputy Director for Health Care Delivery
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Gregory Downing, Director, Office of Technology and Industrial Relations
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette 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. Ernest T. Hawk, Director, Office of Centers, Training, and Resources
Dr. John Niederhuber, Deputy Director for Translational and Clinical Sciences
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Acting Associate Director, Center to Reduce Cancer Health Disparities
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

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

TABLE OF CONTENTS

DAY ONE: TUESDAY, DECEMBER 6, 2005

DAY TWO: WEDNESDAY, DECEMBER 7, 2005

DAY ONE: TUESDAY, DECEMBER 6, 2005

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

Dr. Daniel Von Hoff, Senior Investigator and Director of Translational Research, Translational Genomics Research Institute, called to order the 136th NCAB meeting. He welcomed and introduced *ex officio* members of the Board in attendance: Dr. Louisa Chapman, Office of Science and Technology (OST); Dr. Allen Dearry, National Institute of Environmental Health Sciences (NIEHS); Ms. Raye Anne Dorn, Veterans Health Administration (VHA); and Dr. Peter Kirchner, Department of Energy (DOE). He introduced and welcomed liaison representatives and thanked NCI staff for their help in organizing this meeting. Members of the public were welcomed and invited to submit to Dr. Paulette Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Von Hoff then reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the September 20-21, 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, and he reminded members that the next meeting will be held on February 6-8, 2006.

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

Dr. Andrew von Eschenbach, Director, NCI, announced that he would be calling attention to several themes, beginning with the whole area of communications. He emphasized the importance of keeping the cancer research community informed of activities related to NCI's diverse and complex portfolio and the active engagement of various parts of the NCI in that portfolio and, in particular, of the coordination and integration that is occurring among all of those programs. Dr. von Eschenbach reminded members of NCI's constant emphasis on communication to the Board, the larger community, stakeholders, collaborators, and partners to ensure that all have an opportunity to grasp the total dimension of the activities that are occurring. To that end, the Office of Communications (OC) has been tasked with specific directives to create an overarching plan that focuses on both the content and how it is communicated to ensure that the entire community understands the impact of the NCI and its leadership role in the National Cancer Program (NCP). As examples of initiatives in the plan, Dr. von Eschenbach called attention to changes that have been made to the NCI Web Site to make certain that this critically important modern tool of communication is being used effectively to give specific information and, at the same time, present a cohesive and coherent NCI perspective. The Web site has been the winner of a number of prestigious awards and has received recognition for its effectiveness and impact. An important feature on the Web site is the *Cancer Bulletin*, which provides weekly information on NCI initiatives, as well as the strategy and thought processes behind them.

Another recent initiative has been to ensure that the portfolio of information being communicated by NCI's operational units in their publications have a common look and feel in spite of the diversity, uniqueness, and specificity of the information. Dr. von Eschenbach noted that the common look and feel of the publications reflects what is at the core of and central to the culture of the NCI. The concept is that

the NCI is a group of diverse components pursuing unique opportunities and making specific contributions in a way that is coordinated and integrated. This theme of collaboration and coordination has continued to be engendered within the NCI itself and reflected across the broad NCP and cancer community. The coordination and collaboration extends to many initiatives beyond the NCP in an effort to bring the richness of extramural expertise and contributions into the NCI's directed mission and vision to contribute to achieving the goal of eliminating the suffering and death due to cancer by the year 2015.

Dr. von Eschenbach concluded that collaboration and cooperation is the important theme to be shared, as well as the fact that it is reflected in the NCI strategy of communications and is one manifestation of the culture that has been created, nurtured, and shared throughout the community. He pointed out that the theme of collaboration and coordination begins with the NCAB, which includes representatives of other federal agencies who are important to the NCI's ability to accomplish its mission, become a resource, and contribute to the mission of their agencies. As an example of collaboration with other federal agencies, Dr. von Eschenbach described a meeting held the previous day at the National Aeronautics and Space Agency (NASA) with the director of the Johnson Space Center and scientists involved in research under NASA auspices related to the manned mission to Mars. One result of the meeting was to look for opportunities to create common interactions focusing on emerging areas, specifically in this instance, the area of nanotechnology. He noted that these interactions become a platform and opportunity to coordinate NCI nanotechnology for cancer programs with initiatives being developed for widely different and divergent applications and take advantage of the potential for synergism. One application of interest to the NCI is NASA's research into the use of nanoparticles as radioprotectors to reduce the risk of radiation exposure in human space flight.

Dr. von Eschenbach emphasized that such collaborative, cooperative, and integrated efforts will continue to be a high priority for the NCI. The NCI leadership is committed to finding and exploring those opportunities within the NIH. For example, the Human Cancer Genome Project (HCGP) is being launched in collaboration with the National Human Genome Research Institute (NHGRI). Collaborations are occurring with other agencies in the Department of Health and Human Services (DHHS), and collaborations outside the DHHS include those with the Department of Commerce, the National Institute for Science and Technology (NIST), and the DOE. Dr. von Eschenbach cited other examples: (1) the relationship that has been developed between the Cancer Center and School of Engineering at Vanderbilt University and Oak Ridge National Laboratory (ORNL) to bring high-end computing into research on mass spectrometry for proteomics; and (2) University of New Mexico collaborations on nanotechnology with Sandia and Los Alamos. He pointed out that the NCI is looking forward to extending these geography-specific initiatives into more of a national network of networks so that opportunities available locally to Vanderbilt, for example, can be disseminated to other parts of the NCP and, specifically, to the efforts occurring within other NCI Cancer Centers. Dr. von Eschenbach reported that the Cancer Centers Directors at their recent retreat have actively engaged in a process to look at the 2015 goal and begin to map opportunities to integrate their activities and apply them across the discovery to delivery continuum in a coordinated and collaborative effort among the Cancer Centers and their assets. The local relationships with national laboratories, the extensive developments in the area of biotechnology that map to the Cancer Centers, and integration of the clinical trials infrastructure are areas where this effort is underway.

Dr. von Eschenbach stated that collaboration, integration, and coordination will continue to be part of the culture that the NCI will foster and support, not only as it relates to functioning and interacting, but also as it relates to synergizing the effort, talent, and available resources to preempt the cancer disease processes. He emphasized that this commitment will not change, regardless of the change that has occurred over the past months with regard to his role and functions at the NCI. Members were reminded of the circumstances under which he accepted the responsibility to be Acting Commissioner at

the Food and Drug Administration (FDA) while continuing in his role as Director of the NCI. Dr. von Eschenbach explained that, to accomplish this within ethical and legal constraints, he has taken a leave of absence from his administrative responsibilities. Those responsibilities have been delegated to Dr. John Niederhuber, Special Advisor to the Director for Clinical and Translational Sciences, as Chief Operating Officer responsible for day-to-day operations of the NCI. While acknowledging this change in his role, Dr. von Eschenbach emphasized that nothing has changed with regard to vision, mission, strategic direction, and work of the NCI. He credited this continuity to the fact that these areas have been led, nurtured, and supported by the entire leadership infrastructure of the NCI and have not been the function of the Director only. With the support and leadership of Dr. Niederhuber, the Deputy Directors, and senior leadership at the Division and Center levels, the NCI remains directed, focused, and effective, and will continue to remain so for as long as this situation exists. Likewise, the ability to create and continue to nurture the relationships the NCI has across the continuum within the DHHS and with other agencies and organizations has not changed. Dr. von Eschenbach assured the Board that the alterations and changes that have occurred with regard to his dual roles have been well defined, circumscribed, and organized so that both organizations continue on the trajectory of work and mission for which they are responsible. He expressed appreciation for the personal and professional support he has received at the NCI and FDA and across the entire community. He turned the podium over to Dr. Niederhuber for the remainder of the Director's report.

Dr. Niederhuber reminded members that one challenge facing the NCI is maintaining the momentum regarding the strategic direction, mission, and vision that have been articulated over the past 5 years. A second challenge is to recognize the need for and apply the principles of adaptability and creativity to the budget planning process in light of the fiscal projections through FY 2006 and beyond. A third challenge is to follow the NIH reauthorization legislation that is being considered by the Congress. As opportunities for meeting the challenges, Dr. Niederhuber listed: (1) investing in the NCI's intramural program; (2) optimal management of NCI's research investments, including the establishment of a balanced portfolio and investment in enabling science and technologies to speed progress; and (3) public-private leveraging.

NCI FY 2006 Budget Update. Dr. Niederhuber reminded members that the NCI has been operating under a continuing resolution since the beginning of Fiscal Year (FY) 2006 on October 1 and the prospect is that the continuing resolution could be extended through January 2006. Members were reminded further that the NCI budget of $4.866 B in FY 2005 represented a 3 percent increase over FY 2004, but the operating level after $74 M in taps was $4.825 B, a 1.6 percent increase. In like manner, uncertainties exist about enactment of the President's FY 2006 Budget request for the NCI of $4.842 B, which represents a 0.3 percent or $16.516 M increase over the NCI's FY 2005 operating level. Dr. Niederhuber noted that, although NCI planning has taken into consideration that there could be a government-wide reduction in budgets and additional taps and assessments at the NIH level, the NCI remains committed to maintaining the momentum, addressing its strategic priorities by funding new initiatives, maintaining the number of competing awards, and ensuring that new investigators are funded.

NCI Appointments. Dr. Niederhuber listed the following appointments: (1) Dr. Sanya Springfield, Acting Associate Director, Center to Reduce Cancer Health Disparities, Office of the Director (OD); (2) Dr. Jerry Collins, Associate Director, Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Development (DCTD); (3) Dr. Kenneth Buetow, Associate Director, Bioinformatics and Information Technologies, OD; (4) Dr. Shobha Srinivasan, Health Disparities Research Coordinator, Division of Cancer Control and Population Sciences (DCCPS); (5) Dr. Kishor Bhatia, AIDS Malignancy Program; (6) Dr. Jaye Viner, Deputy Director, Office of Centers Training and Resources (OCTR), OD; (7) Dr. Asad Umar, Acting Chief, Gastrointestinal and Other Cancers Research Group, Division of Cancer Prevention (DCP); and (8) Dr. Gilles Thomas, Scientific Director, Cancer

Genetic Markers of Susceptibility, Division of Cancer Epidemiology and Genetics (DCEG). Dr. Niederhuber announced that Dr. J. Carl Oberholtzer, Associate Professor, Pathology and Laboratory Medicine, and Vice Chair, Division of Neuropathology, University of Pennsylvania, has accepted the position of Associate Director for Training, OCTR, and will be arriving in January. Dr. Oberholtzer will be responsible for providing leadership and vision to trans-NCI basic, clinical, translational, prevention, control, behavioral, and population sciences training. In this position, he will be able to foster collaborations between the intramural and extramural training programs and implement programs that meet the community needs. Recruitments are underway for Center for Cancer Research (CCR) personnel in the intramural areas of medical oncology, genetics, radiation oncology, and pathology.

Updates on NCI Initiatives. Dr. Niederhuber announced that the Human Cancer Genome Pilot Project was approved by the Board of Scientific Advisors (BSA) and is to be announced at a press conference scheduled on December 13 by Drs. Von Eschenbach and Francis Collins, Director, NHGRI. This pilot project will be funded jointly by the NCI and NHGRI. The first meeting of the Principle Investigators (PIs) for the Nanotechnology Alliance was held in November. Awards for $26.3 M have been made to seven Centers of Excellence; awards in the amount of $7 M (12 R01s) have been made to Platform Partnerships; and training awards amounted to $3.2 M. The Characterization Laboratory is to be located at NCI-Frederick.

Dr. Niederhuber reported that implementation of the recommendations of the Clinical Trials Working Group (CTWG) will accelerate in December with the successful completion of project management staffing. The NCI Clinical Trials Operations Committee was approved by the Executive Committee (EC) and will hold its first meeting in December. The Working Group on Clinical Trials Oversight is under development. To ensure operational efficiency, the Cancer and Leukemia Group B (CALGB) Operations Office has been completed. The Investigational Drug Steering Committee is scheduled to hold its first meeting in March 2006, and Scientific Steering Committees will be implemented in 2006.

In presenting the final update, Dr. Niederhuber emphasized that the Translational Research Working Group (TRWG) is intended to build on the CTWG initiatives, which are being implemented to ensure that the appropriate organizational structure and prioritization strategies are in place to move translational research into a new era of broad discovery.

Announcements. Dr. Niederhuber reminded members that the NCAB will participate in a joint retreat on January 10, 2006, with NCI's BSA and Board of Scientific Counselors (BSC) to address budget issues. A special meeting of the combined budget subcommittees of the three Boards will be held prior to the joint retreat.

In other announcements, Dr. Niederhuber noted that the Eastern Cooperative Oncology Group (ECOG) recently celebrated its 50th anniversary at a meeting in Florida, and the DTP's 50th Anniversary Symposium was held the previous week on the NIH campus. He commented briefly on the return to the NCI of former leaders whose contributions were recognized at the symposium entitled "A History of Success and Leadership in Anticancer Drug Development," including Dr. Susan Horwitz, currently a BSA member; Dr. Vincent DeVita, former Director, NCI; Dr. Bruce Chabner, former Director, DCTD; Dr. Michael Boyd, former Associate Director, DTP; and Dr. Michael Greever, also former Associate Director, DTP. Dr. Niederhuber reminded members of the 39 drugs for oncology that were marketed with DTP involvement, many of which are still vital to the treatment of cancer.

Next, Dr. Niederhuber reminded members that this meeting would focus on a review of NCI's intramural research program, which is carried out in the CCR under the leadership of Dr. Robert Wiltrout,

Director, and the DCEG, under the leadership of Dr. Joseph Fraumeni, Director. To give an indication of the size of the NCI intramural program, Dr. Niederhuber noted that the CCR has 295 PIs and 1,080 trainees working in laboratories on the NIH campus and across the Nation. The DCEG has 66 PIs and 58 trainees, including research and clinical fellows. Dr. Niederhuber called attention to the 2 percent growth in 2005 in NCI patient admissions to the NIH Clinical Center, as well as a 2 percent growth in visits by NCI patients being treated as outpatients. In addition, the NIH campus now has a lodge similar to the Children's Lodge, where adults associated with the cancer program can be housed.

Dr. Niederhuber called attention to core-type resources that have been developed and are located at NCI-Frederick, and he asked the Board for help in communicating their availability to the extramural community. The resources are in the areas of genomics, proteomics, advanced imaging technology, nanotechnology, advanced biomedical computing, research animal programs, and national repository resources.

Dr. Niederhuber concluded his report by commenting on scientific accomplishments of NCI investigators. As an example of the NCI effort against cervical cancer, he cited a study of cervical cancer risk in oncogenic Human Papilloma Virus (HPV) DNA-positive women by Dr. Philip Castle, DCEG. This work led to the recommendation that women 30 years and older whose screening Pap tests show equivocal or minimal cytologic abnormalities should undergo HPV testing, and the test should be repeated in 6-12 months in those found to be oncogenic HPV+. Further study of the cumulative incidence rate of cervical intraepithelial neoplasia grade 3 (CIN3) suggests that the addition of testing for HPV16 and HPV18, the most significant types of HPV infection, would provide additional evidence for determining those at high risk for developing CIN3. Dr. Niederhuber noted that a Consensus Development Conference on Cervical Cancer Screening Guidelines will be held at the NIH in September 2006 to consider these findings for possible changes in the approach to screening for women 30 years and older.

In his second example, Dr. Niederhuber briefly reviewed a study by Dr. Kent Hunter, CCR, and colleagues entitled "A Polymorphism in the Sipa1 Gene Modifies Metastasis Risk." This study, which shows that the existence of germline mutations can influence metastatic potential, has added new knowledge to the former view of tumors as autonomous cell masses whose progression is driven by genetic alterations. The mouse model study also suggests a strategy for reducing the metastatic potential in patients found to have that germline mutation. In his third example, Dr. Niederhuber described the NCI effort in patients with hepatocellular carcinoma to test the hypothesis that the expression profiles of cancer contain "prognostic information" at presentation prior to treatment and that computer algorithms can utilize this to predict outcome of individual patients with no prior knowledge. He closed by emphasizing that the focus of the work of intramural investigators and the NCI-sponsored extramural investigators is on making a difference in patients with cancer.

Questions and Answers

Dr. Von Hoff asked that copies of the slides used by Dr. Niederhuber in his presentation be distributed to the Board. Mr. David Koch, Executive Vice President, Koch Industries, asked Dr. von Eschenbach for further comment on his meeting with NASA scientists and whether the money for a manned mission to Mars might be better spent expanding cancer research. Dr. von Eschenbach explained that the meeting was successful in building relationships and coherence among the two agencies, as well as commitment to carrying out individual missions in a way that is complementary and synergistic. Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, commented favorably on NCI's HPV studies and suggested that challenges still exist in the high proportion of people who do not get screened and do not benefit from the findings. He suggested that questions yet to be

answered include why 80 percent of those who get oncogenic HPV infections do not progress to CIN or cancer and how to apply HPV vaccines for the greatest benefit. He then noted concern in the community about potential or real conflicts of interest in the dual roles of Director, NCI, and Acting Commissioner, FDA, and asked for and received assurance that Dr. von Eschenbach would be recused and have no involvement in decisions that relate to drugs, devices, or products under review by the FDA.

Dr. Carolyn Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, called attention to concern in the community about the release of the Request for Applications (RFA) for Translational Research Centers. She asked for clarification as to whether that will mean that a choice must be made by institutions between having an NCI-designated cancer center or a translational research center. Dr. Niederhuber explained that the GCRC is an NIH instrument and that cancer centers have historically been major players in that instrument. He expressed the view that the RFA is an attempt to create a program with the translational research centers that meets the needs of the next decade and would be phased in gradually. Dr. von Eschenbach added his view that the translational research center is a concept that is in evolution and is continuing to be refined. He explained that the first effort within the NIH Roadmap did not quite accomplish the larger vision with regard to the impact of translational and clinical research and the present RFA evolved from that realization. The concept behind the RFA was to strengthen and enhance the role of the GCRC but the concept has been developing along lines that look very much like a cancer center, hence the concern about a conflict. Dr. von Eschenbach expressed the view that work is still in progress and the challenge will be to continue the evolution but ensure that the two types of centers are not in conflict and not mutually exclusive. He suggested the need for participation by and interaction between cancer center directors and their institutional leadership so that, as the evolution is occurring, these problems will not arise and the outcome is appropriate and complementary. From the NIH perspective, the responsibility will be to ensure that, as the initiative is evolving and emerging from the NIH Roadmap, it becomes a contribution to and not in conflict with what has been established by the NCI and that the end product is something stronger. Dr. Von Hoff asked that the NCAB be kept informed of and involved in the process.

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

Dr. LaSalle Leffall, Charles R. Drew Professor of surgery, Howard University College of Medicine, and Chair, President's Cancer Panel, reported that, in October, the Panel concluded its 2005-2006 series of four meetings on the topic "Assessing Progress, Advancing Change." The first two meetings were held in August and addressed high-priority recommendations the Panel had made to the President and Congress in its 2003 annual report entitled "Living Beyond Cancer: Finding a New Balance." The final two meetings in October discussed recommendations from the Panel's 2004-2005 report entitled "Translating Research Into Cancer Care: Delivering on the Promise."

On Monday, October 24, two separate expert roundtables were convened. The first addressed the Panel's recommendations for changing the culture of research and advancing team science, which has been identified as the new paradigm for accelerating translation of basic science discoveries into clinical practice. These recommendations suggested modifying existing institutional reward systems, promoting collaborative science through new funding mechanisms, and examining peer review systems relative to basic and clinical research support. Dr. Leffall noted that the group recognized and discussed the fact that larger systemic and societal/cultural barriers impede team science and was able to offer some suggestions for improvement. For example, formal recognition of multiple lead authors on publications by both journals and institutional tenure committees would provide greater incentives for collaborative research. Institutions and professional societies could also encourage team science by acknowledging group initiatives through their existing awards processes.

Dr. Leffall noted that formal training was identified as the best predictor for success in clinical research careers; thus, roundtable participants proposed expanding formal programs to train individuals who want to pursue careers in this area. It was further suggested that clinical and translational research should be added to general medical school curricula to promote understanding of the importance of clinical research and the role of physicians in referring patients to clinical trials. Dr. Leffall noted that several organizations made commitments to increase emphasis on clinical and translational research and team science in career development programs, including the creation of clinical practice fellowships. Roundtable participants also supported the implementation of the NCI CTWG recommendations to contribute to the advancement of team science.

The second roundtable on October 24 addressed workforce infrastructure issues relative to attracting young investigators to and retaining them in careers in translational and clinical research. Participants recognized that, because a shortage of physicians is projected, new incentives would be needed to motivate students to pursue careers in medicine as well. Of particular importance for the advancement of translational and clinical research will be increasing enrollment in M.D./Ph.D. programs and encouraging these students to pursue specialties in clinical research, behavioral science, and informatics. Dr. Leffall noted that roundtable participants expressed the need for forming new peer-review panels and study sections to allow appropriate, unbiased review of translational research. Protected research time beyond the fellowship stage was also considered critical to fostering the academic advancement of those interested in the field, particularly female investigators and members of underrepresented populations. Roundtable participants also suggested that the pharmaceutical and biotechnology industries be engaged as partners in training young scientists.

On Tuesday, October 25, the Panel shifted its focus to revisit recommendations regarding dissemination and community participation as they relate to translation of treatment advances into clinical practice. With approximately 80 percent of cancer patients and survivors being treated in the community, it was recognized that there is a critical need to disseminate cancer prevention and treatment advances to community health care providers and the public and engage them in research-based activities. Roundtable participants discussed the idea of creating sustainable community relationships to gain community trust in the research process. Although NCI-designated Comprehensive Cancer Centers are required to document their outreach and education efforts, funds are not currently allocated to implement this mandate. Financial support to establish dedicated dissemination staff within the Centers would greatly enhance the efficiency of efforts in this area. Additionally, an evidence base for dissemination must be generated by scientifically evaluating and measuring the effectiveness of existing programs. Dr. Leffall noted that many of the identified barriers to translating research transcend cancer and are relevant to other diseases. Many participants expressed the need for further collaboration on broader systemic health issues to leverage resources and optimize gains in overall public health and awareness.

Dr. Leffall announced that one-page summaries of key findings from the 2005-2006 meetings are posted on the Panel's Web site, and the minutes will be posted there in the near future. He stated that the Panel's 2005-2006 Report to the President and Congress will summarize progress, report on commitments made by roundtable participants, and propose actions to be taken to advance change in the areas of survivorship and translation of research into effective cancer care. The Panel's next series of meetings is entitled "Promoting Healthy Lifestyles To Reduce the Risk of Cancer." Areas of particular interest will include the impact of tobacco use, environmental tobacco smoke, obesity, physical activity, and nutrition on the risk of developing cancer. The meetings will focus on current knowledge and the identification of areas needing increased research. Existing model programs that might serve as approaches to risk reduction also will be explored. Tentative meeting dates and locations are: September 11, Minneapolis, MN; October 23, Lexington, KY; December 5, Portland, OR; and February 12, 2007, Jackson, MS. Dr. Leffall noted that each of these locations provides a unique setting in which to discuss healthy

lifestyles. The University of Minnesota Comprehensive Cancer Center has an NCI-funded program on transdisciplinary research on energetics and cancer. Oregon was the only state to demonstrate no increase in the incidence of obesity in 2005. Kentucky and Mississippi display some of the highest rates of tobacco use and obesity in the country and are home to distinct underserved populations. In addition, Minneapolis, Portland, and Lexington have all taken steps to improve the health of their populations by adopting smoke-free legislation. Dr. Leffall concluded by welcoming Board comments and suggestions as the Panel moves forward in the planning process for this set of meetings.

