DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
146th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 17–18, 2008

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

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The National Cancer Advisory Board (NCAB) convened for its 146th regular meeting on 17 June 2008, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 17 June 2008, from 8:30 a.m. to 2:45 p.m., and Wednesday, 18 June 2008, from 8:30 a.m. to 10:50 a.m., and closed to the public from Tuesday, 17 June 2008, 2:45 p.m. to 5:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala (absent)
Dr. Bruce A. Chabner
Dr. Moon S. Chen, Jr.
Dr. Donald S. Coffey
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Dr. Lloyd K. Everson
Ms. Kathryn E. Giusti (absent)
Mr. Robert A. Ingram (absent)
Mr. David H. Koch (absent)
Dr. Diana M. Lopez
Dr. Karen Dow Meneses
Ms. Lydia G. Ryan
Dr. Daniel D. Von Hoff (absent)

President's Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson)
Dr. Margaret L. Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC
Dr. Patricia Bray, OSHA/DOL
Dr. Allen Dearry, NIEHS
Dr. Diane C. DiEuliis, OSTP
Dr. Michael Kelley, VA (absent)
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE (absent)
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Dori Reissman, NIOSH (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Advanced Technology and Strategic Partnership
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
Ms. Kathy McBrien, Administrative Resource Center Manager
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Lawrence Ray, Deputy Director for Management and Executive Officer
Dr. Craig Reynolds, Associate Director, NCI-Frederick
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Jaye Viner, Acting Director, Office of Centers, Training and Resources
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Steven Klein, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Brenda Nevidjon, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Leo Giambarresi, American Urological Association
Ms. Christy M.P. Gilmour, American Academy of Orthopaedic Surgeons
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. David Lofye, Lance Armstrong Foundation
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 5–6 FEBRUARY 2008 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 146th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz 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 5 - 6 February 2008 NCAB meeting. The motion was seconded and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2009.

III. NCI DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Dr. John Niederhuber, Director, NCI, welcomed Board members. He noted that, overall, NCI's significant budgetary challenges still were outweighed by the opportunities available to the Institute.

NCI Fiscal Year 2008, 2009, and 2010 Budgets. Dr. Niederhuber stated that the fiscal year (FY) 2008 operating budget was approximately $4.8 B, a slight increase of $7.5 M (+0.16%) from the FY 2007 budget. The end-of-year payline for R01 competing grants is estimated at the 14th percentile (approximately 1,283), and new investigator end-of-year paylines are expected to be at the 19th percentile (a target of 217 for the NCI and 1,547 for the NIH as a whole). A total of approximately 5,000 research project grants (RPGs) will be funded in FY 2008. The NCI is focusing attention on directing resources to new assistant professors in the early part of their careers; the first renewal of a grant is the key to whether this group of applicants will remain successful in academic medicine or competitive in basic science departments. The NCI has been addressing the approximately 11 percent of the competing pool of dollars reserved for exceptions funding throughout FY 2008. In addition, the NCI has participated in NIH's bridge award program by submitting applications (particularly for A2 grants) that meet the program's criteria; Type 5 grants received a 1 percent cost of living allowance (COLA) increase; Special Programs of Research Excellence (SPOREs) and Cancer Centers program funding remained unchanged from FY 2007; and group and training program funding, although initially maintained at the FY 2007 level, received increases of approximately 5 percent.

Dr. Niederhuber noted that the President's Budget (PB) for FY 2009 is $4.8 B, which includes an increase of $4.7 M (+0.1%) from 2008. The budget is not expected to be completed until after the Presidential Inauguration in January 2009; it is possible that the NCI will operate on a continuing resolution throughout FY 2009 with an appropriation consistent with the FY 2008 budget. The NIH already is working with the Office of Management and Budget to create the 2010 budget. The NIH budget has experienced many increases and decreases in budget growth since 1971, but this is the first time that the budget has been flat for such an extended period of time (2005-2010), which makes planning difficult. NIH Division, Office, and Center leadership will discuss concluding and managing FY 2008, planning for FY 2009, and preparation for the submission of the FY 2010 budget at the annual executive

leadership retreat to be held at the end of July. Additional needs for the conclusion of FY 2008 include funding for the following: items not previously started and current underfunded programs; new scientific opportunities; and urgent facility and infrastructure needs. Some of these may be funded if monies are redistributed from other areas of the budget before the end of September 2008. In planning the FY 2009 operating budget, it was decided that Division, Office, and Center budgets should anticipate a 3 percent reduction from FY 2008 funding levels. However, Cancer Centers ($262 M), SPOREs ($123 M), Clinical Cooperative Groups ($145 M), and Community Clinical Oncology Programs ($88 M), which are critical to the success and maintaining the momentum of the NCI, will be funded at the listed FY 2008 levels. The NCI leadership is developing the progress report and bypass budget, and has received input from leaders in science and in the science of cancer. The NCI also continues to execute the recommendations and implementation strategies set forth in NCAB's Clinical Trials Working Group (CTWG) report "Restructuring the National Cancer Clinical Trials Enterprise," and NCAB's Translational Research Working Group's (TRWG) report "Transforming Translation—Harnessing Discovery for Patient and Public Health." The NCI's flat budget of the past 4 years is thought to contribute to the decline in the number of Letters of Intent for Phase I and Phase II trials (from 450 to 50) over this time period. The Cooperative Group Concepts for Phase III cooperative group trials also have decreased. However, Dr. Niederhuber noted that these numbers are estimates only, and may show an upturn in 2009, but the NCI is concerned by these decreases.

Drug Development. Dr. Niederhuber stated that the NCI's development of drug discovery and translation into clinical use is the platform that connects academic laboratories, university laboratories, the private sector, and government agencies. The NCI is working to increase its capacity in a number of areas related to drug development, including the following TRWG initiatives: small molecule screening and discovery; the Chemical Biological Consortium (CBC); the Rapid Access to Intervention Development (RAID) program; the Small Business Innovation Research (SBIR) Phase IIB award; the Developmental Therapeutics Program; and the Advanced Technology Partnerships Initiative. In particular, the SBIR program has been very successful. The NCI has created an office that serves as a model for the NIH and may service some of the smaller institutes, and the first Phase IIB awards will be made early in 2009. In terms of novel agents, Dr. Niederhuber mentioned four new inhibitors in the Cancer Therapy Evaluation Program (CTEP) portfolio; the NCI is pursuing seven additional inhibitors and one TRAIL agonist.

The Advanced Technology Research Park is a positive addition to NCI's drug development efforts. It will be located near the Frederick campus; the NCI will conduct technology research and many drug development activities there. The park will encourage collaboration among the NCI and the private and academic sectors. Other advances based on the CTWG report include development of clinical trial registration at the NIH Clinical Research Center and possible collaborations with the future Walter Reed National Military Medical Center and Suburban Hospital. Additionally, the National Cancer Policy Forum will address multicenter Phase III clinical trials and cooperative group structures.

Opportunities and Challenges. Dr. Niederhuber noted additional investment opportunities for the NCI, including molecular prevention, theoretical cancer biology, and development of shared intramural and extramural services and resources. The Cancer Genome Atlas (TCGA) pilot project includes work on glioblastoma, ovarian, and lung cancers. Other opportunities in science include transcriptional regulation, epigenetics, and whole tumor sequencing. Because cancer can serve as a model for both studying disease (such as HIV/AIDs and heart disease) and for health care delivery (as in the use of interdisciplinary clinical care teams), an investment in cancer is an investment in the understanding of biology and biologic mechanisms, which affect all disease.

An NCI-sponsored workshop on theoretical physics was held at the end of February 2008, to explore opportunities to create incentives for collaboration among leaders in physics, chemistry, mathematics, and cancer research. Several ideas to involve the physical sciences in cancer research include: the development of a field of theoretical cancer biology; tumor cell complexity in association with the microenvironment requires mathematical models (e.g., cell communication, metastasis); and the impact of basic physical principles and laws (mechanical forces, energy and energy transfer, cell shape, dimensions of time). The role of tumor cell evolution should be better understood. An annual meeting on translational research will be held November 7 - 9, 2008 and will be co-chaired by Drs. Sheila A. Prindiville, Director, Coordinating Center for Clinical Trials (CCCT), and Lynn Matrisian, Vanderbilt University; it will replace the summer SPORE meeting. Challenges faced by the NCI include the NIH Research, Condition, and Disease Categorization (RCDC) project, Roadmap/Common Fund: Transformative R01s, common language, patient reimbursement, aging infrastructure such as NCI Frederick, recruiting young investigators, international activities, contract renewal regarding the Frederick campus, FY 2010 Bypass Budget, molecular prevention, immunology (immunotherapy network and AIDS/Cancer vaccine initiative), and the NCI Community Cancer Centers Program (NCCCP).

Dr. Niederhuber closed with a statement made by Senator Edward M. Kennedy on May 8, 2008: "We've come a long way in fighting cancer since we passed the National Cancer Act 37 years ago. Americans lived in fear that they or someone they loved would be lost to this dread[ed] disease. Today, we still have that fear, but we're better equipped for the fight."

Questions and Answers

Dr. Moon Chen, Associate Director, Population Research and Cancer Disparities, University of California Davis Cancer Center, asked about NCI's plans to address the cancer burden in all communities. Dr. Niederhuber responded that the NCI has the opportunity to serve all communities through the NCCCP at major research universities; in addition, the NCI has conducted a small pilot project in direct investment in the community that has received an enthusiastic response, and the NCI will be able to carry its research, science, education and Phase I trials to the communities if the program is developed. Dr. Niederhuber has encouraged Cancer Center directors to work, with the backing of their universities and health care systems, to conduct outreach in their communities as well.

Dr. Jean deKernion, Professor and Chairman, Department of Urology, and Senior Associate Dean for Clinical Operations, David Geffen School of Medicine at the University of California, Los Angeles (UCLA), commended the relationships that the NCI has developed with industry, and asked about CTEP's process for discovery and collaborations with industry, and whether a private developer was funding the new research park. Dr. Runowicz queried whether industry had an advantage in conducting clinical trials because they can be performed abroad less expensively and more rapidly, or because they have more funding, or both. She also asked for the details about the reduction in letters of intent (LOI) between 2005 and 2008. Dr. Niederhuber explained that a private company will be developing the research to NCI's specifications, and the NCI will lease the building to tenants involved in biomedical research and drug discovery. Dr James H. Doroshow, Director, Division of Cancer Treatment and Diagnosis, NCI, explained that LoIs for Phase I and Phase II trials decreased because LoIs have historically decreased at the end of a 5-year funding cycle, and the NCI did not issue solicitations because a large number of trials were ongoing. Based on recent substantial demand from industry, the number of LOIs should increase next year. Dr. Niederhuber noted that industry may have economic reasons not to develop a product, but if it is scientifically viable, the NCI can take over the development. Dr. Doroshow added that the activities that the NCI is conducting to enhance the timeliness of its clinical trials system will make partnerships more desirable for industry.

Dr. Donald Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, John Hopkins University School of Medicine, said that the theoretical physics meeting was a fascinating discussion that approached cancer as an evolution problem; the enthusiasm of the attendees demonstrated that including the physical sciences in the fight against cancer was an excellent idea.

