DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
140th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
November 30-December 1, 2006

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 140th regular meeting on Thursday, 30 November 2006, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Thursday, 30 November 2006, from 8:30 a.m. to 4:30 p.m. The meeting was closed to the public from 4:45 p.m. until adjournment at 5:15 p.m. The meeting was open to the public on Friday, 1 December 2006, from 8:30 a.m. until adjournment at 10:30 a.m. 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 Allan Chabner
Dr. Moon S. Chen, Jr.
Dr. David S. Coffey
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Dr. Lloyd K. Everson
Dr. Judah Folkman
Ms. Kathryn Giusti (absent)
Mr. Robert A. Ingram
Mr. David Koch
Dr. Diana M. Lopez (absent)
Dr. Karen Dow Meneses
Dr. Franklyn G. Prendergast
Ms. Lydia G. Ryan
Dr. Daniel D. Von Hoff

President's Cancer Panel
Dr. LaSalle D. Leffall, Jr. (Chairperson)
Mr. Lance E. Armstrong (absent)
Dr. Margaret Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael Babich, CPSC
Dr. Allen Dearry, NIEHS (absent)
Dr. Arispe, OSTP
Dr. Raynard Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. T. G. Patel, VHA
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Dorie Reissman, NIOSH
Dr. Donald Wright, OSHA (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. John Niederhuber, Director, National Cancer Institute
Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Mark Clanton, Deputy Director for Health Care Delivery
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis
Dr. Gregory Downing, Director, Office of Technology and Industrial Relations
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Mr. John Hartinger, Associate Director, Office of Budget and Financial Management
Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources
Dr. Thomas Hooven, Deputy Director for Management
Dr. Alan Rabson, Deputy Director, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Acting Associate Director, Center to Reduce Cancer Health Disparities
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, National Coalition for Cancer Research
Dr. Eve I. Barak, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Nancy Riese Daly, American Society of Clinical Oncology
Ms. Georgia M. Decker, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Mr. Steven Friedman, National Coalition for Cancer Survivorship
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Mr. John Huber, American Urological Association
Ms. Alexine Clement Jackson, Intercultural Cancer Council
Dr. Lovell A. Jones, Intercultural Cancer Council
Dr. Martha M. Kendrick, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. W. Marston Linehan, Society of Urologic Oncology
Dr. Bernard Levin, American Gastroenterological Association
Ms. Jennifer Padberg, American Society of Therapeutic Radiology and Oncology
Dr. William F. Regine, American Society of Therapeutic Radiology and Oncology
Ms. Christy Schmidt, American Cancer Society
Dr. John Stevens, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Mr. Douglas Ulman, National Cancer Institute, Director's Consumer Liaison Group

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THURSDAY, NOVEMBER 30, 2006

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF SEPTEMBER 2006 MINUTES— DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 140th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reminded members that they represent all patients with cancer, for whom NCAB actions are important. She then reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations

Motion. A motion was made to approve the minutes of the 6-7 September 2006, 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 2008 and reminded members of the January 8 joint advisory boards retreat.

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

Dr. John Niederhuber welcomed members and expressed appreciation for the time and effort they dedicate to regular NCAB meetings and subcommittee work.

Fiscal Year (FY) 2006—Closing Out the Budget Year. Dr. Niederhuber reported on the status of the various funding mechanisms as of the close of the FY 2006 budget year that saw a mid-year increase by almost $4 M in taps for utility costs. The end-of-year payline was increased to the 12th percentile and the *R01s (for first-time investigators) were increased to the 18th percentile. An additional number of *R01s above the 18th percentile were funded on the basis of their scientific potential and with the help of the 15 percent of the competing pool that had been reserved for exceptions. Type 5 grants were generally 2.35 percent below the commitment of record, and Special Programs of Research Excellence (SPOREs) were 6.1 percent below FY 2005. Funding to the Cancer Centers increased by 3.9 percent from FY 2005, and Training grants were 1 percent above the FY 2005 level.

FY 2007—Operating Budget Development. Members were reminded that the NCI continues to operate on a Continuing Resolution (CR) pending passage of the FY 2007 appropriations and that NCI works within the context of the NIH as a whole and not in isolation. Considerations in developing the FY 2007 NCI budget include: 1) the decrease by $36.5 M in the FY 2007 President's budget compared with FY 2006 obligations (a -0.8 percent change); 2) the potential for the NIH Director and Department of Health and Human Services (DHHS) Secretary to exercise their transfer authorities (estimated at $20 M); 3) a $14.548 M increase in the NIH Roadmap contribution; 4) NCI-wide requirements that include mandated salary increases estimated at $7 M and rent, lease, and utilities increases estimated at $10 M; 5) participation in trans-NIH initiatives including Genes and the Environment (estimated at $7.8 M) and Pathways to Independence Career Program (estimated at $25 M); and 6) the NCI Director's reserve of $25 M. On the basis of these considerations, the subtotal of available funds would be -$122.598 M, if the President's budget with $4,753,609 for the NCI is enacted, a -2.6 percent decrease compared with FY 2006 obligations. Dr. Niederhuber described the intensive review process undertaken across the NCI

to identify funds that could be recovered and redeployed. The process has yielded about $175 M, which would cover the projected deficit of $122.598 M and make about $52.402 M available for new initiatives and expansions. He cautioned, however, that only $4.866 M would be available if Congress applies a 1 percent across-the-board reduction in the discretionary portion of the budget, which includes NIH funding.

FY 2007 Appropriation Status. Members were reminded that the CR under which the NCI is operating is due to expire on December 8. Congress will return from recess on December 5 and is expected to pass another CR that will be in effect through January or February 2007. Dr. Niederhuber reviewed the trend of NCI's Congressional appropriations from FY 1998 to FY 2007. The investment in the cancer program went through a period of significant growth from FY 1998 to FY 2003 (an 80 percent increase for the NCI). As a result, the number of applicants and applications has increased and the curve continues upward, but the budget has reached a plateau. In addition, there has been a -8.3 percent loss in purchasing power since 2004 because of the higher rate of inflation for biomedical research and development. The challenge for the NIH is to maintain research enterprise vitality in light of reduced purchasing power and increased demand. Members were reminded that the more than $15 B in new research facilities built since 1998 has resulted in renegotiation of indirect costs by the academic institutions and higher indirect costs being applied to investigators' grants.

Members were given a fiscal-year-end summary of NCI FY 2006 allocations and actions compared with previous years: 1) 1,280 competing research project grants (RPGs) were awarded, down from 1,492 in FY 2004; 2) 5,172 RPGs were awarded, up from 5,070 in FY 2004; 3) average cost per competing grant was $324 K, down from $346 K in FY 2003; 4) 7 percent of the competing pool went to Request for Applications (RFAs), down from 9 percent in 2004; 5) 5,679 individual investigators were supported, up from 5,636 in FY 2004; and 6) $42.8 M was allocated to Roadmap, up from $16.2 M in FY 2004. The NCI was able to create a pool of about $60 M in FY 2006 to recognize specific projects and opportunities within the portfolio, compared with $108 M in FY 2005.

Ongoing Scientific Initiatives. Dr. Niederhuber reviewed the status and progress being made in several cross-cutting initiatives through which the NCI is promoting multi-disciplinary collaboration to address cancer problems.

The Cancer Genome Atlas (***TCGA***). For the pilot project, which is co-supported by the NCI and the National Human Genome Research Institute (NHGRI), glioblastoma, lung cancer and ovarian cancer were announced on September 1 as the first tumor types to be studied, and the Cancer Genome Characterization Center awards were announced on October 16. NHGRI announced its awards for Cancer Genome Sequencing Centers on November 20.

NCI Alliance for Nanotechnology in Cancer. At the first Alliance meeting, which was held in October, more than 200 scientists focused on cancer issues. They included representatives from the eight Centers for Nanotechnology Excellence, the 12 platform projects, and four NCI-National Science Foundation (NSF) Integrative Graduate Education and Research Traineeship Programs plus principal investigators (PIs) and Co-PIs, postdoctoral fellows, and students. The 28 oral presentations and 75 poster presentations represented six major areas of focus. Four technical sessions and several translational issues forums were held. A considerable effort focused on ensuring the next generation of nanotechnology leadership and the integration of the NCI's Cancer Bioinformatics Grid (caBIG™).

Clinical Proteomic Technologies Initiative for Cancer. On September 2, five awards to lead institutions were announced for the Clinical Proteomic Technology Assessment for Cancer initiative. Breast cancer has been chosen as the common human cancer type to be studied, and the first benchmark

study—a protein mix study—is ongoing. On September 27, 14 awards were announced for Advanced Proteomic Platforms and Computational Sciences. A Request for Proposals (RFP) for the Clinical Proteomic Reagents Resource is anticipated in 2007.

Integrative Cancer Biology Program (ICBP). This program currently supports six full and three planning centers. Progress includes the development and validation of an siRNA library of cancer genes, sponsorship of an American Association for Cancer Research (AACR) symposium, an integrative cancer biology summer training program, and a Tumor Modeling Workshop. Future planned meetings include workshops on cancer modeling in December and cancer data integration in January 2007, as well as a Cambridge ICBP/Cancer Systems Biology meeting in June 2007.

Office of Biorepositories and Biospecimen Research. The *First Generation Guidelines for NCI-Supported Biospecimen Resources* has been revised in response to public comments and is scheduled for Federal Register reposting in January 2007. With the Rand Corporation, a prototype of a searchable web-based tool for published biospecimen research has been built. The Biospecimen Research Network is collaborating with investigators from the three NCI campuses, Walter Reed Medical Center, private industry, and academia to develop RFPs for additional projects.

Therapeutically Applicable Research to Generate Effective Treatments (TARGET). Dr. Niederhuber described TARGET as an effort to leverage the scientific talent within the NCI and extramurally with the private sector to bring additional resources into research. TARGET is a collaborative project of the NCI and the Foundation for the NIH (FNIH) for target identification and validation for childhood cancers. State-of-the-art technologies will be applied in this coordinated research effort, with the goal of making major advances in target identification for two or more childhood cancers within 2 years of project initiation. General principles guiding implementation are: 1) move quickly to begin TARGET initiative research projects; 2) leverage with ongoing NCI activities including TCGA, Children's Oncology Group (COG), and Strategic Partnering to Evaluate Cancer Signatures (SPECS); and 3) leverage with ongoing industry and research activities through "in kind" support. Scientific oversight will be provided by a Subcommittee of the Board of Scientific Advisors (BSA).

Research focuses for the TARGET initiative include: 1) high-throughput array-based technologies to comprehensively characterize genomic and transcriptomic profiles; 2) gene resequencing to identify genes that are consistently altered in specific childhood cancers; and 3) high-throughput RNA interference (siRNA) and small molecule screening methods to identify and validate therapeutic targets. Acute lymphoblastic leukemia (ALL) has been chosen as the pilot TARGET project in a collaborative effort by the COG, St. Jude Children's Research Hospital, and the NCI. Currently, the project is analyzing high-resolution genomic and transcriptomic profiles for about 240 leukemia cases. Upon completion of this analysis, about 200 genes will be selected for resequencing, which will begin in the first half of 2007. Experience gained from the pilot project will inform similar efforts for the overall initiative. Awards are anticipated in four research areas: tumor/sample component with associated disease expertise; genomic and transcriptomic characterization; DNA sequencing; and RNAi and small molecule screens.

Bringing Science to Patients. Dr. Niederhuber presented his vision for the NCI as he assumes leadership of the NCI and in working within the NIH. Conversations with various stakeholders to determine what the cancer research community is being asked to do have led to the characterization of cancer research needs in a continuum of science that comprises three areas: chemical, biological, and translational. In the chemical space, the research effort should focus on a molecular targets development program, connectivity mapping, development of a complete chemical library, and development of a

chemistry resource for re-engineering molecules. Dr. Niederhuber briefly outlined NCI efforts to invest in and expand these areas as a resource for both the private sector and academic centers.

To address biologic research needs, Dr. Niederhuber noted, the NCI is continuing to invest through the R01 and RFA mechanisms in signal pathways that become abnormal; tissue microenvironment, angiogenesis, cancer-activated fibroblasts; and the biology of cancer stem cells and the so-called stem cell "niche." In regard to the latter, a Stem Cell Mini Retreat was sponsored recently by the NCI with participation by intramural and university scientists. As a result, a Stem Cell Biology Program is being initiated by the NCI to be modeled after the Trans-NIH Angiogenesis Research Program (TARP).

In the translational space, the NCI research investment is focusing on animal models, first-in-human studies to identify targets and biomarkers that will inform drug development, and molecular imaging. In this area, the NCI is promoting the Clinical Center as a resource for the entire community. As an example of this, a pilot program is bringing extramural investigators to the Clinical Center for work in advanced medullary thyroid cancer in children. Another example is the recent meeting on the NIH campus that focused on developing IL-15 for clinical use. Resources in the intramural program are being devoted to producing IL-15 in a quantity and grade that can be taken to patients, and first-in-human studies are planned to be conducted in the Clinical Center.

Dr. Niederhuber briefly described the state-of-the-art vaccine facility built at NCI's Frederick Cancer Research and Development Center (FCRDC) in collaboration with the National Institute for Allergies and Infectious Diseases (NIAID). Vaccines are produced there for clinical testing. The NCI also has the capacity through the Rapid Access to Intervention Development (RAID) program at FCRDC to create biologics and other agents to take into clinical trials. Dr. Niederhuber noted that expansion of the RAID program is needed and on the agenda. Finally, members were reminded of other scientific initiatives that are being implemented on a trans-NCI basis and also extend into other Institutes and in the extramural research community. These include computational biology, cancer stem cells, the lung cancer program, population science research, the Breast Cancer Stamp pre-malignancy program, and the TARP.

Questions and Answers

Mr. David Koch, Executive Vice President, Koch Industries, commented on the time and resources required of scientists who apply for a research grant, and he asked whether there are plans for simplifying the process. Dr. Niederhuber noted that such policies and decisions are made at the NIH level, and he asked Dr. Gray, who sits on the NIH-wide Extramural Program Management Committee (EPMC), to provide additional comment. Dr. Gray briefly outlined changes that are occurring to streamline the application process and reduce the time from receipt of the application to the review. She suggested that Dr. Anthony Scarpa, Director, Center for Scientific Review (CSR), be invited to a future NCAB meeting to present his expectations and actions relative to streamlining the peer review process and making other programmatic changes. Dr. Donald Coffey, Professor of Urology, Oncology, Pathology, Pharmacology and Molecular Science, Johns Hopkins University School of Medicine, asked Dr. Niederhuber to address how the NCAB might be more helpful. Dr. Niederhuber reminded members that the NCAB serves in an advisory capacity and has certain legal responsibilities in terms of signing off on grants. He emphasized that communicating the national cancer story to colleagues and patients in the extramural community and to legislators is hugely important. In addition, Board members provide scientific expertise and input for particular programs. Dr. Runowicz pointed out that NCAB members might work more actively through the NCAB subcommittees on a number of issues.