Questions and Answers

Dr. Von Hoff observed that some legislators have expressed the view that too many people are receiving M.D./Ph.D. training, thereby accounting for low percentage of people receiving funding, and he asked whether the Panel had heard something similar in its interactions around the country or meetings with various legislators. Dr. Leffall commented that the Panel hears statements on both sides of the issue and these will be taken into consideration in Panel deliberations.

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 included $4.8 B for the NCI, was announced on February 7. The House version of the bill with $4.8 B for the NCI was passed on June 24 and referred to the Senate. The Senate version with $4.96 B for the NCI passed on November 3. Conference Committee action on the legislation included a report filed on November 16 with $4.8 B in NCI funding. On November 17, the conference report was defeated in the House. On November 18, the Senate voted to instruct the Conference Committee to reconsider the bill and to restore funding for the NIH to the level requested in the Senate bill.

Ms. Erickson reminded members that the NCI is operating under a continuing resolution at the FY 2005 funding level, which is due to expire on December 17. She reviewed several scenarios that could apply at that time, including the possibility of an extension of the continuing resolution. Concerning NIH reauthorization legislation, Ms. Erickson reviewed the timeline of the bill that was drafted on July 19, 2005, following a series of hearings conducted between 2002 and 2005. The second draft of the bill was completed on August 22, and the next step will be introduction of the bill, although there is no clear indication of when that will happen. Ms. Erickson reviewed the names and chairpersons of the committees that are involved in activity related to NIH reauthorization legislation: House Energy and Commerce Committee, chaired by Congressman Barton, Congressman Dingell is ranking Democrat; Health Subcommittee chaired by Congressman Deal with Congressman Brown as ranking Democrat. If the bill is introduced in the House, it would be taken up in the Senate by the Health, Education Labor and Pensions Committee, which is chaired by Senator Enzi, with Senator Kennedy as ranking Democrat.

Next, Ms. Erickson reviewed legislation of interest to the NCI and the Board. A 2-year extension of the Breast Cancer Stamp was signed into law in November. The bill authorizes issuance of the stamp through 2007, and the extra 8 cents charged for each stamp goes into a research fund, which is divided between the NIH and DOD. Ms. Erickson noted that the bulk of the NIH fund goes toward NCI research, with a small amount to the National Institute of Environmental Health Sciences (NIEHS) for environmental concerns related to breast cancer.

In reviewing other legislation, Ms. Erickson commented that health awareness resolutions have been a growing area in Congress. Although they do not mandate any particular action by anyone, they provide an opportunity for a member of Congress to call attention to a specific disease by designating a

week or month to raise awareness about a disease. In recent years, breast and prostate cancer awareness resolutions have been joined by those raising awareness to pancreatic cancer, childhood cancer, and sun safety. Ms. Erickson noted that resolutions are being tracked to keep the Board aware of them.

Questions and Answers

Mr. Koch asked for an estimate of the amount of proceeds realized from the sale of the breast cancer stamp and received the answer that the NCI receives about $5 M. He asked about the status of the prostate cancer proposal and Ms. Erickson noted that she would check on that. Dr. Runowicz pointed out that there had been some activity regarding an ovarian cancer research stamp also, and she commented that the stamps are important in that the public has an opportunity to cast a vote as to whether they believe the research funded by the stamps is a wise investment. She noted, moreover, that they represent a source of funding for the NCI and a pledge of willingness by Americans to foot the bill.

VI. RECENT SCIENTIFIC ADVANCES FOR THERAPY OF MALIGNANT GLIOMAS—DRS. HOWARD FINE AND HENRY FRIEDMAN

Dr. Howard Fine, Chief, Neuro-Oncology Branch (NOB), CCR, announced that the intention today is to provide selected examples that represent the current direction of research into therapy for malignant gliomas and a more promising outlook for patients with the disease. He noted that he would discuss intramural NCI research and Dr. Henry Friedman, James B. Powell, Jr., Professor of Neuro-Oncology, The Preston Robert Tisch Brain Tumor Center at Duke University, would discuss his efforts at Duke and through the extramural community as a whole.

To characterize the problem being addressed, Dr. Fine reminded members that primary brain tumors are the leading cause of cancer-related deaths in children and are fourth in people under the age of 54, although there also has been a significant increase in incidence in people over the age of 60. He emphasized that it is important to understand that many subtypes of diseases are included under the primary brain tumor rubric, all of which have different biologies. Although progress has been made in treating some of the less common types of brain tumors, the numbers are quite depressing as they relate to the treatment of gliomas, the most common brain tumor type, and particularly glioblastomas, which are the most deadly and aggressive form of gliomas. To illustrate this point, Dr. Fine reviewed the median survival times for patients with glioblastomas who undergo treatment with surgery, radiation (XRT) plus surgery, or chemotherapy plus XRT plus surgery. He concluded that there has been no highly significant improvement in survival in the last 20 years. Moreover, the few long-term survivors face life-long neurocognitive deficits, either from the tumor or the treatments.

NOB Glioma Therapeutics Development Program. Dr. Fine explained that the NOB was created in 2000 as a joint effort between the NCI and National Institute of Neurological Diseases and Stroke (NINDS) with the specific mission of conducting translational and clinical research to develop better therapeutic agents for patients with brain tumors. It is divided into two sections; one devoted to translational/biological approaches; the other a new drug development program. Both sections are supported ultimately by the NCI clinical trials program. As an illustration of ongoing research into translational/biological approaches, Dr. Fine described a collaborative effort with NINDS investigators on a new glioma treatment using marrow-derived neural competent stem cells (MDNCC), which has been published in *Cancer Research*. Mouse model studies have shown that MDNCCs can be transduced with transgenes that are conditionally cytotoxic, will migrate through the brain, reach infiltrating glioma cells, express the cytotoxic gene, and kill the tumor cells. Dr. Fine noted that an investigational new drug (IND) application is pending before the FDA, and a pilot Phase I trial at the Clinical Center is expected to begin within 6 to 12 months.

Dr. Fine stated that many of the new therapies to be presented would involve the process of tumor angiogenesis, whereby solid tumors obtain a needed source of blood supply through the activation and proliferation of endothelial cells by nearby capillaries. He explained that it is now also known that a process called vasculogenesis contributes to the development of tumor neovasculature by activating distant endothelial progenitor cells (EPCs) and causing them to migrate towards the tumor. Dr. Fine noted that this process has been exploited in another of the NOB's translational/biological studies called "EPCs as Real-Time Surrogate Markers for Angiogenesis." The study shows that: (1) human and mouse EPCs migrate, incorporate into, and can deliver transgenes into sites of glioma-mediated vasculogenesis; and (2) EPCs incorporating into glioma-associated vasculogenesis can be labeled and visualized *in vivo* by magnetic resonance imaging (MRI). Dr. Fine noted that the NOB holds the IND and is working with the FDA on a clinical trial that is anticipated to begin within the next 3 months. The trial will involve labeling EPCs, injecting them back into patients with recurrent malignant gliomas undergoing surgical re-resection, imaging them for 2 weeks, and then resecting the tumors to confirm that the MRI pictures are correct and that the EPCs have incorporated into the developing neovasculature.

Dr. Fine turned next to a discussion of the NOB's novel drug development program, which he described as a major emphasis since the branch was created and a major effort in collaboration with the pharmaceutical and biotechnology industries and with the Cancer Therapy Evaluation Program (CTEP), DCTD. The preclinical screening program involves a number of *in vitro* and *in vivo* screens as well as bioassay and biomarker development. The clinical trials program is carried out in the NOB Brain Tumor Clinic for pilot, Phase I, and early Phase II trials, and in CTEP-sponsored brain tumor consortia and cooperative groups for the most promising agents. Dr. Fine noted that this highly active drug development program has 38 institutional review board (IRB)-approved and NOB-activated clinical trials for primary brain tumor, including 28 adult and 10 pediatric. Over the past 12 months, 220 patients were accrued to NOB clinical trials, more than 500 new glioma patients were seen, and 2,500 were seen in followup. In addition, free film review is offered for about 200 patients, to check their eligibility for NOB trials locally or at cooperating institutions nationwide. The NOB has more than 25 pharmaceutical and biotechnology partners, has established 6 Cooperative Research and Development Agreements (CRADAs), is currently negotiating 2 additional CRADAs, and has signed more than 20 active confidential disclosure agreements with these partners for co-developing new agents, many of which will lead most likely to additional CRADAs. The NOB has more than 35 agents in its portfolio for preclinical and clinical development and is currently running more than 20 translational and new drug development clinical trials that are a direct result of the glioma therapeutics program.

As an example of the NOB's preclinical and clinical development of promising new antiglioma drugs, Dr. Fine discussed in detail the work being done on LY317615 (Enzastaurin). LY317615 (LY) was developed by Eli Lily as a potent and selective inhibitor of PKC-Beta isoenzyme and considered promising against gliomas because that isoenzyme is important in the signaling of vascular endothelial growth factor (VEGF), a key angiogenic factor for tumors in general and gliomas in particular. Based on promising preclinical and Phase I clinical data, the NOB was asked by Eli Lily to conduct a Phase II trial. The objectives of the study were to determine the activity of LY in patients with recurrent high-grade gliomas and obtain pharmacologic and toxicity data. Patients were stratified according to whether they were on antiseizure medications or not, to enable the investigators to address the effects of these enzyme-inducing antiepileptic drugs (EIAED) on currently administered agents. The original enrollment of 90 patients has been expanded to 120 based on encouraging data from the first 90. The majority of patients had glioblastomas, and all had been highly pretreated (between one and nine prior therapies). The summary and conclusions based on data to date are: (1) LY is well tolerated in patients with high-grade gliomas; (2) thrombocytopenia is the only consistent adverse event clearly attributable to the drug; (3) drug metabolism is significantly affected by EIAEDs; and (4) objective radiographic responses occur in

about 25 percent of the heavily pretreated patients with recurrent glioblastoma multiforme (GBM), and another 20-25 percent of the patients were stable (from 3 months to almost 2 years).

Dr. Fine pointed out that these data raised the question of why a significant rate of objective tumor shrinkage (rather than stable disease) was mediated by a drug that supposedly only inhibits angiogenesis. Two possible answers were: (1) what was seen was a radiographic phenomenon secondary to the inhibition of VEGF, thereby stabilizing tumor-associated blood vessel permeability; or (2) LY does have primary cytotoxic effects against glioma cells. Given the number of patients stable so long after treatment, it was decided to pursue the second possibility, and with encouragement from Eli Lily, LY was subjected to additional testing in the NOB laboratories. Conclusions from the laboratory studies that will affect clinical drug development for gliomas are: (1) LY has direct cytotoxic effects on glioma cells, independent of its antiangiogenic effects, both *in vitro* and *in vivo*; *a Phase I pharmacologically driven trial in patients with recurrent gliomas is ongoing at the NIH*; (2) LY is a potent inhibitor of glycogen synthetase kinase (GSK)3B as well as PKC-Beta; *a clinical trial is being conducted at the NIH to evaluate whether the inhibition of GSK3B phosphorylation in peripheral blood mononuclear cells (PBMCs) will be a useful biomarker*; (3) GSK3B inhibition results in profound glioma cell death and, therefore, is a promising new molecular target for glioma therapy; *a number of small molecular inhibitors of GSK3B are currently being screened*; and (4) LY is synergistic in combination with other cytotoxic agents; *Phase I trials of LY with carboplatin, radiation, and Temodar® are ongoing at the NIH and through CTEP-sponsored brain tumor consortia*.

In summary, Dr. Fine stated that NOB's experience with LY has driven home the lesson that translational research means that laboratory advances go to the clinic, the clinic can inform the laboratory, and the laboratory, in turn, can inform the clinic. The LY experience also has emphasized the importance of collaboration between the private sector and the NCI's intramural and extramural programs. Dr. Fine pointed out that, as a result of this translational research as practiced by the NOB, a multinational, FDA-approved Phase III trial of LY317615 versus the best standard therapy, in patients with recurring glioblastoma, is scheduled to start in February 2006, less than 3 years from the time the drug was first given to a patient with a glioma at the NIH. Dr. Fine stated that the NOB aims to achieve the type of patient to bench translational research that goes from clinical trial to imaging trials to registration and sample collection to genetic analysis and laboratory studies, all of which ultimately inform the design of the best clinical trials to the benefit of the patient. He closed by acknowledging the commitment and work of NOB colleagues.

Extramural Research Into Therapeutic Strategies for Malignant Glioma. Dr. Friedman began by affirming Dr. Fine's assertion that progress in neuro-oncology is the result of the partnership that has been established among academic institutions, pharmaceutical companies, and the NCI and NINDS Neuro-Oncology Branch. He called attention to the poor prognosis for patients undergoing the current standard of care that includes radiation or radiation plus temozolamide, which underscores the need for new therapeutic options for patients with brain tumors. Dr. Friedman then stated that the research he would be presenting would focus on chemotherapy, another antiangiogenic agent, monoclonal antibody (mAB)-targeted therapy, and molecular pathway inhibitors.

Dr. Friedman prefaced his discussion of a Phase II study of bevacizumab in combination with irinotecan for malignant gliomas with the story behind initiation of the trial at Duke University. The husband of a patient with malignant glioma or GBM who had failed many therapies insisted that his wife be treated with a drug regimen that was approved for colorectal cancer (avastin/CPT-11/5FU), citing the high levels of VEGF found in both colorectal cancer and GBM as a basis for his request. The doctor acquiesced to the husband's request and the wife achieved a complete response (CR) that continues to the present. Dr. Friedman noted that FDA approval was obtained for the study, based on the rationale that the

aberrant vasculature in tumor blood vessels, particularly VEGF, is a particular target of avastin, and VEGF is highly expressed in human GBM, making it a rational target. The objectives of the study are to determine the safety of bevacizumab in combination with irinotecan and estimate the activity of the combination as measured by progression-free survival (PFS). Dr. Friedman briefly reviewed the study design, outcome measures, inclusion and exclusion criteria, treatment plan, and patient characteristics. Of the 32 patients (23 with GBM) accrued to the study, 9 came off due to toxicity, and 14 remain in the study and have completed 3, 4, 5, or 6 cycles of the 6-treatment regimen. The best radiographic responses to date are 3 percent CRs and 62 percent PRs, and the responses have been durable. Dr. Friedman noted that the length of the patients' event- and progression-free survival begin to have biological significance in terms of the value of this intervention. Other interim results of the study are: (1) 18 patients received more than 18 weeks of treatment; (2) 14 are still on treatment after 4.5 months; and (3) 75 percent are alive after 4.5 months. Plans are to accrue an additional 32 patients to the current trial and to plan for and add additional studies for recurrent and newly diagnosed patients. Dr. Friedman noted that, in collaboration with Genentech, a four-institution study is in process of development to look at GBM patients in their first or second relapse. They will be randomized for avastin alone or avastin plus CPT-22 to try to prove the benefit of this therapy and get it into the clinic as an approved intervention.

Next, Dr. Friedman presented an update on research in progress at Duke's Tisch Center in the area of radio-immunotherapy (RIT) for patients with malignant glioma. This research involves the use of mABs and is based on the premise that the majority of tumors recur locally. The therapy involves the delivery of mAB 81C6 directly to the tumor via a surgically created resection cavity; the target is tenascin-C, which is an abundant target in malignant glioma and not expressed on normal brain tissue. Dr. Friedman noted that the advantage of local therapy is that the targeted area has a high concentration of residual tumor cells after resection. Three-arm Phase I/II trials of "Fixed Dose" ^{131}I-81C6 have been conducted, combining carefully delivered RIT with systemic therapy. Patients with newly diagnosed malignant glioma made up two of the arms and received the mAB either before or after RIT. Patients with recurrent disease were treated on the third arm. Dr. Friedman reported that patients with recurrent disease at the Phase I and then Phase II level had reasonable mean survivals for recurrent malignant glioma compared with historical controls, and the results were even better for newly diagnosed patients. These Phase I/II trials have either been published in the *Journal of Clinical Oncology* or submitted for publication in that journal. The lessons from these "fixed-dose" studies related to poorer control when patients get lower doses because of rapid antibody clearance and to radionecrosis when clearance is too slow. These issues are being addressed in a pilot study of ^{131}I-labeled anti-tenascin mAB 81C6 administered to deliver a targeted radiation boost dose of 44 Gy to the surgically created cystic resection cavity perimeter in the treatment of patients with newly diagnosed primary and metastatic brain tumors. The objectives are to determine feasibility of the regimen, further define safety and toxicity, and evaluate the clinical activity of this approach. Dr. Friedman summarized the results in the 21 patients accrued to this study: (1) the therapy is feasible, with 20 of the 21 patients achieving the target 44Gy boost; (2) toxicity was minimal—less than 15 percent acute reversible hematologic activity, no significant delayed neurologic toxicity, no patients requiring additional surgery for radionecrosis; and (3) overall survival was highly encouraging, with median for newly diagnosed patients with GBM at 90.6 weeks.

Dr. Friedman informed members that the next step in this research area would be a multi-institutional randomized registration trial to identify the molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. Rationale for the research is that EGFR is an attractive target in GBM, but response to EGFR inhibitors is limited to a subset. Dr. Friedman described studies at the University of California-Los Angeles (UCLA) that attempted to identify the molecular determinants of response in glioblastoma as well as EGFR kinase domain mutations. The finding was that glioblastoma patients whose tumors co-express EGFRvIII and PTEN are significantly more likely to respond to EGFR

kinase inhibitor response. An EGFRvIII/PTEN coexpression had a sensitivity of 86 percent, specificity of 89 percent, and positive predictive value of 75 percent. A validation set, which was performed under the direction of scientists at the University of California-San Francisco, confirmed those findings. The validation studies were conducted in collaboration with the North American Brain Tumor Consortium. The results were confirmed in the UCLA laboratory through a series of isogenic model systems. Dr. Friedman pointed out that, although the response to EGFR kinase inhibitors could be considered marginal, this is a very fine therapy for those with the right genetic parameters. He emphasized that this is another example of the value of correlating results seen in the clinic with tissue studies in the laboratory. He identified, as roadblocks to progress in neuro-oncology, the nihilism of most health care professionals and refusal of insurers to allow patients to leave their network, enroll on clinical trials, or use commercially available drugs in off-label settings. He concluded that new therapeutic strategies are likely to increase survival in patients with malignant melanoma, and he urged modification of the current allocation of federal research dollars.

Questions and Answers

Mr. Koch asked whether the use of radiosensitizers had been studied to improve the outcome of patients with brain tumors, and Dr. Friedman replied that there has been a tremendous effort in that area but no success to date. Dr. Von Hoff asked about evidence that CPT-11 irinotecan seems to be involved in normalization of blood vessels and to mediate better drug concentrations. Dr. Friedman replied that there are no data confirming or negating that evidence and that the question may be able to be addressed in laboratory studies. Dr. Fine added that an imaging-intensive trial of avastin alone in patients with recurrent gliomas is soon to be initiated in the Clinical Center by the NOB to begin to address the question of whether that is a primary vascular effect. Data from that trial will be passed on to the extramural community to further develop the drug. Dr. Kirchner observed that the clinical studies to date appeared to have been done in adults, and he asked whether more side effects from antiangiogenic factors could be expected in children. Dr. Friedman replied that the question is going to be addressed by the Pediatric Brain Tumor Consortium, which is planning a study of avastin and CPT11 in a pediatric population.

VII. CANCER STATISTICS: PARTNERSHIPS, RATES, TRENDS, AND DISSEMINATION—DRS. ROBERT CROYLE AND BRENDA K. EDWARDS

Dr. Robert Croyle, Director, DCCPS, reminded members that the update for NCAB on Surveillance, Epidemiology and End Results (SEER) cancer statistics is an annual responsibility, and he emphasized that thousands of different statistics and types of data are available from which to select for the presentations. He noted that members would be steered toward resources on the Web and elsewhere where more information can be obtained. He also pointed out that NCI's Surveillance Research Program has the function of responding to the many questions received daily about cancer incidence, survival and mortality statistics, and trends, and that questions from the Board are welcomed year round. Referring to Dr. von Eschenbach's earlier comments on the theme of collaboration and integration, Dr. Croyle noted that the surveillance program is a good example. For the past 8 years, the NCI, Centers for Disease Control and Prevention (CDC), American Cancer Society (ACS), and the North American Association for Central Cancer Registries (NAACCR) have collaborated to develop reports on cancer incidence, trends, and statistics in many forms and formats, including the *Annual Report to the Nation*. Another investment over the past few years has been to increase the usability of cancer statistics for many different audiences. Dr. Croyle explained that the Surveillance Research Program plays a key role not only in collecting and integrating cancer incidence data, but also in developing statistical methods to interpret those data. One NCI-funded extramural initiative in this regard is CISNET, a cancer surveillance modeling network. He

introduced Dr. Brenda K. Edwards, Associate Director, Surveillance Research Program, DCCPS, to present the annual update.

Dr. Edwards began by recognizing the organizations with which the NCI partners in the task of maintaining national cancer surveillance: NACCR, ACS, American College of Surgeons, National Cancer Registrars Association, International Association of Cancer Registries, International Agency for Research on Cancer, World Health Organization, and CDC. The complementary and collaborative infrastructure of this group of organizations includes a National Coordinating Council for Cancer Surveillance (NCCCS), Task Force Workgroups, Technical Groups, and established communications and interactions. The *Report to the Nation* is a product of this collaboration and for the third time in 8 years, the NCI has been the lead institution. Dr. Edwards pointed out that a different topic is featured each year to characterize what is behind the national trends in cancer incidence rates for that year. The focus this year is treatment trends, and data pm Hispanics will be featured in 2006. She invited suggestions for topics from the Board. Dr. Edwards noted that much of what is done in the surveillance collaboration is to develop common data standards and share technology consistent with the NCI's Cancer Bioinformatics Grid (caBIG). She called attention to the publication written by the National Cancer Surveillance Coordinating Committee entitled "A National Framework for Cancer Surveillance in the United States."