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

Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel (PCP, the Panel) and Charles R. Drew Professor of Surgery, Howard University Hospital, thanked the NCAB for the opportunity to present the Panel's update, and expressed appreciation for the PCP members and staff for their excellent work.

Themes covered in the Panel's 2007-2008 meeting series "Strategies for Maximizing the Nation's Investment in Cancer" included: the role of the NCI in the Nation's cancer enterprise; patient-centered cancer research and care; coordination across the cancer enterprise; innovative scientific discovery; and application of current knowledge. Other common themes included access to quality cancer care for all; smoking cessation and prevention; regulatory barriers; technology development and application; workforce issues; sharing knowledge and resources; strong leadership; and the need for a unified message and vision within the cancer community. The Panel is preparing its final conclusions and recommendations from this series of meetings; a final report will be presented to the White House later in the summer.

The 2008-2009 meeting series "Environmental Factors in Cancer" will be held in East Brunswick, NJ; Indianapolis, IN; Charleston, SC; and a city in the west yet to be determined. The focus of the meetings will be cancer-causing pollutants found in air, soil, food, and water; workplace exposure to arsenic, asbestos, and cadmium as well as job-specific chemical use; and other factors such as nuclear fallout, electromagnetic fields, and radiation exposure. Possible outcomes of this series are to: determine the role of the NCI as it relates to environmental causes of cancer; identify research needs and potential new areas of collaboration among federal agencies; increase public awareness of environmental and occupational hazards; and develop recommendations for regulating toxic and other potentially hazardous chemicals and materials and for reducing exposure to cancer-causing pollutants. Dr. Leffall directed the Board to the Panel's Web site (http://pcp.cancer.gov) for further information.

Questions and Answers

Dr. Runowicz noted that, according to Dr. Harold Freeman, Center for Cancer Care and Prevention, Harlem, NY, patients present with very late-stage cancer because they lack medical insurance until they are diagnosed. It must be stressed that access to early cancer care is key; when the disease is caught at an early stage, there is a far better outcome. Dr. Leffall agreed, and added that encouraging cancer screening also would decrease the incidence in all populations.

Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center and Chief of Hematology/Oncology, Massachusetts General Hospital, noted that last year NCAB had urged the administration to ratify the World Health Organization Framework Convention on Tobacco Control (FCTC), and asked if the PCP had considered taking a similar stance. Dr. Leffall responded that the Panel has addressed the FCTC, and that tobacco control will be an integral part of the report to the President this year.

Dr. Coffey asked what amount of funds the PCP suggested that the President should spend to optimize the Nation's investment in cancer, and stated that some committee, possibly the PCP, should

determine this amount as well as effective strategies to prevent smoking and to decrease health disparities. Dr. Leffall replied that the PCP did not address the dollar amount, but did state that more research funding is needed to recruit young investigators; the annual report will contain examples of strategies that have worked and should work. Dr. Niederhuber explained that the NCI has the responsibility of reporting to the President through the Bypass Budget, but capacity has to be built. With an additional $2 B per year, the NCI could develop incentive programs to recruit young researchers, and later shift some of the funding toward research; this would be an investment that could improve the country's health and economy. Dr. Kenneth Cowan, Director, UNMC Eppley Cancer Center, University of Nebraska Medical Center, agreed that spending more on training and ensuring there is a new generation of scientists is critical. The flattening of the NIH and NCI budgets has had a negative impact on science, and a discussion of what portion of the federal budget should be invested in biomedical research is needed. It is possible that additional funding could ensure that the United States has a leading role in biomedical research in the future. Advocacy groups would be helpful in developing some of these concepts and in supporting training, infrastructure, biomedical research, economic impact, and the impact of research on health care and health care dollars. The NCI and NIH should lead discussions that demonstrate how science is leading to improvements that aid the economy. Dr. Niederhuber agreed, and added that the country needed to recognize the importance of science and mathematics to continued growth and prosperity.

Dr. Coffey commented that the Cancer Act created the PCP and the Bypass Budget, but these may not have enough impact on the President or Congress; NCAB should consider the role of the PCP and its own role in advising the government on cancer. Dr. Chabner added that the PCP should simplify the message it sends to the President and the public. The Panel should tell the President that an additional $1 B is needed for cancer research, and tell the public to "stop smoking." Dr. Leffall thanked the NCAB, and noted that he and the recently deceased Dr. Judah Folkman had discussed the benefits of cancer research on the treatment for macular degeneration, an example of cancer research's broad application. Dr. Runowicz added that the American Cancer Society (ACS) determined that the tobacco tax has been the most effective means of reducing smoking.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), reported on the status of appropriations, hearings, and briefings that have occurred since the last meeting and presented highlights about health-related legislation.

Appropriations Status. The FY 2009 appropriations cycle began on February 4 with the announcement of the PB, which provided $29.3 B for the NIH, with $4.8 B allocated to the NCI. The House has scheduled the Subcommittee markup for June 19 and the full Committee markup for June 25. In the Senate, a Subcommittee hearing is planned for July 16. The War Supplemental Spending Bill is progressing through Congress. The House version, which was passed on May 15, did not include increases in domestic spending. The Senate amended the bill by adding some domestic spending, including $400 M to the NIH; it passed on May 22 and was returned to the House.

Hearings and Briefings. On May 8, Sen. Edward Kennedy (D-MA), Chair of the Senate Health, Education, Labor, and Pensions (HELP) Committee, convened a hearing entitled "Cancer: Challenges and Opportunities in the 21st Century." Sen. Kennedy and Sen. Kay Bailey Hutchison (R-TX) announced their intention to introduce legislation renewing the war against cancer. Goals of the bill include removing barriers to cancer research and treatment, improving access to early detection and cancer care, increasing enrollment in clinical trials, and reducing disparities in cancer treatment. The House Energy and Commerce Subcommittee on Health held a hearing on May 21 to receive input on two bills: H.R. 1157

and H.R. 758. H.R. 1157, the Breast Cancer and Environmental Research Act, authorizes a $40 M grant program to fund research on environmental factors causing breast cancer. H.R. 758 requires health insurers to extend coverage for a minimum of 48 hours in the hospital for women undergoing mastectomy or lumpectomy. The first two panels focused on H.R. 1157—Dr. Deborah Winn, NCI, the musician Sheryl Crow, and others testified. Dr. Winn represented the NIH and NCI position on the Senate version of the bill (S 579) as well as the House version (H.R. 1157). The NIH and NCI do not support either House or Senate bills because of the "disease-specific" nature of the legislation, but do not oppose the Senate bill. Both bills would establish a Breast Cancer and the Environment Research Panel. The two versions of the bill differ slightly in how the Panel would operate. The House bill mandates that NIH is bound to follow the funding recommendations of the Panel, which is seen to circumvent peer review. The Senate bill calls for the NIH to consider, but not necessarily follow, the Panel's recommendations—this difference allows the NIH and NCI to take a position of not opposing the Senate Bill. In additional news, Dr. Niederhuber met with members of the House Appropriations Subcommittee: Rep. James Walsh (R-NY), Rep. Betty McCollum (D-MN), and Rep. Mike Simpson (R-ID). He also met with Rep. Niki Tsongas (D-MA) and Rep. Nancy Boyda (D-KS), new House members who have long-standing interests in cancer issues.

Legislation of Interest. Ms. Erickson referred members to their Board books for extensive synopses of health and cancer-related legislation, including the Conquer Childhood Cancer Act; the Small Business Innovation Research Program/Small Business Technology Transfer Program (SBIR/STTR) Reauthorization Act; and the Pediatric, Adolescent, and Young Adult Cancer Survivorship and Quality of Life Act. Members received an overview of the Genetic Information Nondiscrimination Act (GINA), which was signed into law on May 21 (PL 110-233). GINA prohibits discrimination in health insurance and employment discrimination on the basis of genetic information. It restricts companies from adjusting premiums or contribution amounts based on genetic information. Insurers are not allowed to require patients to undergo genetic tests. GINA authorizes penalties if companies base eligibility on genetic information or base exclusion of preexisting conditions on genetic information. Other key employment provisions are: employers must treat genetic information as a confidential medical record; they may not limit, segregate, or classify employees based on genetic information; and they may not request an employee's genetic information. Because of rapid advancements in the genetics field, Congress established a Study Commission to review the developing science and provide recommendations to Congress in 6 years. The bill addresses genetic services in clinical trials, including the potential for discrimination that exists based on the fact that the mere action of requesting a genetic test could seem to imply that a participant possessed a genetic disorder; the bill bans discrimination based on genetic services.

Questions and Answers

Ms. Lydia Ryan, Service Line Clinical Director, Hematology and Oncology/Stem Cell Transplantation, Children's Healthcare of Atlanta, AFLAC Cancer Center, noted that the young adult cancer survivor bill (S. 2877) includes guidance for the states to work in collaboration with NCI's Director to incorporate strategies targeting comprehensive cancer plans, and develop systems for tracking cancer survivors. She asked about NCCCP efforts on outcome metrics and tracking of cancer survivorship. Dr. Niederhuber responded that the survivorship was one of the issues considered when designing the NCCCP, particularly the linkage of the programs to academic cancer centers and the public health arena. He mentioned that Dr. Julia Rowland, NCI, who is heavily involved in NCCCP, currently is planning a meeting on cancer survivorship with the involvement of the ACS and Mr. Lance Armstrong.

VI. UPDATE: RESEARCH, CONDITION, AND DISEASE CATEGORIZATION (RCDC)—MR. LAWRENCE RAY AND MS. LISA KRUEGER

Mr. Lawrence Ray, Deputy Director for Management, NCI, and Ms. Lisa Krueger, Research Analysis and Evaluation Branch, DEA, NCI, provided an update on the scientific coding system, called RCDC, mandated by Congress.

Scientific coding provides science-based budget information through the analysis and classification of research projects for scientific content. An analysis of this information reveals the distribution of funds across research areas and serves as a basis for budget projections. Scientific coding is needed to answer inquiries on both the scientific and budgetary aspects of NIH- and NCI-funded research. The NCI is authorized and mandated, as leader of the National Cancer Program, to collect and disseminate cancer research data, and NCI's coding approach, employed for more than 25 years, analyzes the entire project and prorates dollars based on percent disease relevance. Across the NIH as a whole, coding has been varied in its approach as well as its breadth and depth. The NIH Reform Act of 2006 required that the NIH establish an electronic system to uniformly code research grants and activities. The NIH reports to Congress annually how much is spent on approximately 360 research, condition, and disease categories; approximately 14 of those are cancer specific. The RCDC will automate coding across the NIH to: create trans-NIH definitions (or fingerprints) for each of the RCD categories; eliminate the differences in 27 Institute and Center (IC) coding methodologies; and improve transparency by providing project listings for each category. The RCDC will analyze each project title, abstract, and specific aims, and adhere to an "all or nothing" budget rule, which counts any category identified in the matching process at 100 percent in the overall project listing and budget distribution pattern.