Dr. Franklyn Prendergast, Director, Mayo Clinic Comprehensive Cancer Center, commented on the need for: 1) a definition of what constitutes "advisory;" 2) a feedback loop that provides members with an indication of the consequences of their advice; and 3) more direct and tangible engagement by the NCAB in its capacity as the voice, on behalf of both the investigators and the public, on matters that are germane to the overall responsibility of the NCI. Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, observed that Cancer Centers and the NCI through the FNIH are targeting the same funding sources, and he suggested the need for a discussion with Cancer Center Directors. Dr. Runowicz pointed out that the Cancer Centers Subcommittee might want to address this issue as an agenda item.

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

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Howard University Hospital, reminded members that the President's Cancer Panel has begun its 2006-2007 series of meetings entitled "Promoting Healthy Lifestyles to Reduce the Risk of Cancer." This series focuses on ways to reduce cancer incidence and mortality through the promotion of healthy lifestyles.

At the first meeting on September 11 at the University of Minnesota Cancer Center, the Panel heard testimony on how obesity, physical activity, and nutrition affect cancer risk and learned about community-based programs in these areas. Statistics presented on obesity rates indicate that a dramatic increase has occurred since 1980 across every age group and among all populations. Approximately 70 percent of the U.S. population is overweight, and 30 percent is obese. The Panel heard that a considerable amount of research, including clinical trials, has been done demonstrating that dietary factors affect health outcomes. It is also likely that diet plays a role in the risk of many common cancers, although research in this area is not yet conclusive. Similarly, the overall benefits of participation in regular physical activity are well-known. However, the evidence base is still emerging relative to the effects of physical activity on cancer risk. The evidence linking nutrition and physical activity to cancer risk is strongest for breast and colon cancer. A knowledge gap identified by participants is the paucity of research looking at multiple associations between weight control, physical activity levels, and cancer risk. The biological mechanisms associated with lowered cancer risk also are not well understood. Panelists addressed limitations in collecting and analyzing data on physical activity and nutrition. These include the variability in quantifying items, such as the level and duration of physical activity, and complexity in collecting objective, self-reported data.

A variety of programs to improve healthy lifestyles was presented. A comprehensive approach that includes informational, behavioral, social, and environmental strategies was recommended.

Speakers noted, however, that the effectiveness of *ad hoc* community-based programs is not always clear because funding for evaluation is limited. It also is difficult to develop programs that are effective across populations in the absence of a strong scientific evidence base. This gap raised the question of what action can and should be taken now while research is ongoing. A number of speakers emphasized that many lifestyle factors relative to cancer risk are also germane to heart disease and diabetes. There are connections on the causal side that could and should be linked and leveraged as part of broader public health campaigns.

On October 23, the Panel held its second of four meetings in this series at the Markey Cancer Center in Lexington, KY on effects of tobacco and environmental tobacco smoke, on cancer risk. At this meeting the Panel gathered testimony on effective policies and programs to combat the problem of tobacco-related disease in the United States. Dr. Leffall reminded members that tobacco use is the single leading preventable cause of death in this country. Since publication in 1964 of the first Surgeon

General's report on the health consequences of smoking, approximately 14 million Americans have died prematurely due to tobacco use. More than 440,000 Americans continue to die each year from tobacco-related diseases. Smoking accounts for some 30 percent of cancer deaths. Data analysis also confirms that there is no risk-free level of exposure to secondhand smoke and that exposure contributes to cancer and other diseases. Despite such grim statistics, significant tobacco use, primarily smoking, persists. It is estimated that 21 percent of adults in the United States still smoke. While there has been a decline in smoking prevalence in most age groups, the Panel heard that the rate of decline has stalled among adolescents. The Panel also heard that socially disadvantaged populations, generally poorer and less educated, have higher smoking rates, further increasing health disparities in such groups.

Effective evidence-based interventions exist to prevent initiation of smoking and to promote cessation activities. State tobacco control programs have provided evidence of the value of a comprehensive approach for reducing tobacco use. Such an approach combines educational, clinical, regulatory, economic, and community-based strategies. However, such programs are severely underfunded. Of the more than $21 B that states received in 2005 from tobacco excise taxes and master settlement agreement payments, less than 3 percent of those funds were invested in tobacco control. The reasons identified by speakers for the nation's continued tobacco dependence in spite of proven risk include the following: 1) an industry—the tobacco industry—that invests more than $15 B per year promoting tobacco products; 2) the extremely addictive properties of nicotine; 3) introduction of new products, for example, smoke-free tobacco; 4) the influence of media on youth, particularly smoking images in popular movies; 5) industry promotions lowering the cost of cigarettes; 6) misperceptions about the effectiveness of pharmacologic treatment and cessation counseling programs; and 7) lack of healthcare system support in preventing and treating the problem.

On a positive note, the Panel heard that there has been an increase in the number of states with smoke-free air laws. By 2007, 22 states and the District of Columbia will have at least partial statewide indoor smoking bans in place, which means that smoking will be banned in at least one of three categories—workplaces, restaurants, and bars. Given that risks of tobacco use are undisputed and methods to address them are proven, speakers asked what more can be done to rid this country of tobacco-related disease. This challenge was presented as a moral obligation and one that also extends to developing nations.

Dr. Leffall reminded members that the Panel will hold two more meetings in this series—the next in Portland, OR on obesity, physical activity, and nutrition and the final meeting of the four in Jackson, MS on issues related to the impact of tobacco use and environmental tobacco smoke on cancer risk.

Questions and Answers

Dr. Runowicz applauded the Panel for working to address such challenging issues. She initiated a discussion as to how the NCAB could help turn the Panel's reports into action items. She cited as an example working to get state legislators to invest a greater percentage of the excise tax settlement monies in tobacco control. Dr. Leffall explained that the tobacco topic was chosen in recognition of the fact that tobacco use remains an important issue even though the Surgeon General's report on the health consequences of tobacco use was released in the early 1960s. He suggested that the NCAB could give the Panel report even greater strength by continuing to emphasize the importance of eliminating this preventable cause of cancer in its reports. Dr. Coffey called attention to and commended the current American Cancer Society (ACS) campaign to enlist grassroots support in solving the cancer problem. Dr. Chabner observed that the impact of smoking on deaths and the cost to society exceeds some of the current political issues that receive greater attention, and he asked for a follow-up report on the response of the President and the Administration to the Panel's report. Dr. Runowicz pointed out that the NIH

campus is not yet smoke free. She suggested that the NCAB might consider sending a letter advocating such action and was informed that an NIH Tobacco-Free Campus Policy is currently being implemented and that the FCRDC already has responded to the DHHS Secretary's directive for tobacco-free government campuses.

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences (DCCPS), pointed out that the next round of decisions that states make about how to use master settlement agreement dollars will occur in 2007, so the timing is right for taking action. Dr. Croyle also updated the board on the new NCI Smoke-Free policy relating to NCI-sponsored meetings. Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, agreed to work with Dr. Gray to draft a letter or statement to Congress expressing the Board's consensus regarding the issues being addressed by the President's Cancer Panel. A letter or statement also will be drafted endorsing consideration to use the master settlement agreement dollars at the state level for health programs in tobacco control; this letter or statement will be distributed to coincide with the Panel report for utilization by advocates at the state level. The documents would be circulated for members' approval before distribution.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, Office of Policy Analysis and Response (OPAR) , reminded members that the President's budget, which was announced in February, contained allocations of $28.6 B for the NIH and $4.75 B for the NCI. The bill was passed by the House Committee on June 13 with identical allocations and by the Senate Committee on July 20 with the same figure for the NIH and an increase to $4.99 B for the NCI. A CR was passed on September 29 to prevent a government shut-down after the close of the fiscal year. Congress passed a second CR on November 17 before recessing for Thanksgiving, with additional legislative work scheduled for the week of December 4. Ms. Erickson noted that Congress, when it returns from recess, is most likely to pass another CR, which will extend beyond the swearing in of the 110th Congress during the first week of January 2007. Possible actions by the new Congress are to include the Labor, HHS appropriations in an omnibus bill or pass another CR.

Ms. Erickson briefly reviewed the legislative and organizational outlook for the 110th Congress with Democrats in the majority. Legislative possibilities include an increased focus on health and science issues and new life for old issues such as stem cell research. Committee leadership will change in both the House and Senate. Probable committee leadership in the House includes: 1) Representative David Obey (D-WI) as Full Appropriations Committee and Subcommittee Chair; 2) Representative John Dingell (D-MI) as Chair, Energy and Commerce Committee, which is responsible for NIH authorization, and Representative Waxman as Health Subcommittee Chair; and 3) Representative Henry Waxman (D-CA) as Chair, Government Reform Committee which has NIH oversight authority. In the Senate, probable leadership includes: 1) Senator Robert Byrd (D-WV) as Chair, Full Appropriations Committee and Senator Harkin as Chair, Appropriations Subcommittee; 2) Senator Edward Kennedy (D-MA) as Chair, Health, Education, Labor, and Pensions (HELP) Committee, which is responsible for NIH authorization; and 3) Senator John Rockefeller (D-WV) as Chair, Homeland security and Government Affairs Committee, which has oversight authority.

Potential issues to be addressed by the 110th Congress include stem cells, NIH reauthorization, and a comprehensive cancer bill. Ms. Erickson noted that a stem cell bill was passed this year by both Houses of Congress but was vetoed, and that the issue is likely to be addressed by the new Congress. The NIH reauthorization legislation, if it is not passed by the 109th Congress, will need to be reintroduced in the 110th Congress. Ms. Erickson reported that the NCI has received inquires from some members of Congress that suggest they may be working on a comprehensive cancer bill similar to that introduced in

the 109th Congress. She indicated that she would monitor activity in all three areas and keep the NCAB informed of the details.

Questions and Answers

Dr. Chabner asked about the status of the World Health Organization (WHO) treaty on smoking control relative to ratification by the United States. Dr. Croyle explained that the Framework Convention for Tobacco Control has had a significant impact in the countries where this global health initiative has been ratified, for example, in Ireland where Dr. Niederhuber witnessed the phenomenon while working there on a renewal of the All-Ireland Consortium. He noted that the United States has initialed the Framework Convention, but the treaty has never been submitted by the President to the Senate for confirmation. He mentioned also that a few investigators in one of NCI's Trans-Disciplinary Tobacco Use Research Centers (TTURCs) have played a leading international role in conducting research to evaluate the impact of the implementation of the Framework Agreement in a number of countries around the world. Dr. Chabner proposed that this topic be placed on the February NCAB agenda to obtain more specific information in preparation for more definitive action instituted by a motion or perhaps by working with the President's Cancer Panel.

VI. FREDERICK CANCER RESEARCH AND DEVELOPMENT CENTER (FCRDC)— DRS. JOHN NIEDERHUBER AND CRAIG REYNOLDS

Introduction. Dr. Niederhuber reminded members that understanding the organization and activities of the NCI intramural program was identified at a recent retreat as helpful to the Board in its advisory capacity with respect to supporting intramural program leadership and scientists. At that time, it was decided that the December meeting would be devoted primarily to the intramural program. He reminded members in advance that the NCI authority to use the contract mechanism evolved from discussions of the Yarborough Committee as to how the cancer research engine could be moved forward at a more rapid and integrated pace. The reasoning was that the authorization to enter into contracts would permit the NCI to direct research and attract individuals to cancer research who might not otherwise be able to do so. Dr. Niederhuber emphasized the importance of the FCRDC in terms of NCI's ability to engage in a number of different research agendas, but especially technology development, as well as the ability to work with the private sector.

Overview. Dr. Craig Reynolds, Director, FCRDC, informed members that the FCRDC (NCI-Frederick) mission is to provide a unique national resource for the development and application of advanced technologies to meet the most urgent and challenging research and development needs of the NCI and the nation. NCI-Frederick was established in 1972 by Presidential directive to convert the former Department of Defense (DOD) Biological Defense Research laboratories at Ft. Detrick into a center for cancer research. The directive also stipulated that "operation of NCI-Frederick should be by private contractor to allow the necessary flexibility, which would be difficult under direct Government operations." In 1975, NCI-Frederick was formally designated as a Government-owned, contractor operated (GOCO) Federally Funded Research and Development Center (FFRDC). There are about 38 FFRDCs throughout the nation including the Lawrence Livermore National Laboratory under the Department of Energy (DOE) and the National Defense Research Institute under DOD. NCI-Frederick is the only FFRDC in the DHHS and the only one in the nation dedicated solely to biomedical research. Dr. Reynolds explained that FFRDCs are designated by the NSF and authorized by Congress to meet specific and urgent needs of the nation. The FFRDC authorization allows NCI-Frederick to function under a broad charter and provides, through the Federal Acquisition Regulations (FAR), a number of unique acquisition capabilities. These capabilities provide the NCI with enhanced flexibility, rapid response capability, and increased efficiency. In return, the FFRDC authorization designates that NCI-

Frederick must focus its efforts on meeting the most urgent and difficult-to-achieve needs of the NCI, not those that can be met by using other funding mechanisms.

Dr. Reynolds presented an example of NCI-Frederick's rapid response capabilities in the past. Responding to the need for a diagnostic AIDS blood test, NCI-Frederick began production of large amounts of the AIDS virus in April 1984; by June quantities of virus-infected cells were provided to each of five companies charged by the NCI with development of the blood test. By March 1985 the FDA had approved the first assays to test blood supplies, and by 1989 the number of individuals in the United States infected via contaminated blood transfusions was reduced to fewer than 450. Dr. Reynolds cited the AIDS Vaccine Program (AVP) as an example of how NCI-Frederick has become a unique resource for the NCI intramural and extramural investigators, other Institutes, other government agencies and NCI corporate partners. Since 1983 more than 100,000 liters of HIV/SIV products were produced and distributed to more than 200 AIDS researchers nation- and worldwide; antigen-capture kits for both HIV p24 and SIV p27, with an estimated value of more than $7 M, were provided to more than 300 investigators; about 3,000 viral load and related assays were provided to intra- and extramural programs doing AIDS research; retroviral nucleocapsid proteins are provided on a yearly basis to more than 60 investigators; and large number of unique HIV and SIV serological reagents are shared freely with the NCI/NIH intramural and extramural communities.