Next, Dr. Edwards presented data from the *2005 Report to the Nation*, which tracks the status of cancer from 1975 to 2002. Incidence rates of all cancer sites and both sexes combined have been stable since 1995. By sex, the data show that rates for men are higher but have been stable since 1995. For women, the long-term increase in rates has slowed and increases have been 0.3 percent per year since 1987. Dr. Edwards noted that prostate cancer, which is the most common cancer diagnosed in the United States, explains much of the higher incidence rates for men. The 2005 data show an increase in incidence among white men and leveling off the rate for black men, although Blacks have the higher rate. U.S. death trends for cancer of all sites have shown a decline of -1.1 percent since 1993 for both sexes, with a slightly greater decline for men. The decline continues for cancer of the prostate, breast, colorectal, lung in males, and many other sites. However, the death rate for lung cancer in women is increasing. After decades of increasing trends, mortality has declined since the early 1990s, in men, for 12 of the 15 major sites and, in women, for 9 of the 15 major sites.

Dr. Edwards pointed out that the 2005 estimates of the U.S. cancer burden (expected cases and expected deaths) are based on combined data from NCI SEER 1979-2001 and CDC NCHS 1969-2002. Five years of high quality incidence data are available for more than percent of the U.S. population. The challenge has been to make a coherent estimate inasmuch as some geographical areas are not covered by quality incidence registries receiving federal funds; statisticians at the NCI have been using statistical modeling to fill in the missing data. Dr. Edwards pointed out that incidence and mortality data on the top 15 cancer sites have been reported separately for Blacks and whites since 1975 and for Hispanic, Asian/Pacific Islanders, and American Indians since 1992. The NCI is currently working with the CDC and Indian Health Service on a monograph to characterize data trends for the American Indian/Alaska Native population to improve classification and address the problem of undercounting.

Next, Dr. Edwards called attention to the information on population-based trends in cancer treatment that is a special feature of the *2005 Report to the Nation*. She noted that the strategy to reduce deaths and improve survival requires that evidence-based cancer treatment services be available and accessible to all. The SEER program has a long history of working to improve the data for surveillance of cancer care and surveillance; the NCI has sponsored a number of Patterns of Care/Quality of Care (POC/QOC) studies; and the SEER and Medicare databases are being linked to provide U.S. claims-based information. This feature of the Annual Report synthesizes the information from those sources and a number of publications to characterize trends in delivery and determinants of cancer treatment focusing

this year on breast, colorectal, non-small-cell lung, ovarian, and prostate cancers. Dr. Edwards explained that the POC/QOC studies are evaluating the dissemination of state-of-the-art cancer therapy into community practice, disseminating the findings in scientific journals and at professional meetings, and working with professional organizations to develop training opportunities to improve the use of state-of-the-art therapy in community practice. She showed data from the POC/QOC studies on the percentage of patients offered or receiving adjuvant therapy for Stage II and III colon cancer, and data from SEER-Medicare studies on trends in treatment for early-stage prostate cancer to show how the data can be mined to provide a picture of dissemination trends. Another set of data on non-small-cell lung cancer showed patterns of chemotherapy use among the different age groups and races, and another example showed the survival differential that exists by race according to whether the treatment for lung cancer is surgical or non-surgical.

Concerning the issue of information dissemination, Dr. Edwards explained that data are available from the network of registries and from the SEER Web site (SEER.cancer.gov), which includes a guide for finding and using cancer rates and trends data. Fast*Stats is another feature of the Web site that enables the user to customize reports using reports and data that have already been generated. The *Annual Report to the Nation* and links to other agencies also are available. Dr. Edwards pointed out that the Web site has recently been redesigned, with input from advocacy participants, surveys, e-mails, and 9 months of measures from the American Customer Satisfaction Index (ACSI) Web survey financed by NIH evaluation funds. Dr. Edwards noted that the post-redesign testing continues, to ensure customer satisfaction with services. The SEER Web redesign was undertaken to improve navigation and make it easier to locate products and resources, add Cancer Stat Facts, enhance Fast*Stats, and link to resources beyond SEER. Examples of the latter are Cancer Control PLANET, State Cancer Profiles, and NCI's Cancer Trends Progress Reports. Dr. Edwards noted that a SEER-Advocacy workshop held in April 2005 provided additional information for addressing SEER Web site dissemination issues. The Workshop did influence the redesign and prompted the adding of a few new features. Other outcomes were a followup teleconference in participation with the Office of Liaison Activities and a presentation at the Office of Communication (OC) staff retreat.

Plans for the future include working with the Cancer Information Service (CIS), OC, in their Partnership Program to build a distance learning series and another advocacy workshop. The focus of the next workshop will be on increasing material on the Web site related to interpretation and use of SEER data. In addition, the Surveillance Research Program staff will be working to place new information on the Web site and in other appropriate media. In conclusion, Dr. Edwards noted that the Surveillance Research Program will continue to work with its partners to improve data collection, quality and standards, reporting, and access to cancer statistics. This will include a focused effort to interpret health disparities, an example of which is the current work on the *2006 Annual Report to the Nation* feature on Hispanics. Also in the future are additional advocacy workshops and continued Web site evaluation and improvement. Dr. Edwards closed by inviting NCAB input and suggestions.

Questions and Answers

Dr. Moon Chen, Professor, Public Health Sciences, University of California-Sacramento, asked whether a printed version of the updated *Racial/Ethnic Patterns of Cancer in the United States* would be available or just an electronic version. Dr. Edwards replied that the NCI is currently updating that publication to reflect the 2000 census data. Dr. James Armitage, Joe Shapiro Professor of Medicine, University of Nebraska College of Medicine, asked whether future data collection would reflect what is known about the biology of cancer as a disease and not just a disease site. Dr. Edwards prefaced her reply by noting that presentations usually focus on major cancer types, but the SEER database includes information by histology as well as anatomic site, which can be accessed through the Web by researchers

who need those types of information to answer a particular question. She then acknowledged that capturing information on the biological features characterizing cancers will be a challenge at the population level where SEER operates, but one that no doubt will be addressed in the future. Currently, efforts are being made in the SEER system to allow for adding site-specific information to the standard data collection activity by building coding schemes and nomenclature that will allow that level of detail. Dr. Edwards reminded members that three SEER registries are now collecting tissue and building tissue microarrays using virtual repository kinds of concepts.

Dr. Kirchner observed that the advent of noninvasive and invasive techniques allows cancers to be diagnosed at much earlier stages and may cause a dramatic change in apparent incidence (for example, the spike in prostate cancer incidence in 1992) that may relate in some way to a change in diagnostic criteria or approach. He asked how the SEER data would be adjusted should such a circumstance occur to avoid misinterpretation of the data. Dr. Edwards noted that the prostate cancer diagnosis, and overdiagnosis in some cases, has been discussed in a number of settings, and SEER is now characterizing those data by stage. Through SEER-Medicare linkage, it was shown that many of those cases followed the use of needle biopsy. She added that there are a number of other situations where screening or early detection do apply, that breast and prostate data are being reported by stage, and that lung data will probably follow. Dr. Freedman asked whether the SEER database has been able to capture information on barriers in addition to the availability of state-of-the-art treatment in the community. He asked also whether the NCI is monitoring utilization of the information, for example, to change state or local policies. Dr. Edwards replied that the Applied Research Program, DCCPS, is the part of the NCI surveillance team that interacts with the public and private sector on these issues. In addition, other NCI-sponsored initiatives complement this population-based surveillance component, including the Cancer Research Network, the CANCORS project, and CISNET. Dr. Croyle added that the SEER-Medicare data linkage is a heavily used resource for answers to questions about disparities and access, as well as the work of the President's Cancer Panel and many of the professional organizations. He briefly reviewed the intensive effort being made within the NCI and across the country to identify where the breaks in the chain occur in terms of health disparities, and he suggested an update on those activities as a future agenda item for the NCAB.

VIII. NCI'S FIRST GENERATION BEST PRACTICES GUIDELINES FOR BIOREPOSITORIES—DRS. ANNA BARKER, CAROLYN COMPTON, AND JAMES VAUGHT

Dr. Anna Barker, Deputy Director for Advanced Technologies and Strategic Partnerships, OD, reminded members that, in the area of biorepositories, the NCI has been working to build a foundation for personalized medicine of the future, most particularly for molecular oncology. One issue to be addressed was how to collect, store, distribute, and provide access to biospecimens in the future. Over the past 3 years, the NCI has undertaken many meetings, reports, and analyses that have resulted in a group of White Papers around biorepository issues, as well as a series of workshops with experts from many sectors. Progress in these efforts has been reported to the NCAB and BSA, and the first-generation guidelines have been finalized and are being brought forward in accordance with the NCAB charge to the NCI. Dr. Barker stated that during this period the Biospecimen Coordinating Committee (BCC) was established with membership from Divisions and Centers across the NCI. The BCC's role is to interface with the Office of Biorepositories and Biospecimen Research (OBBR) to coordinate what is being done across the various biorepositories and sectors. Dr. Barker called attention to a November meeting that brought together representatives from biorepositories worldwide for an exchange of information. She noted that the Board will be kept informed of the activities that will flow from this internationalization of biorepositories and NCI's leadership role in it. She introduced Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research, OD, and Dr. James Vaught, Special Assistant for Biological

Resources, DCEG, to present the guidelines and discuss future steps.

Dr. Compton reminded the Board that the biorepositories initiative began several years ago upon realization that there were no national biorepository standards. Moreover, NCI's current systems did not enable accurate accounting or analysis of funded biospecimen resources and did not provide guidance for quality control; ethical, legal, and policy (ELP) issues; access or retention. Given these issues, it was realized that data supporting certain areas of science may be in doubt. Dr. Compton acknowledged the enormity of preparatory work that had already been done and highlighted the many activities that occurred in 2005: the BCC was formed to advise the OBBR and coordinate over-arching guidelines for NCI-supported biorepositories; the BSA Tissue Subcommittee was formed; the National Biospecimen Network (NBN) Prostate Special Program of Research Excellence (SPORE) Pilot was launched; White Papers were finalized from background documents and prior years of analysis and meetings; two multi-sector workshops were convened, the NCI OBBR was established; and the first generation NCI guidelines were finalized and are being presented for NCAB approval.

Areas targeted as needing attention by the Workshop participants were: implementing first-generation Best Practices for NCI-supported biorepositories; addressing complex ELP issues; establishing a management structure to coordinate NCI's future efforts; and evaluating current biorepositories. Dr. Compton summarized strategies and actions that have been undertaken to address those areas, as presented to the NCAB in September. The guidelines will be submitted for public feedback and implemented across NCI-supported biorepositories on a voluntary basis following the comment period. ELP issues that remain to be addressed will go forward through BCC to the NIH and other government agencies for solution. NCI will deal with those policy issues that are under their control. The guidelines will constitute a foundation for the future evaluation of existing biorepositories and provide guidance for prospective collections. All recommendations have been grouped into categories of those that can be implemented immediately and those needing prioritization for future action.

In presenting NCI's First Generation Best Practice Guidelines for Biorepositories for NCAB consideration and approval, Dr. Vaught explained that the actual publication has four sections-a checklist version, two additional versions, and a slide presentation. The Guidelines include recommendations for common best practices for research biorepositories, Quality Assurance/Quality Control (QA/QC) programs, implementing informatics, addressing ELP issues, establishing reporting mechanisms, and providing administration and management structure. The two major categorizations are Technical and Operational Guidelines and ELP Guidelines. The Technical and Operational Guidelines deal with: (1) specimen collection, processing, storage, retrieval, and dissemination; (2) collecting and managing clinical data; (3) QA/QC; (4) biosafety; and (5) biorepository informatics, including data management, inventory control, and tracking. The ELP Guidelines cover informed consent, access to biospecimens and data, privacy protection, ownership/custodianship, and intellectual property (IP). Dr. Vaught then guided the Board through a review of the short version, commenting on various aspects.

Concerning the Technical and Operational Guidelines, Dr. Vaught noted that they build on practices that are in place in other organizations and are fairly well established. It is expected that larger repositories will be able to meet these guidelines and smaller ones will consider upgrades if they cannot. In terms of collecting and managing data, Dr. Vaught stated that the NCI will be recommending a universal minimum clinical dataset that has not yet been established, but will probably build on guidelines in the National Biospecimen Network Blueprint. He expressed the hope that the various biorepositories and clinical centers will provide feedback on what they think should go into the dataset, and he emphasized the importance of having quality data associated with specimens. Dr. Vaught noted that additional discussion is needed to resolve discrepancies between the Health Information Portability and Privacy and Accountability Act (HIPAA) and the Common Rule related to how privacy rules are applied,

and that the NCI will need to work with other agencies on resolutions to that problem. The QA/QC guidelines require that biorepositories follow basic QA/QC principles and have a plan in place to manage the quality of specimens and their associated data, as well as the quality of equipment. In terms of biosafety, Dr. Vaught noted that the guidelines follow the rules, regulations, and procedures laid out by the CDC and Operational Safety and Health Administration (OSHA), so compliance is mandatory. In the area of informatics, Dr. Vaught pointed out that the First Generation Guidelines are attempting to bring biorepositories into line with NCI Center for Bioinformatics guidelines as a first step, then are recommending "silver level" compliance with caBIG programs.

Dr. Vaught stated that informed consent will take additional work to achieve standardization, and the NCI is working with other agencies, NCI grantees, and the intramural program to develop a standard consent template. A proposed template in included in the Guidelines index. Dr. Vaught noted that access to biospecimens and data has been a repeated topic in meetings and workshops. The Guidelines specify that each biorepository should have clear policies in place for sample distribution and clinical data sharing; that investigators should have timely, equitable, and appropriate access to specimens without undue burden; and that charges to be implemented for samples cover costs only. Other access issues relate to the disposition of samples if a biorepository needs to close, patient identity protections, and restrictions regarding use of specimens for research only. Concerning ownership or custodianship guidelines, Dr. Vaught expressed the view that custodianship is the more appropriate term because there are many issues where ownership of specimens is not well understood or regulated. The Guidelines specify that each repository should have a plan for handling and disposing of the specimens they hold and their associated data at the end of a grant period, when research objectives are accomplished, when specimens are depleted, or when clinical data endpoints are achieved. Conflict-of-interest guidelines apply to individuals who control access to samples and/or data, and informed consent language should disclose that specimens may at some point be used for and have commercial value. Regarding IP issues, the Guidelines specify that the Material Transfer Agreement (MTA), NIH's Simple Letter of Agreement (SLA), or the Uniform Biological Material Transfer Agreement (UMBTA) is to be used for transfer of materials. Dr. Vaught called attention to an MTA template included in the appendix and noted that it is an attempt by NCI staff to create a unified document for use by the biorepositories. The IP guidelines also specify that biorepository staff are not considered inventors and that biorepositories have no inherent rights to future IP and research data obtained through the use of specimens or data made available to the research community. Finally, Dr. Vaught pointed out that the First Generation Guidelines are an empirical product, having been assembled from previously documented best practices, discussions, and federal regulations. The goal in the future is to produce a data-driven set of guidelines based on solid research. He turned the presentation over to Dr. Compton to discuss plans and strategies for achieving that goal.

Dr. Compton pointed out that the First Generation Guidelines are broadly applicable to good practice within the entire laboratory, but do not provide guidance as to what to do to get the best possible analytic results from a particular analysis platform. The goal over the next few years will be to develop an evidence base, where the guidelines that are produced will be specific to the type of specimen and analysis platform being used and the question to be answered. The process will begin immediately. There is a small amount of solid scientific data on which to base such bench-top level guidelines, but that amount is not known because there have been no publications or funded research in this area. Dr. Compton pointed out that a process is needed to locate this information and bring it together to produce evidence-based data that can guide investigators through the entire biospecimen life cycle that includes acquisition, handling/processing, storage, distribution, quality control, and restocking. Dr. Compton observed that when biobankers talk about process related to biorepositories, they are talking about post-acquisition processes, when in fact pre-acquisition variables also should be considered. She briefly reviewed the types of pre- and post-acquisition variables that could potentially change the biology of

specimens dramatically and within minutes and noted that these variables will be the focus of a Biospecimen Research Network being established by the OBBR to study them in a systematic fashion. The conceptual framework within which this will be approached is the so-called "ice cube tray concept of biospecimens." Standard operating procedures (SOPs) filling any of the cubes will need to be informed by the biomolecule of interest, analysis platform, type of analysis, and, in some cases, special specimen handling and storage requirements dictated by the technological approach. Dr. Compton stated that the schema is complicated , and initial plans are to hold workshops polling investigators who have produced this kind of data, published or unpublished. The objective will be to see which cubes can be filled in immediately with data-driven SOPs and which are totally devoid of any hard scientific evidence that would guide SOPs on a specific level. Priorities will be set up within the research network to capture the expertise of the investigators in the network and attempt to fill the ice cube tray in a systematic manner so that the Second Generation Biorepository Guidelines can be generated.

Dr. Compton stated that the OBBR, and BCC comprise the administrative infrastructure within the NCI and the NCI's Biospecimen Research Network will consist of the intramural division of experts in both the Bethesda and Frederick campuses and extramural community of investigators, with caBIG as the platform for exchange. Research data produced by the Network will lead to the generation of laboratory- and specimen-specific SOP guidelines that will be useful for investigators on a bench-top level. Dr. Compton noted that the current concept is that the expertise of colleagues from organizations and agencies outside the NCI-such as the College of American Pathologists, ISBER, NIST, and advocacy groups-will be enlisted for the actual development of the Second Generation Guidelines. With the First and Second Generation Guidelines in place, in the future it will then be possible to build a Biorepository Accreditation Process for oversight and training to ensure that all NCI-funded biorepositories are operating on common principles down to the level of data-driven standards that are, therefore, applicable universally. Following NCAB action today, the First Generation Guidelines will be released IN the Federal Register for public comment, finalized, and distributed to the cancer research community.

Motion. A motion was made to accept NCI's First Generation Best Practices Guidelines for Biorepositories for posting on the Federal Register for public comment. The motion was seconded and approved.

Questions and Answers

Dr. Von Hoff observed that legal issues would present the greatest challenge. Dr. Freedman suggested that harmonization of the rules set forth by the CDC, HIPAA, and FDA is needed and that it should be possible to develop innovative approaches to dealing with a complex legal system and, at the same time, maximize the efficiency of acquiring specimens. Dr. Barker agreed that the NCI could address ELP issues to a certain extent, but issues of policy are in the purview of the DHHS, and the NCI is working through the NIH to promote harmonization. In that regard, an NIH subcommittee is planned, and Dr. Compton has been appointed delegate to the NIH committee that will be dealing with federal agency policy discrepancies. Dr. Compton noted that she will report to the BCC on what transpires in the NIH committee, but the NCI will go forward in implementing those ELP recommendations that came from the workshops, coordinating its activities with whatever transpires at the NIH level. Dr. Barker pointed out that action may ultimately be needed at the Congressional level. She clarified for Mr. Koch that the biorepositories affected by the Guidelines are those in the extramural community that are partially or fully funded by NCI dollars on which NCI-funded investigators depend to get specimens for their funded research. Mr. Koch asked whether access to the specimens and information is easy to obtain. Dr. Barker answered that access was one of the most difficult issues addressed in both of the summer workshops. The Guidelines are addressing it by requesting that each biorepository establish access rules and abide by them. Mr. Koch asked about the possibility that institutions housing such a repository

would charge high fees to outside investigators, and Dr. Barker noted that cost recovery was another of the major controversial issues addressed at the workshops. She reminded Mr. Koch that the Guidelines specify that costs can be recovered, but the idea of selling tissue is similar to that related to trafficking of human organs. The same thinking has not yet been applied to biospecimens, but soon will be, as biospecimen collections become of enormous value to investigators for defining, for example, proteomic signatures in certain diseases. Dr. Barker pointed out that this ownership issue adds further emphasis to the need for federal regulations, but in the meantime, the First Generation Guidelines will level the playing field to ensure the quality of the research data that is produced.

Dr. Armitage commented that his institution has a large collection of lymphoma samples that have been distributed outside the University of Nebraska and the big debate has been about whether a particular project is a good use of the resource, not about who should pay. He pointed out that patients, doctors, pathologists, and institutions could all claim ownership of the biospecimens, and he asked whether it is known definitively who owns them. Dr. Compton replied that the financial aspect is unresolved but will come to the fore when the guidelines are implemented and require additional time and input by pathologists. Dr. Diana Lopez, Professor, Department of Microbiology and Immunology, University of Miami School of Medicine, pointed out that basic scientists are required by law to share information and products developed with NCI or NIH funding, and asked whether those rules applied to biorepositories. Dr. Barker agreed that it is the responsibility of the funded researcher to put new information in the public database. She pointed out that biospecimens are in transition from a time when an individual investigator assumed that they owned them and controlled access, to the time of protected genetic information and high through-put science in support of personalized medicine when tissues and their data likely will have to be more broadly available.

IX. PROGRAM REVIEW OF CENTER FOR CANCER RESEARCH—DRS. ROBERT WILTROUT, LALAGE WAKEFIELD, LEN NECKERS, YVES POMMIER, SRIRAM SUBRAMANIAM, MURALI KRISHNA, AND PETER CHOYKE

Dr. Robert Wiltrout, Director, CCR, reminded members that the CCR has been in the midst of a reengineering program for the past several years. The philosophy of the reengineered program has been to focus intramural efforts in key areas of science where the CCR has strength in basic, translational, and clinical science. Those areas of science are supported by an emphasis in advanced biomedical technologies. He highlighted areas of emphasis in the reengineered CCR: molecular targets and molecular oncology; immunology and the immunotherapy Center of Excellence, and imaging and biomarkers. The overall goal is to focus the basic discoveries from the intramural program toward delivery in the extramural community clinics by emphasizing communication and integration. Dr. Wiltrout noted that the CCR is moving toward development of a Phase 0 clinical trial concept in partnership with the DCTD. Therapies produced in the intramural laboratories will receive initial vetting in intermediate types of review groups and then be prioritized for early-phase clinical trials in the CCR. The objective is to move rapidly from discovery to development and delivery for the benefit of the patient. He introduced CCR investigators to present highlights of some of their research in the areas of molecular oncology, immunology, and imaging.

Development of Molecularly Targeted Agents

Targeting the Transforming Growth Factor (TGF)-Beta Pathway: Potential for Cancer Therapy. Dr. Lalage Wakefield, Senior Investigator, Laboratory of Cell Regulation and Carcinogenesis, CCR, began by reminding members that TGF-Betas are highly pleiotropic polypeptide growth factors whose ligands and receptors are widely expressed. They play key roles in development, adult homeostasis, and response to injury, and they have complex roles in tumorigenesis. Dr. Wakefield noted

that much of the TGF-Beta story has been an NCI story, from the time of its identification and purification as a cancer promoting factor in 1981 by Drs. Sporn and Roberts, CCR, to the ongoing development of TGF-Beta antagonists for treating advanced cancer by Drs. Wakefield, Berzofsky, Roberts, Letterio, Mitchell, and Morris, CCR. Opposing findings with TGF-Beta over those years were rationalized by work from her group and others when they demonstrated that TGF-Beta has two types of activity. It begins as a tumor suppressor but switches to become a pro-metastatic factor during cancer progression. To progress from normal epithelium to invasive metastatic cancer, there seemed to be a change in the output of the TGF-Beta signal that mediated a progressive decrease in tumor suppressor activity, an increase in the pro-progression activities, and a switch point where the pro-progression activities dominate. To try to correct defects in the system, the choices were to restore normal TGF-Beta response or reduce the elevated TGF-Beta signal, and the latter was chosen as the starting point by the Wakefield group. Dr. Wakefield noted that they expected this type of approach to be broadly applicable because TGF-Beta expression is increased in many advanced human cancers and correlates with enhanced invasion and metastasis.