The NCI has a representative on 14 RCDC working groups, including the Point of Contact group, which coordinates the identification of the subject matter experts needed to create these definitions, distribute assignments throughout the ICs, and ensure that they are completed and returned to the RCDC. The RCDC thesaurus is a combination of several biomedical thesauri, including the NCI thesaurus. The NCI has approximately 90 subject matter experts assisting in the development of the definitions. Once the experts agree on the fingerprints, the current versions are applied to a fiscal year database and a project list is generated and sent to the ICs for review. The NCI has returned approximately 35,000 comments to the RCDC. An NCI Intranet Web site has been created for the RCDC initiative, and a town hall meeting was held to keep the NCI informed on the project. Validation of the fingerprints against the FY 2007 dataset has begun, and the goal is to complete the fingerprints by November so that the RCDC can prepare a 2008 report for Congress. The RCDC also will post the 2007 data (referred to as the FY 2007 Crosswalk) at that time. Comparison of the results of the RCDC system with the NCI coding process is ongoing. The NCI is committed to working with the NIH to yield a more accurate and transparent reporting system, and with the NIH Office of Portfolio Analysis and Strategic Initiatives (OPASI) to develop a communication plan.

Questions and Answers

Dr. Diane C. DiEuliis, Senior Policy Analyst, Office of Science and Technology Policy, Executive Office of the President, noted that the public uses the Computer Retrieval of Information on Scientific Projects (CRISP) database to search for funded grants in particular disease areas, and asked if the coding terms that are used for the RCDC match those in CRISP. Ms. Krueger responded that CRISP terms can be used because the CRISP thesaurus is included in the RCDC thesaurus. Dr. deKernion expressed concern that only 14 cancers were included in the RCDC system, because there are many more cancers, as well as research that does not apply to one specific cancer, and wondered who would be using the RCDC system. Mr. Ray responded that there are plans for the RCDC to incorporate more cancer

categories in the future, with the NCI coding system to be used for reporting purposes in the interim, and that there are hundreds of requests for spending patterns throughout the year from Congress, advocacy groups, individuals, and corporations that could be answered by the RCDC.

Dr. Coffey asked how special requests that fall outside of traditional cancer science would be handled. Ms. Krueger responded that the NCI and other ICs have their own methodologies in place to answer those questions. Dr. Paulette S. Gray, Director, DEA, NCI, explained that there are two different methodologies that are used to code the research grants currently in place; the legislatively mandated NIH system must be an electronic system, and the NCI still is doing manual coding. She expressed concern about the accuracy of the data that may be reported by the NIH, but mentioned that the NCI and NIH are working to ameliorate the inaccuracies that may result from the two methodologies. Dr. deKernion asked whether the current NCI coding system could provide information on the amount being spent on a particular type of cancer. Ms. Krueger confirmed this, and Dr. Gray noted that one thing the new system should be able to do is to report all funds that are allocated to cancer research across the NIH; at present, the NCI only reports its own appropriations. Mr. Ray added that there will be differences in the two systems that will pose challenges. Dr. Runowicz asked if it was correct that the RCDC system would aggregate information that is separated in the NCI system. Ms. Krueger responded that if a category of cancer requires use of the automated RCDC system, only the RCDC would be used to create a subreport. Dr. Gray said that the reporting to Congress of dollars allocated across the NIH to cancer research is to be done through the new system.

VII. VITAMIN D AND CANCER—DR. LEE HELMAN

Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research (CCR), NCI, said that vitamin D can be categorized as a potential chemopreventive agent, and recently has received a great deal of media attention. In addition, the NIH has held several conferences on vitamin D in recent years (one in 2003 and two in 2007).

Most vitamin D comes from dietary sources, and is activated by two metabolic enzymes: calciferol-25-hydroxylase catalyzes a 25-hydroxylation in the liver, and subsequently 1-alpha-hydroxylase in the kidney creates the active form of vitamin D, 1-alpha 25-dihydroxy-vitamin D_3. The catabolic enzyme 24-hydroxylase is part of the cytochrome p450 system referred to as CYP24A1, which catalyzes a
24-hydroxylation that leads to excretion of either 25 or 1,25-vitamin D, a fat soluble vitamin. In general, epidemiologic studies measure the circulating level of 25-hydroxyl vitamin D_3 because its half-life is 15 days, versus the 1-alpha-25, which has a much shorter half-life measured in hours. In terms of the tumor microenvironment, some recent studies have implicated vitamin D in inhibiting proliferation, inducing differentiation, and inhibiting angiogenesis. All of these actions, as well as the vitamin D receptor, must be considered when analyzing study data. Epidemiologic evidence implicates potential roles for vitamin D in preventing various tumors, including lung, breast, colon, prostate, and pancreas. Conflicting evidence exists that makes the topic controversial, however. Vitamin D emerged as a protective factor in a cross-sectional study of more than 3,000 adults, predominantly males who underwent colonoscopy; those with the highest vitamin D intakes had significantly lower risk of lesions. A Women's Health Initiative study examined supplementation of calcium with vitamin D (400 IU) for 7 years and found that it had no effect on the incidence of colorectal cancer among postmenopausal women. A third study that focused on bone health showed, in just under 1,200 postmenopausal women, that subjects supplemented with calcium (1,400-1,500 milligrams) and vitamin D_3 (1,100 IU) had a significantly lower incidence of cancer over 4 years compared to women taking placebos. If the cancers that develop within the first year of the study are discarded, there was still a significant protective effect on the women treated with calcium and

vitamin D. However, calcium alone did not show a statistically significant impact. The primary difficulty with this study is that cancer was not a primary outcome variable.

The overwhelming majority of studies on vitamin D and colorectal cancer show a ratio that favors vitamin D decreasing the odds of developing colorectal cancer. NCI's Division of Cancer Epidemiology and Genetics (DCEG) has completed a number of vitamin D studies that examine the prospective relationship between the vitamin D metabolite 25-hydroxy Vitamin D in serum and cancer mortality. A decrease in colorectal cancer mortality was found; patients with 25-hydroxy vitamin D levels greater than 80 nmols per liter showed a 72 percent risk reduction compared to those at less than 50 nmols per liter. The Web site ClinicalTrials.gov lists 571 trials on vitamin D, 217 of which are on vitamin D and cancer; 77 of the latter are sponsored by the NIH. CRISP FY 2008 data show 67 NCI-funded grants, including 41 R01s, 9 R03s, and a variety of other mechanisms. Ongoing studies at DCEG include an examination of the relationship between the metabolites 25- and 1,25-dihydroxy vitamin D and a study on the methodological issues in blood sample measurement of 25-hydroxy vitamin D. Vitamin D binds to the vitamin D receptor, which functions as a transcriptional activator much like the retinoid receptor; the vitamin D receptor binds with the RXR receptor to activate a number of vitamin D responsive downstream genes. Several polymorphisms exist in the vitamin D receptor gene. One, Fok1, contains a T to C polymorphism (F allele or ff allele) that leads to a shorter vitamin D receptor with greater transcriptional activity, producing higher vitamin D levels. One study found that among prostate cancer patients, those with the ff allele and low Vitamin D levels had a higher likelihood of a more aggressive histology. However, a previous study found the ff allele from the Fok1 polymorphism was associated with less aggressive histotype; gene-nutrient interactions such as this must be considered when studying the literature.

A study on cancer mortality by annual sun exposure demonstrates a higher age-adjusted colon cancer and breast cancer mortality in those geographic areas that have lower sun exposure due to the climate, implicating that less sun means lower vitamin D levels associated with a higher colon and breast cancer mortality. The synthesis of vitamin D due to UV radiation in the oils of the skin also is related to pigmentation; the more darkly pigmented an individual, the less vitamin D is synthesized. An Agency for Healthcare Research and Quality (AHRQ) report asks if there is a level of sunlight exposure sufficient to maintain adequate vitamin D concentrations without increasing the risk of skin cancer, but more information is needed on the synthesis mechanism and the relationship among the vitamin D polymorphisms to answer this question. An understanding of the level of degradation based on the cytochrome p450 enzymes as well as the alpha-hydroxylation to activate vitamin D that appears to occur in cells other than kidney also is needed. There is evidence that vitamin D demonstrates anticancer properties both *in vitro* and *in vivo*, but many questions remain. Future studies should consider metabolism, catabolism, and polymorphisms in vitamin D receptors and in both the metabolic and catabolic enzymes that activate and inactivate this particular transcription factor. The methodology of the measurement of vitamin D levels must be addressed, and ideally, biomarkers should be determined.

Questions and Answers

Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP), NCI, commented that some people think vitamin D is a hormone, not a vitamin, because a precursor of vitamin D is ingested or absorbed from sunlight, and vitamin D itself is converted to the active form in the kidney. A problem with a number of the studies mentioned is that 25-hydroxyl vitamin D_3, an inactive form, is being measured. Tissue levels of calciferol should be measured. Dr. Helman added that the vitamin D receptors also must be known. Dr. Greenwald noted that vitamin D might protect against early polyp formation, but might have no effect later on the progression to cancer, so the time of exposure must be known. One concern is that some supplement companies are beginning to use the active form in the pills, which bypasses the

homeostatic mechanism. Additionally, there is evidence that in whites, approximately 15 minutes in the sun will provide more vitamin D than supplements, and the homeostatic mechanisms in the skin then will stop absorption. Deltanoids, which are vitamin D analogs that will not cause hypercalcemia, may be useful in studying chemoprevention.

VIII. STRATEGIES AND OPPORTUNITIES FOR CANCER THERAPY WITH VACCINES INDUCING T CELLS OR ANTIBODIES—DR. JAY A. BERZOFSKY

Dr. Jay A. Berzofsky, Chief, Vaccine Branch, CCR, said that one approach to cancer therapy is the development of vaccines that induce T cells or antibodies targeted against the tumor itself. B cells can be induced to make antibodies against specific antigens, and cytotoxic T cells can kill cancer cells. Antibodies are potentially highly potent, but can detect only proteins expressed on the surface of the cancer cell; many cancer antigens are expressed only within the cell. To permit detection of internal antigens, the immune system has developed an internal surveillance mechanism, in which a portion of every protein made in the cell is degraded to peptide fragments that are transported to the endoplasmic reticulum, where they bind major histocompatibility complex (MHC) molecules that then carry the peptides to the cell surface and present them for recognition by receptors on cytotoxic T lymphocytes (CTLs). CTLs then can destroy cancer or virus-infected cells.

Tumor antigens suitable for targeting by vaccines should be tumor selective to allow targeting of only the cancerous and not the normal cells. The antigen also should be part of a protein that is essential to tumor cell survival so that the tumor cannot evade destruction by downregulating that gene. To use a T cell-based vaccine, the antigens must be processed and presented at the cell surface by MHC molecules and must be immunogenic. There are several potential mechanisms by which antibodies can be targeted to tumor cells. Antibody-dependent cellular cytotoxicity (ADCC) involves natural killer (NK) or other cells with Fc receptors that can bind immunoglobulin molecules and use those to target cells for killing. Another approach is to use antibodies to inhibit function of a molecule required for oncogenicity. Herceptin, a monoclonal antibody that targets Her2/neu and inhibits its activity, has been successful in the treatment of breast cancer; however, vaccines to induce these antibodies in the patient are lacking.