In a more cancer-focused example, Dr. Reynolds noted that the Biopharmaceutical Development Program (BDP) at NCI-Frederick was able to help Dr. Elizabeth Jaffee develop new pancreatic cancer vaccines for use in translational research. Organizationally, the BDP is supported by the Developmental Therapeutics Program (DTP) of the Division of Cancer Treatment and Diagnosis (DCTD), and was established in 1993 to provide, not only vaccines, but also monoclonal antibodies, recombinant proteins, peptide, oncolytic viruses, gene therapy products, and other biological agents in support of intra- and extramural investigators. The BDP provides complete cGMP-compliant support from feasibility testing through product development and manufacturing to filing of regulatory documentation. Since inception, the BDP has completed more than 100 projects, of which 68 have gone to clinical trials.

The NCI's Nanotechnology Characterization Laboratory (NCL), a component of the Alliance for Nanotechnology in Cancer, also is located at NCI-Frederick. The NCL objectives were to create an environment for the confluence of nanotechnology disciplines of physics, chemistry, engineering, and mathematics with the biosciences. In collaboration with the National Institute of Standards and Technology (NIST), robust protocols are developed for product validation, comparison, and evaluation. In collaboration with the Food and Drug Administration (FDA), a critical pathway is being developed toward clinical translation of new nanotechnology products.

Dr. Reynolds cited the newly completed Vaccine Pilot Plant (VPP) as an example of the NCI-Frederick helping in the missions of other Institutes. In response to an urgent request from the President and Congress, NCI-Frederick worked with the NIAID Vaccine Research Center to increase NIAID's capacity for the production of pilot lots of vaccines for emerging infectious disease needs. The VPP was completed by NCI-Frederick on schedule, under budget, and in just 36 months from the lease of land to delivery of the first cGMP product. The Plant is a state-of-the-art multiproduct facility for the production of biological products from prokaryotic or eukaryotic cells. The result of this effort was a significant increase in NIAID's capacity to produce vaccines for HIV and other emerging infectious diseases such as avian flu, SARS, Ebola, and West Nile encephalitis.

Dr. Reynolds presented a summary of activities in recent years. During past 5 years, NCI-Frederick has: 1) provided basic and clinical research services to 25 of the 28 NIH Institutes and Centers (ICs) and the Office of the Director (OD), NIH; 2) published more than 4,000 peer-reviewed

research articles; 3) executed 3,067 Material Transfer Agreements and 77 collaborative research agreements with numerous universities and industry collaborators; 4) was cited by *The Scientist* as a top ten "Best Places to Work" for U.S. research institutions and was in the top ten "Best Places to Work" for postdoctoral fellows. In the past 2 years, NCI-Frederick: 1) provided advanced technology expertise and support to the Department of Homeland Security (DHS), DOD, FDA, and United States Department of Agriculture (USDA); 2) produced more than 40 novel biopharmaceutical products and vaccines through two cGMP manufacturing programs; 3) supported more than 300 NIH-sponsored clinical trials to test innovative cancer and AIDS treatments; 4) acquired or stored more than 1.5 million clinical samples in support of cancer and AIDS clinical trials worldwide; 5) provided more than 1 million novel research animals to about 1,100 investigators at more than 200 U.S. institutions; 6) acquired, produced or distributed more than $10 M in quality biological research reagents at no cost to investigators through the NCI-Frederick Preclinical Repository; and 7) provided advanced biomedical computing expertise and support to more than 1,800 users from the world's largest, high-performance computer resource dedicated solely to biomedical research.

Questions and Answers

Mr. Koch asked for clarification of the process for developing the novel products discovered at NCI-Frederick into commercial products. Dr. Reynolds explained that the FCRDC works with industry to bring a larger number of the novel agents through early clinical trials where an assessment can be made as to whether they are good or bad candidates for further development. The goal is to turn products over as quickly as possible to a corporate partner for major manufacturing, development, and Phase III trials. Mr. Koch asked whether the novel products could be licensed to industry and how that could be accomplished. Dr. Reynolds explained that the cancer agents coming through the biopharmaceutical production facility from extramural investigators are returned to them for the initial clinical trials and licensing by their institutions. About 25 percent come from the intramural program and are NCI agents. These are processed through the NCI Technology Transfer Branch and the NIH Office of Technology Transfer, which protects the intellectual property that belongs to the government by filing invention reports and patents and then makes the product available to investigators.

In response to a question from Dr. Kenneth Cowan, Director, UNMC Eppley Cancer Center, Dr. Reynolds explained that the NCI-Frederick is reimbursed for work contracted for other ICs or government agencies, and the NCI budget is preserved for cancer research. Dr. Cowan asked how the NCI-Frederick budget is allocated to research versus support activities. Dr. Reynolds explained that NCI-Frederick does two things—provide dedicated support services to its customers through its dedicated facilities and makes resources available on a shared services basis. Shared services run the gamut from facilities maintenance and engineering programs, to a laboratory animal sciences program that provides transgenic animals and animal holding for the entire NCI, to more advanced technologies such as the research technologies program and the advanced biomedical computing center.

Dr. Coffey commended the NCI-Frederick as a model for a controlled contract process that is worthy of amplification and replication for university, industry, and government interactions. He suggested that a future report should deal more specifically with issues such as intellectual property.

VII. CENTER FOR CANCER RESEARCH: CLINICAL PROGRAM—DRS. JOHN NIEDERHUBER, ROBERT WILTROUT, AND LEE HELMAN

Introduction. Dr. Niederhuber reminded members that, during the 5 years when the budget was growing, the NCI spent much of the time reengineering and downsizing the intramural program. This was accomplished with the help of members of the Board of Scientific Counselors (BSC) who provided

rigorous scientific reviews of the individual laboratories. As a result, only about 9 percent of the NCI budget goes to personnel and supplies in laboratories in the intramural program, down from a high of 10 percent in 2002. He called attention to the ranking in a recent publication of the intramural molecular biology and genetics laboratories as number one among government laboratories and the immunology laboratory as number two.
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Overview. Dr. Robert Wiltrout, Director, CCR, reminded members that the CCR is one of two intramural components of the NCI. The Division of Cancer Epidemiology and Genetics (DCEG) is primarily population science-based and the CCR provides most of the on-site basic translational and clinical research in support of the NCI. The Intramural Research Program (IRP) originally comprised two divisions—Basic and Clinical. In 2001 the IRP was reengineered to merge the two divisions to form the CCR. Collaboration was emphasized and facilitated, with strategies for rewarding team science as a new paradigm for conducting complex interdisciplinary research. Faculty and working groups were formed, leading to the establishment of Centers of Excellence. Closer ties between clinical and basic research have led directly to translational and research advances. Dr. Wiltrout noted that reengineering continues to be a dynamic process of integration and optimization of resources.

The CCR mission is focused on patient benefit. Its primary role continues to be knowledge generation that leads to increased discoveries in basic and clinical cancer research and, ultimately, to the development of novel therapeutic interventions for adults and children with cancer or infected with HIV. The CCR seeks to achieve its mission by: 1) performing rigorous basic scientific research into fundamental mechanisms of biology and cancer; 2) translating these advances rapidly from the laboratory to the clinic; 3) developing innovative technologies that enable more accurate detection, diagnoses, and treatments; 4) pioneering novel interventions for underserved patient populations and rare diseases; 5) sharing expertise, scientific data, and technologies to broaden the impact of intramural research and enhance the overall productivity of the cancer research community; and 6) providing a unique environment to cultivate and train future physician-scientists and biomedical researchers.

Dr. Wiltrout noted that one measure of the success of the CCR research program and its impact is a recent survey of the 250 most highly cited investigators, which revealed that 25 (or 10 percent of the list) resided and functioned within the CCR. He listed examples of high-risk, high-impact advances coming out of the intramural program that have been highlighted in various ways: 1) adoptive therapy advances; 2) development of new vaccine approaches; 3) unraveling the biology of TGF-b and its role in hematopoiesis, carcinogenesis, and basic cancer biology; 4) a distinctive interdisciplinary renal carcinoma research program; 5) gene expression profiling to inform treatment decisions; 6) cutting-edge childhood rhabdomyosarcoma research; 7) HPV research and a vaccine that are having a global public health impact; 8) world-class leaders in AIDS pathogenesis, comparative genomics, comparative virology, and bioinformatics; and 9) a novel noninvasive imaging method to detect sentinel lymph node involvement.

Dr. Wiltrout reminded members that the CCR philosophy and culture includes the support of long-term, high-risk, paradigm-shifting research. He gave as examples of such research: 1) the progress achieved in Birt-Hogg-Dube disease, a subset of kidney cancer, which was published in the October *Proceedings of the National Academy of Science*, and 2) a seminal study in distinguishing lymphoma subtypes, which was published in the June *New England Journal of Medicine*. As an example of CCR research that addresses an unmet medical need, Dr. Wiltrout cited a study on adenovirus-based long-term HIV vaccine, which was published in the September *Virology*. This approach is being pursued in collaboration with NIAID. Dr. Wiltrout noted that the CCR works to develop technologies that empower and benefit the entire community, and he cited work to develop a library or "molecular taxonomy" of cancer that can be used to identify critical targets for drug development for different cell types in different

cancers. The technology and methodology are easily exported for use in the broader community. This work was published in the May *Nature*.

Next, Dr. Wiltrout addressed the role of collaborations in CCR culture and philosophy. He noted that fulfilling the CCR mission requires extensive collaborations at the laboratory or branch level, across the NCI and NIH, and with extramural investigators, industry partners, partners in other federal agencies, and national and international consortia. At the same time CCR scientists participating in such interactions are reviewed, recognized and rewarded for the team science. To accomplish the latter, the CCR works in partnership with the BSC to change review guidelines for the intramural program so that critical aspects of team-oriented science are defined and rewarded at the time of the intramural reviews in addition to the reviews of their independent science. Dr. Wiltrout noted that this has helped the CCR move toward a culture where team-oriented interdisciplinary science predominates. Evidence of this is that 70 percent of all publications from the CCR are based on collaborations, and half are collaborations with extramural investigators, many with universities and Cancer Centers. As part of its research mission, the CCR produces many things that are shared with the extramural community. These include cell lines, many reagents, and transgenic animals and new technologies that are provided for the benefit of the broader research community. In the area of technology transfer, the CCR has a strong record of generating intellectual property. CCR scientists produce a large number of the extant Material Transfer Agreements. CCR holds 27 percent of NIH Cooperative Research and Development Agreements (CRADAs) and brings in 33 percent of NIH's royalty dollars.

Dr. Wiltrout described the CCR as being organized for convenience as clinical branches or basic laboratories; however, the integrative structures in place make such designation artificial to a degree. Organizationally, the clinical branches include virtually all of the clinical areas of expertise and support not only the CCR's research program, but also the entire NIH in particular areas such as surgery and pathology. The basic laboratories constitute a critical mass of expertise, which contributes to the distinctiveness of the intramural program in terms of interdisciplinary research. Dr. Wiltrout noted, however, that the laboratories and branches are woven together around several strategic goals where integration between basic and clinical research is important and laboratories and branches are melded together by technologies and new approaches to translation. For example, the CCR is engaged in a partnership with the DCTD to develop and validate novel targeted therapies to improve cancer treatment. Other strategic goals include developing new approaches to combat HIV/AIDS and AIDS malignancies; harnessing the immune system to combat cancer; discovering and developing novel approaches for early cancer detection, diagnosis, and prevention; and interrogating the molecular genetics of cancer to individualize medicine.

Dr. Wiltrout announced the successful recruitment of Dr. Paul Meltzer as Head, Clinical Molecular Profiling, and Chief, Genetics Branch; Kevin Campausen as Chief, Radiation Oncology Branch; Dr. Deborah Morrison as Laboratory Chief, Laboratory of Cell and Developmental Signaling; and Dr. Giorgio Trinchieri, as Director, Cancer and Inflammation Program, and Chief, laboratory of Experimental Immunology. Dr. Wiltrout observed that ongoing recruiting challenges include conflict-of-interest and salary issues within the government and the significant competition from public and private sector for top researchers, but the CCR continues to move forward with successful recruitments. He noted that the quality of investigators in both the basic and clinical side of the CCR is evidenced by the number of offers they receive to move off to Cancer Centers. He concluded with a brief summary of the additional topics and presenters in the CCR review.

Questions and Answers

Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at UCLA, commented on how the successful intramural program in the CCR must either grow or die, and he asked how that could happen in the current fiscal climate without adversely affecting the extramural program. Dr. Wiltrout noted that every Cancer Center and Academic Medical Center director is facing the same challenges and that the CCR budget did not grow at the same rate as the NIH budget during the doubling period. He explained that the recent downsizing conducted with BSC help has made it possible to reprogram dollars and to think this year about recruiting a few tenure tracks. On the other hand, he pointed out, the CCR has been successful in retaining its critical mass of the best science and is looking to a time when the budget will begin to recover. He emphasized that the concern should be that great science is done and that there is support for that science wherever it is done. Dr. Coffey cautioned that the infrastructure of the NCI could begin to be taken apart as the budget goes down and the hiring of support staff is frozen. He commented on the need to look at the quality of research and recognize that the intramural program cannot continue to be cut back. Dr. Prendergast expressed the view that the serious needs of the physical plant at NCI-Frederick need to be addressed formally in terms of both current and longer term needs to preserve the effectiveness of the operations there. He commented that the expert advice provided to institutions such as his has been enormously effective and helpful.

CCR Clinical Program. Dr. Lee Helman, Acting Scientific Director for Clinical Research, CCR, noted that the operative perspective in the clinical program is that the next 10 years will see a paradigm shift in cancer treatment from 20th century empiricism to 21st century mechanism. Treatment will be proactive, more rational, and less toxic, and quality of life will be improved. From a strategic point of view, the Clinical Program believes that predictive medicine is an important focus inasmuch as it is increasingly possible now to know an individual's complete genome and proteome, assess for tumor rejection antigens, use multiparameter diagnostics to visualize a patient in the present and predict the future, and select drugs to redesign the behavior of biologic systems. Dr. Helman cited the new approach to diagnosis that is resulting from CCR studies. In particular, gene expression profiling of large B-cell lymphomas (LBCL) revealed distinct histologic entities with different responses to standard chemotherapy for LBCL; this has increased understanding of and the need for different therapeutic choices. Dr. Helman called attention to individualized medicine as the hope for the future, where molecular diagnostics will make it possible to individualize treatment based, for example, on whether the tumors are Akt-driven or EGFR-driven rather than whether they are breast, prostate, or lung cancer tumors.

Dr. Helman noted that imaging is another key component of the intramural research program and that molecular imaging promises to be key to making earlier and better decisions about the effectiveness of a particular treatment. New imaging approaches will be used to analyze the effect of targeted treatment on a specific target, alter treatment in real time, and determine activation of a pathway related to oncogenesis. Dr. Helman concluded that these are the future directions for the intramural and clinical programs and expressed confidence that they would be addressed within the next 10 years in a collaborative way that benefits the entire cancer community.