Dr. Wakefield demonstrated how her group overcame the therapeutic challenge of selectively neutralizing the pro-metastatic effects of TGF-Beta, while sparing the desirable effects on normal homeostasis and tumor suppression. In early preclinical studies, the Wakefield group was able to show that an antibody-like TGF-Beta antagonist can suppress metastasis without any of the predicted adverse effects that could have come from systemic neutralization of TGF-Beta. Dr. Wakefield noted that this was an encouraging outcome, despite the underlying complexities of biology, and that development of this type of agent for clinical use might be feasible. To expedite development of this approach, a CRADA partnership was advertised for and formed with Genzyme Corporation, based on Genzyme's large portfolio of appropriate monoclonals, infrastructure for pharmacokinetic and pharmacodynamic toxicology, and experience in obtaining INDs and supporting clinical trials with TGF-beta antagonists in fibrotic diseases. The CRADA, as it was set up, involves multiple PI groups within the CCR, all attempting to develop these agents for various different applications in the cancer setting. The Wakefield group is looking at TGF-antibodies for suppression of metastasis; other groups are focusing on hematopoietic recovery (Letterio group), radiation therapy (Roberts and Mitchell), and immunotherapy (Berzofsky group). Genzyme, CRADA partner, in addition to the PK/PD and toxicology, is focusing on the development of these agents to suppress bony metastases and on possible combinations with conventional chemotherapy.

Dr. Wakefield then reported work that has occurred in the CRADA. Her group is focusing on mechanisms of metastasis suppression by TGF-Beta antibody monotherapy. They have shown that anti-TGF-Beta antibodies act primarily by unmasking effective antitumor immunosurveillance and that, by enhancing endogenous immune surveillance, TGF-Beta antibodies "raise the bar" for successful metastasis. Genzyme Corporation is studying TGF-Beta antibody effects on bony metastasis and has shown that the antibodies promote survival in a bony metastasis model. The Berzofsky group is studying TGF-Beta antibodies in cancer immunotherapy and have found that they enhance the efficacy of antitumor vaccines. The Letterio group is focusing on TGF-Beta antibodies for hematopoietic recovery following cancer chemotherapy, and has shown that they have the potential to reduce chemotherapy-induced myelosuppression. Dr. Wakefield concluded by reporting that encouraging preclinical data have led to the expansion of the CRADA to include clinical trial components. A Phase I clinical trial of GC1008 anti-TGF-Beta antibody in advanced cancer is in planning stages in the Metabolism Branch, CCR, and should begin enrollment in 2006. A companion animal trial also is being considered to be conducted in the Comparative Oncology Program, CCR. Large-scale trials on genetically outbred animals are envisioned to help in patient stratification.

Targeting the Molecular Chaperone HSP90 as a Novel Approach to Cancer Therapy. Dr. Len Neckers, Senior Investigator, Urologic Oncology Branch (UOB), CCR, explained that 10-15 years ago heat shock protein (HSP)90 was considered a housekeeping gene responsible for the folding and maintenance of proteins in the cell. Work in the UOB has suggested a much more important role in tumor cells and potential as a novel molecular target. It is now known that: (1) HSP90 is a molecular chaperone, comprising 1-2 percent of cell protein under unstressed conditions; (2) HSP90 client proteins include key components of multiple cell growth and survival pathways; and (3) HSP90 functions as part of distinct multi-chaperone complexes. He reminded members that HSP changes its conformation depending on nucleotide binding, and that its different conformations attract different co-chaperones with different activities. This was not known when his group began to explore the activities of a molecule called geldanamycin, which is a representative of a class of natural substances known as benzoquinone ansamycins, which have been known since the late 1970s. The proposed mechanism of action was tyrosine kinase inhibition, but Dr. Neckers' group and others found this to be secondary to kinase degradation. In the early 1990s, his group found direct binding of these drugs to HSP90, their true molecular target, and published those findings. A few years later, they found and published that a highly analogous derivative of geldanamycin, 17-allylamino-17-demethoxygeldanamycin (17-AAG), had the same activity and could be given *in vivo* at effective doses. Dr. Neckers pointed out that, since their first paper, there have been nearly 500 others using geldanamycin to study HSP90, which further informs the future clinical development of these agents.

In terms of its mechanism of action, Dr. Neckers showed that geldanamycin was found to replace the nucleotide in HSP90 and short circuit chaperone cycling. He noted that, when their investigations began, the client proteins of HSP90 were primarily steroid receptors. Use of these drugs has led to finding a large and growing number of protein client classes relevant to cancer, indicating that HSP90 is involved in many different processes in the cell. By inhibiting HSP90, there is a definite possibility that growth and survival of tumor cells can be affected. Dr. Neckers described studies showing that HSP90 inhibitors affect both the stability and activity of client proteins, and that the most sensitive HSP90 client protein uncovered to date is HER2 (ErbB2), which is important in prostate, breast, and other cancers.

Dr. Neckers pointed out that HSP90-directed translational research has led to the initiation of several clinical trials at the NCI: (1) one looking at kinase-domain mutated KIT in mastocytosis; (2) one targeting HIF-1Alpha in hereditary clear cell renal carcinoma; and (3) one combining HSP90 inhibition with proteasome inhibition. Papers leading to establishment of these trials came from the UOB group. Another collaboration with the Radiation Oncology Branch, CCR, has shown that HSP90 inhibitors are potent radiosensitizers. Dr. Neckers then called attention to the number of clinical trials that are ongoing in the United States and the United Kingdom. Phase Ib combination trials are incorporating 17-AAG, the first HSP90 inhibitor to reach the clinic, with a number of chemotherapeutic agents. A number of Phase II trials are using 17-AAG as a single agent in a variety of cancers, related to the fact that some HSP90 clients are highly important in the establishment and development of those cancers. Phase I trials of 17-AAG also are open in pediatric malignancies at a number of institutions, and a second Hsp90 inhibitor, 17-DMAG, is in Phase I trial in patients with solid tumors at the NCI and several other U.S. cancer centers. He concluded by describing briefly the current status of HSP90 inhibitor drug development.

Topoisomerase I (TOP1) Inhibitors. Dr. Yves Pommier, Chief, Laboratory of Molecular Pharmacology (LMP), CCR, reminded members that TOP1 is an essential enzyme in humans and animals in that it is able to relax supercoils in the DNA so that transcription and replication processes can proceed. TOP1 came to light when NCI-funded investigators discovered that camptothecins extracted from the *Camptotheca acuminata* tree had potent anticancer activity; the same team discovered taxol. At present, Topotecan (Hycamtin) and CPT-11 (Campto) are the only two camptothecin derivatives in clinical use, and they are used in solid tumors. Dr. Pommier noted that camptothecins have been a remarkable

resource for pharmacology and a lesson in natural products. They are one of nature's paradigms for drugs called interfacial inhibitors. NCI investigators knew that camptothecin binds neither to DNA nor to TOP1 and were able to propose an answer to the question as to how it works. It was 10 years before extramural investigators were successful in developing a co-crystal structure of TOP1 DNA and camptothecin, and the structure was exactly as predicted by the NCI. Dr. Pommier pointed out that new TOP1 therapies are needed: (1) because camptothecins are among the most effective anticancer drugs recently introduced in cancer chemotherapy, TOP1 is a validated target for cancer treatment; (2) novel agents with common targets are known to exhibit different anticancer activity; and (3) camptothecins have pharmacological limitations. To look for camptothecin inhibitors with the same activity profile, a COMPARE analysis was performed in the Developmental Therapeutic Program's (DTP's) NCI *In Vitro* Anticancer Drug Screen and the first indenoisoquinoline (NSC compound 314622) was discovered. Using this compound as seed, other drugs with the same profile were identified, and most were camptothecins, indicating the selectivity of this drug toward TOP1. The similarities of camptothecin, NSC314622, and topotecan were demonstrated further in a mean graph representation of their cytotoxicity profiles in the 60 cell lines of the screen. Dr. Pommier stated that CCR and DTP investigators have been collaborating with Dr. Mark Cushman of Purdue University, who had discovered NSC314622, in synthesizing derivatives that would show greater activity as TOP1 inhibitors and anticancer agents. As a result of that collaboration, a class of derivatives called indenoisoquinolines was discovered. In comparison with the camptothecins, the indenoisoquinolines are more potent inhibitors of TOP1 and are more stable chemically. Eight lead compounds have been selected for joint development by DTP and CCR from about 300 derivatives. The patents are held jointly by the NCI and Purdue, and some of the derivatives have recently been licensed to drug companies for formulation. Dr. Pommier noted that Dr. William Bonner, LMP, discovered and holds the patent for the histone gamma-H2AX as a pharmacodynamic biomarker for indenoisoquinolines. This biomarker will be available when the drugs are tested in Phase 0 and Phase 1 clinical trials. Dr. Pommier concluded by thanking LMP, DTP, CCR, and Purdue collaborators in this research.

Questions and Answers

Dr. Von Hoff commented that it is incumbent on the investigators to identify the kinds of clinical trial situations where the new TOP1 inhibitors would be used. He suggested that many think that the camptothecin CPT-11 would be an active agent for non-small-cell lung cancer, but it was never developed for that disease. He observed further that CPT-11 was not found to be very active in breast cancer until it was administered as an oral form, and he suggested that these findings should be considered in testing the new molecules. Mr. Koch asked about plans for using carbon nanotube technology to deliver toxins to receptors on cancer cells. Dr. Wiltrout replied that new imaging technologies are being developed in the Laboratory of Cell Biology, CCR, to integrate and interface with the nanotechnology world in terms of characterizing nanoparticles and, ultimately, guiding research with nanoparticles in the CCR.
Dr. Runowicz asked about the toxicity profile of HSP90 inhibitors and whether they are well tolerated. Dr. Neckers replied that there have been no target-related toxicities seen as yet for 17-AAG, only those that are due to hepatic metabolism, and these have been very limited to date. Dr. Lopez asked whether there is any improvement in the innate immunity compartment (e.g., macrophages) when patients are treated with the TGF-Beta fusion protein. Dr. Wakefield noted that NK is the only component looked at so far, and no activation of the NK by the antibody treatment was seen. She agreed that looking at the macrophage compartment would be worthwhile. Dr. Von Hoff asked that the NCAB be kept informed of clinical trials of the new agents.

Dr. Wiltrout stated that the three presentations on molecularly targeted agents were chosen as examples of the ability of NCI's intramural program to move a basic science observation through long-

term, high-risk research to a point where questions can be answered and clinical trials considered. The next set of presentations relate to approaches that are currently being taken with imaging.

Imaging: From Molecules to Man

From Molecules to Tissues: Bridging the Imaging "Gap." Dr. Sriram Subramaniam, Chief, Biophysics Section, Laboratory of Cell Biology (LCB), CCR, reminded members that the sizes of objects of biological interest range in size from small molecules to macroscopic entities like humans, a rate difference of about 27 orders of magnitude. Imaging technologies based on x-ray and nuclear magnetic resonance (NMR) have had an impact at both ends of the spectrum—x-ray crystallography and NMR spectroscopy at the small end and computed tomography (CT) and MRI at the macroscopic end. Investigating subcellular architecture in the middle range has largely been the realm of conventional electron microscopy. However, an important gap in imaging technologies exists for biologic entities in the size range of viruses, multiprotein assemblies, and small subcellular organelles (e.g. mitochondria). They are too large or too heterogeneous to be investigated by the more high powered structural methods like x-ray crystallography or NMR spectroscopy or are such that the level of information desired is not easily accessible by methods such as electron or light microscopy. Dr. Subramaniam stated that bridging that gap has been the focus of work in the LCB. The objective is to gain a greater understanding of the dynamics in biology in terms of the spatial and temporal architecture of various changes taking place in the human body all the time. The main tool in use today to approach that type of information is the electron microscope, which produces three-dimensional (3-D) images that can be integrated to make a cellular or molecular tomogram, providing information about the internal architecture of those entities. Dr. Subramaniam stated that he would be presenting examples of LCB efforts to use this type of technology to image molecular machines, cells and viruses, and tissues in the absence of staining so that they can be studied in their natural state.

In the area of molecular imaging, one focus has been the molecular complexes in the mitochondria, to understand the difference between normal and defective mitochondria and, in particular, to visualize the various molecules that bring metabolites to the mitochondria and generate the molecules needed for energy production in the cells. Electron microscopy has been used to look at structural changes in the molecules that function as membrane transporters. As an example of this, Dr. Subramaniam noted that it is now possible to understand how a molecule called the oxalate transporter works to transport oxalate across a membrane. In related studies, the LCB is looking at a much larger multiprotein complex called the pyruvate dehydrogenase complex. With the help of electron microscopic images of the various complexes of pyruvate dehydrogenase in different states, LCB investigators have been able to synthesize nearly three decades of biochemistry on the enzyme complex, including the structures of all the pieces that comprise an enzyme that is 500 axons across. It has been possible to learn much about the mechanics of how small molecules like acetyl Co enzyme A (acetyl CoA) are synthesized by the multiprotein complexes in cells. Dr. Subramaniam noted that there are thousands of complexes that they would like to understand at this level of detail.

In a similar way, the LCB extended electron microscope technology to look at larger, more heterogeneous assemblies by co-viruses, for example, direct imaging of HIV and SIV in infected cells. A tomogram assembled from 3-D images of HIV virus allows the visualization of individual virions at a high level of detail, such that individual microprotein molecules on the surface can be seen. The biological focus of this work is to understand the molecular basis of antibody neutralization of HIV—why some antibodies neutralize and others are ineffective even though they bind to the HIV. Dr. Subramaniam noted that LCB also is actively working to catch HIV in the act of entering a cell. Electron microscopy is being employed unconventionally to look at the virus in as close to the native state as

possible to promote understanding of the molecular nature of the fusion core and how various inhibitors might affect its structure.

In a third example, Dr. Subramaniam noted that LCB is extending these EM methodologies to locate nanoparticles in tissues. In collaboration with Dr. Tracey Roualt and colleagues at the National Institute of Child Health and Human Development (NICHD), LCB was able to visualize neuronal degeneration in the IRP2 -/- mouse model. A conventional optical microscopic picture showing the build up of ferritin in the drugs led to the presumption that the degeneration was caused by the presence of ferritin in the axons of the mice. However, an extension of the studies by using electron tomography to produce 3-D images of the axons at 10 times higher resolution showed a different picture. The ferritin was seen to be localized in the enabling oligodendrocyte cells, not the axons. Dr. Subramaniam commented that this study emphasized the importance of using multiple approaches at multiple levels of resolution to understand where molecules travel in tissue and in which cells they are formed.

Dr. Subramaniam stated that a CRADA partnership has been established with in FEI Company in Oregon to develop new technology for automated tissue imaging. The objective is to eliminate the need for conventional modes for using an ultramicrotome that involves manual sectioning. With the new microscope, it has been demonstrated that whole cell pellet or tissue samples can be sliced electronically with a focused ion beam, one surface at a time, and the images taken in sequence can be combined to produce 3-D images, for example, of a dividing yeast cell. This technology has been extended in the past few months to look at frozen tumor tissue, demonstrating that it is possible to look rapidly and in a short-timeframe at the ultrastructure of freshly frozen tissue. An extension of this technology would be in the direction of locating nanoparticles in the context of the tissue. A final example of the power of electron microscopy is in the context of nanoparticle imaging and standardization. Dr. Subramaniam showed an image of a nanogold particle in which the location of each gold atom could be seen clearly. He noted that not all applications will need this level of resolution, but the LCB is committed to developing these methods both for automation and for higher resolution, to characterize nanoparticles. In the long term, the NCI vision is to develop these technologies to the point where automated 3-D imaging can be used as a tool to standardize various nanoparticles. The vision is that automated sample delivery systems will ultimately lead to automated 3-D imaging of particles. Dr. Subramaniam concluded by noting that, although most of the LCB studies address the gap that is centered in the nanobiology and nanotechnology size range (1-100 nanometers), the hope is to contribute to an understanding of other-sized entities in the spectrum.

Radiation Biology Branch (RBB) Functional Imaging Program. Dr. Murali Krishna, Chief, Biophysical Spectroscopy Section, RBB, CCR, stated that he would report on work in the RBB on the MRI assessment of tissue oxygen level and redox status, using stable free radicals as tracers and contrast agents and low-field MRI called electron paramagnetic resonance (EPR) imaging. These studies evolved from earlier findings by Dr. James Mitchell, RBB, that some stable free radicals can be antioxidants and whole body radiation protectors with specificity for normal tissue. He reviewed the rationale for measuring tissue oxygen levels: hypoxia in tumors can negatively influence radiation and chemotherapy; hypoxia is associated with tumors that are more likely to metastasize; hypoxia regulates a number of genes via the HIF pathway that can be associated with tumor progression and poor prognosis; and non-invasive assessment of tumor hypoxia may allow for more effective individualized treatment. Another potential medical application is the monitoring of ischemic diseases.

Dr. Krishna compared NMR spectroscopy, which detects nuclei with magnetic moments, with EPR spectroscopy, which detects paramagnetic species like free radicals. He noted that free radicals are preferred for ease of imaging in biological systems because they can be detected at room temperature. He pointed out that the unique advantage of using free radicals in functional imaging is that the oxygen

molecule is a unique MRI contrast agent and EPR spectral imaging is extremely sensitive to oxygen. From images, it is possible to distinguish differences in oxygen in the range of 0-5 percent. In this regard, the RBB and CRADA partners have been developing novel prototype MR scanners and MRI methodology for small animal imaging applications. Dr. Krishna noted that the requirements for EPR tracers include water solubility, kinetic and metabolic stability, and nontoxicity at the concentrations required for imaging. One tracer being used by the RBB is the triphenylmethyl radical, which was found to have a long enough half-life for imaging purposes and to be well tolerated *in vivo.*

Dr. Krishna explained that the imaging system in his laboratory is low-field MRI (OMRI), a hybrid consisting of MRI plus EPR imaging. Using weak magnetic fields reduces the cost of the magnet, and free-radical paramagnetic contrast agents are used. Combining OMRI with endogenous oxygen as the contrast agent produces high-resolution MR images at a low magnetic field. Anatomical images are co-registered with pO_2 images. Dr. Krishna demonstrated that MR images produced in the presence of a contrast agent have a higher resolution. The image intensity is enhanced by contrast agent concentration and the extent of the hypoxia. When there is less oxygen, the image intensifies, so there is good mapping in ischemic areas. Dr. Krishna demonstrated this with another set of images, which showed that oxygen maps from OMRI correspond with changes in tissue oxygenation, and that dynamic changes in pO_2 can be monitored. Dr. Krishna noted that the power of this technique is that changes in pO_2 can be monitored in medical imaging time scales of 15 and 30 minutes. Thus, it is possible to see the consequences of an intervention in terms of tissue oxygen measures. In a series of images taken minutes apart in a 2-50 minute timeframe, Dr. Krishna demonstrated that EPR imaging with this methodology enables the monitoring of dynamic changes in pO_2. Currently, the capabilities of this technique are such that pO_2 in a mouse model can be mapped with a precision of plus or minus 2 millimeter mercury with a spatial resolution of 1 millimeter cubed in less than 5 minutes. Dr. Krishna noted that plans to integrate EPRI with anatomic imaging modalities such as MRI are progressing. The techniques have been protected with patents, and corporate partnerships are being considered for licensing. The ultimate goal is oxygen tissue imaging in humans. Applications include the assessment of tumor and normal tissue pO_2 and the noninvasive mapping of ischemic regions.

Dr. Krishna then described further exploration of the discovery by Dr. Mitchell that nitroxide free radicals are novel antioxidants. They had been shown to be radiation protectors *in vitro* and *in vivo* and to have promise as functional EPRI and MRI agents. Dr. Krishna noted that these agents had been evaluated as MRI contrast agents in the early days of MRI but abandoned because their relaxation profile was poor compared with gadolinium complexes. However, a recent collaboration with the University of Pennsylvania showed that one nitroxide compound topically applied to the scalp of humans receiving whole brain irradiation therapy prevented limited radiation-induced alopecia. Dr. Krishna pointed out that the study showed that derivatives of nitroxide, with a molecular weight less than 200, can be functionalized to localize at specific compartments. He then described further studies in the RBB that confirmed that: (1) nitroxides provide useful T1 contrast at doses well tolerated; (2) the change in contrast as a function of time is dependent on tissue redox status; (3) nitroxides, which are effective radioprotectors of normal tissue, can be monitored by clinically available MRI scanners; and (4) as small organic molecules, they can be directed to specific cellular and subcellular compartments. Research opportunities presented by these findings include: (1) discovering whether temporal profiles of nitroxide levels in normal and tumor can be used to determine timing of radiation to yield maximal radioprotection in normal tissues; (2) assessing intra- and extracellular redox status utilizing the vast array of available nitroxide analogs; and (3) monitoring production of oxidants by administering hydroxyalamines.

Radiolabeled Herceptin™ for Imaging and Therapy. Dr. Peter Choyke, Chief, Molecular Imaging Program, CCR, stated that he would be discussing an upcoming Phase 0 clinical trial of radiolabeled herceptin for imaging and therapy. The trial will target Her2/neu, which is a widely

expressed epithelial growth factor found in many tumor types, and features the human monoclonal antibody (mAB) Herceptin™ that has shown efficacy in monotherapy and combination therapies. The trial is a collaboration with the Radiation Oncology Branch (ROB), CCR, and will follow more than 4 years of preliminary research in imaging and radioimmunotherapy using radiolabeled Herceptin™ in rodent models of cancer. The rationale behind designing a "Herceptin™ scan" is that it will provide a first look at the biodistribution of Herceptin in humans, identify sites of disease expressing Her2/neu and potentially quantifying Her2/neu expression, monitor disease response to Herceptin therapy, provide dosimetry for radioimmunotherapy, and provide a basic molecular platform for launching alpha- and beta-emitting radioisotopes for therapies. The chelate CHXA DTPA was chosen for mAB conjugation because it has sufficient thermodynamic and kinetic stability to prevent loss of radionuclide *in* vivo and does not alter mAB specificity or rate of mAB catabolism. It can attach to a number of pertinent radioisotopes, including ^{111}Indium for imaging and ^{86}Y, ^{212}Bi, and ^{213}Bi for therapy. Dr. Choyke noted that the chelate was designed by Dr. Marin Brechbiel, ROB, and is the intellectual property of the DHHS, making the combination with the Genentech-owned mAB less complicated. CHXA has been used in a number of clinical trials around the world, as well as the NCI, and has proved to be safe, successful, and particularly stable.