To induce anti-Her2/neu antibodies, an adenovirus-based vaccine that expresses the extracellular transmembrane domains of Her2/neu was tested in a mouse mammary carcinoma model. One round of immunization with the vaccine caused regression of large, established mammary carcinomas in almost every animal tested. Recurrence was not observed as long as a year after immunization. Lung metastases can be generated in mice by injecting breast cancer cells intravenously. By day 15, large tumors in the lung are visible to the eye and will kill the animal by day 30. If the mice are immunized with the Her2/neu vaccine at day 15, tumor growth still occurs at day 35, but by day 48 the tumors have disappeared and recurrence is not observed. This mechanism is mediated completely by antibodies and does not involve T cells. In contrast to Herceptin, which depends on Fc receptors and requires ADCC, the adenovirus-mediated approach blocks the activity of the oncogene product itself (Her2). The vaccine raises antibodies that block oncogene phosphorylation and function and inhibit the growth of these tumor cells in the absence of other immune system components. Advantages to this vaccine over Herceptin include its ability to directly inhibit the function of the oncogene. The polyclonal antibodies elicited by the vaccine also may target multiple Her2 epitopes and thus may be less susceptible to escape mutations than a monoclonal antibody to a single epitope. In addition, continuous antibody production by the breast cancer patient herself avoids the need for repeated monoclonal antibody administration, which can cost approximately $100,000 a year over multiple years. The next goal is to translate this approach into a clinical trial in breast cancer patients.

Many tumor antigens are self antigens to which the host is tolerant. Because self-tolerance is primarily against dominant epitopes, subdominant epitopes must be targeted. This avoids tolerance, but epitope enhancement, which involves modification of the interacting sequence to improve binding to MHC molecules, is needed to raise a strong response. In addition, because tumors downregulate MHC molecules or processing machinery to avoid detection by the immune system, induction of high avidity T cells is needed to respond to low densities of MHC molecules. Cytokines such as IL15 can increase CTL avidity, induce long-lived CTL memory, and function as a substitute for CD4 helper cells, which can be inadequate in patients who have received certain types of chemotherapy. Tumors also evolve to suppress the immune response by utilizing natural brakes in the immune system; this negative regulation needs to be blocked. Antigens can be optimized by changing amino acids in the peptide presented to the T cell receptor to improve the interactions of the peptide with the MHC molecule and increase affinity. Such peptides are more immunogenic, but are recognized by the T cells in the same way as the natural antigen. Vaccines raised against optimized antigens have been observed to protect against higher titers of virus challenge.

In collaboration with Ira Pastan, a vaccine directed against T cell receptor gamma Alternative Reading frame Protein (TARP), which is a prostate cancer antigen expressed in approximately 95 percent of prostate cancers and 50 percent of breast cancers, was developed. The TARP peptide was enhanced by replacing the 9th (final) amino acid from HLA-A2 with a valine substituted for the leucine residue. Because TARP 29-37 is a subdominant epitope, self-tolerance is unlikely to interfere. Human CTLs raised against the epitope-enhanced TARP peptide killed human tumor cells that express both TARP and HLA-A2, but not tumor cells that express only one of these molecules. This vaccine will be tested in clinical trials soon.

Cytokines also can be used to increase the magnitude of the immune response. Because cancer cells often downregulate expression of tumor antigens, MHC molecules, and antigen processing machinery, high avidity CTLs are needed to kill these cells. IL-15, which is made by dendritic and other stromal cells, can enhance CTL avidity. IL-15 is related to IL-2, but while IL-2 contributes to antigen-induced T cell death, IL-15 protects against T cell death and is important for long-term CD8 T cell memory. Vaccination with a vaccinia virus expressing the HIV envelope protein plus IL-15 generated higher avidity CTLs than using HIV protein alone. The inclusion of IL-15 selected for cells with higher levels of the IL-15 receptor alpha chain, which allowed the cells to respond more effectively to low levels of IL-15 without needing another cell to present it. In addition, because IL-15 is required for homeostatic proliferation, which compensates for gradual attrition of CTLs over time, the high avidity cells survived longer and therefore the average avidity of the population increased. IL-15 also upregulates the CD8 co-receptor on the CTLs, which contributes to their functional avidity.

IL-15 can substitute for CD4 helper cells to induce long-lived CTL memory. Immunization in the absence of IL-15 resulted in a response that fell over time; in contrast, inclusion of IL-15 resulted in a similarly high peak response but a much higher plateau that lasted at least 14 months. Helper T cells provide help for CTLs by activating dendritic cells to upregulate co-stimulator molecules and synthesize cytokines such as IL-15. Helper cells may induce the cell that presents the peptide MHC complex to the T cell receptor to also present IL-15; this process was mimicked by using the vaccinia virus that expressed both antigen and IL-15 in the same cell. A cancer patient with deficient helper T cells or an HIV-infected patient would be unable to induce dendritic cells to synthesize IL-15; thus, immunization would not induce CTLs of sufficient avidity or longevity. Including IL-15 in the vaccine compensates for this loss.

To better understand this process, mice were analyzed a year after immunization with the vaccine with IL-15 or the vaccine without IL-15 in animals depleted or non-depleted for CD4 cells. CD4-depleted mice had essentially no specific CTLs a year after immunization. However, CD4-depleted mice

immunized with the vaccine that expressed both the antigen and IL-15 had CTL levels almost as high as non-depleted mice. This demonstrates that IL-15 can substitute for CD4 cells. Including IL-15 in a vaccine induces longer lived memory and higher avidity CTLs and overcomes the need for CD4 help. Thus, IL-15 is a promising candidate to enhance the efficacy of vaccines for use in HIV-infected or cancer patients who have a deficiency of CD4 help.

Cancer vaccines often have been able to induce measureable levels of CTLs, but have not been successful in inducing clinical regression. This is likely due to negative regulation of immune functions by the tumor, which can produce immunosuppressive cytokines, evade immune recognition, and produce "off" signals, such as CTLA-4 or PD-1, on T cells. Tumors also can induce suppressor cells such as myeloid-derived suppressor cells and CD25 positive T regulatory cells, as well as a suppressive type of natural killer (NKT) cell. Unlike NK cells, NKT cells express a T cell receptor but have an unusual restriction to a nonclassical MHC molecule called CD1d that presents a lipid rather than a peptide antigen and permits the immune system to detect lipids. NKT cells also are among the first responders in many types of immune responses and influence the subsequent immune response. Masaki Terabe discovered that when mice were given an immunogenic tumor that could induce CTLs that would cause tumor regression, the regression was incomplete and the tumor recurred because the tumor also induced a type of NKT cell that synthesized IL-13, which suppressed the CTL response. IL-13 acted on myeloid cells that express an IL-13 receptor (CTLs do not have this receptor), inducing these cells to synthesize transforming growth factor beta (TGF-β), which prevents CTL activation. Removal of the NKT or myeloid cells, or blocking IL-13 or the TGF-β reduced the number of lung metastases in one model and tumor recurrence in another model. Clinical trials are underway in melanoma with a monoclonal anti-TGF β. Inhibiting IL-13 is another strategy under consideration.

Surprisingly, other groups have observed that NKT cells can protect against tumor formation. Two major types of NKT cells exist; Type 1, or classical NKT cells, are CD1-dependent, have an invariant T cell receptor, and recognize only certain lipids, while Type 2, or nonclassical NKT cells, also are CD1-dependent but have diverse T cell receptors and recognize several different lipids. Type 1 NKT cells promote both NK cell- and CTL-mediated killing of tumors, but Type 2 NKT cells must be suppressed to achieve tumor regression. Type 1 and Type 2NKT cells also inhibit one another's activity, which defines a new immunoregulatory axis that may be important for immune-based approaches to therapy, especially because NKT cells are among the first responders in an immune response and influence the type of response and subsequent adaptive immune response. Other factors such as T regulatory cells and molecules such as PD1 and CTLA-4 may need to be blocked to remove all suppression of tumor-killing cells. This combinatorial approach to cancer vaccines, which features epitope enhancement to optimize the antigen, and use of cytokine co-stimulatory molecules, receptor ligands, and blockage of negative regulators to improve the quality of the immune response, is being pioneered through the intramural program at the CCR. Tom Waldmann has provided IL-15 for use as a vaccine adjuvant. Jeff Schlom's group has pioneered the use of co-stimulatory molecules as vaccine adjuvants. Dennis Kleinman was one of the discoverers of CpG molecules that currently are being tested in this approach. Steven Rosenberg has performed clinical trials to test the effects of blocking CTLA-4.

Questions and Answers

Dr. Diana M. Lopez, Professor of Microbiology and Immunology, University of Miami Miller School of Medicine, asked about the mechanism by which NKT cells suppress the cytotoxic response. Dr. Berzofsky responded that IL-13 acts on cells that have the same properties as the myeloid-derived suppressor cells and induces these cells to synthesize TGF-β. Other mechanisms involving arginase and nitric oxide also have been described. In the early stage of the response, increased numbers of cells are

not observed, although their numbers greatly increase later in the response. Efforts are underway to better define the cell involved and its relationship to cells that synthesize arginase and other relevant molecules.

Dr. Lopez asked Dr. Berzofsky to comment on incorporation of IL-15 in anti-HIV vaccines. Dr. Berzofsky answered that the vaccine trial planned by the Vaccine Research Center is based on a DNA prime followed by adenovirus boost strategy but does not involve cytokines or other stimulatory molecules. Groups at the CCR are developing DNA vaccines that optimally express high levels of IL-15; these optimized genes will be used in adenovirus vectors. Another goal is to demonstrate that IL-15 works in mucosa, and attempts to produce mucosa vaccines to HIV using IL-15 in a vaccine vector are underway.

Dr. Niederhuber commented on interactions between Dr. Robert Gallo and Dr. Berzofsky regarding vaccine development for HIV that results in information useful for the development of cancer vaccines. Dr. Berzofsky agreed that there are many parallels between cancer vaccines and HIV vaccines. Both cancer and HIV cause chronic diseases and suppress the immune system. Better interaction among investigators working on HIV vaccines and those working on cancer vaccines would promote progress in both fields. This cross-fertilization is a mission of the Vaccine Branch that Dr. Berzofsky heads.

IX. VISIONING THE FUTURE OF THE NIH CLINICAL CENTER—DRS. JOHN NIEDERHUBER, STEPHEN KATZ, AND JOHN GALLIN

Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS), described current and future challenges facing the NIH Hatfield Clinical Research Center (CRC). The CRC is dedicated to improving human health by providing an outstanding environment that facilitates the development of diagnostics and therapeutic interventions; training; and processes to ensure safe, efficient, and ethical conduct of clinical research. Groundbreaking for the CRC began in 1997 and a dedication ceremony was held in 2004. The first patient was admitted in April 2005. Dr. Katz explained that patient census levels and equity in funding among Institutes and Centers (ICs) are recurring issues facing the NIH Director, with no single solution acceptable to all ICs. Several advisory committees have made recommendations to improve the CRC, some of which have been implemented but many of which have been ignored. In July 2007, an IC Directors' Mini Retreat focused on these issues and proposed that the CRC could encompass a Trans-NIH initiative on inflammation, immunology, and autoimmunity, as well as focus on interesting cases or patients with rare or difficult problems. Other ideas from the retreat included the identification of "Manhattan-like" projects and an emphasis on the recruitment and retention of clinical investigators.