Dr. Helman presented a listing of the types of credentialed physicians in the Clinical Program of the CCR. Of the 396 total, 163 are senior physicians, 148 are fellows, and 85 are other types of physicians, including consultant, adjunct, and research. He called attention to honor society memberships held by senior CCR physicians: 17 are members of the American Society for Clinical Investigation, 6 are fellows in the American Association for the Advancement of Science, 3 are Institute of Medicine members, 6 are members of the Association of American Physicians, and 13 are members in Clinical Specialty Societies. He emphasized that the NCI intramural CCR is not a large-volume, full-service cancer center, but is the largest cancer-focused clinical research center in the world. It is capable of performing patient-intensive clinical research focused on developing new approaches for prevention,

diagnosis, and treatment of cancer. The vision for the future of clinical research at the NCI is to focus on testing new science-based hypotheses interrogating a disease or disease process, and to maximize understanding of how to intervene in the disease process by interrogating the cancer network using genetic, proteomic, and imaging tools. Dr. Helman noted that the CCR Clinical Program's commitment is to protocol-driven clinical research with a mandate to test innovative therapeutic approaches. If the job is done well, successful studies will be fed into the extramural community to be tested in Phase II and broader Phase III studies, and this will be a measure of success.

Dr. Helman reported that an early action as Acting Scientific Director was to establish a clinical molecular profiling core headed by new recruit Dr. Meltzer, a world expert in molecular profiling since its inception. Dr. Helman stated that expression profiling, array CGH single nucleotide polymorphisms (SNP) analysis, and resequencing elements already are in place and micro-RNA technology is being developed for use in the Clinical Program. A developmental core also is in place to keep the NCI at the cutting edge, and the technologies can be applied in real time to patients on clinical protocol. Dr. Helman called attention to the work and credentials of Drs. Campausen, the new head of the Radiation Oncology Branch, and the fact that Dr. Giuseppe Giaccone, currently Chief of Medical Oncology at Vrije University in Amsterdam, will be coming to the NCI as Chief, Medical Oncology Branch. Recruitment is underway for a new Chief of the Laboratory of Pathology.

Dr. Helman concluded that opportunities for the future include intramural and extramural collaborative studies and pilot prevention studies with validated surrogates. Members were told that much work remains to: 1) accelerate the pace of drug discovery and development; 2) advance conduct of rationally based combination clinical trials; 3) integrate and leverage use of advanced biomedical technologies; 4) optimize use of information, making data accessible to all; 5) standardize biospecimen collection approaches; and 6) work with industry to facilitate intellectual property issues.

Questions and Answers

Mr. Koch observed that the NCI Clinical Program appears to be organized around basic functions rather than cancer types, and he asked about the underlying rationale. Dr. Helman noted, first, that the Clinical Program is organized by subspecialty and the clinical investigators have a disease focus. However, the Program also has a number of basic researchers with focuses on pathways or a few cancers. The current practice is to think about how a program in breast cancer, for example, might also cross cut with another type of tumor because the pathways or targeted therapies might be the same. The thought is that findings could be exported across diseases and there is a need for flexibility. Dr. Chabner commented that clinical programs in the Cancer Centers must be organized around diseases to offer state-of-the-art therapy and to conduct clinical research. He noted that multidisciplinary clinical groups are accepted now in most of the country's Cancer Centers and that interdigitation of basic and clinical science can be accomplished through disease programs—one basic scientist can interact with multiple disease programs.

VIII. CENTERS FOR CANCER RESEARCH: MEETING NIH'S MANDATE FOR RARE DISEASE RESEARCH: CLINICAL DEVELOPMENT OF TREATMENTS FOR NEUROFIBROMATOSIS TYPE 1 ASSOCIATED TUMORS—DR. BRIGITTE WIDEMANN

Dr. Widemann, Investigator, Pediatric Oncology Branch, CCR, stated that her objectives as a clinical tenure track investigator within the Pharmacology and Experimental Therapeutics Section have been the development of new treatments for refractory childhood cancers and, most recently, the clinical development of a treatment program for Neurofibromatosis Type 1 (NF1)-related tumors. She reviewed

the characteristics of the disease: 1) NF1 is the most common single gene disorder; 2) it is diagnosed by the presence of cutaneous stigmata; 3) affected individuals are prone to development of a variety of benign and malignant tumors, including plexiform neurofibromas (PNs), malignant peripheral nerve sheath tumors (MPNSTs), optic pathway and low-grade gliomas, and leukemias; and 4) NF1 can manifest itself in essentially any organ system and requires a multidisciplinary care approach. One rationale for development of anti-NF1 agents is that neurofibromin, the NF1 gene product, is known to function as a GTPase-activating protein, which facilitates the conversion of active GTP-bound RAS to an inactive status. Moreover, additional targets for NF1 have been identified, many of which overlap with targets for human malignancies for which treatment agents are in development.

Dr. Widemann noted that her initial focus for treatment was on PNs, which are benign tumors that involve multiple nerve fascicles and branches. They are diagnosed in approximately 25 percent of individuals with NF1. The natural history of these tumors is not well known but many believe these are congenital tumors that have an erratic growth, large size and complex shape and, while not malignant *per se*, they cause significant disfigurement, functional impairment, and potentially life-threatening complications such as compression of the trachea. Up to 13 percent of these tumors undergo malignant transformation to MPNSTs. Surgical resection is the only standard treatment but is not feasible in many cases; thus, the development of medical treatments could reduce the morbidity of these tumors and potentially prevent cancers.

Dr. Widemann noted that it was necessary to create an NF1 clinical trials infrastructure because none existed in the NCI or elsewhere, and many issues had to be addressed prior to successfully developing clinical trials. To solve the need for endpoints to measure these large, complex, slow-growing tumors, Dr. Widemann, in collaboration with Dr. Jeff Solomon, developed the methodology for volumetric magnetic resonance imaging (MRI) analysis. A randomized, placebo-controlled crossover trial was designed because many agents are unlikely to shrink these tumors whose natural history is unknown. Access to agents was important because these tumors occur in predominately young children who have a chance of growing to adulthood, and this problem was solved by working with the Cancer Therapy Evaluation Program (CTEP), pharmaceutical companies, and the FDA. A number of collaborations were initiated including an informal consortium, a DOD-sponsored NF1 consortium to facilitate the clinical trials, and a partnership with the Sarcoma Cooperative Group (SARC). Funding for the initial NF 1 clinical trials came from two DOD clinical trial awards and an NIH Bench to Bedside Award. Dr. Widemann noted that the ability to accrue patients by nationwide referral made it possible to build a patient referral base; currently, 80 patients are being followed actively at the NCI Pediatric Oncology Branch. Finally, the capability for central response evaluation in the clinical trials was established at the NCI and is currently being implemented in four multicenter clinical trials.

Using an MRI image, Dr. Widemann showed the size and complexity of PNs, indicating that the standard response criteria and validation of these tumors would have limited applicability. She demonstrated how the automated volumetric MRI analysis methodology, which had been developed in the CCR, was able to address the complexity of these tumors on MRI. This methodology is being used to analyze PNs in clinical trial. Dr. Widemann described studies in which the growth rate and pattern of PNs were analyzed using volumetric MRI. Conclusions reached were: 1) volumetric MRIs sensitively measure PN growth; 2) growth rate varies among patients but is constant within patients; 3) PNs grow more rapidly in young patients, and age stratification should be considered for clinical trials; 4) body growth alone does not account for the more rapid growth of these tumors; and 5) drug development for PNs should target young patients even though this is a more difficult task.

In collaboration with Texas Children's Cancer Center and Cincinnati Children's Hospital, a Phase I study of the farnesyltransferase inhibitor Tipifarnib was developed. Children, age 2-18 years old, with

NF1 and solid tumors were eligible for the study. Tipifarnib, which is designed to inhibit RAS activation and has activity in leukemias and breast cancer, was administered orally twice daily for 21 days. The endpoints were maximum tolerated dose (MTD), toxicities, pharmacokinetics (PK), and pharmacodynamics. The findings were that: 1) children with NF1 were substantially younger than children with solid tumors; 2) baseline absolute neutrophil count and the decrease in absolute neutrophil count was comparative for both groups, even though children with NF1 had not received prior cytotoxic treatment; 3) children with NF1 received many more treatment cycles prior to progression, as measured by standard WHO criteria, compared with children with solid tumors; 4) cumulative toxicity could not be identified in NF1 patients, suggesting that, for noncytotoxic agents, separate Phase I trials may be needed for children with NF1 given that they stay on trials much longer; 5) MTD was equivalent to that for adults; 6) PK for the MTD in NF1 and solid tumors was comparable; and 7) dosage and concentrations achieved were those applied for inhibition of proliferation *in vitro*, and inhibition of the target farnesyltransferase was shown empirically in blood mononucleotides.

On the basis of these findings, a Phase II trial of Tipifarnib has been designed for children with progressive PNs. Dr. Widemann noted that the decision was made to use a double-blind, placebo-controlled, flexible crossover trial design, given the unknown natural history of these tumors. The primary endpoint is time to progression, which is measured as a 20 percent volume increase. Children with progressive tumors are randomized to initially receive drug or placebo, followed by volumetric MRI until they progress on this first treatment phase. Then they were crossed over from placebo to drug or vice-versa, followed in identical fashion, and removed when they progress on the second phase. The crossover is flexible in that it is defined by progression and not by a predefined time point. In regard to the status of the trial, 58 patients with a median age of 8 years have been enrolled, out of the accrual goal of 60 patients; 22 are stable on Phase A; 27 progressed and crossed over to Phase B, and of those 11 are stable; and 12 were removed from the study for progression in both cases. Thirteen patients were removed from the study for reasons other than progression, only four because of toxicity. Conclusions from this ongoing trial are that: 1) the Tipifarnib and placebo toxicity are, for the most part, indistinguishable; 2) volumetric MRI analysis is more sensitive to measure progression for these complex tumors than standard criteria; 3) volumetric MRI analysis is a valid trial endpoint; 4) the randomized flexible crossover design is feasible; and 5) the placebo arm will serve as a historical control group in several other ongoing clinical trials for NF1 and PNs.

Next, Dr. Widemann discussed research related to MPNSTs, which have a high death rate, particularly in NF1, and are a leading cause of death. In a comparison of MPNST incidence in NF1-associated and sporadic tumors, the findings were: 1) MPNSTs are diagnosed at a younger age and more frequently in individuals with NF1 (approximately 50 percent); 2) typically, NF1 develop in preexisting benign PN; 3) clinical findings such as pain, rapid growth, and neurologic compromise are features indicating malignant degeneration, but they often preexist in PNs, which makes diagnosis more difficult in NF1-associated tumors; 4) the molecular biology of these two types has not been described as distinct; 5) the chemotherapy response rate in NF1-associated tumors may be worse than in sporadic cancers, according to a small retrospective study; 6) with one exception, all studies show that the overall survival and 5-year survival in NF1-associated tumors is worse. Dr. Widemann described an ongoing CCR Phase II trial of neoadjuvant chemotherapy for sporadic and NF1-associated high-grade unresectable MPNSTs. The primary goal is to define separately for NF1-associated and sporadic tumors what the response is to standard chemotherapy agents, including ifosfamide, doxorubicin, and etoposide. The primary endpoint is response after four treatment cycles, as measured using standard WHO criteria. Secondary endpoints in the study include answering imaging questions and understanding the molecular biology and epidemiology of these tumors. The study is a collaborative effort of the NCI, SARC (which is coordinating the study), and NF1 centers. Funding has been obtained for the participating sites and the five coordinating centers through a DOD grant.

Dr. Widemann concluded with a review of her current activity and future directions in the area of NF1 research. These include: 1) a collaborative, trans-NIH natural history study using available NIH resources such as those related to geno- and phenotyping, optic gliomas, hormonal influence, and cognitive function; 2) separate NF1 Phase I trails after the cancer trial to develop endpoints for the Phase II trials; 3) Phase II PN trials within the DOD NF1 Consortium; 4) FDG-PET for the diagnosis of MPNSTs within PNs; 5) Phase II trials in recurrent MPNSTs within the DOD NF1 Consortium; and 6) development of sensitive methods to measure dermal and spinal neurofibromas with the goal of designing clinical trials for these tumors. With regard to the latter, Dr. Widemann noted that a natural history and biology study of these tumors was conducted in collaboration with NHGRI investigators, and one of the goals was to monitor these tumors using a method called volume photography over time. The hope is that this method will assist in measuring the growth rate more precisely and can ultimately be incorporated into the clinical treatment studies.

Questions and Answers

Dr. Chabner commended the intramural program for mobilizing research around rare diseases like PNs and MPNSTs and providing unique opportunities for everyone to learn and to conduct trials that would otherwise be impossible. He asked how drugs were selected to take into the clinic. Dr. Widemann replied that farnesyltransferase inhibitors are a focus of good basic research and *in vitro* and *in vivo* models are being developed to evaluate agents that are undergoing clinical testing. Dr. Helman pointed out that the cancer community is currently helping the neurofibromatosis community in the area of clinical trials. Dr. Judah Folkman, Director, Vascular Biology Program, Children's Hospital of Boston, observed that many children's tumors, especially the vascular malformations, explode when puberty arrives; he suggested that Dr. Widemann's studies provide a clue that may point to an answer. Dr. Widemann noted that a rapid increase has not yet been observed because the cohort is very young, but the plan is to follow them longitudinally and see what happens at that time.

IX. CENTER FOR CANCER RESEARCH: IMMUNOLOGY CENTER OF EXCELLENCE—DRS. ROBERT WILTROUT, CRYSTAL MACKALL, TOM WALDMANN, AND JAY BERZOFSKY

Dr. Robert Wiltrout introduced Drs. Crystal Mackall, Acting Chief, Pediatric Oncology Branch, CCR; Tom Waldmann, Chief, Metabolism Branch, CCR, and a member of the National Academy of Sciences; and Jay Berzofsky, Chief, Vaccine Branch, CCR. They described some of the NCI's work in immunology and cancer.

Preclinical and Clinical Development of rhIL7: A Potent Immunorestorative and Vaccine Adjuvant. Dr. Mackall explained that cytokines may be useful for improving the effectiveness of immunotherapy for cancer. For treatment of solid primary tumors, for example, Ewing's sarcoma, patients usually have normal T cell populations with normal function at the time of diagnosis. After receiving multi agent chemotherapy, almost always including cyclophosphamide, the tumors are eradicated to the point of no evident disease, but lymphocyte populations are severely repressed. Because of this immune system depression, the tumor may recur in the ensuing months after completion of therapy but before recovery of the immune system. One approach for circumventing this problem is to manipulate the immune system during the time point at which remission has been induced and there is minimal residual neoplastic disease.