Concerning the use of CHXA in imaging Herceptin, Dr. Choyke noted that his laboratory has done multiple trials in various cell lines that do not express Her2/neu in high levels and found good biodistribution. He made the point that high expression of Her2/neu is not needed for images; therefore, the regimen has the potential for wider application and not just highly amplified tumors. In that regard, he showed an image obtained from athymic mice bearing interperitoneal human colon carcinoma xenografts following intravenous administration of ^{111}In-CHX-A"-Herceptin™, which showed a significant uptake within the tumor even though it does not highly express Her2/neu.

Dr. Choyke stated that this research is culminating in a Phase 0 trial in early 2006. Criteria for a Phase 0 trial are that it be the first-in-human study and that it be authorized through an exploratory IND indicating that the study drug is administered directly to the patient with a minimal number of toxicity studies. The chelated Herceptin will be manufactured according to GMP standards and the ^{111} Indium added in the NCI radiopharmacy. It is a microdosing study utilizing less than 1 percent of the clinical loading dose of Herceptin and has no therapeutic intent. The primary endpoint is safety. Entry criteria are: women with Stage I and II breast cancer; standard of care therapy; and immunohistochemistry (IHC) demonstrating 1+, 2+, or 3+ Her2 expression. Breast and whole-body imaging will be done at baseline and after completion of therapy. Spot scans at 6 hours through 72 hours will look for various toxicities and at the pharmacokinetics of blood clearance. In addition to safety, secondary outcome measures will be uptake versus IHC expression and the determination of the optimal scanning time after injection. Dr. Choyke stated that a CRADA has been established with Genentech and a GMP manufacturer has been identified and has begun making the chelate. The clinical trial protocol itself is under review with the NCI PRMC and IRBs.

Dr. Choyke stated that future plans include using this regimen as a molecular platform for treatment given the fact that it has the potential to image or get a therapeutic agent to tumor cells other than those for which Herceptin alone is designed. These include several kinds of radioimmunotherapies, some of which already are being studied in animal models. A protocol has been proposed for a collaboration with the Surgery Branch, CCR, to treat patients with peritoneal metastases who have failed the standard debulking and perfusion therapy. Patients would undergo a repeat debulking followed by imaging with ^{111}In-CHX-A"-Herceptin™ and treatment with ^{213}Bi-CXH-A-Herceptin™. Dr. Choyke pointed out that Herceptin imaging is a place holder for other targeting ligands. His laboratory has experience with Avastin and erbitux and both are promising. He concluded that CHX-A Herceptin radionuclide imaging is a starting point, but it will be possible to look later at other kinds of imaging,

including Herceptin-activatable optical imaging, Her2 affibody imaging, Her2-targeted iron nanoparticles, and Herceptin-targeted MR lymphangiography agent. He thanked colleagues in the Radioimmune and Chemistry Section, ROB; Cancer Imaging Program, CCR; Medical Oncology Clinical Research Branch, CCR; and DCTD for their contributions to this research.

Questions and Answers

Dr. Freedman observed that one of the limitations of radioimmunotherapy has been that only a single dose has been given, and he asked whether the possibility of multiple dosing is being considered. The response was that this simply is not a true limitation, but rather one that has been either self-imposed or FDA imposed. The origin of this concept is historical and dates back to the time of murine monoclonal antibodies and their associated immune response; the field has moved beyond this with chimeric, "humanized", or human monoclonal antibodies to obviate the concern over repeated administration. Thus, use of Herceptin traverses this concern. Additionally, ongoing radioimmunotherapy trials at the NCI are designed to be multi-dosing and the value of this becomes clear in the context of fractionated delivery of radiation and chemotherapeutics. Dr. Freedman noted that he was referring to patients who have been debulked chemotherapeutically and experience expression changes, and the possibility that multiple dosing is needed to target the expression changes effectively. Dr. Choyke explained that the alteration of antigen expression is possible and probably impacts chemotherapy as well, but this possibility then justifies imaging studies coupled with an option to proceed forward with a potential therapy arm. Dr. Von Hoff added that Avastin might mediate better penetration. Dr. Choyke agreed that was an intriguing possibility and pointed out that his laboratory is considering the idea of cocktails of targeted agents given the basic platform. However, due to regulatory issues, an initial trial will probably require investigation of the single agent not in combination with Avastin. This would be an interesting combination therapy trial. The requirement of combination therapies and that radioimmunotherapy is not envisioned as a stand-alone therapy but rather should be incorporated into a standard therapeutic regimen. Dr. Von Hoff expressed the view that there is a need for developmental therapeutics researchers to have easier access to emerging imaging technologies. Dr. Choyke agreed that this is a deeply appreciated position that the collaborative activities seek to fulfill. Mr. Koch asked why bismuth as an alpha emitter was selected and what regulatory and practical problems are encountered in the preparation of a mAB with a radioisotope. Dr. Choyke replied that the choice of bismuth was a matter of chemistry and that the more complex question is matching the mAB to the emitter, which has to do with biologic biodistribution and clearance of the mAB. The regulatory and practical problems at this time are minimal in many ways since there is a close association with the first such trial using Bi-213 at Memorial Sloan Kettering, as well as another ongoing in Bi-213. Thus, these experiences can be drawn upon directly. Additionally, since the NCI was the source of the chemistry that made those trials possible, they have already established and validated the exact chemistry that would be employed in any studies with Bi-213 here at the NCI. Additionally, the NCI is uniquely situated to conduct such trials as the research group that has promoted and championed the use of antibody targeted alpha-emitters as a therapeutic option resides within this same institute. Dr. Kirchner commended the work being done, and asked if a bismuth-labeled molecule is known to exhibit the same kinetics as an indium-labeled molecule. Dr. Choyke pointed out that these studies have already been executed and published; Bi-205/6 was used as a tracer for Bi-213 and stability vs. both I-131 and In-111 labeled monoclonal antibodies with this chemistry has been established and validated. Dr. Von Hoff expressed the opinion that the research that has been presented should be communicated to the outside world in some concentrated forum. Dr. Wiltrout noted that the intramural program has been begun a more aggressive program of communication. He called attention to a brochure summarizing intramural program activities in the recent past and that is ongoing, and pointed out that high-profile meetings are being held to bring the extra- and intramural communities together.

X. HPV PROPHYLACTIC VACCINES TO PREVENT CERVICAL CANCER— DRS. ALLAN HILDESHEIM AND JOHN SCHILLER

Dr. Wiltrout introduced Drs. Allan Hildesheim and John Schiller who presented developments around the human papilloma virus (HPV) prophylactic vaccine to prevent cervical cancer.
Dr. Hildesheim began with the observation that one in every five cancers diagnosed worldwide each year is attributed to an infectious agent; this problem is higher in developing nations, where more than one in every four tumors can be attributed to an infectious agent. In a large proportion of cases, cancer can be called an infectious disease. Dr. Hildesheim listed a number of infectious agents, many of them viruses, including HPV, that have been linked to cancers. HPV are DNA viruses that have evolved slowly. There are more than 100 HPV types, which can be classified into two categories: the cutaneous (which infect the skin) and the mucosal types. The mucosal HPVs number more than 40, which are mostly oncogenic (that is, linked to the development of cancer) or non-oncogenic. Fifteen HPV types are linked clearly to the development of cancer; HPV Types 16 and 18 account for approximately 70 percent of all tumors diagnosed. There is a tremendous amount of evidence linking papilloma viruses to the development of cervical cancer. This evidence comes from clinical and molecular studies that have demonstrated the presence of the virus in cancers and precursors to those cancers. Experimental data from the laboratories have shown that HPV genes are tumorigenic. More recently, epidemiological studies have shown that HPV is a necessary cause and the major risk factor for the development of cervical cancer.

CCR/DCEG Joint Project: HPV Prophylactic Vaccines To Prevent Cervical Cancer.
Dr. Allan Hildesheim, Division of Cancer Epidemiology and Genetics, described a cohort study, sponsored by the NCI and led by Dr. Mark Schiffman in NCI's Division of Cancer Epidemiology and Genetics, of 20,000 women who were enrolled through Kaiser Permanente and then followed for 11 years. It was one of the large epidemiological studies recently completed. After excluding women who had disease at the time they were enrolled, women were tested and divided into whether they had an HPV infection or were HPV negative. Women who were infected with either HPV Type 16 or 18 have an absolute risk of between 10 and 15 percent to develop high-grade precursor lesions, called CIN3, or more severe disease during followup. This is much higher than women who either were HPV negative when they were tested at entry and have very low rates or who are HPV positive for oncogenic types other than 16 and 18.

Nearly 100 percent of all cervical cancers are HPV positive; because of the propensity of HPV Types 16 and 18 to progress more rapidly than other types of HPV, they account for about 70 percent of all cervical tumors worldwide. Most genital-mucosal HPV infections occur shortly after sexual debut and are transient. In older age groups, the rate of HPV prevalence declines. Cervical cancer is the second or third most common cancer diagnosed among women worldwide, with approximately 600,000 new cases diagnosed yearly and 200,000 deaths. Approximately 10 percent of all tumors diagnosed among women worldwide are cervical cancer.

In countries with active and effective cervical cancer screening programs, such as the United States, in addition to the mortality burden, there is also a tremendous morbidity burden associated with cervical cancer and its prevention. It is estimated that between 2 and 3 million women are diagnosed with low- or high-grade cervical cancer precursors at the time of screening; now that HPV DNA testing has been incorporated into screening programs, the number of individuals found to have either a precursor lesion or an oncogenic infection likely will number in the millions each year. Vaccines to prevent other viral diseases, such as small pox, are among the most successful and cost-effective public health interventions. Dr. Hildesheim commented that if sexually transmitted HPV infections can be prevented, the burden associated with cervical cancer should be reduced.

The prophylactic vaccine that is being tested in clinical trials is based on purified papilloma virus like particles (VLPs), which are empty virions or shells of the virus, with no DNA inside. Generated in either yeast or insect cells, they are composed of a major capsid protein of the HPV. Because they are empty shells and neither infectious nor oncogenic, the VLPs are promising candidates for vaccine.

Three animal models—two oral models in cows and dogs and a cutaneous model in rabbits—used in initial preclinical studies to evaluate VLP vaccines have shown that they are effective at preventing infection of the virus. In the animal studies, the effect appears to be purely prophylactic, that is, the vaccine provided no therapeutic effect for the animals if they had been exposed previously to the virus. The effect appears to be type specific; vaccinations against one animal type protect only against that type.

These promising animal studies led to the Phase I vaccine trials in humans that were designed to look at toxicity and safety of the vaccine as well as immunogenicity. A Phase I trial that was conducted by the NCI at the Johns Hopkins Center for Immunization Research reported that, compared with the use of placebo, individuals who were vaccinated experienced higher rates of local responses that were largely attributed to local pain and, to a lesser extent, to redness and hardening at the site of injection. This is consistent with most childhood vaccinations that have been used for many years. The systemic side effects appear to be low; most were headaches that lasted for 1 or 2 days. In the early trials, the vaccine appeared to be safe. The vaccine induces a very strong immune response. The enrollees received three doses of the HPV 16 L1 VLP vaccine intramuscularly over 6 months. One month after the last dose was given, the titers of antibodies against HPV 16 were much higher among the individuals who got the vaccine compared with those in the placebo group. These levels of antibodies that are seen after vaccination are somewhere between 40 and 100 times higher than one sees after a natural infection with HPV.

In a follow-on Phase II study, a group of 200 women at Johns Hopkins was vaccinated with 50 μg of HPV 16 VLP. The vaccinations were given as three doses over 6 months. The study revealed that very high levels of antibodies were generated and present at the month following the last dose. Six months after the last dose was given, the titers lowered, but they were still about 20 times or so higher than what is seen following a natural infection. The study also determined that antibodies were present at the genital tract, which is where those antibodies would need to be to prevent infection, in addition to being in the blood. The early phase trials indicated that the vaccine was well tolerated with no serious adverse events reported. Systemic vaccination of HPV 16 L1 VLP induced consistent and high levels of serum IgG antibodies. These were durable for 6 months or longer; the levels were much higher than those seen after natural infection, and antibodies were detectable in cervical secretions. This led to a series of three proof-of-concept efficacy trials. Two of them—one published in 2002 and the other in 2005—were conducted and sponsored by Merck Pharmaceuticals, and a third one was published in 2004 by GlaxoSmithKline Biologicals; these companies have undertaken commercial development of the vaccine.

The studies involved between 450 and 1,500 women who were followed for 1.5 to 2.5 years. The first study has now been followed for 3.5 years and has yielded similar results. There was evidence of near complete protection against persistent infection as well as any clinical outcomes, albeit the number of clinical outcomes was very small. Persisting oncogenic HPV infections are the most important determinant risk of progression to precancers and cancers, even more important than the presence of a low-grade, abnormal pap smear.

Large Phase III trials are using two vaccines produced separately by Merck Pharmaceuticals and GlaxoSmithKline (GSK) Biologicals. The GSK vaccine is a bivalent vaccine that has the two most

important oncogene HPVs. The Merck vaccine includes the same two cancer-associated HPV types as well as HPV Types 6 and 11, which are linked to the development of genital warts. The Merck vaccine is adjuvanted with a common adjuvant, alum; the GSK vaccine has an adjuvant that contains alum and monophosphoryl lipid A (MPL). Whether these different adjuvants will make differences in the performance of the vaccine is unclear at this time.

Three large-scale efficacy trials are underway. Two of them, conducted by Merck and GSK, are large (involving more than 15,000 women), multicentric, and encompassing more than 20 countries and 100 sites. Each one is testing its own vaccine. The NCI is conducting a third trial in Costa Rica in collaboration with investigators in Costa Rica within a population the NCI has worked with for many years. The study is using the GSK biological bivalent vaccine under a clinical trials agreement and has enrolled more than 7,000 women. The NCI's Costa Rica vaccine trial targets young women between the ages of 18 and 25. Women were randomly assigned to one of two arms and received three doses over 6 months of either the GSK bivalent vaccine or the control vaccine, the hepatitis A vaccine Havrix®. Enrollment is nearing completion, and the women will be followed for 4 years annually or at more frequent intervals as needed. The NCI has made a commitment to the participants in the trial to crossover with the HPV and Havrix vaccines if the HPV vaccine is found to be as effective as expected. This study's objectives are to: (1) evaluate the safety and efficacy of the HPV vaccine against high-grade cervical precursors and persistent infections associated with HPV 16/18; (2) evaluate the durability of protection; (3) report on other potential vaccine effects, including cross-protection and secondary therapeutic effects; (4) evaluate the cost effectiveness of the vaccination relative to other established methods of prevention; (5) understand the mechanisms of protection and failure; (6) develop surrogate markers of protection for rapid evaluation of second generation vaccines; and (7) make all results publicly available.

Merck recently reported interim results from its large Phase III trial and very recently filed the data with the FDA; there could be a vaccine available for use within the year. The trial is a double-blind study, placebo-controlled, involving approximately 12,000 young women (ages 18 to 25), who have been followed for about 1.5 years. The vaccine was found to be well tolerated with only about 0.2 dropout rate and the equivalent dropout rates in the vaccinated and placebo groups. It was very immunogenic, with nearly 100 percent seroconversion with very high titers of antibodies developed after vaccination. The trial results showed that the vaccine's efficacy was extremely high at almost 100 percent efficacy against the development of high-grade cancer precursors (CIN2 or 3) that were associated with HPV 16 or 18. Two analyses were conducted. One counted women as events or cases that were included only if they were HPV 16 and 18 DNA negative and seronegative at the end of the vaccination phase and had received all three doses of the vaccine. In addition, a modified intent to treat analysis was performed in which events were counted as early as 1 month after vaccination, meaning 1 month after the first dose was given, but before the complete series was given. Women were excluded based on DNA and serology on day 1; if they acquired HPV after initial enrollment, they were still counted. In both cases, vaccine efficacy was close to 100 percent.

Regarding when the vaccines might be available to the public, Dr. Hildesheim noted that Merck has filed with the FDA in December 2005, and a decision is possible within 6 months of filing. This means that a vaccine could be available in the United States by late summer of 2006. In addition, GSK Biologicals has stated that it likely will seek regulatory approval in the first half of 2006, with initial filings in Europe. Dr. Hildesheim acknowledged collaborators within the NCI and other institutions in the United States and in Costa Rica for their work on this project.

Questions and Answers

Dr. Lopez asked about the proportions used in Merck's vaccine, which targets four HPV types. Dr. Schiller replied that 20 to 40 micrograms was included for each of the four types. Dr. Koch wondered about potential side effects of the vaccine and whether any side effect might cause extreme legal liability that would prevent bringing the vaccine to market. Dr. Hildesheim responded that there has been no evidence throughout the Phase I through Phase III trials in Costa Rica that the vaccine is unsafe. Dr. Runowicz posed several questions to confirm the number of injections necessary, the durability of the response, the cost of the vaccine, and societal and ethical considerations. Dr. Hildesheim noted first that Dr. Schiller would be covering most of these in his presentation and then explained that the cost is estimated at $300 for the series (about $100 per shot). Dr. Freedman queried whether any of the virus types could mutate over time and so escape. Dr. Hildesheim acknowledged that all viruses evolve, but noted that, HPVs are DNA viruses that evolve very slowly and that, once inside a host, they do not change. A theoretical concern is that, after HPV 16 and 18 have been eradicated, other oncogenic types might populate the cervix for biological reasons; the Costa Rica cohort should consider looking at the distribution of specific HPV types before and after vaccination to determine if there is any evidence of replacement of one HPV type with other HPVs. Dr. Schiller added that the other HPV types are not as oncogenic. Dr. Armitage shared concerns with Dr. Runowicz; he posed the question as to whether vaccines will target more viruses than just two HPV types. Dr. Hildesheim acknowledged that this vaccine is targeted against two types that account for about two-thirds of the disease. At least one of the vaccines that Dr. Schiller will discuss is potentially a more broad-spectrum, second-generation vaccine that could protect against more types. Dr. Kirchner asked if there was intent to follow up to look at the cancers that do develop despite the vaccine to locate the site of failure and achieve better protection. Dr. Hildesheim replied that, in the longer term, if the vaccine over the 4 years is as effective as it seems to be over a period of 2 to 3 years and there is 100 percent efficacy, even after crossover in the trial in Costa Rica, individuals could continue to be followed for breakthrough infections and lesions, and thereby determine when boosters may be needed. In further discussion, Dr. Hildesheim confirmed that at most less than 1 percent of individuals contract cervical cancer without infection.

Papillomavirus Vaccines To Prevent Cervical Cancer. Dr. John Schiller, Center for Cancer Research, presented information to answer outstanding questions regarding the biology, virology, and immunology of the vaccine; implementation issues; and the development of second-generation vaccines. Regarding the outstanding biologic and immunologic questions, duration of protection is really the key question. The Merck trial of the HPV 16 monovalent vaccine has yielded encouraging data where, after 3.5 to 4 years of followup, patients still have 100 percent protection from persistent infection. Because the antibody titers tend to drop tenfold or twentyfold in the first year or two and then remain stable, this vaccine could provide long-term type-specific protection.

Regarding cross-protection against other HPV types, GSK recently presented data that showed significant protection (about 50 percent for certain types) against persistent infection from other related high-risk HPV types. However, this vaccine might provide only short-term cross-protection. During *in vitro* neutralizing assays, cross-protection was found to be about one hundredfold to one thousandfold lower titers, suggesting that cross protection titers might be less durable than the type-specific protection. For prevalent infection, the vaccine potentially could prevent successive rounds of autoinoculation under the presumption that the initial infected cell does not have the propensity to progress to cancer. Hopefully the ongoing Phase 3 trials will determine whether vaccination might interrupt viral persistence and progression to cancer in such instances.

No data exist regarding protection for males. Because of the difference in the male genitalia, which is not bathed in mucus that contains neutralizing antibodies, it should not be assumed that this vaccine will work for men. As a cautionary note in this regard, a recent GSK trial of a herpes simplex vaccine demonstrated protection in women but did not work in men.

Lastly, an immune correlate of protection could short-circuit many subsequent trials to introduce additional types in the vaccine or introduce fundamentally different vaccines. The most likely correlate of protection is neutralizing antibodies. The NCI recently has developed a high-throughput assay to evaluate the potential of the vaccine to induce neutralizing antibodies that are type specific as well as cross-neutralizing. The vaccine likely will not be effective in destroying an existing lesion because L1 is not expressed in the cells of the lesion where the infection is being maintained. In a productive lesion, L1 is expressed only in the terminally differentiated cells at the upper layer while the infection is maintained in the lower layer basal cells. In progression, these cells become more dedifferentiated to the point where L1 is no longer expressed. Therefore, it is hard to see how L1 T-cell responses would clear infection. For this reason, this vaccine is being considered as a prophylactic, and no true therapy is expected from it.

Dr. Schiller noted that those who should receive the vaccination, in the descending order of importance, are: (1) 10 to 13 year-old girls (the ultimate target group as they have not yet been exposed to these sexually transmitted viruses); (2) "older" women (some might not yet have been exposed to these viruses, and the vaccine might reduce auto-inoculation and transmission); and (3) adolescent boys and men (only if the vaccines are shown to prevent infection).

Dr. Schiller highlighted several concerns, including the price of the vaccine, which Dr. Hildesheim had noted earlier might cost as much as $300 for the series of three vaccinations. Dr. Schiller pointed out that this price also was the original cost for the hepatitis B vaccine, but UNICEF currently buys the hepatitis B vaccine from an India manufacturer for 30 cents per dose. There is also the issue of delivering three intramuscular doses to young adolescents. To bring young women or boys into the clinics three times in 6 months, new programs will need to be developed. Some people in the vaccine and other adolescent-health arenas are excited about this vaccine because it could become the platform for pre-adolescence health care interventions for youth who normally would not visit the clinics. The effect of the vaccine on cervical cancer compliance is also an issue of concern. There likely will not be any initial changes in recommendations for screening; however, there is a possibility that vaccinated people will decide to forego their normal cervical cancer screening tests. This could be a disaster because screening alone prevents at least 80 percent of cervical cancer in the United States, including cervical cancers by HPV types not contained in the vaccine, whereas expectations are that the vaccine could prevent at most two-thirds to 70 percent. Lastly, there is the issue of marketing the vaccine as a cancer vaccine versus a vaccine against a sexually transmitted disease.

Dr. Schiller commented that education of the parents makes a difference for acceptability of this vaccine for vaccination of adolescents. A clear and consistent message for young women, parents, and health care providers is needed that: (1) cervical cancer is caused by a sexually transmitted virus; (2) becoming HPV infected is almost synonymous with being sexually active (the lifetime risk is greater than 70 percent); (3) the vaccines will likely be most effective if given before the onset of sexual activity; and (4) the vaccines will neither replace Pap screening, nor prevent all abnormalities detected in screening programs. Dr. Schiller noted that acceptance of the vaccine will not be universal. It is unlikely that the vaccine will be mandated in the United States. Recommendations by the CDC's Advisory Committee for Immunization Practices (ACIP) and professional medical organizations will be important to get large-scale coverage of this vaccine. In addition, parents will need to be convinced that the vaccine is more of a red light against cervical cancer than a green light for promiscuity.