Clinical Center Financing. Dr. Katz briefly reviewed the history of the CRC finance models, which ranged from bed allocation (implemented in 1953) and quarterly (1986) or annual (1993) usage to a school tax (2000) and noted that several advisory committees have made recommendations about the CRC. The school tax was adopted because it de-linked cost from usage, encouraged utilization, and provided a more predictable cost based on the Intramural Research Program (IRP) budget. The CRC planning and budget review currently is an extensive process that involves fulfilling program requirements and holding five reviews by cross-NIH groups that meet each year.

In December 2007, Dr. Elias Zerhouni, NIH Director, charged the Management and Budget Working Group to address CRC financing, including the best ways to allocate costs and increase the Center's vitality. In comparing CRC assessed costs against the budget, the costs declined as a percentage of the IRP budget between FY 2001 and 2005, and they increased between FY 2005 and 2008 as the IRP budget became more constrained. Since FY 2006, costs have been identified that are more appropriate to charge to ICs directly, resulting in a higher proportion of IRP budget. For the long term, it is assumed that

there will be no increase to the IRP budget, and that costs will increase either 3.5 percent (same as FY 2006–2008) or 6 percent (closer to the hospital rate of inflation) per year. By FY 2013, costs as a percentage of IRP are expected to increase to 16 or 18 percent. Costs will continue to increase even if utilization remains stable or declines. The use of CRC inpatient and outpatient services generally increased through FY 2004 following school-tax implementation in 2001; however, its use since FY 2004 has held steady or declined, with beds filled to two-thirds of capacity.

The Financing Committee identified three financing options: 1) the school tax, which is the current method; 2) CRC Appropriation, authorizing funding from the total amounts appropriated for the NIH; and 3) IC Consortium, a hybrid model in which some costs are assessed by utilization and others by a formula such as the school tax. In March 2008, it recommended the continuation of the school tax for the short term and a fundamental review of the mission of and opportunities for the CRC for the long term. This review should be undertaken by an outside panel with expertise in both clinical research and hospital administration as quickly as possible. The recommendations were adopted by the IC Directors. Dr. Katz noted that no option was agreed upon unanimously.

IC Directors' Budget Retreat. Dr. Katz described the May 2008 retreat and shared some of the presentation by Dr. Niederhuber, who led the discussion at the retreat. The funding option to continue the school tax is an acceptable approach, but it is not working well with less-than-inflation budgets. Other considerations are that the ICs benefit from a corporate NIH image, the tax is not tied to IC usage but offers a predictive model of assessment for ICs. Recent history has shown that the tax does not create incentives for CRC usage. There has been a steady movement during the past several years to "cost shift" expenses to the ICs, which raises a number of issues, including: the CRC's role in setting the NIH apart as an exceptional research enterprise, NIH and IC commitments for the CRC in a time of constrained budget, the possibility of a direct tie to the overall NIH budget level, relationship between CRC budget growth and either IR or RMS budget lines, and the possible need for another Blue Ribbon Panel review. If the CRC did not exist, the NIH would lack the ability to attract outstanding clinical scientists, the study of rare diseases would be compromised at the NIH, and translational research would not occur at the NIH. In addition, the NIH would lack a unique Federal resource as it is the Nation's largest hospital devoted entirely to clinical research; about one-half of the 1,500 protocols are Phase I and II clinical trials. The NIH FY 2008 budget allocates approximately $352 M (1.2%) to the CRC. An additional increment of $45 M increases the total CRC budgeted amount to near $397 M. An option is to engage a professional consultant to advise about the most appropriate management structure and tracking system to collect real-time, actual operational cost data. Thoughts about the IC Consortium include that the NIH would need to commit to adequate growth of the CRC. Up to seven ICs account for 80 percent of census, and contributions from these ICs could be negotiated separately within the IC budgets. Other IC needs could be met on a fee-for-service basis thereafter.

The IC Directors agreed to continue the school tax and establish a Scientific Management Review Board, as authorized by Congress in 2007. The Board will be composed of IC Directors and representatives from outside the NIH. The Board will undertake a fundamental review of the mission of, and opportunities for, the NIH CRC.

Questions and Answers

Dr. Chabner asked whether the focus on a trans-NIH initiative on inflammation, immunology, and autoimmunity or on rare cases, "Manhattan-like" projects, and recruitment of clinical investigators would address the issue of CRC usage. Dr. Katz said that research on rare diseases could assist with future transplant programs; the initiative could increase the number of patients if it included novel

approaches. Dr. John Gallin, Director, NIH Clinical Center, added that the reduction in the number of principal investigators (PIs) is a key element affecting the decrease in inpatient occupancy.

Dr. Niederhuber said that the CRC involves a complicated management structure. He acknowledged the efforts of Drs. Gallin and Helman to work toward a more effective information system and a cost accounting of the pharmacy, respectively, to help inform leadership in decisions about the CRC. Dr. Katz noted that the Foundation for the NIH (FNIH) has agreed to assist with the issue of paying for drugs to use in the clinical research environment.

Dr. deKernion suggested that the CRC should be treated either as a business or as a research endeavor; as the latter, Congress could make it a separate funding entity as part of the NIH. Dr. Niederhuber said that it is research laboratory, and that as an NIH enterprise, it would seem to make sense if were at the top of the NIH budget in a budget line with a formula attached to it that addressed that issue from the NIH budget perspective. Dr. deKernion said that another option is to consider the CRC as part business and part research with an outpatient and inpatient business; the outpatient business could be operated with the pharmaceutical industries to help pay for the protocols and drugs, and the possibility of billing third parties for inpatient services could be investigated. Dr. Gallin said that the placement of the CRC as a line item on the NIH's budget has been discussed since its inception. He also observed that appropriation language allows the NIH to collect third-party recovery and to keep the funds, but that issues arise with trial patients who already are close to their lifetime insurance cap. For these and other reasons that have been reviewed extensively, the NIH has opted not to collect third party funds.

Dr. Chabner commented that some of the trends that Dr. Katz described also are being seen in the extramural community and that most cancer care and experimental care is provided in an outpatient setting; he suggested that the NCI carefully consider funding trials that will require very expensive drugs that will need to be purchased and also actively engage with pharmaceutical companies to cover radiology, associated laboratory, and pharmacy costs. Dr. Niederhuber noted that at times, though, NCI's scientific endeavors might not be supported by industry because new side effects of a specific agent might be found that were not seen earlier, and to conduct a study, therefore, the NCI must assume the cost of drugs. Dr. Cowan said that manpower, the number of beds, and the pharmacy budget should be considered in relation to the proper size needed to fulfill NCI's mission of being distinctive or strategic; this should be reviewed through a 5-year or longer perspective. Ms. Ryan suggested determining the mix of research to non-research, applying to the ICs what is purely research, and finding another financial mechanism for the standard, as well as exploring point payers. Dr. Gallin stated that the CRC is moving away from its existing activity-based costing system and toward a real-time finance tracking system analogous to a billing system. Currently, about one-third of Clinical Center costs can be attributed to research and two-thirds to standard care. He added that the need for revenue to pay for escalating costs is critical and pointed out that a critical number of patients is needed to sustain accreditation by the Accreditation Council for Graduate Medical Education (ACGME). Dr. deKernion reiterated the ideas of separating inpatient and outpatient services and cutting costs. Dr. Helman pointed out that the cancer community believes there is a unique place for the CRC at the NIH, and that successful CRC studies should complement work in the extramural community. He also noted that the NCI's utilization of the CRC is growing by approximately 1 percent per year.

Ms. Ryan asked for further details about collaboration with and the use of financial models from hospitals, such as Suburban Hospital. Dr. Katz replied that such collaborations can be quite beneficial; the NIAMS' intramural musculoskeletal research program, for example, does not focus particularly on orthopedic surgery, for which there is a great national need, and an orthopedic surgery unit is costly. Dr. Gallin said that the close proximity to the NIH campus makes the collaboration with Suburban Hospital desirable.

Dr. Pazdur, Division Director, Division of Oncology Drugs, U.S. Food and Drug Administration (FDA) asked whether the trials conducted at the CRC are unique or could be conducted at major clinical centers or university cancer centers. Dr. Niederhuber said that the CRC has advantages for imaging technologies and tissue sampling. Dr. Helman agreed, citing Dr. Bill Dahut's work using bevacizumab and radiation with a cytotoxic T cell immunization in prostate cancer, as well as quadrant-based biopsies with special imaging techniques for expression profiling. Dr. Katz added that studies of some rare diseases in cancer—such as patients with xeroderma pigmentation in terms of chemoprevention studies—would not be conducted elsewhere.

Dr. Coffey encouraged the development of a strategic plan to guide long-term interactions between ICs and hospitals. Dr. Chabner agreed and said that controlling expenses should be seen as part of a short term solution: in this context, it is essential to know the costs of a trial and to justify this expense in terms of the priority of the proposed study. Dr. deKernion said that the CRC's purpose appears to be training and clinical and translational research that cannot be conducted elsewhere; trials that do not support these goals should be trimmed. Dr. Runowicz encourages the NCI to consider strategic partnerships with venture capitalists and cancer organizations, such as the ACS, to avoid duplication and develop innovative funding strategies.

X. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 552b(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 that their participation in the deliberation of any matter before the Board would be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

The *en bloc* vote for concurrence with IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,004 applications were reviewed requesting support of $577,682,069.

WEDNESDAY, JUNE 18, 2008

XI. CELL TRANSFER IMMUNOTHERAPY AND GENE THERAPY FOR PATIENTS WITH CANCER—DR. STEVEN A. ROSENBERG

Dr. Steven A. Rosenberg, Chief, Surgery Branch, CCR, NCI, said that adaptive immunotherapy, which involves the passive transfer of immune cells with anti-tumor activity to the cancer-bearing host, is an effective way to harness the immune system to mediate cancer regression. Advantages to this form of cell transfer therapy include the ability to: identify cells with high avidity for tumor antigens and grow them to large numbers outside the body, relieve the cells of their inergic and tolerizing signals to maximize anti-tumor effector function, administer large numbers of the selected high avidity cells back to the patient, and manipulate the host prior to the cell transfer to provide an altered environment for the transferred cells.

The first steps in the development of adaptive immunotherapy included isolation of immune cells from the patient and identification of the highest avidity CD8+ killer that could recognize tumor antigens

in vitro and establishment of cultures from these high avidity cells. Techniques were developed that allowed growth of up to 10^{11} of these cloned lymphocytes. The total body burden of lymphocytes is approximately $5x10^{11}$, meaning that nearly an entire body burden of cloned lymphocytes would be administered to the patient along with the requisite growth factor IL-2.

A series of 13 patients with metastatic melanoma were treated with cells that could recognize 0.1 nanograms of the melanoma antigen gp100. None of the patients responded and all died of melanoma, because the cells did not persist in the body; by 2 to 3 days after administration of 10^{11} cells, none were found in the circulation. The number of lymphocytes in the circulation is limited to approximately 10^6 per milliliter of blood; at this level, the lymphocytes saturate the IL-15 made by stromal cells. It was hypothesized that by eliminating the body's natural complement of T lymphocytes, IL-7 and IL-15 would act only on the administered cells and sustain their survival. Thus, patients were treated using a non-myeloablative regimen commonly administered to patients receiving mini-allotransplants for the treatment of leukemia and lymphomas to eliminate all T cells for approximately 8 to 10 days. Once T cells were completely depleted, 10^{11} cloned anti-tumor cells selected for high avidity along with IL-2 were administered. Fifteen patients were treated, including six who received the highest numbers of cells along with maximum depleting chemotherapy, but no patients responded. No administered cells could be found in the patients' circulation a few days after administration.