Recovery from lymphopenia and T cell regeneration can take place by one of two pathways. In the first pathway, T cells could be sent from the bone marrow through the thymus and into the periphery.

This approach is not efficient because the thymus involutes relatively early in life; chemotherapy and cancer itself also are toxic to the thymus. The second pathway, called homeostatic peripheral expansion (HPE), is characterized by mitotic expansion of mature T cells in response to both self antigens and any present cognate antigen, leading to replenishment of the peripheral T cell pool. Although this pathway is functional in cancer patients, it is not able to completely normalize T cell numbers; patients remain lymphopenic up to a year or two after completion of therapy. Immunization during HPE can skew the T cell repertoire toward particular antigens of interest, presenting an opportunity to improve the effectiveness of tumor vaccines.

To harness the HPE process to allow normalization of T cell numbers, the biology and function of suppressor cells must be understood. The most well-studied subset of suppressor cells is the CD4+ CD25+ regulatory T cells. These cells are crucial for normal immune function; mutations in the *FOXP3* gene, a transcription factor necessary for development of these cells, leads to an autoimmune disease characterized by development of diabetes mellitus early in life, diffuse polyendocrinopathy, diffuse enterocolitis, and death. Restoring this population of cells by bone marrow transplant leads to a cure. Regulatory T cells are important for establishing self tolerance at birth; however, there is evidence that regulatory T cells may be a major way in which tumors evade the immune response.

The function of regulatory T cells in lymphopenic patients was examined as part of a clinical trial in which attempts were made to immune-reconstitute patients treated with intensive chemotherapy for childhood cancer. The patients were given either a dose of their own T cells that had been collected prior to therapy or their own T cells plus IL2 as a growth factor to enhance immune reconstitution, and their immune reconstitution in the months post-therapy was followed. Patients who received only their own T cell did not show significant improvement in the numbers of T cells. Patients receiving T cells plus IL2 had an increase in CD4+CD25+ regulatory T cell counts to levels above those seen in healthy people. Using the proliferation marker Ki67, it was determined that these cells entered the cell cycle as part of the HPE process. This work showed that regulatory T cells expand during lymphopenia and during treatment with cyclophosphamide; cyclophosphamide profoundly depletes the entire compartment of CD4+ cells, but leads to a relative increase in regulatory T cells, which is detrimental for suppression of tumor growth. Adding IL2 exaggerates the relative increase in regulatory T cells, which is undesirable in the context of immune-based therapies.

Another cytokine, IL7, is required for the development of T cells and for maintenance of T cells throughout life. There is interest in using IL7 as an immunorestorative and as part of a variety of vaccines. In one study, female mice were given male cells and development of immunity to male antigens or rejection of tumor cells that express male antigens was analyzed. Treating the female mice with IL7 increased the frequency of cells responding the male antigen, demonstrating that IL7 significantly enhances vaccine responses to a greater extent than IL2. IL7 was the most effective at preventing tumor recurrence in female mice challenged with a male antigen (HY) expressing tumor. A Phase I clinical trial of IL7 was recently completed. Administration of IL7 resulted in dose-dependent increases of circulating T cell counts (CD4+ and CD8+). Using the Ki67 proliferation marker, the increase in T cells was attributed to an increased rate of cell cycling, rather than redistribution of T cells. The secondary lymphoid organs (spleen and lymph nodes) of the patients increased in size, further demonstrating an increase in total T cell mass. Quantitative PCR analysis of FOXP3 showed that, in contrast to IL2, IL7 did not disproportionately increase the regulatory T cell fraction of the CD4 compartment.

A remaining question to address concerns the extent to which IL7 can increase the repertoire diversity of the T cell pool; this is important to allow induction of immune responses to the very weak antigens that tumor antigens would represent. If the subset of cells believed to represent recent thymic

emigrants are examined after IL7 treatment, the cycling of these usually naïve, quiescent cells is substantially increased. There also is evidence that emigration of cells from the thymus is increased. Thus, IL7 therapy is capable of expanding numbers of cells and repertoire diversity. A number of therapies currently exist to drive development of different erythroid progenitors, i.e., epopoietin for red cells, and GM-CSF and G-CSF for myelomonocytic progenitors. IL7 is a potential agent for inducing expansion of the broad repertoire of naïve T cells and the memory T cell pool.

Questions and Answers

Dr. Bruce Chabner asked whether early experiments were performed using low dose daily cytoxan rather than the high dose Dr. Mackall is using, and whether this could account for some of the results. Dr. Mackall answered that it is possible that certain doses of cyclophosphamide could selectively deplete regulatory T cells, but in her opinion the augmented immune reactivity observed after cyclophosphamide treatment is more likely to be the response to lymphopenia. Dr. Chabner asked Dr. Mackall to discuss the possible role of anti-CTLA4 or anti-CD3/CD28, both of which are believed to be immune-enhancing, and asked whether Dr. Mackall would consider combining them with IL7. Dr. Mackall answered that anti-CTLA4 appears promising, but there are limited data concerning how it works. Understanding its mechanism will be necessary before anti-CTLA4 can be made more effective. Dr. Wiltrout commented that early dose chemotherapy studies that examined reduction of suppressor cells were based on functional assessments because cell markers were not yet available.

IL15 in the Life and Death of Lymphocytes: Implications for Cancer Therapy and Vaccine Design. Dr. Waldmann stated that the human T cell lymphotrophic virus-1 (HTLV-1) was the first retrovirus found to cause a disease in humans, adult T cell leukemia. The virus encodes a transcription factor that transactivates genes encoding IL2 and the IL2 receptor (IL2R) and also IL15 and its receptor (IL15R). Infected T cells display between 10,000 and 35,000 IL-2 receptors on the cell surface, compared with uninfected cells, which display fewer than 500. The discordance in receptor expression between normal and infected cells provides a target for monoclonal antibody therapy. Daclizumab, a monoclonal antibody to IL2R, blocks the interaction of IL2 with the receptor and has been used effectively to treat adult T cell leukemia and other conditions including organ allograft rejection, multiple sclerosis, T cell-mediated uveitis, pure red cell aplasia, psoriasis, and aplastic anemia.

Further study of patients with adult T cell leukemia led to the discovery of a novel cytokine, IL15. The IL2 and IL15 receptors share common beta and gamma chains, but have unique alpha subunits. Both IL2 and IL15 stimulate proliferation of a number of T cell subsets, co-stimulate immunoglobulin synthesis and differentiation of B cells, and, especially for IL15, are essential for maintaining and generating natural killer (NK cells); in the absence of IL15, NK cells die within 24 hours. However, IL2 and IL15 have distinct functional roles in adaptive immunity. IL2 predominantly prevents a T cell immune response to self, through co-apoptotic or inhibitory mechanisms. It is involved in the phenomenon of activation-induced cell death (AICD) and in the maintenance and fitness of CD4/CD25 regulatory T cells. IL15 inhibits IL2-mediated activation-induced cell death, and is not critical for maintenance of regulatory T cells, but instead is required to maintain NK cells and memory CD8 T cells, which are involved in maintaining a long-lasting and robust immune response to invading pathogens. Knockout experiments showed that loss of IL2 or its receptor alpha subunit results in massive enlargement of peripheral lymphoid organs, high levels of certain immunoglobulin classes, and development of an array of autoimmune disorders. In contrast, loss of IL15 or its receptor alpha subunit does not result in lymphoid enlargement, but instead is characterized by reduction in NK cells, inter-epithelial intestinal lymphocytes, and memory CD8 cells.

The differences in phenotypes resulting from the knockout of these two interleukins can be

attributed in part to different distributions of their unique receptors. IL2 alpha subunits are expressed on activated T cells, and IL15 alpha subunits are expressed on activated monocytes and dendritic cells, i.e., antigen presenting cells (APCs). Furthermore, in contrast to IL-2, IL15 works as part of an immunological synapse. When monocyte or dendritic cells are stimulated with interferon, coordinated simultaneous expression of IL15 and IL15R alpha is induced on the cell surface. IL15 and IL15R alpha recycle through endocytic vesicles and are maintained on the cell surface for days. APCs with IL15 and IL15R alpha on their surfaces trans-present IL15 to NK or CD8 cells that express the other components of IL15R; this trans-presentation is required for NK cell survival. IL2 may cause activation-induced cell death (AICD) of cytotoxic lymphocytes; thus, IL15, as a facilitator of effector and memory CD8 cells, may be superior to IL2 as a component of a vaccine to treat cancer.

In animal experiments, colon carcinoma cells were introduced intravenously into wild type mice or mice transgenic for high levels of IL15; the animals expressing IL15 at high levels did not develop tumors. If the colon carcinoma tumor cells were transfected with IL15R alpha, small quantities of circulating endogenous IL15 were sufficient to induce tumor cell death through activation of NK cells. This approach also was successful for models of melanoma. A collaborative effort between NCI and NIAID through the Centers of Excellence/ BDP at NCI for good manufacturing practice (GMP) production of IL15 and development of an array of assays for IL15 and antibodies directed to it is underway. Because of the mode of action of IL15, IL15 as a monotherapy likely will be effective, but not optimal. To augment IL15 effectiveness, the goal is to induce IL15R alpha so that administered IL15 can bind to this receptor and be transpresented.

Because IL15 has a major role in immunological memory, it may be useful as a component of molecular vaccines for HIV, tumor antigens, or bioterrorism targets. Co-administration of HIV vaccine vectors with vaccinia virus expressing IL15 resulted in robust CD8 T cell-mediated cytotoxic immunity lasting for at least 12 months. However, because IL15 is an inflammatory cytokine that induces expression of TNF alpha and IL1 beta, inhibits self tolerance, and facilitates memory CD8 T cell survival, disordered IL15 and IL15R alpha expression can have serious consequences. Dysregulation of this cytokine and its receptor has been observed in inflammatory autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis, as well as HTLV1 mediated diseases. A humanized Mik-∃1 antibody directed toward IL2 and IL15R beta produced under GMP effectively inhibits IL15 trans-presentation and blocks IL15 action on CD8 and NK cells; this antibody also prolonged cardiac allograft survival. In mice, an antibody against IL2 and IL15R beta blocks IL15 action and leads to the disappearance of NK cells.

In summary, IL2 and IL15 have contrasting roles in the life and death of lymphocytes. IL2 is involved in the checkpoint control of T cells required for self tolerance and prevention of autoimmunity. In contrast, IL15 is anti-apoptotic and favors survival of CD8 memory T cells, leading to the persistence of an immune response. IL15R alpha and IL15 are produced together and IL15 recycles with its receptor and presents IL15 in trans as part of an immunological synapse with neighboring NK and CD8 T cells. The demonstration that IL15 is a critical factor for the proliferation, activation and function of NK and memory CD8 T cells supports its use in the prevention and treatment of cancer, especially in those cases where IL2 has already been approved by the FDA, such as for metastatic renal cancer and metastatic melanoma, but also could be used in lieu of IL2 in HIV protocols in patients receiving HAART therapy. The incorporation of IL15 in molecular vaccines for cancer and AIDS provides a robust, sustained, high avidity cytotoxic T cell immune response. Finally, humanized antibody Mik-∃1 has been produced here by the BDP of the NCI and developed to use as a therapy for CD8 leukemias and lymphomas and for treatment of an array of autoimmune diseases.

Questions and Answers

Dr. Runowicz asked whether humanized Mik-∃1 had been given to humans. Dr. Waldmann answered that a single dose of humanized Mik-∃1 per patient was given to six patients with T cell LGI with granulocytopenia as part of a dose escalation trial. He hopes to complete studies involving saturating doses within the next few months. Currently, there have been no reports of drug-related toxicity in either animals or humans.

Mr. Koch asked how long the project took to complete and about the size of the team involved. Dr. Waldmann answered that the antibody to CD25 was made 25 years ago. His group has 15 researchers, plus a clinical trials team. The group is organized around three areas: 1) basic science, involving the discovery of new cytokines and cytokine receptors, their signaling pathways, and how they contribute to disease; 2) preclinical models of human adult T cell leukemia mice for initial testing of drugs; and 3) clinical trials involving a group consisting of two senior physicians, two research nurses, and nurse practitioners. Clinical trials involving diseases other than cancer are performed as collaborative trials with other institutes or institutions. GMP production of IL15 involves the BDP, NCI.

Dr. Prendergast asked whether Dr. Waldmann had developed toxicity profiles for IL15. Dr. Waldmann answered that this work had not yet been completed in humans. However, at doses of 10 micrograms per kilogram, IL15 is effective in cynomolgus monkeys. No toxicity has been observed at doses to 100 and 200 micrograms per kilogram in these animals. Specific toxicities he has assessed include capillary leak syndrome (analogous to that seen upon treatment with IL2) and evidence of autoimmunity, neither of which has been observed. Another agent in combination with IL15 could cause large strains on the lymph nodes, similar to that observed with megadoses, but at present toxicity with IL15 in mice has not been observed at a level equivalent to 1,000 micrograms per kilogram. The expected human dose will likely be between three and 20 micrograms per kilogram and at that dose there has been no toxicity.

Dr. Prendergast related his experience with T cell leukemia in the 1960s and 1970s. At that time, patients presented with severe lymphadenopathy that responded well to chemotherapy (cytoxan), but recurred quickly, leading to patient death. He asked if this could be attributed to cytokine responses in the patients. Dr. Waldmann agreed that many of the T cell malignancies are orphan diseases for the pharmaceutical industry because they are quite rare relative to B cell leukemia and lymphoma. He speculated that treatment for adult T cell leukemia will require multidrug therapy, rather than monoclonal antibody therapy alone. Radiolabeled monoclonal antibodies have shown some effect. In a trial involving 17 patients with Hodgkin's disease, treatment with Yttrium-labeled daclizumab resulted in a complete response in seven of the patients and a partial response in five.

Dr. Folkman asked whether IL15 counteracts the vascular leak syndrome of IL2. Dr. Waldmann answered that he had not looked at that specifically. His group has looked for vascular leak as a comparison dose by paired dose and found that at a dose above the effective dose, IL15 does not cause capillary leak syndrome in mice.

Dr. Coffey commented that estrogens have an effect on autoimmunity and asked if they have an effect on the IL2 and IL15 system. Dr. Waldmann answered that Dr. Lou Staudt would address this later in the meeting. He added that the gene encoding IL15R alpha is expressed discordantly in women. He also mentioned work on a soluble IL15R alpha assay that could be used to assay activation of IL15R alpha anywhere in the body and to determine whether it is elevated in autoimmune diseases; if so, IL15R alpha could be a target for receptor-directed therapy.

Dr. Coffey mentioned that nanotechnology particles often travel to the spleen, and asked if anyone had studied whether this has an effect on the immune system or the spleen. Dr. Waldmann answered that he had not examined this.