If VLP vaccine protection is predominantly type-specific, then (1) it will prevent most high-grade cervical dysplasias and cervical cancer, but cancer rates will not decrease for many years; (2) it will not prevent many of the low-grade cervical abnormalities that appear soon after infection and are routinely detected in Pap screens; and (3) women and health care providers need to know that the vaccine may be

working, even if many vaccinated women develop low-grade Pap smear abnormalities or HPV DNA positivity. Dr. Schiller observed that increasing the valency of the vaccine might help cover more of these types to reduce low-grade abnormalities. He noted that including the four most prevalent HPVs in the vaccine would account for about 80 percent of cervical cancers. In terms of the overall cervical cancer prevention, the vaccine is part of a shift to HPV-based cervical cancer prevention.

Eighty percent of cervical cancers occur in developing countries. It will be difficult to develop sustainable vaccination programs for disadvantaged women with the current VLP vaccine because (1) the VLPs are expensive to manufacture and need to be generated from cultured insect cells or in yeast by a multistep purification process; (2) the vaccine will be expensive to distribute, involving needle injection in cold chain; (3) and the logistics of implementation will also be complex. To address these implementation issues, especially for worldwide use, attempts are underway to develop second-generation vaccines with better characteristics. One approach is live bacterial vectors that express VLPs. The advantage is that live bacteria could generate VLP antibodies and could be grown inexpensively. However, initial trials would be expensive because these would be genetically modified organisms and there might be more variability of response. This approach has not been tested clinically, but there has been promising preclinical data from an NCI collaborator, Dr. Denise Nardelli, published in the *Journal of Virology*. She showed that if the strain of *Salmonella* that has been used in millions of people worldwide as a *Salmonella* vaccine (TY21) has a modified L1 (such that it looks like a bacterial gene), then an L1 can be expressed at levels that result in high titers of neutralizing antibodies after mucosal vaccination with the live bacteria. This vaccine is moving toward a Phase I clinical trial in India.

Another vaccine under extensive development is based on L2, which is a minor capsid protein. L1 plus L2 VLPs, like L1 VLPs only, make almost exclusively type-specific neutralizing antibodies; for example, HPV 6 L1/L2 VLPs are good at neutralizing the HPV Type 6 virus but not Types 16 and 18. When removed from its normal context, L2 can induce cross-neutralizing antibodies among the various types although the titers are lower than what is seen with VLPs.

NCI scientists are trying to identify better L2 immunogens for induction of broadly cross-neutralizing antibodies. The that are cross-reactive for L2; the best L2 immunogen that has been found against HPVs, surprisingly, is the first 88 amino acids of bovine papilloma virus Type 1. It induces more neutralizing antibodies against HPV 16 and 18 infection than the corresponding HPV 16 peptide. The next step is to move this vaccine into a clinical trial to determine the levels of neutralizing antibodies it generates in women. The L2 vaccine approach works in an animal model, as shown in rabbits by Neil Christensen, a collaborator. HPV16 and BPV1 L2-based vaccines protected against experimental infection by both cutaneous and mucosal types of rabbit papillomaviruses, which are distantly related to each other, HPV16, and BPV1.

Dr. Schiller concluded his presentation with three ideas: (1) there are high expectations that a safe and effective HPV VLP vaccine to prevent cervical cancer will be commercially available within 1 year; (2) issues of vaccine acceptability and accessibility will dominate in the coming years; and (3) second-generation vaccines might address accessibility issues in developing countries, but safety and efficacy remain to be established in clinical trials.

Questions and Answers

Dr. Lopez commented that the length of the protection is important. Dr. Schiller agreed that some young children should be vaccinated now and followed up to see if they are protected later on. Dr. Chen expressed his enthusiasm at the potential to eliminate disparities, which has tremendous implications. Dr. Freedman wondered about the rates of screening for susceptible women. The answer

given was that the rates of invasive cervical cancer in the United States continue to fall every year, and the CDC offers a successful outreach program for screening of women who are underserved. There are approximately 3,000 cases of cervical cancer a year in the United States, which is much lower than 20 years ago. Dr. Ryan asked what has been observed or learned relative to implementation in NCI's work in Costa Rica. Dr. Hildesheim said that women in Costa Rica have been very accepting of the vaccine. There has been a national debate in that country about this trial, and there is opposition in some sectors of the population to vaccinations as there is in the United States. In general, women are interested in learning about the vaccine, and their willingness to accept it seems to increase with their knowledge.

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.

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There also was a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

DAY TWO: WEDNESDAY, DECEMBER 7, 2005

XII. PROGRAM REVIEW OF DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS —DR. JOSEPH FRAUMENI

Dr. Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), began by noting the parts of the Division's portfolio to be discussed today: (1) highlights from the Radiation Epidemiology Program, (2) the development and application of predictive risk models, (3) an international collaborative study into the origins of lymphoma and the merging of new genetic technologies with epidemiologic strategies, and (4) a project designed to identify susceptibility genes in both prostate and breast cancer.

High-Yield Cancer Data From Low-Dose Radiation Exposures. Dr. Fraumeni introduced Dr. Martha Linet, Chief, Radiation Epidemiology Branch, who discussed high-yield cancer data from epidemiologic studies of low-dose radiation. Ionizing radiation has long been known to cause several types of cancer. Until recently, however, most epidemiological studies focused on quantifying radiation-related cancer risks from high-dose exposures, yet low-dose exposures are more prevalent. Increasingly, fluoroscopic-guided diagnostic and interventional radiological procedures are being employed, with the latter rising exponentially because of lower morbidity, mortality, and cost. It is estimated that there are about 2.3 million radiation-exposed medical and nuclear workers worldwide. Public concern and fear are two of many reasons to study the health effects of low-dose radiation.

Ionizing radiation is an excellent model for studying carcinogenesis. Current efforts emphasize quantifying risks and clarifying mechanisms, but an increasing amount of attention is being given to a better understanding of individual susceptibility. Research also is focusing on improving various diagnostic and therapeutic modalities that involve radiation exposures, and helping to develop radiation protection standards.

Dr. Linet presented a pie chart that showed the sources of exposure to ionizing radiation: radon, 50 percent; medical, 14 percent; gamma, 13.5 percent; cosmic, 12 percent; internal, 10 percent; and the remaining 0.5 percent coming from discharges, products, fallout, and occupational hazards. She noted that approximately three-quarters of the exposure come from background radiation.

The highest doses result from fractionated radiotherapy exposures. Diagnostic exposures comprise a wide range, with more than one-hundredfold differences in various forms of diagnostic radiation exposure. The exposures from the followup studies of the Japanese Atomic Bomb survivors are comprised of even wider range exposures; the majority of survivors had relatively low dose exposures in the form of a single acute dose. In contrast, medical and nuclear workers experienced protracted doses, which are repeated small doses that accumulate and ultimately range from a low to moderate dose. Lastly, most people are exposed to low chronic range of doses from environmental sources. Dr. Linet defined dose as the amount of energy absorbed, which is now considered in Gy, with 1 Gy equaling 100 rads. The relative biological effectiveness of radiation characterizes its ability to produce a specific disorder, such as cell death, chromosome aberration, or cancer. The unit of biological dose equivalents is called the sievert. One sievert equals 100 rad in the old terminology.

The premier radiation study is the 55+ year followup study of the atomic bomb survivors. This study covers more than 100,000 survivors, 60 percent of whom had doses under 0.1 Gy. Fifty percent of the survivors are still alive, as many of them (85 percent) were under age 20 at the time of the bombings. This is the largest followup study of children exposed to low doses. NCI's collaborative studies with Japanese colleagues at the Radiation Effects Research Foundation are now employing 2002 new DS02

organ dose estimates, and the current work is focusing on followup of cancer incidence from 1958 through 1998. The greatest numbers of expected cancers from the atomic bomb survivors are projected to occur in the next 20 years. Approximately 7 percent of the cancers occurring in the atomic bomb survivors are thought to be caused by ionizing radiation from the atomic bombing. The most recent followup study is focusing on 17,000 total cancers, the majority of which are from the digestive tract (10,000) and respiratory (2,000) and then (in declining order) female genital, breast, urinary, and thyroid. The dose-response relationship is linear, at both high and low doses, and statistically and significantly different than expected at the low-dose levels. Other results from this investigation include excess risks, which persist more than 50 years after the bombings. The excess rates increase throughout a person's lifetime for all ages at the time of exposure and are higher for women then men.

The NCI Chernobyl Research Program also has been studying the issue. The Chernobyl accident occurred on April 26, 1986; following the accident in Chernobyl and surrounding regions of Belarus, Russia, and Ukraine, there were 10 days of releases of fallout into the atmosphere. Some areas that received substantially more radiation exposure are not adjacent to the closest areas, as the deposition of fallout was affected by rain, wind, and other weather patterns. Soon after the accident, approximately 100,000 people were evacuated from nearby areas, but 5 million people who resided in the contaminated regions were not evacuated.

The NCI collaborative studies were undertaken following a binational agreement signed by President Reagan and Russian President Gorbachev to address the issues of nuclear safety and to cooperate in radiation-related research to improve the situation. The studies include two cancer types: leukemia (not discussed here) and thyroid. In the thyroid studies, 25,000 children who were under the age of 18 resided in the contaminated area (Belarus and the Ukraine) at the time of the accident were screened every 2 years. The children had to have their thyroid radiation activity measured so that their doses could be calculated. The screening was carried out by palpation, ultrasound, and fine needle aspiration as needed; thyroid function tests and a questionnaire were used to try to better understand the doses.

As the dose increases, risks rise dramatically to fifteenfold at the highest dose levels. A strong linear dose response has been seen, and it has been estimated that about 75 percent of the thyroid cancer cases occurring in these populations are caused by radiation. The risks are higher in females than in males, and risks are higher in those who were younger at the time of the accident than older children.

Dr. Linet next presented data on other environmental exposures that the NCI has worked on both in the United States and abroad. These involve studies on radon and lung cancer, including a large lung cancer case control study in the Ganzu Province in China. The people in Ganzu Province live in unusual dwellings that are constructed underground; this area was studied because of the very wide range of radon levels and the low mobility of the population. It is more difficult to study radon when a population moves around because every single home that a person lived in would need to be measured. In this study, lung cancer risks have been shown to be equal or exceed extrapolations from the studies of uranium miners who also inhaled higher doses of radon.

In the area of occupational exposures, the NCI is conducting a large, nationwide cohort study of U.S. radiologic technologists to determine the risks of cancer and other diseases. Like nuclear workers, these workers are exposed to protracted low-dose radiation, which accumulates during a lifetime and can reach more substantial levels. This study is unique in that it primarily addresses female workers, whereas most radiologists and radiologic technologists focus on male workers. Potential genetic variation and radiation susceptibility are current topics of interest. This followup study involves 146,000 technologists who belong to the American Registry of Radiologic Technologists and who were certified for 2 or more

years between 1926 and 1982. The subjects, three-quarters of whom are women, responded to between one and three self-administered questionnaires, which were administered in the mid 1980s and mid 1990s, with the third survey being completed now. A very sophisticated ionizing radiation dosimetry is being developed, and this is one of the few cohorts in which lifetime sun exposure assessments also have been evaluated. Because of the nationwide characteristic of this particular study, the exposures to a wide range of latitudes and the effects of ultraviolet (UV) rays on cancer risk will be examined in this study. Doses vary widely by facility and time period; there is a dramatic difference between the level of exposure to the workers before 1940 and later.

Dr. Linet described the relative risk for breast cancer based on the number of years worked by the radiology technologists and the risks by decade—specifically, the calendar year in which persons first worked. The exposures of people who first worked in the 1940s have led to substantially higher risks than the referent group, who are workers exposed who began work in 1960 or later. The number of years worked does not appear to be as important as the year first worked, with the highest risks for those working before 1940. There is a little bit of evidence among those who have worked the longest periods of time but began working in the 1960s.

In terms of the other findings from the study besides breast cancer, increased risks for leukemia, nonchronic lymphocytic leukemia, and skin cancers have been found. Increased risks were anticipated for basal cell carcinoma, but the high risk seen for melanoma was unexpected. There is not evidence of significantly increased cancer risks among recent workers; it is believed that the almost absence of increased risks for more recent workers is linked to the marked improvements in radiation protection standards that have reduced exposure—specifically, the workers are working with technically better machines, less scatter, and more protection. Continued followup of these workers is necessary because of the lifetime cumulative nature of the risk.

Dr. Linet presented a followup study (Brenner and Elliston, 2005) of cancer risk following radiation exposure from computed tomography in children and adolescents. The use of a CT scan in children has dramatically increased since the early 1980s, with an exponential increase in the past 15 years. CT scans are increasingly considered to be the gold standard for diagnosis of appendicitis, as well as for diagnosing various other conditions and looking at brain injury. This research is potentially of great impact, and NCI's intramural program has undertaken this partly because it is not easy to find populations where one can measure doses in these children. There is an urgent need for empirical data to push for dose reduction following David Brenner's first paper (2001), which theoretically estimated the lifetime cancer mortality expected from the use of the substantial higher dose procedures compared with typical diagnostic medical x-rays. Consequently, manufacturers who had been unaware of the problem worked rapidly to develop software that set doses that are more appropriate for children. Previously, the equipment was used at settings that were proper for adults, not children. This study aims to evaluate and quantify cancer risk, as well as quantify trends in pediatric CT scan use. The approach will be the retrospective cohort study method; the NCI had to scour the world to find places to collect lifetime electronic radiology department records to estimate dose, which will be assessed by counting the number of CT scans. Various dose surrogates and a series of different approaches are being used to estimate dose more accurately. Cancer incidence will be ascertained by linking the children who undergo these procedures with data from population-based cancer registries. Because of the movement of most of the American population into and out of health maintenance organizations, the study is being conducted in the United Kingdom. It will be quite large and have good statistical power to be able to calculate risks even at quite a low level, including risks of leukemia in someone under the age of 2 years and brain tumors around the age of 2 years.

Recently, the NCI has been designated as a major research center for the national and international concern about potential health effects of radiological terrorism. There is an emphasis on developing medications that can be taken by the population to minimize the health effects and risks from radiation disasters. Radiation disaster covers dirty bombs, improvised nuclear devices, and a wide range of potential exposures. The unique effort that the NCI contributes is to be able to employ its long-standing epidemiologic approach to develop approaches quickly, efficiently, and cost effectively for rapid response of physical dosimetry in collaboration with various consortia. This effort is funded by the National Institute of Allergy and Infectious Diseases through funds from the Division of Homeland Security. The NCI also will be working with these groups to develop cutting-edge methods for dosimetry that can be conducted cheaply and on a large scale. The NCI is trying to make others aware of the need to monitor late effects. The acute effects are more dramatic, but the late effects impact many more people. Because the radiation scientific community is aging, the NCI will be training a cadre of dosimetry experts and teaching radiation epidemiology to basic and clinical scientists who are part of the consortium.

Questions and Answers

Dr. Ralph Freedman commended the work being performed in the pediatric population as very important, especially considering that the pediatric population of cancer patients is surviving longer, as well as in relation to clinical trials where multiple diagnostic radiological studies are conducted on this population. He expressed hope that there will be some positive guidelines as to the frequency with which these studies are done in relation to the diseases. Dr. Carolyn Runowicz noted that children have CT scans either because of trauma or history of cancer and wondered if there were plans to stratify looking at secondary cancers in these two groups or to lump these together. Dr. Linet responded that she is looking at late effects among children who have undergone treatment for cancer, most of whom have had high-dose radiation exposure. The NCI is collaborating with extramural investigators in a followup of the children cancer survivors study cohort; Dr. Fraumeni has been one of the leaders of the study, concentrating on children with retinoblastoma. The CT scan study, however, focuses on primarily healthy children who undergo CT scans. Through the National Health Service in the United Kingdom, the NCI has identified electronic listings of the CT scans; because it is a national health service, lifetime data are available. An important part of the research is to consider potential confounding exposures for the CT scans. This will be addressed through the medical records that are available through the National Health Service.

Dr. Von Hoff queried whether laboratory workers were being studied. Dr. Linet stated that the NCI currently does not have studies of laboratory workers. Many worker groups have approached the NCI, including, for example, a task force of interventional radiologists from four societies who normally are competitors but have banded together because of concerns about cancer risks and other health effects in that population. The NCI tries to be responsive when populations of various types approach the NCI or members of Congress, and it collaborates with others who are undertaking studies.

Dr. Cowan noted that CT scans will be used increasingly as a screening technology for heart disease, lung disease, and even lung cancer. He wondered what the data showed about safety issues at the lower dose use as well as whether patient samples were available for study. Dr. Linet replied that an increasing number of samples is being collected to examine the underlying biology, specifically DNA repair and other radiation damaged areas, including cellular, stroma, and matrix damage. In terms of risks at low doses, it has become apparent that the proportion of people exposed to high doses is much smaller than the proportion exposed to low doses. The NCI has an active high-dose program, but low-dose exposures present many challenges, such as the quantity of patients who need to be studied. When specific cancer subtypes are focused on, however, the numbers quickly start to dwindle; cancer is rare and, of course, pediatric cancer is even rarer. In terms of studies of adult diagnostic exposures, the NCI

has two ongoing population studies, including a study of girls who underwent multiple diagnostic x-rays for evaluation of scoliosis. This is a vulnerable population as most of those x-rays occurred during adolescence, and there are elevated breast cancer risks. Dr. Linet noted that the NCI also has been following up with older populations of people who underwent repeated x-rays, diagnostic x-rays, and fluoroscopy during the early days of tuberculosis treatment.

Dr. Ryan commented that the issue of CT scans and x-rays is becoming a hot issue in the pediatric arena. Pediatric hospital administrators are noticing that many children are sent into the community for their scans and x-rays. He wondered if there has been any link made between the utilization of scans in healthy patients and the locations they occur, or if there are any patterns in primary and secondary institutions versus tertiary care institutions. Dr. Linet agreed that it is important to recognize that the community of pediatricians and pediatric oncologists are quick to be concerned about the exposures because they recognize the vulnerability and increased risks seen with exposures during childhood. She expressed her amazement at the dramatically fast response of all of the manufacturers when Dr. David Brenner brought to their attention the potential danger of the CT scan and the fact that machines were not being calibrated for children. The Society for Pediatric Radiology is sponsoring meetings at which the NCI will be presenting about health effects in terms of interventional radiology. Moreover, the American Academy of Pediatrics has been concerned, and its committees—the Committee on Radiology and the Committee on Environmental Health—continue to examine these issues to develop policy guidelines that respect the power and advantage that these diagnostic and interventional tests offer while still being aware that children need special consideration in terms of a dose that is large enough to provide good images but small enough to minimize the risks. Pediatricians are collaborating with the NCI to produce informational brochures to educate the entire pediatric community.

Absolute Risk in Clinical Research and Patient Management. Dr. Fraumeni introduced Dr. Mitchell Gail, Chief, Biostatistics Branch, and called attention to the Gail Model, a pioneering effort that predicts the individualized risks of breast cancer and which has been widely used in clinical research and in patient management. Dr. Gail presented some refinements in the model for breast cancer and discussed its extension to other forms of cancer. He distinguished between absolute and relative risk and provided examples of both. He explained that, using the model, the relative risk of breast cancer of a 40-year-old woman—who began menstruating at age 14 (which is a baseline category in the NCI Risk Disk model), had no children (which increases her risk a little compared to baseline), had no biopsies (which is a baseline risk), and whose mother had breast cancer (which increases her risk compared to baseline)—is determined to be 2.76 times increased risk compared with a 40-year-old woman with all risk factors at baseline. This is a useful concept for understanding the importance of the various risk factors, but it does not tell the woman exactly what her risk is. It tells her what it is compared to someone else. Absolute risk, on the other hand, will provide a number that she can use by asking a different question: what is the chance that the woman will be diagnosed with breast cancer in the next 30 years between ages 40 and 70? The number that comes out of the NCI Risk Disk is .116 or 11.6 percent. This number can be compared with other absolute risks for other health outcomes.

Several factors influence absolute risk, including: (1) the age of the person who is coming for counseling because most cancer age-specific incidence rates increase with age, and this is an important factor in computing absolute risk; (2) the age interval during which the risk projection is being made—the chances of developing the disease over a long interval are greater than over a short interval; and (3) an individual's particular risk factors and competing risks (for example, a person at high risk of dying of cardiovascular disease has a reduced chance of developing breast cancer over a given interval).

Dr. Gail discussed examples from the NCI Risk Disk. One woman, who has no affected first-degree relatives, is 40 years old and would like a 10-year projection of her risk; her 10-year projection is

3.6 percent, with a confidence interval of 3.0 to 4.3 percent. Another woman, with two affected first-degree relatives, is 30 years old and wants a 30-year projection; her projected risk is 33 percent, with a confidence interval of 21 to 47 percent. Depending on the age interval, the age of the woman, and the risk factors present, there can be quite a variation in these risk projections.

For specialized cases, Dr. Gail presented the example of a 20-year-old woman whose treatment for Hodgkin's lymphoma involved 40 Gy to the chest for radiation but no alkylating agents. Her 30-year breast cancer risk just to age 50 is 19 percent, which is very high. Dr. Gail noted that a person carrying the BRCA mutation would have this sort of risk. If the woman had been treated with alkylating agents, her risk would be lower because the alkylating agents reduce the functioning of the ovaries, which offers some protection to the breast.

The uncertainties associated with using the NCI Risk Disk include random error (confidence intervals) and systematic errors (i.e., risk factor is not in the model). The latter include factors such as recent immigration from low-risk area, previous breast cancer, proven BRCA1 linkage in the family, chest radiation for Hodgkin's lymphoma, and anunscreened population. Projections for African American and Hispanic women were subject to more systematic uncertainty than for white women, from whom the model was largely developed.

Absolute risk can be used when counseling patients, designing clinical trials, assessing the burden of disease in populations, and comparing risks and benefits of interventions of interventions, such as tamoxifen, because absolute risk can be computed for breast cancer and other health outcomes. The absolute risk is the commensurable quantity that allows one to begin to weigh these risks and benefits. Dr. Gail presented a publication by Bernie Fisher, et al., from the National Surgical Adjuvant Breast and Bowel Project (NSABP), showing the effects of tamoxifen on life-threatening events, in which tamoxifen reduced the risk of invasive breast cancer by slightly less than one-half; unfortunately, the paper showed that the risks of endometrial cancer were increased, the risks for stroke were increased by about 60 percent, and the risk of pulmonary embolus were roughly tripled. Regarding severe events (as opposed to life-threatening events), tamoxifen reduced the *in situ* breast cancer incidence by 50 percent, but there was an increase in deep vein thrombosis. Dr. Gail cautioned that the benefits must be weighed against the risks.