At this time, evidence was accumulating that CD8 killer cells depend on CD4 helper cells for sustained survival; administration of IL-2 with the cloned anti-tumor cells was insufficient to compensate for the absence of CD4 cells. Thus, a technique to grow and select both CD8 and CD4 cells with anti-tumor activity and high avidity for tumor recognition was developed. The first patient treated using this approach was a 16-year-old male with node-positive melanoma that recurred after treatment with interferon and IL-2. The patient was treated with nonmyeloablative chemotherapy and large numbers of cloned anti-tumor cells were administered, but the tumor continued to progress. This patient was then treated with a preparation of CD8 plus CD4 cells along with nonmyeloablative chemotherapy and his cancer regressed. A large axillary mass shrank to a small lesion consisting only of scar tissue, as did a large lesion in the pelvis. In all, nearly a kilogram of tumor disappeared. Analysis of circulating lymphocytes found that 75 percent of these cells were the cloned anti-tumor cells; thus, these cells can be stimulated to proliferate and expand up to 1,000-fold within the body, and they maintain their anti-tumor activity.

A 58-year-old male with metastatic melanoma also had a dramatic response to this therapy, and anti-tumor lymphocytes also were maintained in his circulation and detected in the tumor and in the lymph nodes. The cells persist for years after administration; a residual 20 percent of the patient's original cells are sufficient to prevent opportunistic infections. In 2002, 6 of 13 patients had objective regression in response to this treatment, as defined by a minimum 30 percent decrease in the sum of the perpendicular diameters of all tumors with no new lesions or tumor growth. Currently, 43 patients have been treated and the objective response rate is 49 percent; some patients have been observed for as long as 5 years and remain cancer-free. Efforts are underway to identify receptor agonists that would mimic a graft-versus-host disease complement of cytokines to help sustain survival of the administered cells.

Because work in animals suggested that extensive depletion of lymphocytes resulted in a more active and effective treatment, the treatment protocol was modified by adding 200 Centigray of whole body irradiation to the chemotherapy regimen. Treatment of 25 patients with this regimen resulted in an objective response rate of 52 percent, with sustained survival of the patients. Recently, a trial was completed in which 25 patients with metastatic melanoma were treated with the maximum tolerated lympho-depleting regimen (cyclophosphamide-fludarabine regimen with 1,200 Centigray of whole body irradiation) and given stem cells to replete the hematopoietic system along with cloned anti-tumor cells.

All patients survived and recovered, and the objective response rate was 72 percent. In comparison, the only two FDA-approved treatments for metastatic melanoma (IL-2 and decarbazine) have objective response rates of approximately 13 to 15 percent. Treatment with cloned anti-tumor cells induces regression fairly quickly, with nearly complete regression of large masses observed within approximately 3 months. This treatment also can cause regression of lesions on the heart, brain, liver, and lung metastases and of multiple large cutaneous and subcutaneous lesions.

The therapy works by creating a lymphopenic environment that eliminates T regulatory or suppressor cells, thus eliminating competition for homeostatic cytokines such as IL-7 and IL-15 that are vital for T cell survival. Thus, only the anti-tumor cells administered to the patient are exposed to these cytokines. These lymphocytes proliferate, persist in the circulation, and infiltrate organs and extravasate into tissues. The persistence of the transferred cells correlates highly with regression. In addition, longer telomeres in the transferred cells indicate that the therapy is more likely to be successful; phenotypic markers of relative dedifferentiation, such as CD27, also correlate with the success of the treatment. Overall, this work shows that immunotherapy using a highly avid cloned T cell population can mediate the regression of large vascularized invasive melanoma in humans.

Work is underway to improve response to this therapy. T cells recognize antigens expressed on tumor cell surfaces through their receptors, which are composed of alpha and beta chains. The genes that coded for alpha and beta chains capable of recognizing melanoma from one treated patient were cloned into a retrovirus, which was used to insert the genes into the patient's normal lymphocytes to convert them into cells capable of recognizing the cancer. In this way, cells from any patients can be converted into cells that are capable of recognizing a cancer by genetically engineering the appropriate T cell receptor into the cells. This approach has been used to treat 16 patients. Only two had objective regression of the tumor and metastases (liver and lung), but both patients have been disease-free for nearly 3 years. An additional 15 patients also have been treated, and two regressions were observed, resulting in a response rate of only 13 percent; however, these results indicate that using a patient's own normal genetically engineered cells can cause tumor regression.

Options to improve this cell transfer therapy include identification of higher affinity T cell receptors and avoiding mispairing of the genetically engineered chains with the patient's normal chains. To identify higher affinity receptors, lymphocytes from a large number of patients were cloned and cultured to identify those with receptors that were highly sensitive for recognizing the tumor. A T cell that secreted 20,000 picograms of interferon gamma upon encountering the tumor antigen was identified; this was 10 to 100 times more potent than the T cell from which the first receptor chains were cloned. Alpha and beta chain genes from this highly avid T cell receptor (DMF-5) were cloned into an improved retrovirus that permits gene transfer into 80 to 90 percent of lymphocytes. Treatment of 20 melanoma patients with this improved receptor has resulted in an objective response rate of 30 percent.

Patients treated with this approach developed lymphoid infiltrates of the skin that initially resembled a second degree burn with recovery similar to a bad sunburn. These lymphocytes were found to be recognizing individual melanocytes, which are the cells of origin of the melanoma, in the basal layer of the epidermis. Because of this, nearly all patients develop a depigmentation syndrome; if some cells persist in the hair follicles, repigmentation can occur.

Response rates using the new receptors are approximately 30 percent, and patients with hundreds of lesions have had dramatic responses to this therapy. Staining for CD8 cells that were administered to the patients showed that by day five, these cells had infiltrated the tumor. Between days 6 and 9, the cells were observed to be destroying the tumor. Lymphocytes were isolated from biopsies of the melanoma lesions and grown in culture; 99 percent of the cells were those that expressed the receptor chain that

recognized the tumor antigen. Although less than a year has passed since administration of the cloned receptor chain genes, the cells expressing these genes appear to persist in the body at levels representing between 30 and 40 percent of circulating lymphocytes.

Along with identifying high affinity T cell receptors, this treatment also can be improved by avoiding mispairing of the alpha and beta chains of the receptor. Each lymphocyte expresses its own T cell receptor; when genes encoding the chains of the high affinity receptor are added, the alpha chain of the high affinity receptor could combine with the existing beta chain and form a non-productive receptor. To prevent this mispairing, a mouse constant region can be placed in the human constant region of the receptor, which will prohibit pairing with the endogenous receptor chains. Additionally, a new cysteine residue can be introduced to promote disulfide bond formation between the two exogenous chains; cysteines necessary for this bond formation do not exist in the patient's own alpha and beta chains. Inclusion of the mouse constant region or cysteine residues increases expression of the anti-tumor receptor, and use of both modifications simultaneously further increases expression. These receptors currently are being prepared for use in clinical trials.

Cell transfer immunotherapy could be used to treat patients with common epithelial cancers by raising highly avid T cells targeted against tumor antigens found in these cancers. T cells specifically targeted against the cancer testes antigen NY-ESO-1, which is expressed by 25 to 30 percent of common epithelial cancers but not by adult human tissues, were identified. It has been difficult to generate large numbers of T cells reactive against NY-ESO-1, but genes coding for the alpha and beta chains of the receptor of just one reactive cell can be cloned into the retrovirus and used to convert large numbers of patients' lymphocytes into cells that recognize this antigen. Lymphocytes that express this receptor recognize tumors that express NY-ESO-1, including small cell lung cancer, osteogenic sarcoma, breast cancer, neuroblastoma, small cell lung cancer, glioblastoma, and Ewing sarcoma. The p53 tumor suppressor gene is overexpressed in approximately one-half of common epithelial malignancies, and because it causes a peptide epitope to appear on the tumor cell surface, T cell receptors that recognize this epitope can be generated and used against breast, esophageal, and liver tumors as well as sarcomas. Clinical trials using these two specifically targeted receptors are underway.

In another approach, a monoclonal antibody that recognizes a cell surface molecule can be used to create a chimeric T cell receptor using the antigen-combining regions of the variable region of the heavy and light chains of the antibody. These variable regions are combined into a signal chain and then attached to lymphocyte signaling chains such as CD28, 41BB, and zeta. This gene then can be transduced into lymphocytes, which provide the T cell with the recognition capability of the monoclonal antibody. This method has been performed using the Her2 antibody to develop treatments for breast cancer and may be useful for treatment of other Her2-expressing tumors such as some colon and ovarian cancers. The ability to generate genetically modified lymphocytes provides an opportunity to introduce other genes to improve lymphocyte anti-tumor activity, such as BCL-2 to reduce apoptosis, telomerase to prolong *in vivo* proliferation, and other modifications to permit these cells to produce cytokines such as IL-2 and IL-15. Antigen receptors also could be combined to avoid antigen escape.

Cell transfer immunotherapy can mediate the regression of metastatic cancer in humans. Autologous peripheral lymphocytes genetically modified to express anti-tumor T cell receptors can mediate cancer regression *in vivo*, and the ability to genetically modify human T cells opens new possibilities to improve the effectiveness of these cell transfer therapies and possibly extend them to the treatment of common epithelial cancers.

Questions and Answers

Dr. Coffey asked for clarification on the effect of telomere length, given that telomere lengths in rodents are longer than in other animals due to inbreeding. Dr. Rosenberg answered that activation of lymphocytes upregulates telomerase, which mediates the length of the telomere; telomere shortening limits the survival of cells. If telomere length can be sustained after administration of the cells to the patient, cells with longer telomeres will have a higher proliferative potential. Experiments in which the telomerase gene is introduced into lymphocytes have shown that these cells survive longer *in vitro*.

Dr. Coffey asked about the response to therapy using the NY-ESO-1 cancer antigen. Dr. Rosenberg explained that in the trials to test therapies directed against NY-ESO-1, patients' tumors first are analyzed to ensure that they are overexpressing this cancer antigen; only patients who overexpress NY-ESO-1 are included in the trial. In addition, epigenetic methylation of NY-ESO-1 and other cancer testes antigens suppresses expression of the antigens in the adult except in tumors.

Dr. Coffey asked whether gene delivery using nanoparticles would be useful. Dr. Rosenberg answered that his team is beginning to explore the use of nanoparticles to insert the genes *in vivo*, as opposed to inserting them *ex vivo*. However, it has been challenging to target the nanoparticles to only the types of lymphocytes or tumor cells of interest.