A Promising Candidate To Enhance Vaccine Efficacy Against Cancer and HIV: IL15. Dr. Berzofsky stated that CD8 killer T cells, or cytotoxic T lymphocytes (CTLs) kill virus-infected cells to prevent the virus from spreading to other cells, thus avoiding infection. CTLs also can kill cancer cells and cause tumor regression, but high avidity and a long-lived memory are required for this. Activation of CTLs requires presentation of antigen by a Class 1 MHC, such as an HLA molecule, or a professional antigen presenting cell, such as a dendritic cell. For optimal activity resulting in long-lived memory CTLs, the dendritic cell must be activated by CD4 helper T cells, which recognize a different antigen presented by the Class 2 MHC molecule on the dendritic cell. Dr. Berzofsky addressed the role of IL15 made by dendritic cells or provided by a vaccine in mediating help and inducing high avidity and long-lived memory CTLs.

To determine the effect of IL15 on T cell activity after vaccination, mice were vaccinated with vaccinia recombinants expressing the HIV envelope protein alone or the envelope protein and IL15. Up to 14 months after vaccination (even though the vaccinia had been cleared within the first month), CTLs in the group immunized with envelope protein + IL15 showed tenfold higher avidity than the group vaccinated with vaccinia expressing the HIV envelope protein alone. Functional avidity includes the thermodynamic affinity of the T cell receptor as well as the density of the T cell receptor and the CD8 co-receptor. High avidity cells are more effective at clearing a viral infection because such cells can recognize recently infected cells that express very little viral protein, thus killing the infected cells earlier and avoiding the viral replication cycle. Transferring high and low avidity CTL lines to immunodeficient SCID mice showed that the high avidity CTLs resulted in a three log reduction in virus titer, whereas the low avidity CTLs had no effect, despite the ability of the low avidity CTLs to kill virus-infected cells *in vitro*. A similar effect was observed for the killing of tumor cells.

A goal of this work is to use a vaccine to selectively induce high avidity CTLs. The discovery that IL15 can increase CTL avidity will aid this work; however, the mechanism by which IL15 increases avidity must be understood. Flow cytometry experiments showed that high avidity cells express the IL15 receptor alpha chain at levels five- to tenfold higher than low avidity cells. If IL15 induces homeostatic proliferation, the high avidity cells, with their higher levels of receptor, would undergo proliferation at a higher rate. Using a dye that allows monitoring of the number of cell divisions, it was found that 87 percent of the high avidity cells had undergone proliferation, compared to half as many of the low avidity cells. It also was determined that high avidity cells become dominant in the population because they survive longer than the low avidity cells. A second mechanism by which high avidity cells become predominant involves upregulation of the coreceptor, CD8, by IL15. High avidity T cells are more responsive to IL15 and thus undergo a 2.5-fold increase in CD8 expression. CD8 expression contributes to functional avidity, thus further increasing the avidity of the high avidity cells. In summary, expression of IL15 in a vaccine results in selection for cells with high levels of IL15 receptor alpha chain, increasing the sensitivity of these cells to endogenous levels of IL15 even in the absence of antigen. This results in both selection at the population level to increase survival and homeostatic proliferation, increasing the average avidity of the population, and induction at an individual cell level of increased CD8 expression, which contributes to higher avidity.

Another aspect of enhancing vaccine efficacy is maintenance of long-term memory cells. Comparison of three vaccinia viruses expressing antigen alone, or also expressing IL15 or IL2 showed that mice receiving IL15 had persistence of long-term memory at a higher level for as long as 14 months;

this can be attributed to selection for cells that express higher levels of IL15 receptor alpha and therefore undergo greater homeostatic proliferation.

Helper T cells, which upregulate dendritic cell co-stimulator molecules and induce expression of IL15, also are necessary for the development of long-lived memory CD8+ T cells. This process involves presentation of antigen to the T cell receptor and IL15 to the CTLs by the same dendritic cell; a recombinant vaccinia virus expressing both the antigen and the IL15 to the same cell mimics this process. To test whether this was the mechanism by which helper cells mediate induction of long-lived memory cells, mice undepleted or depleted for CD4 cells were examined a year after immunization for numbers of antigen-specific cells. The CD4-depleted group did not have long-term memory cells. However, if the CD4-depleted mice were immunized with a vaccinia virus that also expressed IL15, long term memory persisted for a year, indicating that IL15 can functionally replace CD4 helper cells. The mechanism by which IL15 mediates production of long-term memory cells involves IL15 blockage of TRAIL-mediated apoptosis of CD8+ T cells that have not received help from CD4 cells, and thus usually undergo apoptosis upon secondary encounter with antigen. Knockout experiments showed that IL15 knockout dendritic cells that present antigen cannot mediate help, demonstrating that IL15 is both necessary and sufficient for the mechanism by which helper cells naturally mediate induction of long-lived memory.

This work has shown that including IL15 in a vaccine induces longer lived memory CD8+ CTLs and induces higher avidity CTLs. This results in higher efficacy for vaccines directed against viral infection and cancer vaccines. Including IL15 also overcomes the need for CD4+ T cell help, which could be significant in AIDS or cancer patients with deficiencies in these cells. IL15 thus is a critical natural mediator by which CD4+ T helper cells elicit long-lived CD8+ memory T cells. Responsiveness to IL15 can account for CTL avidity and maturation through selected survival of high avidity CTLs and induction of CD8 co-receptor expression. IL15 is therefore a promising candidate to enhance the efficacy of vaccines for use in HIV-infected or cancer patients with CD4+ T cell deficiencies.

Questions and Answers

Dr. Coffey raised the issue that fever can be a part of fighting infections. When genetically engineered vaccines are given during some trials, the patient develops a fever, and the patient is treated with aspirin to lower the fever. He asked whether Dr. Berzofsky had looked at the effect of temperature on immunotherapy. Dr. Berzofsky answered that his group had not yet studied this, although it is worth examining because fever clearly has a physiologic function in fighting infection.

Dr. Prendergast commented that *ex vivo* dendritic cell generation with subsequent re-infusion for immunotherapy could be a powerful adjuvant. For example, using peptides or epitopes to evoke a response in prostate cancer has not been greatly successful, but IL15 could be an important component of such therapeutic approaches. Dr. Berzofsky agreed and said that his group has been working on developing methods to circumvent the problems associated with cancer vaccines, such as weak response. It is clear that cancer vaccines can induce killer T cells specific for tumor antigens, but cancer eradication is much more difficult. Inducing higher avidity cells and longer lived memory cells with IL15 could be an important component of this work. Another important component currently being studied is blocking negative regulatory pathways. For example, his group has found a new negative regulatory pathway involving NK T cells that make IL13, which induces TGF beta production that blocks the cytotoxic T cells. His group is trying to develop a "push-pull" approach, in which they attempt to "push" the response by adding cytokines, co-stimulatory molecules, and other adjuvants to enhance the response, and then "pull" by trying to remove barriers to the efficacy of the response, such as negative regulatory cells or negative regulatory molecules such as CTLA4. He speculated that a combination of these approaches

will likely be critical to develop an effective strategy for a cancer vaccine and probably also for a therapeutic vaccine against HIV infection.

Dr. Prendergast asked about using B7H1, 1, 2, 3, or 4 in immunotherapy. Dr. Berzofsky clarified that Dr. Prendergast was asking about PD1 ligands and agreed that these could be important components of immunotherapy. He commented that Dr. Rafi Ahmad's group has shown that the so-called clonal exhaustion of the CD8 cytotoxic T cells seen in chronic viral infection can be overcome by blocking PD1 or its ligand. Dr. Berzofsky's group has set up a collaborative agreement with Drs. Gordon Freeman and Arlene Sharpe at Harvard University; they have monoclonal antibodies to these molecules and also knockout mice.

X. CENTER FOR CANCER RESEARCH: PROFILING AND GENE REGULATION—DRS. LEE HELMAN, LOUIS STAUDT, HOWARD FINE, AND KARLYNE M. REILLY

Dr. Lee Helman introduced three presenters—Drs. Louis Staudt, Deputy Chief, Metabolism Branch, CCR; Howard Fine, Chief, Neuro-Oncology Branch, CCR; and Karlyne M. Reilly, Head, Genetic Modifiers of Tumorigenesis Section, Mouse Cancer Genetics Program, CCR—who described the CCR's work in profiling and gene regulation.

Towards Routine Molecular Diagnosis in Clinical Oncology. Dr. Staudt began the presentation with the idea that diagnosis might or might not be easy, but that a wrong diagnosis leads to a wrong treatment. Gene expression profiling is needed to: 1) provide reproducible, quantitative diagnoses for all cancer patients; 2) clarify diagnostic distinctions that are problematic using current methods; 3) deliver newly defined molecular diagnoses that influence treatment choice and/or prognosis; 4) translate insights from therapeutic trials that incorporate molecular profiling; and 5) promote excellence in clinical science.

Dr. Staudt drew on the work of the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) as an example of gene expression profiling. The NCI started the LLMPP, which includes intramural and extramural programs, to establish a molecular classification of human lymphoid malignancies and define molecular correlates of clinical parameters that are useful in prognosis and in the choice of optimal therapy. There are many human lymphomas, including follicular, mantle cell, Hodgkin's, primary mediastinal, diffuse LBCL, and Burkitt. Making the correct diagnosis of lymphoma is a key to getting the right treatment as each type can react differently to various interventions; Burkitt lymphoma, for instance, requires a different kind of high dose therapy than other lymphomas.

The LLMPP has worked to improve the accuracy and reproducibility of diagnoses by focusing on the distinction between diffuse LBCL and Burkitt lymphoma. Dr. Staudt presented graphs and charts that showed the project's use of gene expression to differentiate Burkitt lymphoma from all subgroups of diffuse LBCL. A molecular classifier was built with 100 percent, or near 100 percent, accuracy in diagnosis of classic Burkitt lymphoma and diffuse lymphomas, respectively. Further analyses of samples reclassified by a hematopathology panel led to the idea that these were discrepant cases that were difficult to classify according to current pathologic methods, and clinical behavior was studied through the use of a CHOP-like chemotherapy and various intensive chemotherapies, including those associated with autologous stem cell transplant. Based on this work, it is believed that one-sixth of the true Burkitt lymphomas is misdiagnosed by current methods and, therefore, would be under-treated by CHOP chemotherapy. For this reason, a molecular diagnosis of Burkitt lymphoma likely will improve patient outcome by optimizing the choice of therapy.

Gene expression profiling also can help clarify the diagnosis of problematic cases. For example, it can assist in defining new molecular subgroups that are invisible by current techniques, such as in the case of diffuse lymphoma, which is the most common type of non-Hodgkin's lymphoma. Approximately one-half of the 23,000 new diagnoses per year in the United States are cured, leaving a large burden of death of about 10,000 per year. Studies of this disease in terms of its molecular characteristics and pathways that it relies upon for proliferation and survival have led to the conclusion that there are three molecularly and clinically distinct diseases involved: a common type called germinal center B cell-like diffuse lymphoma, that has a gene expression profile like that of a normal germinal center B cell; a second common type, called the activated B cell-like diffuse lymphoma (which lacks germinal center genes and its own signature of genes that it shares with mitogenically activated blood B cells); and a third type primary mediastinal lymphoma, that strikingly and unexpectedly is shared by Hodgkin's lymphoma, a very different histological disease. The distinctions account for some of the differences seen in response to CHOP chemotherapy, with germinal center type and primary mediastinal type having a 60 percent 5-year survival and the activated type only a 30 percent 5-year survival. Analyses of the oncogenic abnormalities also have confirmed that these are different diseases; in particular, they use different pathways to prevent programmed cell death. The NF kappa B pathway has been found to be constitutively stuck in the "on" position in the activated type of primary mediastinal type, but not in the germinal center type. The NCI is working with the pharmaceutical industry regarding an antiapoptotic pathway in the cells that relies on a key kinase complex to I kappa B kinase. A small molecule inhibitor of this kinase has been found to kill the cell lines of the activated type of diffuse lymphoma, but not the germinal center lymphoma cell lines. Future clinical trials could investigate whether there is a differential response of diffuse lymphoma patients to such inhibitors.

Dr. Staudt next discussed molecular predictors of outcome in cancer using gene expression profiling. Statistics have been used to develop a gene expression-based survival predictor score that is used to rank and divide patients into four quartile groups, followed by analyses of group survival rates. Within a current diagnostic category, gene expression profiling can identify heterogeneity in cell of origin, oncogenic pathways, and common cellular functions (such as proliferation, survival, and cell-cell interactions); this heterogeneity is present in the tumor at the time of diagnosis.

The LLMPP is working to translate these findings into routine clinical use, particularly through the development of a lymphoma diagnostic microarray using the Affymetrix platform. A total of 515 lymphoma samples were diagnosed by gene expression profiling; aggressive lymphomas were grouped together, divided into three types of diffuse lymphoma as well as Burkitt lymphoma, distinguished from benign conditions, and profiled by the microarray. NCI's Specialized Program for the Evaluation of Cancer Signatures (SPECS) also was utilized in the process. Phase 1 of the project is to examine 2,000 retrospectively ascertained and consecutively ascertained samples of various types of non-Hodgkin's lymphoma, Hodgkin's lymphoma, benign conditions, and other cancers in the lymph node. Phase 2 focuses on generating data for regulatory approval. The NCI recently signed a collaborative agreement with Roche Molecular Systems to partner in the development of this technology and assist with the regulatory approval for diagnostics.

To match changes in cancer treatment, molecular diagnoses will evolve as gene expression profiling works on a need-to-know basis. It is expected that clinical trials would have gene expression profiling incorporated into them, and a new diagnostic would be made based on the outcome of that trial and then brought to the patient's use; this process currently is occurring in a cooperative trial sponsored by the Cancer and Leukemia Group B (CALGB) cooperative group.

Questions and Answers

Dr. Coffey asked whether the arrays are adjusted for age. Dr. Staudt replied that age is a clinical parameter that is important for response to and survival from diffuse lymphoma, but it does not have a known genetic signature that can be matched by the gene expression; there are, however, correlates of clinical parameters.

Dr. Folkman asked about the frequency of a recurrent tumor changing its molecular profile. Dr. Staudt said that most of what is seen in cancer is a stable phenotype and a molecular profile that changes very little. A lymphoma changing to a leukemia likely means that certain chemokine receptors are changed.

Dr. Koch asked why Dr. Staudt chose to work on lymphoma/leukemia, as opposed to other cancers, and whether this approach will be applied to other cancers in the near future. Dr. Staudt indicated that he worked on B cell lymphoma in graduate school and thereafter. He noted that there are many current efforts to bring various molecular diagnoses into cancer studies, particularly into studies of breast cancer. This approach is producing equally good outcomes in breast and other cancers as it is with leukemia.

Dr. Chabner wondered if any insights gained from looking at the gene profile would lead to therapeutic ideas for poor prognosis tumors. Dr. Staudt clarified that genetic expression researchers do not consider prognosis in the same way as a clinician. He confirmed that researchers in molecular diagnostics are systematically examining genes, such as through a systematic RNA interference-based method, to help identify future interventions for a poor prognosis tumor. Dr. Niederhuber added that next steps would involve honing down where the genetic differences are, specifically as reflected in the pathway.

Dr. Prendergast asked Dr. Staudt to comment on the term "standard of care." Dr. Staudt replied that standard of care in the new age would involve a therapy that was based on the molecular characteristics of the tumor. Molecular profiling can add great value in this regard in clinical trials; it is the beginning of an evolution that bundles diagnostic tests with therapeutics. Dr. Everson commented that, in applying any of these technologies at the patient level, reimbursement could bring an added complication.

Malignant Gliomas: A Neural Stem Cell Gone Bad. The Biological and Therapeutic Implications of a Changing Program. Dr. Fine first described the mission of the Neuro-Oncology Branch and then focused on the Branch's efforts in translational research. The Neuro-Oncology Branch is one of the few disease-based programs within the CCR. It also is unique because it is a joint effort between the NCI and the Neurologic Institute. Its mission is to partner with the extramural community and the private sector to develop new therapies for children and adults with brain tumors by leveraging the resources and scientific freedom available from NCI's intramural program. Brain tumors are the number one leading cause of cancer death in children and about the fourth leading cause of cancer death in people under the age of 60. The most common type of brain tumor is glioblastoma. There has been little improvement in the treatment of this disease during the last 3 decades, with the median survival of diagnosed patients being approximately 1 year. Novel therapeutic approaches are needed desperately.

Dr. Fine provided an overview of some of the Neuro-Oncology Branch's current programs, including the Clinical Trials and Drug Development Program and the Drug Development Program for Gliomas. The Branch has activated 43 IRB-approved trials for primary brain tumors; more than 5 years ago, there were no such trials; this robust clinical research program is supported by a busy clinical

program. The Glioma Molecular Diagnostic Initiative (GMDI) is an important program aimed to create a publicly accessible Web-based glioma database, and informatics platform consisting of indepth pathologic, molecular, and genetic data with detailed clinical corollary data for hundreds of brain tumors. This involves a national study to accrue more than 1,000 patients to find new molecular targets. To work with millions of data points from collected biospecimens, the GMDI is using the Repository of Molecular Brain and Neoplastic Data (REMBRANDT) program. The GMDI has completed a retrospective study that involved the molecular characterization of more than 300 gliomas. A prospective study has produced the Branch's first 350 glioma tissue array and accrued more than 400 patients nationally to the trial. REMBRANDT is a mechanism to allow rapid data integration across these disparate data sources from gene expression profiling, SNP arrays, clinical data, and pathology. The REMBRANDT Web site is now accessible, contains comparison and visualization tools, and includes a user interface that allows bioinformaticians and clinicians to traverse seamlessly between genomic and clinical data to produce an integrated analysis. REMBRANDT was awarded the Congressional Service to America Award for Science and Technology in 2006.

Regarding malignant gliomas and neural stem cells, Dr. Fine explained that the premise has been that the efficient development of rational kinds of therapy depends on the knowledge of tumor pathogenesis, pathophysiology and predictive clinical models. A new paradigm is being considered, as astrocytes and glioblastoma cells have very little in common, but gliomas and normal neural stem cells have similar self-renewal capabilities, immortalization potential, proliferation, and the capability of generating a heterogeneous cell population. Gliomas may be a stem cell disease and, therefore, glioma or tumor stem cells may represent a more accurate preclinical model of human tumors than the traditional cell lines. The Neuro-Oncology Branch's work on this recently has been published in *Cancer Cell*.

The hypothesis was that most stem cells, including neural stem cells, terminally differentiate when they are exposed to serum. The study compared two populations of matched cells for various properties, such as tumorigenecity, differentiation potential, molecular and genetic phenotyping, and gene expression profiling. It found that NBE cells represent a subpopulation of cells within primary human gliobastomas (GBMs) that have properties similar to tumor repopulating cells, including: 1) similar gene expression profile to primary GBM; 2) clonogenic *in vitro*; 3) tumorigenic *in vitro*; and 4) NBE tumors *in vivo* are phenotypically similar to primary GBMs. In short, NBE cells are tumor stem cells. Important questions raised by this research include: 1) Are truly relevant molecular pathways being targeted when studying glioma cell lines? 2) Are important pathways of tumorigenicity being missed by not studying TSCs? 3) Will TSCs provide to be a more reliable pre-clinical model for study GBMs than glioma cell lines? Several programs are beginning to look at some of these issues, including collaborative efforts between the NCI and the Broad Institute at the Massachusetts Institute of Technology (MIT) and Harvard, and a tumor stem cell bank that is being established at the NIH.

Questions and Answers

In response to a question regarding the state of stem cell research for all solid tumors, Dr. Fine said that it is a multi-disciplinary arena and that the hematopoietic field is leading the way.
Dr. Niederhuber added that parallel models are being used in breast, prostate, and colon cancer research.
Dr. Folkman wondered whether NBE is unique to neural stem cells or usable across other stem cells.
Dr. Fine noted that it is not known what normal breast (or prostate, for example) stem cell is, so it is unknown whether NBE would be the correct media for those cells. Dr. Niederhuber stated that the current knowledge is that breast will grow in that mammosphere like the neurospheres in the same way, and a lot of the culture media conditions drive cells towards differentiation.

Ms. Lydia G. Ryan, Service Line Clinical Director, AFLAC Cancer Center, expressed her enthusiasm for the work completed so far, particularly the work done in moving REMBRANDT from concept to its current level of use. She noted that this is a good example of collaboration between the intramural and extramural program.

Deciphering the Genetic Barcode of Cancer Susceptibility Using Mouse Models of Astrocytoma, MPNST, and NFI. Dr. Reilly described NCI-supported research on the basic biology of tumors. The fundamental issue is to understand why a particular individual in any population develops cancer, whether because of genetic, diet, environmental, or other factors. Dr. Reilly described the research work being conducted on inherited predisposition as a risk for developing particular cancers.

Cancer is a process of accumulating genetic mutations. Two tumor suppressor genes, the NF1 gene and the p53 gene, for example, are involved in transforming astrocytes into astrocytomas and Schwann cells into malignant peripheral nerve sheath tumors and recent data from Dr. Reilly's lab has shown that modifier genes affect this process. The formation of cancer depends on high-penetrance cancer mutations (rare mutations with powerful effects), low-penetrance modifier genes (common variants with partial effects), and imprinted genes (genome modifications inherited from one parent or the other). Dr. Reilly described work being done using a mouse model of neurofibromatosis to look at the interaction between these different genetic factors on how it affects risk for cancer. Mutations in *Nf1* and *p53*, which are high-penetrance tumor suppressors, for example, predispose individuals to developing particular cancers depending on background modifier genes. Knowledge of a single specific modifier genotype, however, is not predictive, due to the complex interactions of high-penetrance cancer genes, low-penetrance cancer genes, and epigenetic effects. Each of these genetic factors contributes unique information like the bars in a barcode. Some cancers that appear to be sporadic may be the result of a more complicated genetic "barcode," and the layering on of different genetic information make them rarer. Understanding these "barcodes" likely will provide insight into the mechanism of tumorigenesis and may suggest new therapies.

Dr. Reilly noted that in this research a mouse model of familial cancer was used to decipher susceptibility codes that would be too complex to study in sporadic human cancer, but will give insight into general cancer susceptibility. The mouse has a shorter life span, its breeding can be controlled to better understand the genetic background, and the variables of diet and environment can be eliminated. Neurofibromatosis, a common genetic disease, was studied due to its known genetic variability affecting cancer development. It is valuable in cancer studies as it is 100 percent penetrant (i.e., every individual with a mutant *NF1* gene will have the disease), but individuals are variable in how they have the disease. Different phenotypes can exist even within a family; siblings raised in the same environment with the same mutation in *NF1* will still have a more variable disease from each other than monozygotic twins who are genetically identical. The study used *Nf1* mutations in combination with *p53* because *p53* has been shown to be mutated in the transformation of neurofibromas into malignant peripheral nerve sheath tumors. The study found that epistatic and combinatorial effects can mask the genetic component of cancer susceptibility and an imprinted gene(s) near to the Nf1 gene and p53 gene can change what tumors form depending on whether Nf1 and p53 mutations are inherited from the mother or the father.

Mouse models of cancer and human familial cancer syndromes are useful to dissect the components of cancer susceptibility. Modifiers can be mapped by using mouse genetics, taking advantage of the different strains and the SNPs between the different strains to generate backcross progeny mice. This isolates the location of modifiers by allowing a correlation to be drawn from genotypes to the modified phenotype. Chromosome substitution mouse strains are another helpful tool in which all the chromosomes are from one genetic background strain except for one, which is from the strain of interest. These chromosome substitution strains were used to show that different modifier genes

affect resistance to tumors by different mechanisms.

Dr. Reilly noted that mouse models can help with the translational pipeline and described a high throughput screening process using a dual luciferase reporter system to test anti-tumor compounds. Mouse tumor cell lines are useful surrogates for human cell lines in preclinical drug testing and allow testing in immune-competent animals. This has been seen through a collaborative effort with the Molecular Targets Development Program, which has identified a compound called Schweinfurthin A that was derived from a plant found in the Congo; mouse lines are equally sensitive to this drug as human cell lines, and this drug has no effect on normal mouse astrocytes in culture suggesting it will be less harmful to normal cells in patients. Furthermore, brain tumor-specific therapeutics may provide a new, more effective approach for the treatment of astrocytoma and glioblastoma.

Questions and Answers

Dr. Coffey asked whether a change in the animal's diet affected the incidence of cancer, as folate can change some methylation patterns. Dr. Reilly said that her laboratory has not yet studied this.

Dr. Folkman pointed out that Dr. Michael Green (*Science*, August 2006) showed that when *p53* was mutated or deleted, endostatin expression levels dropped, the tumors rose, and that this could be bypassed if the enzyme was replaced and the endostatin was mobilized. Dr. Reilly mentioned that Dr. Roger Reeves would like to test this precisely in the model. She also said that, regarding epigenetics, the model she described is not necessarily a change in methylation.

Dr. Prendergast wondered to what extent epigenetic patterns are genetically driven. Dr. Reilly responded that this is unknown, although the assumption is that they are genetically driven.

Dr. Niederhuber expressed his appreciation for the CCR's work.

XI. 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 552(b)(c)(6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Members were instructed to exit the room if they deemed 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.

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

FRIDAY, DECEMBER 1, 2006

XII. PROGRAM REVIEW OF DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS: MELDING EPIDEMIOLOGY AND GENOMICS—DRS. JOSEPH F. FRAUMENI, JR., ROBERT N. HOOVER, MONTESERRAT GARCIA-CLOSAS, AND STEPHEN CHANOCK

Dr. Joseph F. Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), described NCI's efforts in melding the disciplines of epidemiology and genomics. He was joined in the presentation by Drs. Robert N. Hoover, Director, Epidemiology and Biostatistics Program, DCEG; Montserrat Garcia-Closas, Investigator, Hormonal and Reproductive Epidemiology Branch, DCEG; and Stephen Chanock, Director, NCI Core Genotyping Facility.

From High-Risk Families to Populations. There is a growing consensus in the scientific community that now is the time to incorporate the increasingly powerful genomic tools into epidemiologic strategies designed to uncover the gene variants that contribute to cancer susceptibility in the general population. Dr. Fraumeni noted that NCI intramural scientists are working together with extramural scientists to develop the approaches that integrate epidemiology and genomics in ways that will accelerate progress on a national and international scale.

In the 1960s, the NCI epidemiology program launched an interdisciplinary research initiative in familial and genetic forms of cancer. A multicenter study of Wilms tumor revealed a remarkable association with a pattern of malformations that featured congenital aniridia; the syndrome subsequently was linked to a chromosome deletion that led to the discovery of the Wilms tumor gene, WT1. Another early study at NCI described a series of families prone to a wide variety of cancers, including sarcomas, breast cancer, and other tumors occurring in children and young adults; this observation countered the prevailing dogma at the time, which held that familial occurrences of cancer were limited to single forms of cancer. A long-term follow-up project then identified and characterized 24 families with this rare but devastating syndrome (subsequently called Li-Fraumeni syndrome) and showed that it was dominantly inherited and featured sarcomas of bone and soft tissue, breast cancer, brain tumors, leukemia, and adrenocortical tumors, among others, leading to the discovery of inherited mutations of the p53 gene. In addition, long-term followup studies of children with hereditary retinoblastoma caused by germline mutations of RB1 revealed a striking predisposition to second primary cancers, particularly sarcomas both inside and outside the radiation fields, as well as melanoma and other tumors.

A number of other familial tumor suppressor genes were discovered between 1986 and 1996 and involved the intramural research program. The NCI along with NINDS contributed families with neurofibromatosis 1 and 2 to laboratories that identified and cloned the genes, NF1 and NF2. NCI staff also discovered genes responsible for the von Hippel-Lindau syndrome and other hereditary forms of renal cancer. In familial melanoma, NCI staff uncovered germline mutations in the tumor-suppressor gene CDKN2A, which encodes p16, as well as mutations of the proto-oncogene CDK4. Familial breast cancer research at NCI focused on the Ashkenazi Jewish population and shed light on the effect of founder mutations of BRCA1 and BRCA2. Finally, specimens from families with multiple basal cell carcinoma syndrome led to the discovery by NCI staff of germline mutations of the patch gene. There are now at least 50 cloned genes or classes of genes that predispose to hereditary cancer syndromes.

Although studies of high-risk families have led to the identification of high-penetrant gene mutations, epidemiologic studies of common forms of cancer are the primary means of detecting low-penetrant gene variants that predispose to cancer in the general population. It is possible to distinguish mutations from polymorphic gene variants by their characteristics, including degree of penetrance,

absolute/relative risk, attributable risk, gene frequency, the number of genes involved, the role of the environment, the target tissue affected, and study design.

Despite the recent shift in emphasis from family-based to population or association studies, it is important to continue the study of cancer-prone families, which have provided so many critical insights into the genetic and molecular underpinnings of cancer. Further study of hereditary syndromes will make it possible to identify previously unrecognized mutations, as well as modifier genes that affect penetrance or expression. To accelerate progress in gene discovery, international consortia of investigators including NCI intramural staff are collaborating on the study of several hereditary syndromes, including familial melanoma, testicular cancer, and chronic lymphocytic leukemia.

Questions and Answers

Dr. Folkman asked whether a small group of tumor suppressor or other genes that affect a broad spectrum of tumors could be defined in addition to p53 mutations in Li-Fraumeni syndrome.
Dr. Fraumeni responded that the mismatch repair genes predispose not only to hereditary non-polyposis colorectal cancer but also to cancers of the endometrium, ovary, stomach, bile duct, and urinary tract. In addition, mutations of the *p16* and *BRCA2* genes appear to predispose to various tumors, including breast cancer, melanoma and pancreatic cancer, while RB1 mutations in hereditary retinoblastoma predispose also to sarcoma, melanoma and other cancers.

Key Epidemiologic Challenges. Dr. Hoover discussed the coordinated approaches that were developed at the NCI to overcome the obstacles and accelerate the detection of susceptibility genes and the gene-gene and gene-environment interactions involved both in cancer induction and progression. There has been great enthusiasm for the idea that detecting susceptibility genes will allow the detection of susceptibility in general, gene-environment interactions, and previously unrecognized carcinogens. The main observation from the last 10 years of research in this area is numerous false positive findings that do not replicate in subsequent studies. For example, more than 100 epidemiologic studies have been conducted on smoking and breast cancer, with inconsistent results. Since 1995, 50 studies have examined this relationship in relation to 11 susceptibility genes; recent meta-analysis, however, reveals methodologic limitations (e.g., small sample size, the role of chance, and opportunities for bias) that need to be addressed.

Regarding study size, very big studies with adequate statistical power are needed to detect gene-environment interactions; this likely would entail more than 1,000 cases and 1,000 controls. With respect to the role of chance, basic statistics explain that, with more associations examined in a particular study, the likelihood of finding something statistically significant will increase—and most findings will be false positives. With around 24,000 genes in the human genome and 3 billion base pairs in the human haploid genome, there are 8 million or more common SNPs and, theoretically, any one of these could produce a susceptibility variant. In a gene-environment interaction involving the simplest genetic pathway consisting of two genes and 10 SNPs, to characterize each would require more than 1,300 comparisons to be made. Sorting one or two real and biologic interactions from among an estimated 70 false positives requires replication through several large studies. Bias includes all artifacts that can creep into studies to provide the wrong answer by virtue of design or analysis, and genetic association studies are not immune from the kinds of bias that can be present in environmental studies.

To overcome these and other challenges in gene-environment studies, the following are needed: very large studies; planned and coordinated replication; rigorous, high-quality study design, conduct, and analysis that applies to genomics and epidemiology; and data sharing. To help move this forward, there is an emerging new research paradigm supported by the NCI. This involves consortia of epidemiologists,

clinical, and molecular scientists who collaborate intensely using common protocols and methods, and providing coordinated parallel and pooled analyses. These consortia have developed the means to actually share data.

The Cohort Consortium includes more than 30 large population cohorts, nearly 3 million individuals, and more than 1.5 million DNA samples collected at baseline. It is in the process of conducting studies on breast and prostate cancer looking at 53 genes in steroid hormone and growth factor pathways, as well as genome-wide association studies. An example of current success is the work of the International Lymphoma Epidemiology Consortium (InterLymph), a member of the Cohort Consortium; 21 members of InterLymph are conducting studies that involve more than 18,000 cases of non-Hodgkins lymphoma. Dr. Hoover also illustrated the power of this consortial approach through a NCI-SEER study of the *IL1B* variant using 4,000 cases and 4,000 controls; the study did not report a protective element to this variant. In the absence of this consortium, however, likely German researchers would have reported a statistically significant positive association, and Spanish and other researchers would have reported different findings. Without the consortium, it would have taken years before the conclusion was reached that this is not a good candidate on which to follow up.

In conclusion, there are exciting, unprecedented opportunities for insights into genetic pathways and environmental interactions to determine health and disease. There are daunting, unprecedented challenges to exploiting these opportunities. Emerging science and research paradigms are allowing researchers to overcome these challenges.

Questions and Answers

Dr. Bruce Chabner asked whether other studies with expression profiles showing subsets of disease, such as the multiple forms of diffuse B cell lymphoma, are being incorporated into the Cohort Consortium's research. Dr. Hoover affirmed that this is happening. Dr. Don Coffey said that it is important to consider flora as an epidemiological factor in disease, particularly if it involves processing both the carcinogen and the protective agent. Dr. Meneses asked about the major challenges involved in ensuring that researchers collaborate and share data. Dr. Hoover replied that the scientists put aside their competitive issues, and that the greatest obstacle was combining the new paradigm with existing academic and funding systems.

Dr. Coffey suggested that the NCI should develop a special system to award these individual teams that are uncovering and sharing data. Dr. Runowicz noted that determining the criteria for team science would be a good topic for the NCAB Clinical Investigations Subcommittee to discuss. Dr. Barker added that The Cancer Genome Atlas (TCGA) project has been working to integrate biologists and technologists; both parties have recognized that the integrated dataset being developed through their joint efforts is important as a whole new source of discovery for R01 investigators.

Dr. Runowicz asked about the possibility of the *IL1B511* variant as biologic or artifact. Dr. Hoover commented that all of this variation is consistent with chance. Dr. Coffey queried whether a technique was being developed to better determine the relevance of variants. Dr. Hoover replied that the idea of large studies with immediate coordinated replication is an important answer.

Clues from the Pathway-Driven Approach. Dr. Garcia-Closas presented clues that were derived from the pathway-driven approach in which large-scale epidemiologic breast and bladder cancer studies have focused on the risks associated with candidate genes selected on the basis of their known function or biological plausibility. The technologies have become increasingly robust and now enable the entire genome to be interrogated in the search for genetic effects.

Approximately 5 percent of breast cancers occur with strong familial aggregation, and their etiologies may be driven by high penetrance mutations in breast cancer susceptibility genes. The other 95 percent are considered to be sporadic and may be linked to various environmental exposures, such as reproductive history, exogenous hormones, obesity, alcohol intake, and physical activity. Pathways of interest in breast cancer include established or possible risk factors (e.g., environmental exposures), carcinogenic processes, gene expression studies, and somatic mutations. During the past 10 years, the identification of genetic susceptibility factors has remained a challenge. The Breast Cancer Association Consortium (BCAC) recently was formed; it includes 20 studies involving 28,000 cases and 30,000 controls.

The first BCAC study was a pooled analysis of 20 candidate SNPs that have been evaluated in at least three studies in the consortium. This work showed no evidence for a main effect association for 11 of those candidate genes, and the remaining 9 SNPs revealed promising evidence for an association with breast cancer risk. Additional genotyping showed strong evidence that a polymorphism in one of the candidate genes resulting in an amino acid change, the CASP8 D302H polymorphism, offers decreased breast cancer risk. This is the first common variant with convincing evidence of such an association, but the functional consequences of the variant are unclear.

Bladder cancer is a good model to evaluate genetic susceptibility because it has a homogeneous histology, which makes it an easier cancer to study; it is a chemically induced cancer with tobacco smoking and occupational exposure to aromatic amines accounting for more than 50 percent of bladder cancer cases in males; the genetic variation and the functional consequences of the variation in carcinogen metabolism are well understood; and there is familial aggregation that is not yet explained. Bladder cancer is more common in more developed than less developed countries. Because Spain has one of the highest incidences in the world, it was the site of a case control study that recruited about 1,200 cases and 1,200 controls; this was one of the largest molecular epidemiology studies of bladder cancer.

Carcinogen metabolism is been an important candidate pathway for bladder cancer, in addition to pathways involved in the defense against DNA damage cause by carcinogens, such DNA repair and cell cycle control, as well as genes involved in tumor development and growth. The NAT2 and GSTM1 genes are strong candidate genes for bladder cancer based on their role in the metabolism of carcinogens. Meta-analyses of previous small studies suggested associations with bladder cancer risks, but there were concerns about publication bias and the heterogeneity of findings across studies; there also was strong biological plausibility for an interaction with smoking, particularly with NAT2, which detoxifies aromatic amines that have a known association with bladder cancer. The Spanish bladder cancer study used a sufficiently large sample size to help confirm the association between these variants and bladder cancer risk. About 50 percent of the patients have the slow acetylation genotype, which results in a decreased ability to detoxify aromatic amines, and they are at increased risk of developing bladder cancer. Similarly, about 50 percent of these individuals have a double deletion in the GSTM1 gene, resulting in a lack of enzyme activity; those subjects also exhibited an increased risk. There also was a stronger effect of smoking on bladder cancer risk for NAT2 slow than rapid acetylators.

Dr. Garcia-Closas next described how developments in genotyping technology have facilitated large-scale evaluation of candidate genes for cancer. A recent study evaluated approximately 1,400 variants in about 386 genes for associations with bladder cancer risk in the Spanish Bladder Cancer Study. The most notable finding was from a variant in the 5' untranslated region (UTR) of the vascular endothelial growth factor (VEGF). This initial finding was followed up with a detailed characterization of genetic variance at this locus. In addition to the finding in the 5' UTR, three other variants in the promoter region were found to be associated with similar increases in risk; this was limited to subjects

who carried the homozygous variant genotype. A bladder cancer study has been recently completed in New England, which has some of the highest incidences of bladder cancer for both males and females in the United States; exposures specific to males, such as occupational exposures, are unlikely to explain these high incidences in these areas.

Work in this arena is starting to identify associations unlikely to be false positives. This is possible through large, good quality individual studies; collaborative efforts through consortia; and robust, affordable genotyping technology. Most of the work conducted so far has been on candidate pathways based on current knowledge of the etiology or the biology of cancer; researchers are moving toward finding candidate genes using an approach through genome-wide scans.

Questions and Answers

Dr. Judah Folkman mentioned the recent finding that the angiogenesis regulatory molecules, especially VEGF and PDGF, are scavenged by the platelets from plasma and are stored in alpha granules; plasma and serum give a low representation.

The Promise of Genome-Wide Association Studies (GWAS). Dr. Chanock discussed the promise afforded by incorporated genome-wide scans in a step-wise progression of rigorous and cost-effective population studies aimed at identifying causal gene variants and pathways. The value of GWA studies includes the identification of promising low-penetrance, high-frequency susceptibility loci, and the evaluation of gene-gene interactions and genetic interactions with lifestyle and the environment. In addition, the studies serve as a tool for identifying novel mechanisms in cancer and as a foundation for strategies for presention and intervention. GWA studies are a high priority in the NCI, and much of the effort to capitalize on the revolution in genetics and NCI's investment is in parallel and coordinated with other efforts throughout the NIH. Intramural capabilities at the core genotyping facility also have been important, as have been NCI's investment in cohorts and informatics, particularly caBIG™.

The Cancer Genetic Markers of Susceptibility (CGEMS) Program is a strategic intramural/ extramural initiative that involves experts from Harvard University, the ACS, and a number of cohorts from the Cohort Consortium (called the BPC3). The goals are to conduct: 1) genome-wide SNP scans in prostate and breast cancers and analyze and publish findings; and 2) rapid sequential replication studies under an aggressive timeline. The initial study was in prostate cancer, working with case-control studies from the Prostate, Lung, Colon, Ovary (PLCO) Project and a breast cancer study looking at post-menopausal breast cancer in the Nurse's Health Study.

The general strategy for prostate and breast cancer was to winnow through four phases from roughly 500,000 to 600,000 markers down to first 28,000 SNPs and then 1,500 SNPs, and finishing with a fine mapping of roughly 20 to 30 loci. One of the key issues to face is the power of the first two phases of CGEMS; how to look at this depends on the genetic models used, as the genetic variants may operate in very different ways. For example, two copies may be needed in some circumstances but in another case, one copy may be operative.

Two technologies currently are available for whole genome scans: Illumina and Affymetrix. CGEMS selected Illumina after conducting a thorough analysis. Because of commercial reasons and the development of these tools, CGEMS' prostate cancer scans have been divided into two parts: data for the first scan are now available on the Web, and the analysis is nearly complete for the second scan. A breast cancer scan also is nearing completion; that data will be available in March 2007. All the precomputing information will be fully available without restrictions. Dr. Chanock also described discordance rates in the genotype analysis, noting that the technologies have improved so that the errors are now $2X10^{-4}$. The

technology has allowed data to be looked at in two different ways: by incident density sampling and by comparing the total cases versus the total controls present; Dr. Chanock provided an example of the latter through a QQ plot for about 300,000 SNPs.

Dr. Chanock next described analyses of the PLCO study in terms of population and geographic differences. Because the PLCO recruits individuals from multiple centers across the United States, it presents opportunities even in a study of Caucasian individuals, as the demographics may have quite different histories and the population structure might be different. CGEMS made it a goal to map more than 300,000 genetic markers and now has completed 500,000. Its recomputational capabilities are important to examining empirical data and ameliorating the issue raised about the plethora of false positives in certain subpopulations. Dr. Chanock described CGEMS' value in uncovering the complexity of specific markers, SNPs, and their interactions. CGEMS can provide value-added analysis in the investigation of gene-environment covariates, such as body-mass index (BMI), smoking, and hormone levels; multiple SNP analysis; gene-gene pathway interactions; and followup cohort studies. CGEMS is partnering with NCI's caBIG™ initiative to make the results of pre-computed analyses and genotype data available with no restrictions to epidemiologists and other scientists. Raw genotyping data with case-control studies, age, and family history also will be available to registered investigators addressing many different questions, such as about population frequency. There is a strong effort to look at pancreatic cancer based partly on the recommendation of the Cohort Consortium; a whole genome scan for 1,200 cases and 1,200 controls is being initiated, but the challenge is that data are being pooled from 12 studies.

The next 2 to 4 years likely will bring cheaper and denser SNP technologies that result in better coverage of the genome. In the next 8 years, it is expected that the whole genome will be sequenced; this will replace the study of SNPs and magnify the challenge of confidentiality. Furthermore, there likely will be challenges to classical epidemiology in how information is academically, politically, and medically viewed. The GWAS should lead to clinical implementation. Remaining steps include fine mapping of notable regions; the functional determination of causal variants; design issues for analysis in clinical studies, particularly regarding populations and study sequences; validation criteria; and the commercial development of tests.

Questions and Answers

Dr. Coffey asked about CGEMS in relation to the copy number, methylation, and noncoding of genes. Dr. Chanock replied that all three areas present exciting opportunities for the whole genome scan and in understanding how the genome regulates itself or regulates the host response; he noted that the Illumina technology actually allows researchers to look at copy number variation.

Dr. Niederhuber expressed his appreciation for the CGEMS' work, which keeps the NCI and the NIH in the forefront of the research.

XIII. 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 140th regular meeting of the NCAB was adjourned at 10:22 a.m. on Friday, December 1, 2006.