Dr. Gail explained how to weigh these risks and benefits and present this information to a woman. He suggest using a method recommended by the NSABP that listed the various outcomes and asked the woman to consider what would happen to a population of women just like her. For instance, if there is a 40-year-old white woman with a uterus whose 5-year risk of invasive breast cancer is 2 percent, the following is projected to happen during the next 5 years to a group of 10,000 women just like her: if no tamoxifen were given to this population, then 200 (or 2 percent) of the women would develop invasive breast cancer, as well as 2 hip fractures, 10 endometrial cancers, 22 strokes, and 7 pulmonary emboli. If tamoxifen were given, 97 (almost 50 percent) of the invasive breast cancers and 1 of the two hip fractures would have been prevented; however, 16 additional endometrial cancers, 13 additional strokes, and 15 additional pulmonary emboli would have developed. More information could be provided to the woman by determining the net number of life-threatening and severe events. Using an index of one for life threatening and one-half for severe events, then there would be a net benefit of 54 life-threatening and 38 severe events prevented, for a combined total of 73 net events prevented. Using this index for white women ages 40 to 49, as the risk projection for invasive breast cancer rises, the benefit index increases because there is more breast cancer to be prevented. When a 50- to 59-year-old woman is compared to a 40- to 49-year-old woman, the benefits are less because the background rates of stroke and endometrial cancer increase rapidly with age and the compounding effects of tamoxifen lead to the fact that these adverse events begin to outweigh the beneficial effects. A woman in this age group who has a 2 percent

risk should not take tamoxifen. African American women have a similar pattern but they tend to have smaller net benefits because their background rates of stroke are higher.

Regarding DCEG's ongoing research, a model is being completed that incorporates mammographic density into these risk models. It is a strong risk factor; it is hoped that information about this model will be published in 2006. There also is modeling breast cancer risk with case-control data for African-American women, and a plan for a model focusing on Hispanic women and possibly to try to combine genetic and classical risk factors in a common model. In addition, models are being developed, and some are in press, for colorectal cancer, melanoma, cancer in patients with Franconi anemia, the absolute risk of cervical cancer and precursor lesions, and second cancers. The NCI also is trying to use independent data to validate models that others have developed, as well as working on the statistical methodology side to develop and implement criteria for evaluating risk models and to improve the confidence interval estimation procedures to take into account all sources of variability.

In May 2004, the NCI sponsored a workshop on cancer risk prediction models. It was co-organized by Andrew Freedman of DCCPS and Ruth Pfeiffer of DCEG. Topics included: the strengths and weaknesses of current models, the methodology and validation techniques, the need for models for various cancer sites and for competing risk endpoints, collaboration and data sharing, risk communication, and decision making.

Dr. Gail concluded his presentation by noting that absolute risk is a key tool for counseling, designing trials, assessing disease burden in populations, and weighing the risks and benefits of an intervention. There is a lot of ongoing research to develop new models, validate current models, and improve the methodology. Finally, DCEG is planning to develop a portal to facilitate scientific exchange of models that are in development and would benefit from comments by the general scientific community.

Questions and Answers

Dr. Runowicz commented that, as a clinician, she finds the risk models very useful. She noted that the overall risk was 2.5 for endometrial cancer and the risk under the age of 50 was the same as placebo, thereby making the calculations for the age of 40 a little higher for endometrial cancer risk. Dr. Gail agreed. Drs. Runowicz and Gail then conversed about the minimal effect that alkylating agents likely will have on the ovaries of a 20-year-old woman.

Interlymph: Discovering the Heritability of Non-Hodgkin Lymphoma. Dr. Fraumeni next introduced Dr. Sophia Wang, a tenure-track investigator in the Hormonal and Reproductive Epidemiology Branch, who presented the early results from a study of genetic susceptibility to lymphoma. The study included the development of a collaborative international network that aims to accelerate progress in a coordinated and cost-effective fashion. Dr. Wang shared recent accomplishments from the International Lymphoma Epidemiologic Consortium (InterLymph Consortium) in discovering the heritability of non-Hodgkin lymphoma.

DCEG has had a longstanding interest in understanding the etiology of non-Hodgkin lymphoma (NHL), as rates have been rising worldwide for the past 50 years. One of the challenges in understanding or studying this disease, however, is that NHL includes many clinically and epidemiologically distinct subtypes. There are critical clues in what is known about this disease, including that immune dysregulation is the key cause of NHL; it is a cancer of the immune cells. Individuals who are infected with HIV and AIDS, who have had organ transplants, or who have autoimmune diseases or inherited immunodeficiency syndromes all have much elevated risks for NHL. There is a genetic contribution to this disease, although the exact nature of this contribution has not been defined.

The NCI has taken two approaches to identify the nature of the genetic contribution. The first approach is to evaluate the effects of a family history of lymphoma or leukemia. It has been reported consistently in the literature that individuals who have a family history of lymphoma or leukemia also have elevated risks of NHL. However, this exact pattern of inheritance has been difficult to define mostly because of the small proportion of NHL cases that contain a family history of lymphoma. The second approach is to link common genetic variants with disease, which might reveal critical pathways such as specific immune pathways or genes that would alter risk for NHL, thereby providing important clues to understand lymphomagenesis. Some of the challenges in this approach, however, have been in the feasibility of doing so in population-based studies. Investigators have tried this approach in other tumors, looking at genetic variances of polymorphisms in relatively small case control studies. As a result, there are many false positives and negatives populating the scientific literature.

Fortunately, with the formation of the InterLymph Consortium, as well as in the advent of rapidly advancing technology in the arena of high throughput genotyping, the NCI is well placed to proceed with both approaches. In 2001, investigators in DCEG—Drs. Patricia Hartge, Martha Linet, and Nat Rothman—brought together lymphoma researchers around the world for the first annual meeting of the InterLymph Consortium. At this meeting, the investigators agreed to combine forces as they recognized that there would be no single study large enough to evaluate gene associations or environmental associations with NHL. No single study would be large enough to study the effects by each of the different histologic subtypes of which there are many for NHL. The success of the InterLymph Consortium during the past 5 years provides a platform from which investigators of individual studies can rapidly replicate their own results as well as avoid being misled by chance findings. The InterLymph Consortium is an international consortium of investigators with ongoing or completed case control studies of non-Hodgkin lymphoma. It is an open scientific forum through which collaborative research, including pooled or parallel analyses, is conducted. The consortium currently includes more than 11,000 NHL cases and more than 13,000 controls. The majority of the studies come from Northern America, Europe, and Australia, which are the areas where NHL rates historically have been the highest.

Dr. Wang presented preliminary results from the pooled InterLymph analysis of family history and risk for NHL. The analysis focused on understanding the heritability of NHL and the attempt to identify the exact pattern of inheritance. The case control studies that are participating in the pooled analyses vary in size and include the NCI SEER NHL study led by the PI Dr. Patricia Hartge (DCEG). Some studies have contributed multiple cases with a family history of NHL, ranging from three cases (northern Italy) to as many as 56 cases (United States NCI study). With the pooled analysis, there are more than 22,000 cases and controls and 201 cases with a family history of NHL. Some scientific questions can be asked and analyses performed with the pooled analyses that could not be done with any individual study. Early results confirmed that there is a 1.5-fold increase in risk for NHL for individuals who have a first-degree relative (parent, sibling, or child) with NHL. The pooled analysis further demonstrated that it is the individuals who have a sibling (brother or sister) with NHL who have the highest (2-fold) risk. Because men historically have higher rates of NHL than women, the study looked at them separately. The actual relative's gender likewise was examined separately, as it also relates to the risk for disease in some tumors. For men and women who have a female relative (mother, sister, or daughter) with NHL, there is a moderate risk for NHL: 1.2-fold for men and 1.4-fold in women. There is, however, a 2.4-fold increase in the risk in men and 1.8-fold increase in the risk for women if this relative is male (father, brother, or son). There is nearly a trifold increase in risk if this relative is a brother. Dr. Wang summarized the study by noting that NHL in siblings marks the highest risk, with male relatives indicating a higher risk than female relatives, particularly if this male relative is a brother. In addition, the effects vary by the lymphoma subtype, and family history of other hematopoietic malignancies, such as leukemia and Hodgkin's disease, also relate to NHL risk.

Dr. Wang next turned to a pooled analysis of immune gene variations and risk for NHL, which is NCI's second approach to trying to identify the genetic contributions to NHL etiology. She noted that this pooled analysis was recently published in *The Lancet Oncology*, which is included in the Board's materials.

In selecting candidate genes for the pooled effort and in selecting candidate genes actually as part of the NCI SEER case control study of NHL, the first consideration was that severe disruption of immune function is the primary risk factor for NHL. For this reason, the analysis focused on immune genes and cytokines, a type of immune gene. Immune genes serve as great candidate genes because they are known to alter gene expression and have functional relevance. They have been associated with autoimmune disorders and infectious diseases, two main causes of NHL. In addition, they have large polymorphic variations that can be investigated, and they have been shown to influence clinical outcomes so they have great scientific relevance for NHL. Dr. Wang showed a diagram of inflammatory response to illustrate that while immune genes can be targeted, the actual selection of immune genes and specific polymorphisms is not a simple task as there are numerous immune genes that are involved in T-cell differentiation and B-cell differentiation, and the inflammatory response.

Before the pooled effort, the NCI focused on the key proinflammatory response genes. The NCI SEER study, which examined 57 immune genes, found significant associations with the proinflammatory cytokine pathway, which is significantly associated with some of the more aggressive lymphoma subtypes, including diffuse large B-cell lymphoma. Specific polymorphisms from specific proinflammatory cytokines, including tumor necrosis factor significantly increased risk for diffuse large B-cell lymphoma. A subset of these immune genes was selected for the InterLymph pooling project. The genotyping for the NCI SEER study was completed at the NCI Core Genotyping Facility, which is directed by Dr. Stephen Chanock. They also completed the genotyping for a number of other studies included in the pooled analyses, and they played a critical role in the bioinformatics and quality control of the pooled effort. They provided 102 ethnically diverse DNA samples that were characterized by NCI's SNP500 project for genotyping at each of the participating laboratories, of which there were four. There was found more than 99 percent concordance for the genotyping.

Dr. Wang presented the results from the pooled analyses. The tumor necrosis factor promoter polymorphism due to a G to A substitution at position -308 that is associated with increased risk for diffuse large B-cell lymphoma. This is a rather low frequency allele where 3 percent of the population is homozygotes and 26 percent of the population is heterozygotes. There is a 1.3-fold increase in the risk for heterozygotes and a 1.6-fold increase in the risk for homozygotes. If the risk with each additional variant allele is considered, there is a significant trend of .000055.

Dr. Wang next showed an additive model, which demonstrated the risk for each additional variant allele by individual studies. For all of the studies, all of the risk estimates are above one, indicating an increased risk for diffuse large B cell lymphoma. Only one study—the NCI SEER study—yielded a statistically significant increase in risk. If the confidence of the risk estimate is measured by the 95 percent confidence intervals, then the best confidence is in the pooled estimate.

The pooled analyses also demonstrated an increase in the risk for diffuse large B-cell lymphoma with another cytokine, interleukin-10. This particular genotype at position 3575 is more common. Thirteen percent of the population is a homozygote for this particular polymorphism and 46 percent of the population is a heterozygote. A more modest increase is seen in the risk, a 1.2-fold increase in the risk for diffuse large B-cell lymphoma in heterozygotes and a 1.3-fold increase in risk for homozygotes. Both are

statistically significant and again the trend is statistically significant at 0.006, modeled on each additional variant allele.

If the additive model is examined by study, then the risk estimates by individual study are generally above one, indicating an increased risk for diffuse large B-cell lymphoma. Only a single study was actually statistically significant on its own. The confidence interval was most tight for the pooled estimates.

Because both of these polymorphisms affect or increase the risk for diffuse large B-cell lymphoma, and they are reported to be causal in the proinflammatory pathway, their effects were investigated further in conjunction with each other. Individuals who are homozygous for the TNF promoter polymorphism, as well as individuals who are also either a heterozygote or a homozygote for the IL-10 polymorphism, have the highest risk, a 2.1-fold increasing risk for diffuse large B-cell lymphoma.

One of the great advantages and one of the best illustrations for consortium work is avoiding false positives. Dr. Wang showed the results from another cytokine, interleukin 1B. These are the risk estimates for each individual study for the homozygote variant TT and non-Hodgkin lymphoma. If each of the individual studies had published results on their own, one study would have published a statistically significant decrease in risk for non-Hodgkin lymphoma, and other studies would have followed, trying to replicate this finding. Another study would have published a statistically significant increase in risk for non-Hodgkin lymphoma, which other studies would have tried to replicate, and maybe in several years, no association between this polymorphism and NHL eventually would have been concluded. However, it was demonstrated in a single publication with the pooled analysis that there is no association between IL-1B and NHL.

Dr. Wang concluded that, based on the findings of the pooled analysis, the proinflammatory pathway alters the risk for NHL, particularly for diffuse large B-cell lymphoma. The InterLymph Consortium provided 3,600 cases and 4,000 controls that had DNA available at the time and ready for genotyping. Currently, there are more than 9,000 NHL cases and an equal number of controls now with DNA. It provides a great opportunity for replication of these and individual study findings. The NCI SEER case control study found an association between TNF and diffuse large B-cell lymphoma, and the pooled analyses were able to replicate this finding immediately, clearly demonstrating the power of the consortium. In addition, false leads and misleads were avoided. For TNF and IL-10, only one study was statistically significant for each of those associations. There are currently opportunities for extension to other genes, and the NCI SEER case control study is pursuing them, which hopefully will be replicated in the consortium. There is the opportunity for gene-environment interactions. Some extreme genotyping is ongoing, and within the consortium there may be opportunities for whole genome scans as has been done with other tumors, which Dr. Chanock will discuss. Dr. Wang thanked all of the collaborators who are involved in the InterLymph Consortium effort.

Questions and Answers

Dr. Lopez asked if the functional implication of this genotyping of TNF alpha and interleukin-10 had been examined for higher secretion levels of TNF alpha or interleukin-10. Dr. Wang confirmed that work has been done on the TNF and, although not proved, in a number of models and in cell lines it has been demonstrated that this particular polymorphism is purported to increase levels of TNF. The interesting thing about the interaction or the joint effect of IL-10 and TNF is that it is believed that IL-10 also plays a suppressive role to the tumor necrosis factor alpha protein. The polymorphism for IL-10 actually decreases the level of IL-10 and the joint TNF polymorphism increases the level of TNF, so it is

thought that there is more of the TNF protein making it a potentially good molecular candidate, particularly since it is one of the key stimulatories to the NF kappa B pathway for inflammation.

Dr. Niederhuber wondered if the higher risk group in a family—i.e., siblings, particularly male siblings—had been looked at or if there were germ line gene alterations that would set the background. Dr. Wang explained that analysis has not been performed for this group but that one of the next analyses that the consortium hopes to conduct is merging the family history data with the genotyping data. The family history analysis is being completed now and will be submitted shortly for publication. She noted that the sibling component, and understanding the genetic variation or the general similarities between families, provides leads for pursuing family studies. Looking at siblings for genetic variations in the general population also might be another approach. Dr. Von Hoff added that looking at groups all together does not take in the context of vulnerability or other things not considered. Dr. Wang agreed but noted that one of the first genetic analyses performed was the assessment of the homogeneity between all of the studies. The study might not have accounted for all of the environmental factors, but in terms of the actual heterogeneity among the population for characteristics that were known and measurable, they were extraordinarily homogeneous.

Dr. Barker commented that Drs. Wilson and Staudt have looked at B-cell lymphoma, especially in terms of the somatic mutations; she noted that discovering the genetic background and then adding on the somatic prognostic factors would help to provide direction for some of the newer projects. Dr. Wang responded that the NCI SEER case control study is pursuing this. She said that although the merging of all the pathology slides from the InterLymph Consortium was a little bit challenging at the moment, but that the NCI SEER case control study is proceeding with defining the molecular subtypes for diffuse, large B-cell lymphoma in collaboration with Dr. Staudt. Dr. Wang confirmed that the NCI is planning to look at the genetic variation and how etiology relates to survival.

The CGEMS Project: Cancer Genetics Markers of Susceptibility. Dr. Fraumeni then introduced Dr. Stephen Chanock, Director of NCI's Core Genotyping Facility, to discuss the Cancer Genetics Markers of Susceptibility (CGEMS) project in which genomicists and epidemiologists are joining forces in a systematic search for modifier genes that might raise or lower the risk of prostate and breast cancer. Dr. Chanock began by noting that the Genome Project, the HapMap, and other resources in genomics and epidemiology have converged to focus on central questions about the genetic basis of different types of cancer. For example, breast cancer studies have shown that there are very important highly penetrant germline mutations that represent 5 to 10 percent of cases and are very important in populations and individuals affected with those particular genetic mutations. There also is emerging evidence that there are other genes with lower penetrance that predispose a person to breast cancer.

It is unknown what percentage of cancer is genetic versus environmental. Some have argued that cancer is 100 percent genetic and others say that 100 percent is environmental. Others would argue that it is somewhere in between, and that the numbers add up to 100. If genetics has a role in breast cancer, most of us believe it will be found to be a complex disease with many genetic factors involved. To take advantage of the confluence of opportunities to identify inherited cancer risk, the knowledge gleaned from the Human Genome Project and the HapMap project, which has laid down remarkable scaffolds for genetic variation in human populations, is being combined with the dense SNP technologies that have emerged over the last several years in the private sector. In addition, the tremendous investment in cohort studies and large case control studies on the part of the NCI and other institutions are remarkable resources to bring genetics in sufficiently large enough populations and particularly case control studies (both direct and nested case control studies) to raise questions.

CGEMS has laid out a major goal to attempt whole genome SNP scans. The challenge will be to do this in more than one tumor in parallel with a slight staggering. Prostate cancer was chosen as an initial focus, and the plan is, within a very short period, to initiate a comparable project in breast cancer where rapid sequential replication of studies hopefully will avoid the false positives that exist in many of the association studies involving common alleles with a lower penetrance. The idea is to have everything tagged with one set right after the next to minimize lags of time that can allow particular biases and proclivities to alter the results, which, although not necessarily done consciously, are nonetheless major problems in the field. There is a very aggressive timeline in place, as well as a proposal to conduct the initial scan in two different cohort-based studies, starting with a nested case control study from the PLCO with prostate cancer and then very shortly thereafter going into the Nurse's Health Study looking at postmenopausal breast cancer in comparable size studies. The key opportunities include: (1) replication of findings, (2) rapid dissemination of results, (3) leverage existing infrastructure to reduce cost, and (4) foster intramural/extramural collaboration. The examination of prostate cancer, which is the initial scan of 1,200 cases and 1,200 controls, involves enriching for advanced cases (i.e., 50 percent of the cases have Stage C or D or a Gleason of 7 or greater), which is coming out of the PLCO and includes four or five studies set up for replication. Then there will be up to 7,000 cases and controls for subsequent replication. Similarly, in breast cancer, which began 6 months later, and focuses particularly on postmenopausal breast cancer, replication would be both the cohort-based studies and several pristine case control studies.

Genetic variation and the world of SNPs has taken a remarkable turn in the last several years and posed even more challenges. Current estimates indicate that there are 7 million single nucleotide polymorphisms with a frequency of about 5 percent. There is a history of SNPs in each person in the population, but not all SNPs are unique and unrelated to those around; in other words, SNPs are related to contiguous SNPs and those in the neighborhood through a process that is described as linkage disequilibrium. This provides the opportunity to look at those 7 million SNPs with surrogates rather than test all 7 million. In addition, the number of SNPs also changes when different populations are examined based on the population history.

Dr. Chanock showed a graphic representation of the frequency of SNPs, estimating their numbers in the human genome as a function of their minor allele frequency. The largest numbers of SNPs are between 5 and 10 percent of frequency; higher frequencies result in lower total SNP numbers. Some 250-300 genes have any publications of polymorphisms of SNPs in the literature; there are 20,000 to 25,000 genes and perhaps more when they are extended into RNAs and other important transcripts. So far, only a very small percentage has been analyzed.

Because testing for all the SNPs is too costly in terms of economics, time, and available DNA, the strategy for SNP selection is to examine one region at a time. The technologies have improved to allow an exam of larger sets at a particular time, but looking at each place in the genome is important. The strategy employs an approach that capitalizes on linkage disequilibrium. It divides the genome into "bins" and uses a paralyzed R square through which sets of SNPs that are very strongly correlated with each other can overlap these bins as opposed to the haplotype block definition. A bin has a group of SNPs that are highly correlated by the greedy algorithm of Carlson, et al. (University of Washington), and select one Tag SNP from each bin that would serve as a surrogate for the others. Fifteen percent, however, do not have a strong correlation with other SNPs.

The prostate scan does not look across the entire genome and capture every possible bin but rather focuses on enhancing the unhappy SNPs in candidate regions that have been identified in the family linkage study that was recently published in the *American Journal of Human Genetics* (summer 2005). Genic regions are also being examined, particularly genes using the combined resources of several

different international databases, and conserved regions in the genome. Approximately 3 to 4 percent of the genome is highly conserved between different species, particularly between vertebrates.

The replication strategy for prostate cancer will start with an initial study of 1,200 cases and 1,200 controls and look at 300,000 or more Tag SNPs. It is expected that the number of SNPs will whittle down through the course of four replication studies down to between 10 and 25 loci. CGEMS is a project that purports to identify these; others can perform the full genetic analysis and examine the biologic implication to advance new strategies for prevention and for treatment. The detection probability is at the odds ratio of roughly 1.5 for a particular allele, the likelihood by using the adapted schema of the Carlson approach of an R square of 0.8 could be described as very good power for the entire project when looking at alleles that are greater than 10 percent in the population. The analysis plan involves focusing primarily on the main effects: looking at noteworthy SNPs, performing sequential analysis to identify regions, and adding additional SNPs to help dissect the genetic components; this strategy is designed to minimize false positives. There is excellent power for finding those things with odds ratios of greater than 2.

Information regarding the genotype data, case control status, and the history of prostate cancer will be made publicly available through CaBIG as quickly as possible. Publication of results will also help to develop a foundation for data posting, stimulate new analytical approaches, encourage data mining, and be useful for a forum for analysis workshops and tool development a tremendous amount of information is generated. The mechanics of CGEMS involves a contract for the whole genome scan (such as the RFP for prostate cancer), the Core Genotyping Facility's (CGF) replication studies using the extreme throughput genotyping platforms Illumina and Affymetrix, and analytic capability to look at quality control issues and statistical analysis.

Dr. Chanock noted that CGEMS has been funded through the Office of Cancer Genomics under the leadership of Dr. Daniela Gerhard and conducted in the DCEG and CCR at the NCI Core Genotyping Facility under Dr. Joe Fraumeni. He also recognized Drs. Robert Hoover (DCEG), David Hunter (Harvard School of Public Health and eminent NCI scholar), and Gilles Thomas (DCEG).

Dr. Chanock pointed out that CGEMS is a project or a strategic initiative that is expected to disseminate rapidly the findings of referenced whole genome scans to help define genetic markers for susceptibility and protection and motivate the investigation of the biologic basis of the genetic markers and mechanisms and have this lead to new strategies for treatment and prevention of these major public health problems (i.e., prostate and breast cancers). He reiterated that an aggressive timeline is in place. The first scan, if all goes well, will go out the door in January and data will begin coming in late in the spring and early summer of 2006.

Questions and Answers

Dr. Niederhuber commented that the excellent presentations from both days have provided the Board with a good sense of the activities that are occurring in the intramural program. He and Dr. von Hoff expressed their appreciation on behalf of the Board for the exception accomplishments across the extramural research program, and for the outstanding efforts of the intramural leadership and scientific staff.

XIII. UPDATE: NCI TRAINING COMMISSION REPORT—DRS. ERNEST HAWK AND CAROLYN STRETE

Dr. Hawk represented the NCI Training Commission, which was established by Dr. von Eschenbach in late 2003 to examine what the NCI was doing in training across all of the various divisions and evaluate and envision how it might be improved or facilitated. This resulted from discussions that he had had with Dr. Joshua Lederberg, who was particularly interested in the NCI focusing on translational science. Dr. von Eschenbach commissioned this under the leadership of Dr. Carl Barrett and charged the commission with eight tasks: (1) compile an inventory of training activities across the Institute; (2) promote existing training opportunities; (3) develop new training opportunities particularly related to curricula that did not exist, as well as facilitating translational training; (4) integrate training activities for added value; (5) establish data and tracking systems to monitor training activities more effectively than were present in the past, (6) coordinate fellowship and education offices; (7) promote mentoring; and (8) increase the training of under-represented cancer researchers and continue support for new investigators.

The Commission was challenged midstream with the departure of Dr. Barrett. Dr. Antman subsequently picked it up and then left, whereupon leadership fell to Dr. Hawk earlier this year. There are a variety of other activities that the Training Commission is engaged in and they will subsequently be under the leadership of Dr. Carl Oberholtzer. Dr. Hawk acknowledged his colleagues' work and introduced Dr. Carolyn Strete, who heads the Cancer Training Branch and has been a leader in this aspect of the Training Commission's work. Dr. Strete reported on the activities of the Training Commission Inventory Subcommittee, which was tasked with the Training Commission's first mandate, to compile an inventory of training activities across the Institute. The Subcommittee was to: (1) identify NCI's research training and career development programs; (2) determine the types of data needed; (3) identify data sources; (4) obtain relevant descriptive, quantitative, and fiscal data from all programs; and (5) summarize and report findings. Dr. Strete pointed out that the members of the committee included Drs. Carolyn Strete (OCTR), Demetrius Albanes (DCEG), Jane Daye (CRCHD), Lester Gorelic (OCTR), Kathleen Schlom (OD), and Jonathan Wiest (CCR). She acknowledged the participation of others from a number of branches from across the NCI and the NIH.

Dr. Strete distinguished between training and career development. She described training in terms of institutional curricula-driven programs that combine didactic and hands on research experiences without any defined plan of progression to independence. Career development, on the other hand, refers to a period of supervised research experiences that may integrate didactic studies with laboratory, clinical-based research, population, behavioral sciences, where the proposed research should have intrinsic value, as well as serve as a suitable vehicle for learning the methods, theories, and conceptualizations necessary for a well-trained independent researcher. She cited K career awards as falling under career development.

The sources of information that went into this report came from all of the programs that the Subcommittee inventoried. Other sources included NCI's databases, such as the Extramural Financial Data Branch's database that includes fiscal records on grants, and the NIH-wide data source, the Information for Management, Planning, Analysis and Coordination (IMPAC II) system, which has a huge repository of information on all the NIH grants. Moreover, the Office of Policy Analysis and Resources provided information on the history of legislation governing NCI's training and career development programs.

There are five locations where there are extramural activities in training and career development: Cancer Training Branch, Comprehensive Minority Biomedical Branch, DCP's Cancer Prevention Fellowship Program, Organs Systems Branch (SPORE Program), and the Center to Reduce Cancer Health Disparities (CRCHD). There are two divisions within the intramural program that support training: Center for Cancer Research and the Division of Cancer Epidemiology and Genetics.

In terms of cumulative data for the extramural programs as a whole, the overall numbers in training between FY 1999 and FY 2004, and the dollars awarded to support these training programs, steadily increased. The number of trainees means the number who were in training within each fiscal year rather than the number who were trained. These numbers are underestimated because statistics on trainees in the Comprehensive Minority Biomedical Branch (CMBB), who are supported by the Minority Institution or Cancer Center Partnership Programs, are still being assessed. In addition, the numbers under the Cancer Education R25E grants are not included here. Finally, it is not known how many dollars have been spent to train individuals under the career development component of the SPORE program. The overall increase in numbers in training for the extramural CTB, CMBB, and CRCHD was 22 percent from 1999 to 2004; the increase in dollars for those same programs over those years was 115 percent. In sum, the total dollars awarded by these extramural programs is approximately $881 M. (The Cancer Prevention Fellowship Program statistical data will be reported under the intramural program section because intramural dollars support this program.)

For intramural programs, the cumulative numbers of individuals in training steadily increased from FY 1999 to FY 2003 and then declined in FY 2004 by 145 or by 8.5 percent. However, the dollars awarded to support the intramural training steadily increased by up to 87 percent during that time. The total dollars awarded in the intramural programs was found to be approximately $358.4 M. (This figure includes the Prevention Fellowship Program). The overall cumulative number of individuals in training in all programs combined increased 31 percent from FY 1999 to FY 2003 and declined slightly by 3.3 percent (N=139) in FY 2004. At the same time, overall dollars awarded increases steadily up to 107 percent. The conservative estimate for all extramural and intramural programs combined and applied over the 6 years for training and career development totaled $1.24 B.

Dr. Strete next described the individual programs. The Cancer Training Branch (CTB) manages the extramural research manpower development and cancer education programs and oversees the NIH loan repayment (which is not part of the Subcommittee's inventory, and so is not discussed here). The CTB offers a range of training opportunities, from the predoctoral stage to established investigator or the mentored to independent phases across a career timeline. The Branch focuses on three career tracks: (1) basic research; (2) clinical research, with an emphasis on patient-oriented research; and (3) prevention, control, behavioral, and population science. Dr. Strete presented a table showing individual K awards on those three career tracks as an example of how these mechanisms can be applied. The Branch's strategic plan was put in place in 1999 and 2000; the cumulative numbers of individuals in training and career development increased by 12 percent from 1999 to 2004. The lack of correlation between the increase in the number of individuals in training and career development, 12 percent increase, and the near doubling of the training budget is partially explained by the increase in NRSA stipend support, increase in the cost of tuition and health insurance costs, and the growth in the career award mechanisms in strategic areas that were laid out in the strategic plan, and that is explained in the body of the report. The stipend levels over the years have increased by an average of about 6 percent per year. In terms of the overall CTB trends, roughly $710 M was spent. The Branch awarded 57 percent of the total extramural dollars to training and career development over 6 years. From FY 1999 to FY 2004, there was increase of 12 percent in the number of individuals in training and career development, and the budget nearly doubled. There is a small decrease (53) in the cumulative number of individuals in training between FY 2003 and 2004. (FY 2005 dollars have not been collated.) Again, the increase in dollars relative to the numbers in training is explained partially by the increase in the costs required to conduct training programs.

Dr. Strete turned to the Comprehensive Minority Biomedical Branch, which focuses on training researchers from minority and under-represented groups by broadening their participation through the CURE program and by increasing research capacity at minority serving institutions. This Branch uses a variety of mechanisms (described in Appendix E of the Subcommittee's report) to accomplish its goals.

They supplement six RPG mechanisms plus P20, P30 and P50, T32, R25T, Cancer Education Grants, and the K12 Clinical Oncology Grant, and the Cooperative Planning Partnership Awards, U54 and U56. With regard to training in the latter two mechanisms, the investigators who have the grants develop educational programs for ethnic minority groups entering careers in cancer research and they support pre and postdoctoral training. This Branch also supports four individual K awards. In terms of trends for this Branch, the number of individuals in training and career development increased by 103 percent between FY 1999 and FY 2004, including the supplements (i.e., a person or persons that can be counted) to the P20, P30 and P50 grants. This does not include, however, the trainees under the U54 and U56 so this does not include all of the trainee numbers. The overall number of individuals in training and career development increased steadily during each year between FY 1999 and FY 2004 by 103 percent. The total dollars awarded to training and career development in the Minority Training Branch increased 267 percent between FY 1999 and FY 2004, for a total of approximately $165 M. Dr. Strete showed a graph of the total dollars awarded by the Comprehensive Minority Biomedical Branch with the portion of the support for the centers and partnership programs, which includes the P20s, P30s, P50s, U54s, and U56s separated out.

The Cancer Prevention Fellowship Program (CPFP) aims to train scientists and clinicians from multiple health science disciplines who will become leaders in the cancer prevention and control field both inside the NCI and at outside institutions. There are three key features. (1) Fellows who come into the program without a prior degree in public health epidemiology can obtain training in fundamentals of public health and research methodology during their M.P.H. program experience. (2) Although the CPFP is housed in the extramural DCP, Cancer Prevention Fellows can match with preceptors engaged in cancer prevention and control research anywhere at the NCI, intramural or extramural. (3) The *Summer Curriculum in Cancer Prevention* is a series of courses geared toward clinicians, research scientists, and other professionals interested in cancer prevention and control (20 out of 100 participants are CPFPs). Regarding overall trends, an increase in the total number of fellows across the years coincides with 36 percent increase in the number entering each year. The increase in numbers represents an increase from 11 in FY 1999 to 15 in FY 2004 for a total in FY 2004 of 57 in training. In terms of the dollars from FY 1999 to FY 2003, the dollars awarded to the CPFP increased approximately 24 percent annually but between FY 2003 and FY 2004, the dollars awarded decreased by about 10.5 percent. Dr. Strete reminded participants that FY 2003 was the last year of the doubling of the NCI budget. There was a total of $11.5 M awarded to this program over the years that were inventoried.

The career development component of the Specialized Programs of Research Excellence (SPORE) is designed to accommodate scientists with a wide variety of prior experience and at different stages in their career development. As a consequence, all aspects of this program are designed to be highly flexible and are tailored to the individual needs of the candidate as well as to the particular SPORE. Eligible candidates may be in a postdoctoral phase of their careers or they may be established investigators who wish to develop or refocus their careers on translational cancer research. Predoctoral investigators are not a part of this training and career development component. The SPOREs provide support for salary and research, but the costs are not fixed as they are for the K awards. At the time that the report was drafted, there were 61 funded SPOREs, addressing 14 organ systems. In FY 2004, the total budget was $136 M. Because information about the trainees is not captured in a database, the number of dollars was not included in the report. The Subcommittee is looking for ways to gather data on this important training.

The CRCHD's Training in NCI Networks provides funds to networks of minority investigators who can train students interested in health disparities research. Junior investigators write research proposals that are evaluated as mini-R01 grants. The meritorious ones are funded, and the investigators perform the work and summarize their work and, hopefully, publish it. This program began in FY 2001.

Through FY 2004, both the training numbers (n=46 in FY 2004) and the dollars ($2.3 M in FY 2004) increased steadily up to 155 percent during that time, for a total of $6.8 M.

Dr. Strete next presented information about training in NCI's intramural programs. She explained that she would first describe the two divisional programs separately, and then describe the data on both programs collectively. In the intramural program, there are five support mechanisms. The Cancer Research Training Award (CRTA) is the major mechanism for supporting postdoctoral investigators in the intramural program; it also supports postbaccalaureate fellows, graduate students, and summer students, and many of the summer students are high school or college kids. The Visiting Foreign Fellows Program has postdoctoral trainees in it only. Two other categories include clinical fellows and research fellows. The clinical fellows are junior-level physicians who gather experience in biomedical research relevant to NIH program needs. The position has both clinical and laboratory components, with some time spent in direct patient contact supporting the performance of clinical protocols and in translational research. Importantly, in some cases the clinical fellows may receive approved credit as far as residency training, advanced specialty training and board certification. In terms of the research fellows, the purpose is to provide junior-level scientists who have doctoral degrees with experience in biomedical research while they provide service relevant to NIH's needs; these scientists spend their entire fellowship program in laboratory research.

Dr. Strete then presented training data. When looking at the CRTA, the domestic trainees and the visiting fellows, e.g., foreign fellows, the distribution within the intramural program of the foreign fellows versus the CRTA fellows, the domestic trainees fluctuated between FY 1999 and FY 2004 beginning with 608 in FY 1999, increasing in FY 2003 to 773 and declining to 657 in FY 2004. The number of foreign fellows showed a significant increase from FY 1999 to FY 2001 (329 to 490) and then a gradual increase from FY 2002 to FY 2004 (522 to 535). Combined, the number of fellows increased up to FY 2003 and then declined by an n of 103 in FY 2004.

For intramural pre and postdoctoral trainees, the number of predoctoral investigators fluctuated widely between FY 1999 and FY 2004. The total number of postdoctoral trainees showed a sharp increase in FY 1999 and FY 2001 and then a gradual increase thereafter. There was, however, an overall 27 percent increase in the pre and postdoctoral trainees in training from FY 1999 to FY 2004. (These numbers do not include clinical and research fellows categories, described later.)

In terms of dollars for intramural pre and postdoctoral investigators, the dollars awarded increased gradually from FY 1999 to FY 2004, with the exception of a slight decrease in FY 2004. The dollars awarded to postdoctoral trainees steadily increased from FY 1999 to FY 2004 and overall, the dollars awarded to pre and postdoctoral investigators increased by nearly 67.4 percent over the years FY 1999 to FY 2004.

Regarding the intramural clinical and the research fellows categories, the numbers of trainees in both gradually increased from FY 1999 to FY 2003 and then declined. The dollars gradually increased in all years for the clinical category and increased in FY 2003 and then declined in the research category. The overall budget increased up to FY 2003 and then leveled out. A total of $130 M was awarded during the 6 years that were inventoried.

Among all the intramural programs, the numbers in training increased 34 percent from FY 1999 to FY 2004. There was a slight decline between FY 2003 and FY 2004, caused by budget constraints and FTE caps. The dollars awarded increased 87 percent from FY 1999 to FY 2004. The biggest reason for the increase in dollars and the decrease in the numbers in training is the increase in stipends and health benefits; this amounted to approximately a 6 percent increase per year. The NCI allocated 29 percent

($358.4 M) of its overall training and career development dollars for the years that were inventoried to its intramural training programs.

Dr. Strete showed two graphs that illustrated the number of individuals supported in the extramural and intramural programs together, and the NCI dollars awarded to training and career development by both extramural and intramural programs. She closed with a summary slide that tallied all numbers for both types of programs; in the extramural and the intramural programs, there was approximately $1.24 B awarded.

Questions and Answers

Dr. Von Hoff requested that the Subcommittee continue to work in defining its particular mission. He cautioned about overselling the "cumulative" amount of training, as most are interested in what has been spent in the current year. In addition, he observed that training for extramural investigators costs about $80,000 per trainee and $50,000 for intramural investigators. Dr. Peter Greenwald commented that the Cancer Prevention Fellowship Program has experienced trouble in attracting physicians into the training programs and suggested that the clinical training might be a problem. He also wondered if the budgets in the upcoming years would be sufficient to maintain the training programs of young investigators. Dr. Ken Cowan wondered if there is any followup to determine what happens to these trainees; obtaining some idea might help the Institute determine if the program is accomplishing what it set out to do. Dr. Niederhuber noted that Dr. Carl Oberholtzer, a new Associate Director for training, was present, and invited him to comment. Dr. Oberholtzer observed that the training issue is complex but important. He stated that he is looking forward to working with all of the constituent bodies, including NCAB, and with the people in the community to determine what is the best way to do it and the issues that were raised here regarding the intramural and extramural programs. Dr. Runowicz agreed that training replacements is absolutely essential; she shared her observation that pooling training awards with private foundations and other outside organizations would make better awards available, increase the candidate pool, and help to work around financial constraints and share resources. Dr. Von Hoff commended the idea of public-private partnerships. Dr. Barker noted that the NCI is collaborating with other federal agencies, such as the National Science Foundation and the FDA. Dr. Strete joined in to report further cooperation with the Thoracic Foundation for Research and Education, the American Urological Association, and the American Cancer Society awards some outstanding candidates that the CTB cannot reach for funding. Dr. Von Hoff expressed his and the Board's appreciation to Dr. Strete, the Subcommittee, and others involved in compiling this inventory.

XIV. UPDATE: TRANSLATIONAL RESEARCH WORKING GROUP—DR. ERNEST HAWK

Dr. Ernest Hawk reported on the progress of the Translational Research Working Group (TRWG), which Dr. von Eschenbach initiated in late summer 2006 in an announcement to the NCAB. He reminded the Board of the rationale for the group: (1) advances in cancer biology offer enormous opportunities to improve public education and clinical practice; (2) proliferation of NCI programs over the last decade; (3) limited resources, unlimited potential, and high expectations; and (4) important opportunities to accelerate NCI's progress.

The working group's strategic plan outlined thirteen steps, the first seven of which have been initiated: (1) announce the TRWG plan to the NCAB, (2) define senior leadership, (3) develop membership rosters, (4) share foundational documents, (5) develop a Web-based communication platform, (6) initiate a translational research outcome evaluation, (7) plan the first Roundtable and receive public comment, (8) convene the first Roundtable, (9) develop a draft model of translational research and recommendations, (10) receive public comment on the initial recommendations, (11) convene a second

Roundtable to discuss the draft model, recommendations and suggest implementation strategies, (12) develop an implementation plan, and (13) present the final model, recommendations, and implementation plan to the NCAB. Dr. Hawk reported that senior leadership for the working group includes Drs. Ernest Hawk, Lynn Matrisian, and William Nelson. The membership roster includes 60 individuals coming from 18 states and the United Kingdom, as well as 18 NCI representatives. Each member was chosen strategically based on their expertise and other components that are important to the working group's mission. Other members include: four representatives with industry experiences, two advocates, many experienced with grants, various professional organizations and NCI oversight boards, and the Clinical Trials Working Group (CTWG) members.

Regarding the working group's plan to share foundational documents, several reports have been disseminated to members to review ongoing activities. These reports include the CTWG report, P30/P50 Report, Progress Review Group Reports, the President's Cancer Panel Report, NIH Roadmap initiatives, and NCAB's report "Cancer at a Crossroads." In addition, four pre-planning teleconferences with TRWG membership have been convened to brainstorm the issues and key elements of translational research.

The Web-based communication platform can be found at www.trwg.cancer.gov. It includes information on the TRWG process, its leadership, and members. Additional information will posted as it is available. The site also will be used to receive public comment on key questions at various stages throughout the process.

For the outcome or process evaluation being developed, the first meeting was held during the past weekend, during which a group was commissioned through the Office of Science Planning and Assessment to begin a systematic evaluation, both in terms of a broad portfolio analysis and a more detailed process evaluation, to examine the NCI enterprise to determine which are embodied in the term "translational research." Learning how to identify within the overall grants portfolio those that had a translational impact has been an interesting experience and remains a work in progress. The overall goals are to identify NCI's work in translational research; use it as a tool to identify strengths, limitations, or gaps; and to extract lessons to help envision a more productive and creative future.

The next step in this process has been to plan and ultimately convene the first roundtable to solicit broader community input into the key issues facing translational science from industry, advocates, and investigators engaged in this research. The planning meeting was convened December 4-5, 2005, in Baltimore, Maryland. The TRWG members at that session discussed the issues and elements of translational science and the best structure for the working group to address these issues, including how to use the roundtable for breakout sessions, topics under consideration, and key individuals who are not currently represented on the TRWG but will be important to invite into the process. Moreover, the TRWG process evaluation, how it is going about its work, its goals, and refinement of its activities were discussed. There will be a public comment period that will be focused on specific questions available on the Web site, which likely will start December 20 and close January 20 before the convening of the first roundtable on February 23-24. That roundtable will begin developing a draft model of what translational research would look like and recommendations to get there. It is anticipated that the model will be available for public comment around the end of summer 2006, and a second roundtable will be held to discuss that model with the broader community, recommendations, and results of the process evaluation, as well as a draft implementation plan that will be finalized by the TRWG. It is likely that the implementation plan will be brought to the NCAB in late 2006 or early 2007.

Dr. Hawk closed by echoing Louis Pasteur's idea that basic science is critically linked to applied science. He noted that the goal is to figure out how best to facilitate the discussions between laboratory, clinic, and population to achieve meaningful improvements in the public's health.

Questions and Answers

Dr. Cowan said that he was pleased to participate in this first planning meeting and congratulated Dr. Hawk and the other leaders for an excellent job in organizing it. He looks forward to participating in the working group. Dr. Niederhuber observed that this is an ambitious undertaking and commended Dr. Hawk's leadership. He noted that one of the difficulties has been how to put the limits around what truly is translation, from its start to hand off, and to determine how it works from patient application in the very, very earliest stages to develop patient research where the patient is actually part of the model and then take that information back to the laboratory. He reminded the Board that the TRWG is a natural step in building on the amount of effort that went into the CTWG. Ongoing challenges will be to define coordination of this effort, whether intramurally and extramurally, and prioritize what is being done.

XV. SUBCOMMITTEE REPORTS

Communications Subcommittee—Dr. Lydia Ryan

Dr. Ryan summarized the highlights of the Communications Subcommittee's work during the past 6 months, which includes two conference calls between the leadership staff of the Office of Communication, Nelvis Castro and Mary Anne Bright, and the Subcommittee. NCI's strategic plan has been drafted and was in external review in early November when the Subcommittee met via a conference call. The Office of Communications has undergone a functional realignment and is working actively within the construct of NCI's overall strategic plan to outline those communication activities that ultimately are going to enable the NCI to achieve its strategic objectives. An NCI Steering Committee will be formed to assist the NCI in communicating and pulling together its planning efforts, which have been highlighted for the Communications Subcommittee.

The target date for completion of the first draft of the NCI communication plan is late spring 2006. Ms. Castro will send it to the Subcommittee to look at what may be some key areas for collaboration or advocacy assistance. Within the communication plan, there is a strategic tactic to consider developing an external working group to help the Office of Communication in advocacy, provide guidance, and help communicate and disseminate key elements of the strategic plan. The Subcommittee expects to meet by early June via conference call.

Questions and Answers

Dr. Von Hoff commented that patients and families might like to read the NCAB's and other NCI publications to obtain more information. He referred to a telephone call he received in the morning from a patient with gastro-intestinal stromal tumors who asked for advice on treatment. Dr. Freedman agreed that placing NCI's books within the clinics of major cancer centers for patients to read might be helpful. Dr. Ryan shared that the Office of Communication has redesigned and examined the issue of materials on the Web versus hardcopy, and she pointed out that Dr. Croyle's group is examining how to use some of the Web tools that already are in place. She acknowledged that the dialogue is ongoing and the Office of Communication looks forward to the strategic plan with some tactics that the Office can help market as well.

XVI. ADJOURNMENT—DR. DANIEL VON HOFF

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

There being no further business, the 136th regular meeting of the NCAB was adjourned at 11:27 a.m. on Wednesday, December 7, 2005.