Dr. Niederhuber inquired about the partial responses to the immunotherapy and asked for clarification on the number of active clinical trials underway in the Surgery Branch. Dr. Rosenberg explained that his team uses a strict definition of complete response; for example, a patient with a slight shadow of a tumor would be classified as a partial response, although it is likely that the response was complete. Because many of the patients treated in these trials have visceral disease, they are more likely to have slight scars at the sites of prior lesions and are classified as partial responders if the scar looks as if it could be a lesion. Dr. Rosenberg noted that the NCI Intramural Program and the CCR provided him with the ideal environment in which to perform these studies. These therapies are highly labor-intensive and receiving reimbursement for treating the patients would be difficult. His team has a number of cancer vaccine trials underway, as well as trials to test different ways to genetically engineer CTLs for cell transfer therapies. The Surgery Branch is engaged in approximately 30 ongoing clinical trials.

Dr. Chabner asked if PET scans would be useful for determining whether a residual tumor was present. Dr. Rosenberg answered that although PET scans are useful for patients with melanoma, his team does not use them as a criterion for assessing the presence of tumor. Many of the patients classified as partial responders are PET-negative, but RESIST criteria do not allow PET scans as an indication that the patient is tumor-free. Dr. Chabner suggested searching for circulating tumor cells as a way of determining whether the patient had residual live tumor, and questioned whether Dr. Rosenberg had considered creating vaccines to several of the mutations present in proteins involved in melanoma, such as Raf c-kit or Ras. Dr. Rosenberg answered that others have attempted to immunize patients against those mutant peptides. T cells raised against these peptides may account for up to 30 percent of all circulating T cells following vaccination, but tumor regression did not occur. One problem is the need to suppress regulatory T cells by suppressing the patient's immune system, but this also eliminates the effector cells and thus vaccination will not be successful. A way to selectively eliminate the regulatory T cells is needed. One approach under consideration is use of an IL-2 plus diphtheria toxin conjugate, which would eliminate only T regulatory cells *in vivo*. Dr. Chabner asked if cell transfer immunotherapy could be used outside the research setting. Dr. Rosenberg answered that efforts are in progress to simplify production of the genetically modified CTLs. Johnson & Johnson, which has a small program in cell transfer, has expressed an interest in developing this as part of their business and will be speaking with his group at the behest of Dr. Niederhuber.

Dr. deKernion asked if Dr. Rosenberg had attempted this therapy in renal cell carcinoma and whether surgical debulking had a role in treatment of the patients described in this presentation. Dr. Rosenberg answered that a CG-1 T cell that recognizes renal cell cancer has been identified and that T cell receptor is being reproduced for efforts to treat this cancer. He also noted that his team had not observed any relationship between tumor bulk and the likelihood of an anti-tumor response. Active T cells circulate through the capillaries and organs, and can destroy bulky tumors.

XII. FROM IGF TO mTOR SIGNALING IN PEDIATRIC SARCOMAS: OPPORTUNITIES FOR NOVEL THERAPEUTIC INTERVENTION—DR. LEE HELMAN

Dr. Helman said that IGF-2 was previously observed to function as an autocrine growth and motility factor in pediatric rhabdomyosarcomas. Loss of imprinting at the IGF-2 locus also was observed in these tumors, as well as in Ewing sarcoma. The IGF-1 receptor is required for transformation of fibroblasts by the EWS-FLI-1 fusion protein characteristically observed in Ewing sarcoma. *In situ* hybridization experiments showed that IGF-2 is overexpressed in rhabdomyosarcoma tumor cells, although not in adjacent normal skeletal muscle. Although originally believed to function as a mitogen, IGF-2 likely aids transformation by preventing apoptosis. In C2/C12 normal mouse myoblasts, overexpression of IGF-2 does not cause significant proliferation but does inhibit the G1 checkpoint when cells are exposed to DNA damaging agents. This resistance to DNA damage was correlated with phosphorylation of p70 S6kinase and 4E-BP-1, which suggested involvement of the mammalian target of rapamycin (mTOR) pathway.

Resistance to apoptosis could be overcome by blocking mTOR. When C2/C12 cells overexpressing human IGF-2 were exposed to low doses of the DNA damaging agent cisplatin, downregulation of p70 S6 kinase is not observed, compared to the dramatic downregulation of this protein observed after cisplatin exposure in wild-type cells. Pre-exposure of the cells to rapamycin permits down-regulation of p70 S6 kinase in IGF-2 overexpressing cells and renders these cells sensitive to DNA damage. IGF signaling thus provides a survival signal that contributes to tumor cell resistance to DNA damage-induced cell death. This resistance was associated with mTOR signaling and could be reversed with rapamycin, which blocks mTOR.

In several sarcoma models, aggressive metastatic behavior was associated with mTOR signaling. Blockade of mTOR signaling with rapamycin or its analogs (“rapalogs”) inhibited pulmonary metastasis in an animal model of osteosarcoma. However, clinical studies of rapalogs found that although mTOR signaling was blocked, activation of AKT occurred; this activation was found to be dependent on IGF signaling. Two complexes containing mTOR exist: TORC-1, which is inhibited by rapamycin, and TORC-2, which is not regulated by rapamycin. Blocking IGF receptor results in feedback inhibition of AKT activation. Regulation of this system is related to nutrient and glucose utilization and alterations in these pathways are likely to have significant impacts on cancer. These pathways also are involved in regulation of translation of oncogenes such as cyclin-D1 and myc, as well as of genes that have a role in vascularization, such as HIF-1 alpha and VEGF.

Several pharmaceutical companies have developed human monoclonal antibodies to the IGF-1 receptor. These antibodies were used to characterize IGF-1 receptor density in rhabdomyosarcoma cell lines using quantitative electrochemiluminescent assays. IGF-1 receptor levels ranged from high to barely detectable in several cell lines (30,000 receptors per cell to less than 5,000 receptors per cell) and similar variation was observed in rhabdomyosarcoma tumors. Some cell lines were highly sensitive to these antibodies; for example, low amounts of human IGF-1 receptor monoclonal antibody resulted in marked inhibition of growth of the rhabdomyosarcoma cell line RH4, but had no effect on other cell lines. A linear correlation between IGF-1 receptor density and sensitivity to growth inhibition by monoclonal

antibodies was observed. Cell lines with high IGF receptor levels were observed to have high levels of spontaneous AKT phosphorylation; cells lines with low levels of IGF receptor had low levels of phosphorylated AKT. Exposure of cell lines with high IGF-1 receptor to anti-IGF receptor antibody resulted in marked downregulation of phospho-AKT; the receptor blockade had no effect in cell lines with low receptor density and no endogenously activated AKT. These results indicated that the IGF-1 receptor is responsible for the majority of AKT activation in rhabdomyosarcoma cells. Anti-IGF-1 receptor antibodies specifically downregulate the receptor and AKT in cell lines with high IGF1 receptor. Introduction of constitutively activated AKT could reverse growth inhibition by IGF-1 receptor antibodies, demonstrating a direct correlation between the ability of IGF-1 receptor antibodies to inhibit AKT and its effect on cell growth.

In xenograft studies, anti-IGF-1 receptor antibodies had no effect on tumor cells with low IGF-1 receptor levels, but growth of tumor cells with high receptor levels was inhibited for up to 45 to 50 days. By 70 to 80 days after treatment, however, regrowth of these tumors occurred. Analysis of these tumors found that initial antibody treatment decreased IGF-1 receptor levels and dramatically downregulated AKT. Later in treatment, however, the antibody continued to inhibit IGF-1 receptor levels but phospho-AKT levels had returned to baseline, implying that a different pathway was activating AKT. Treatment with rapamycin in addition to anti-IGF-1 receptor antibody abrogated to some degree the reactivation of AKT. These results suggested that when a receptor is blocked from activating downstream molecules, a different pathway may begin to activate these molecules in its place. Inhibition at one point in the pathway may result in activation of a separate, compensatory mechanism. This suggests that if a patient initially responds to a treatment but then progresses, stopping that therapy may be counterproductive because this would allow signaling through both the previously inhibited and the compensatory pathway. Rather than stopping a seemingly “unsuccessful” therapy, continuing with the therapy and adding an additional therapy may have a better effect on outcomes. Early evidence suggests that it may be beneficial to combine mTOR inhibition with IGF-1 receptor inhibition. The effect of IGF-1 receptor blockade on decreasing phospho-AKT is lost in long-term xenografts, but can be somewhat abrogated by mTOR inhibition.

Several human monoclonal antibodies are being tested in clinical trials. Of note, during Phase I testing in adults, several patients with Ewing sarcoma have had objective responses. Antibody therapy given to one Ewing’s patient with two large pulmonary nodules referred after multiple chemotherapeutic regimens shrank the tumors to nearly undetectable size. Marked shrinkage has been observed in a few other Ewing Sarcoma patients, including a patient with a third systemic relapse and a large mediastinal mass and pulmonary module. This response has lasted through 15 months of treatment without further progressive disease. Based on these results, interest arose in using this approach to treat pediatric sarcomas, leading to development of a Phase 2 study involving approximately Ewing sarcoma, rhabdomyosarcoma, and several other sarcomas in partnership with the Sarcoma Alliance for Research through Collaboration (SARC), using the Hoffman-LaRoche antibody. This is an international study taking place in France, Germany, Italy, and the United States; to date, more than 85 patients with sarcomas have been enrolled.

Recently, a 17-year-old boy with multiple recurrent Ewing sarcoma was treated on this Phase 2 study after failing standard front-line and salvage of drug therapy. He had a dramatic decrease in a chest mass after 5 weekly injections of the antibodies. Patients also report very few debilitating side effects while receiving this treatment. Responses in cases of rhabdomyosarcoma also have been reported. Thus, human IGF-1 receptor monoclonal antibody has shown significant clinical activity in Ewing sarcoma patients, and evidence of efficacy for treatment of rhabdomyosarcoma. Early evidence suggests that combining mTOR inhibition with IGF-1 receptor inhibition may be effective for treating these tumors. A Phase 1 study to evaluate treatment with a combination of rapamycin and antibody is planned.

Although promising, response rates to these therapies likely will be less than 50 percent of patients. Because Ewing sarcomas all bear the same translocation, identifying the 30 to 35 percent of patients who respond dramatically will be challenging. Preclinical data suggest that receptor density may play a role; unfortunately, it may be difficult to evaluate receptor density in the clinical setting. Work is in progress to develop an imaging procedure in which the antibody is linked to an imaging agent such as indium-111, which would allow quantitative data on receptor density to be gathered both pre- and post-treatment. Additional studies are underway to identify patients who are unlikely to respond to antibody treatment. In addition, mTOR kinase inhibitors, as opposed to rapamycin analogs, are being evaluated to identify agents that block both the TORC-1 and TORC-2 complexes. Rapamycin analogs block only TORC-1, which could be problematic because TORC-2 is believed to directly activate AKT. PI3 kinase-mTOR combined inhibitors also may be effective when combined with antibody therapy.

Questions and Answers

Dr. Runowicz asked why Dr. Helman used rapalogs rather than the new analogs. Dr. Helman answered that rapalogs were used because they were available and permitted him to quickly test whether blocking mTOR would have an effect on tumor growth.

Dr. Chabner commented on potential explanations for resistance to therapy. He noted that cMET amplification sometimes is observed in patients whose tumors are resistant to an EGF receptor inhibitor; in addition, multiple kinases may be unpredictably activated in certain tumors. Dr. Helman explained that there is emerging data that suggest crosstalk between EGFR and IGF, but no changes in EGFR have been observed in the sarcomas he has studied. His team is currently analyzing cMET, and because platelet-derived growth factor alpha often is upregulated in rhabdomyosarcomas, a kinome screen is underway to determine which kinases are upregulated after prolonged exposure to the IGF-1 receptor antibody. Dr. Chabner commented that the differences in activation of signaling pathways in tumors suggest a need for individualized cancer therapy.

Dr. Coffey mentioned that evolution should be considered when studying resistance in tumors. Evolution in somatic cancer cells leads to selection; blocking a receptor results in selection of cells that can survive this blockage. Evolution of resistant tumor cells occurs in response to many treatments, such as Gleevec and VEGF inhibitors. Some researchers have suggested that destroying the habitat may be more effective than destroying the tumors, which always will evolve to evade therapies directed against them. Dr. Helman agreed that this could be possible, but noted that ceasing treatment upon evidence of resistance may not be the best approach, at least in patients who initially respond to the treatment.

Dr. Niederhuber asked if Dr. Helman was working with stem cells. Dr. Helman responded that whether tumors have stem cells has not been definitively established. Work with Gleevec suggests that if an oncogenic translocation occurs in a stem cell, a small percentage of patients seem to be cured, but if the stem cell bearing the translocation has not been eliminated, recurrence is likely.

Dr. Lloyd K. Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, commented that testing markers and performing genetic, proteomic, and pathway profiling may allow clinicians to distinguish between responders and nonresponders to a given therapy. Dr. Chabner noted that testing of this sort is expensive and complicated. A few of the cancer centers are beginning to invest in the capability to perform molecular profiling of patients, but it is uncertain whether this will become usual clinical practice. Dr. Niederhuber stated that some discussion has occurred concerning whether the NCI should create independent centers in the country that would provide access to state-of-the-art tools to use for such profiling. Dr. Chabner agreed that the ability of molecular profiling

to have an impact on cancer treatment will require profiling of large numbers of patients and selection of those that have the appropriate molecular profile to fit the trial rationale. This will be complicated because a single type of cancer, for example lung cancer, actually is composed of multiple disease types in subsets of patients. This approach eventually may be cost effective; rather than treating every lung cancer patient with an EGFR inhibitor, only the 10 percent of patients with the appropriate mutation will be treated.

Dr. Coffey countered that discovery work does not take place at centralized centers, but such centers might be useful for development. Some standardization would assist the field, but probably not lead to significant basic discoveries; independent investigators are more likely to contribute in this way. The SPOREs provided a mechanism by which discovery could interface with clinical medicine. A SPORE for translational molecular oncology could be useful for development of better targeted chemotherapies. Dr. Niederhuber expressed skepticism that the current SPORE structure could accommodate such research. Dr. Coffey contended that the nine most significant discoveries related to prostate cancer, including PSA, were developed through SPORE programs. However, the NCI has not made adequate use of these programs; this is an area that the NCAB should discuss with leaders in the field.

XIII. NIH ROADMAP UPDATE—DR. DINAH SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), provided an update on recent changes to the NIH Roadmap for Medical Research and Common Fund. The Roadmap was initiated by the NIH Director in 2003 to address fundamental knowledge gaps, develop transformative tools and technologies, foster innovative approaches to complex problems, and respond flexibly to emerging challenges and innovative new projects. It supports programs for a limited period of 5 to 10 years after which initiatives transfer to an IC or end. In FY 2004 through FY 2006, the Roadmap was funded by a tap on NIH ICs. In FY 2007, it became a line item in the NIH budget, with amounts allocated at $483 M for FY 2007 and $496 M for FY 2008; $534 M was requested for FY 2009, which represents 1.8 percent of the NIH budget. It is estimated that approximately $30 M to $50 M will be uncommitted each year for new initiatives.

Scientific Programs. Two cohorts of programs have been initiated. One cohort was initiated in 2004 and includes NIH Pioneer Awards and NIH Director's New Innovator Awards, among numerous other projects that span the spectrum of biomedical research and training. The second cohort, which is in the process of being launched, includes the Human Microbiome Project and the Epigenomics Program. The Human Microbiome Project was initiated in FY 2008 to generate resources to enable the comprehensive characterization of the human microbiota and analysis of its role in human health and disease. The purpose of the Epigenomics Program, which will be initiated in FY 2008 and 2009, is to examine the role of epigenetic regulation in the origins of health and disease susceptibility, with a focus on epigenetic mechanisms that control stem cell differentiation and organogenesis and contribute to responses to external and endogenous stimuli.

The NIH recently announced a major change with the establishment of a new Transformative R01 Program that will be initiated. The impetus for this new program is the result of recurring themes identified by several NIH working groups focused on high risk and high reward, peer review, and Roadmap leadership. Many details remain to be finalized. This will be a pilot program of $25 M per year from the Common Fund over 5 years. Special focus areas will include: the development of new protein capture technologies, science of behavior change, functional variation in mitochondrial disease, 3-D tissue models, enabling pharmacogenomics such as "My Meds", and acute to chronic pain transition. However, the program will be open to any idea that is thought to be paradigm disrupting or paradigm creating. The applications will consist of an essay format of 5 to 8 pages.

Governance. OPASI is responsible for administering Roadmap and Common Funds and providing guidance to the IC directors on areas in which the Roadmap should focus, who in turn provide guidance to the NIH Director. The OPASI Working Group is a Subcommittee of the NIH Director's Steering Committee and provides policy guidance to OPASI and the IC directors. A recent addition in this process involves the implementation of the Council of Councils, which is composed of 30 individuals from all of the councils of various ICs and other senior leadership; the Council will provide guidance to the IC directors and OPASI on new programs and have a notable role in the selection of ideas through the transformative R01 process.

Selection and Implementation of Roadmap Concepts. The generation and selection of Roadmap concepts begins with a request for information (RFI) Solicitation of Ideas from the scientific community, advocates, and the Council. OPASI clusters ideas with common themes, after which the IC Senior Planning Staff Committee approves or disapproves the concepts. The accepted concepts undergo refinement by the Trans-NIH Working Group and concept clearance by the Council. The concepts then are presented to and approved by IC Directors, and the NIH Director selects concepts to move forward. Implementation starts with the Trans-NIH Implementation Working Groups, who develop Funding Opportunity Announcements (FOAs). A funding plan also is developed. The applications are reviewed and grants or contracts are awarded, which undergo mid-course reviews during the course of a 5- to 10-year life cycle after which the contract ends or transitions to a specific IC.

Questions and Answers

Dr. Niederhuber said that a significant amount of manpower from throughout the ICs, including about 50 NCI staff members, had been invested in the previous Roadmap process that selected and refined six projects. He said that the ICs did not receive prior indication that significant systemic changes would occur, and that many things are unclear, including Roadmap operations, responsibility for managing the grants, and their review. Dr. Everson stated that most organizations generally do not initiate new projects that are resource intensive during a time of stagnant or declining revenue. Dr. Niederhuber said that science has worked best when the science has come from investigators rather than from a fixed amount of money that must be spent.

Dr. Chabner questioned the useful impact of the new program on his hospital's work and expressed the opinion that the CRC represents the ultimate Roadmap project as it promotes integrative interdisciplinary discovery. Dr. Niederhuber said that his efforts to include the CRC on both the budget retreat and the Roadmap were to no avail. Dr. deKernion stated that there are other ways to look at usual or neglected areas within the current structure. Dr. Singer said that three independent groups within the NIH all identified the need to support innovative and creative research; although it is unclear whether the transformative R01 really will achieve this, it is noted that it is a pilot program. Dr. Coffey applauded the work on the Roadmap initiative thus far but expressed concern about the new procedure. Dr. Chabner indicated that he did not see the need for a totally separate, complicated structure. Dr. Runowicz observed that the change has been implemented but that the Board clearly registered its discontent with the change.

XIV. ONGOING AND NEW BUSINESS—DR. CAROLYN D. RUNOWICZ

Subcommittee Report: Communications

Dr. Lopez reported on the NCAB Ad hoc Subcommittee on Communications meeting held on 4 February 2008. Three staff members from the NCI presented information about NCI's offices and efforts related to communications and provided suggestions to support NCI's communications efforts.

NCI Office of Media Relations. Mr. Rich Folkers, Director, Office of Media Relations, NCI, described the new Office of Media Relations, which fields media queries, processes interview requests, and produces press releases and fact sheets to communicate scientific findings from the NCI to major media channels.

NCI Office of Communications and Education. Ms. Lenora Johnson, Director, Office of Communications and Education (OCE), Center to Reduce Cancer Health Disparities, NCI, provided an update about the NCI OCE, which was formed by combining two NCI offices to offer a single point of access for NCI communication. Its work encompasses nine areas: 1) communication leadership for NCI; 2) research, evaluation, and usability analysis; 3) content and materials development and management; 4) information technical services; 5) supporting operations and infrastructure; 6) management of NCI-facing channels; 7) management of partners and public-facing channels; 8) strategic planning, consultation, and support for communications and education initiatives; and 9) management of divisions, offices, and centers accounts.

Division of Cancer Control and Population Sciences (DCCPS) Communications Research. Dr. Brad Hesse, Branch Chief, Health Communication and Informatics Research, DCCPS, NCI, said that DCCPS uses scientifically supported surveys and surveillance reports to gauge public behavior and attitudes. OCE uses these results to tailor NCI messages to intended audiences. Evidence-based approaches in communications are vital for increasing population health. Self-contained applications are effective tools for engaging people in self-administered behavior modification, and are relatively inexpensive when compared with producing print materials that may not reach the public. Current trends include interactive communication, the increased use of the Internet for access to information, and targeted audiences.

Questions and Answers

Dr. Runowicz said that the ACS has worked on communication, including developing an outstanding 800 number for those who are not computer literate or do not have access to a computer savvy resource, and she encouraged the NCI to partner with the ACS to leverage resources. Dr. Chen supported such collaboration and noted that similar efforts are underway in California. Dr. Karen M. Meneses, Professor and Associate Dean for Research, School of Nursing, University of Alabama at Birmingham, lauded Dr. Hesse's presentation and expressed appreciation for his help to the Subcommittee in integrating the communication.

Motion. A motion was made to accept the minutes of the February 4, 2008, Communications Subcommittee meeting with changes, including the addition of the participants list. It was seconded and approved unanimously.

Subcommittee Report: Planning and Budget

Dr. Chabner described the NCAB Planning and Budget Subcommittee retreat held on 4 February 2008. The FY 2009 budget and PB were discussed. The discussion also addressed the IRP and the cost of the CRC. The Subcommittee recommended that a presentation be made regarding the problems faced by the CRC and possible solutions to keep the CRC as a viable research entity. He said that the Subcommittee minutes captured the discussion well.

Motion. A motion was made to accept the minutes of the February 4, 2008, Subcommittee on Planning and Budget meeting with several changes. It was seconded and approved unanimously.

XV. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

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

There being no further business, the 146th regular meeting of the NCAB was adjourned at 10:50 a.m. on Wednesday, June 18, 2008.

Date	Carolyn D. Runowicz, M.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary