

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
128th NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
December 2-3, 2003**

**Building 31C, 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 128th regular meeting on Tuesday, December 2, 2003, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, December 2, 2003, from 8:00 a.m. to 4:25 p.m. The meeting was closed to the public from 4:25 p.m. until adjournment at 5:20 p.m. The meeting was reopened to the public on Wednesday, December 3, 2003, from 8:00 a.m. until adjournment at 11:40 a.m. NCAB Chair Dr. John E. Niederhuber, Professor, Departments of Oncology and Surgery, University of Wisconsin-Madison, presided during both the open and closed sessions.

NCAB Members

Dr. John E. Niederhuber (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Moon S. Chen, Jr.
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Dr. Ralph S. Freedman
Dr. Elmer E. Huerta
Dr. Eric S. Lander
Dr. Susan M. Love
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Ms. Marlys Popma
Dr. Amelie G. Ramirez
Ms. Lydia G. Ryan

President's Cancer Panel

Dr. LaSalle D. Leffall, Jr. (Chairperson)

Alternate *Ex Officio* NCAB Members

Dr. Steven Akiyama, NIEHS
Dr. Peter Kirchner, DOE
Dr. Hugh McKinnon, EPA
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Anna Barker, Deputy Director, Strategic Scientific Initiatives
Dr. J. Carl Barrett, Director, Center for Cancer Research
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. Ellen Feigal, Acting Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Harold P. Freeman, Director, Center to Reduce Cancer Health Disparities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Paulette Gray, Acting Director, Division of Extramural Activities
Ms. Janice Mullaney, Acting Deputy Director for Management, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Roshunnd Drummond, American Society of Therapeutic Radiology and Oncology
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Monica Leibert, American Urologic Association
Ms. Barbara K. LeStage, National Cancer Institute, Director's Consumer Liaison Group
Ms. Judy Lundgren, Oncology Nursing Society
Ms. Mary F. Mitchell, American Society of Therapeutic Radiology and Oncology
Dr. Monica Leibert, American Urologic Association
Dr. Clare O'Connor, National Science Foundation
Ms. Nancy O'Reilly, The American College of Obstetricians and Gynecologists
Ms. Barbara Stewart, Association of American Cancer Institutes
Ms. Julie Taylor, American Society of Clinical Oncology
Ms. Marie Zinninger, American College of Radiology

TABLE OF CONTENTS

DAY ONE: TUESDAY, DECEMBER 2, 2003

I.	Introduction, Welcome, and Approval of September 2003 Minutes—Dr. John Niederhuber.....	1
II.	Future Meeting Dates Confirmed Through 2005—Dr. John Niederhuber	1
III.	Director’s Report—Dr. Andrew von Eschenbach	1
IV.	Fiscal 2004 Budget Update—Mr. John Hartinger and Mr. Stephen Hazen.....	3
	Questions and Answers.....	4
V.	President’s Cancer Panel Report—Dr. LaSalle Leffall, Jr.....	5
VI.	Legislative Update—Ms. Susan Erickson	6
VII.	Special Recognition—Drs. Andrew von Eschenbach, Alan Rabson, and John Niederhuber.....	7
VIII.	Overview: Center for Strategic Dissemination—Dr. Edward Maibach.....	7
	Questions and Answers.....	8
IX.	Overview: Office of Communications—Ms. Nelvis Castro and Ms. Mary Anne Bright.....	9
	Questions and Answers.....	10
X.	Nanotechnology Strategic Initiatives—Dr. Mauro Ferrari	10
	Questions and Answers.....	12
XI.	Working Lunch	13
	Update: Task Force on Advanced Biomedical Technology Initiative—Dr. Eric Lander	13
	Questions and Answers.....	13
XII.	Program Review of Center for Cancer Research	14
	Overview—Dr. Carl Barrett.....	14
	Fundamental Discoveries in Cancer	14
	Role of DNA Breaks in Genomic Instability and Cancer—Dr. Andre Nussenzweig	14
	TGF- β s in Cancer Progression: Complex Roles and Therapeutic Opportunities—Dr. Lalage Wakefield.....	15
	Novel Approaches in Cancer Detection and Diagnosis	17
	Mapping Molecular Network Interconnections Using Protein Microarrays for Patient-Tailored Therapy—Dr. Emmanuel Petricoin.....	17
	Oncologic Imaging: Structure, Function, and Molecular Biology—Dr. Peter Choyke.....	19
	Questions and Answers.....	20
	Immunotherapy	20
	Integrating Immunotherapy Into Cytotoxic Regimens: Pediatric Sarcomas as a Model—Dr. Crystal Mackall	20
	Design, Development, and Delivery of Recombinant Vaccines for the Therapy of Human Carcinomas—Dr. Jeffrey Schlom.....	21
XIII.	Closed Session	23

TABLE OF CONTENTS (continued)

DAY TWO: WEDNESDAY, DECEMBER 3, 2003

XIV.	Intramural Reengineering Initiative—Dr. Carl Barrett.....	23
	Questions and Answers.....	25
XV.	Think Tank Task Forces and Long-Range Scientific Planning—Dr. Dinah Singer.....	26
	Questions and Answers.....	27
XVI.	National Bio-Specimen Network Initiatives—Dr. Anna Barker	28
	Questions and Answers.....	30
XVII.	Subcommittee Reports	31
XVIII.	IOM and NCAB Retreat Reports—Dr. John Niederhuber	31
XIX.	Adjournment—Dr. John Niederhuber.....	33

DAY ONE: TUESDAY, DECEMBER 2, 2003

I. INTRODUCTION, WELCOME, AND APPROVAL OF SEPTEMBER 2003 MINUTES—DR. JOHN NIEDERHUBER

Dr. Niederhuber began by asking for a moment of silence to consider the patients with cancer and those who have passed away from cancer, in particular, Dr. Paul Calabresi, former NCAB and President's Cancer Panel (PCP) Chair. He welcomed members and *Ex Officio* members of the Board; representatives of liaison organizations; members of the PCP; Dr. Paulette Gray, Acting Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), and Executive Secretary, NCAB; other NCI staff; and members of the public. Dr. Niederhuber invited the public to submit to Dr. Gray, in writing and within 10 days, comments regarding items discussed during the meeting.

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

Motion. A motion was requested and made to approve the minutes of the September 2003 NCAB meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

II. FUTURE MEETING DATES CONFIRMED THROUGH 2005—DR. JOHN NIEDERHUBER

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda, which have been confirmed through 2005.

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

Dr. Andrew von Eschenbach, Director, NCI, began his report by thanking NCAB members, NCI staff, and all scientists, clinicians, caregivers, administrators, public servants, patients, and patient advocates for their dedication and commitment to the cancer biomedical research effort. He noted that, for the first time, the possibility of success in eliminating suffering and death from cancer by 2015 can be envisioned. He then reported that the NCI is working on a memorial to recognize and remember Dr. Calabresi, and that a formal presentation will take place at the February 2004 NCAB meeting.

Dr. von Eschenbach announced three new personnel appointments. Dr. Richard Alexander has accepted the position of Deputy Director, Center for Cancer Research (CCR), NCI, and will be serving as liaison for the CCR laboratories and branches to focus on strategic planning and policy setting. Dr. Karen Antman, President, American Association for Cancer Research (AACR), will be joining the NCI as an Intergovernment Personnel Act detailee in the Office of the Director (OD) to assist in the implementation of the P30/P50 working group recommendations. Dr. Mark Clanton will be joining the NCI as a senior policy consultant in the OD to work in the area of cancer care delivery and cancer control.

Dr. von Eschenbach announced that the NCI will be sponsoring a workshop in January as a followup to the Institute of Medicine (IOM) report on NIH reorganization, under the leadership of Dr. Lee Helman, Chief, Pediatric Oncology Branch, CCR, and Dr. Julia Rowland, Chief, Office of Cancer Survivorship, Division of Cancer Control and Population Sciences (DCCPS). Issues surrounding long-term cancer survivorship among children and adolescents will be addressed.

Board members were reminded of the ongoing collaboration between the NCI and the U.S. Food and Drug Administration (FDA). A task force co-chaired by Dr. Anna Barker, Deputy Director, Strategic

Scientific Initiatives, NCI, has been established and a number of joint initiatives have been planned. Dr. von Eschenbach noted that he and FDA Commissioner Dr. Mark McClellan announced two of these initiatives at a recent meeting at the Woodrow Wilson Center. The first is the recreation of the cancer fellowship training programs, which will train physicians and scientists in both institutions to create a corps of experts who are able to transition between the discovery and approval sciences. In the second initiative, the FDA is participating in the NCI Bioinformatics Initiative and will assist in the implementation of the Cancer Bioinformatics Grid (CaBIG). CaBIG will be piloted in the NCI Cancer Centers. Common clinical trial management software will be developed to link researchers with the FDA and the NCI to facilitate electronic transmission of data and the investigational new drug (IND) application process. Other initiatives are in progress and will be reported on as they are finalized.

Dr. von Eschenbach referred to the National Biospecimen Network Blueprint as the product of another fruitful NCI collaboration, this time with the National Dialogue on Cancer. He noted that the Blueprint exemplifies two important principles: (1) it reflects best practices across the sphere of biorepository initiatives, and (2) it reflects a perspective of the entire research community. Board members were reminded that the Blueprint, which is available for public comment on the Web, will allow for the development of individual biorepositories in such a way that a comprehensive national biorepository network is created with the ability to share data across a common platform, based on quality-assured standards. Dr. von Eschenbach noted that this initiative reflects NCI's strategy for enhancing the research agenda by providing standards and infrastructure. CaBIG was cited as another initiative that reflects a similar strategy.

Dr. von Eschenbach briefly referred to other initiatives that reflect important strategies within the NCI. The American Stop Smoking Intervention Study (ASSIST) Evaluation Program is demonstrating that smoking cessation and intervention programs are being jointly structured and supported through state cancer programs and NCI's Cancer Information Network as well as other work in the cancer control area. NCI-funded scientific research is creating the tools that are being applied to address community problem areas through other venues. A similar initiative within the intramural program is the Tobacco Intervention Research Clinic, which is developing pharmacologic- and behavioral-based intervention programs. These evidence-based tools and strategies will be piloted and exported for implementation in the larger delivery structure to have an impact on the problem of tobacco addiction. Dr. von Eschenbach noted that the same principle is being applied to NCI's prevention research emphasis based on the role of energy balance (physical exercise, diet, and nutrition) in addressing the emerging obesity epidemic. The NCI is working on individual programs as well as participating in the trans-NIH obesity initiative and a broad cross-sectional program and conference on obesity sponsored by the National Dialogue on Cancer. Dr. von Eschenbach concluded that these collaborative and cooperative partnerships within the NIH, with other Department of Health and Human Services (DHHS) agencies, and with organizations outside the NCI will continue to be an important part of the Institute's strategy for reaching the 2015 challenge goal.

Dr. von Eschenbach listed other important updates that will be presented: (1) the reengineering of the intramural program, (2) the Division of Cancer Biology (DCB) think tanks for the development of strategic initiatives, and (3) technology development and a strategy for application in the NCI scientific agenda. He announced upcoming meetings, including: (1) the kick-off in February of the NCI Director's Seminar Series with a roster of speakers that includes FDA Commissioner Dr. Mark McClellan; Dr. Julie Gerberding, Centers for Disease Control and Prevention (CDC); and Dr. Carl Feldbaum, Biotechnology Organization; (2) the first Cancer Center Directors Retreat with the Director, NCI, on March 8, 2004; (3) a subsequent 1-day retreat with the Cooperative Group Chairs, and (4) a joint meeting of the Board of Scientific Advisors (BSA) and the Board of Scientific Counselors (BSC) on January 26 to discuss long-range financial strategic planning for the NCI. Finally, Dr. von Eschenbach announced that the Fiscal

Year (FY) 2005 Bypass Budget will be available later in December to provide an opportunity for the community to have broad input earlier in the planning process.

IV. FISCAL 2004 BUDGET UPDATE—MR. JOHN HARTINGER AND MR. STEPHEN HAZEN

Mr. John Hartinger, Associate Director, Office of Budget and Financial Management, NCI, stated that the Board would receive an annual written summary of the distribution of NCI's budget as requested, beginning with the FY 2003 report. He presented a summary of the expenditures contained therein. The NCI received a 10 percent budget increase in FY 2003, or about \$416 M. The increase was disbursed as follows: (1) about \$152 M for Research Project Grants (RPGs)—about \$90 M of that for maintaining RPGs; (2) about \$22 M for extramural training programs; \$53 M for research and development (R&D) contracts, notably, a major bioinformatics initiative, the loan repayment program, and drug development initiatives; (3) about \$38 M (9 percent of the increase) for intramural research; and (4) about \$36 M for cancer prevention and control. Mr. Hartinger noted that taps and assessments amounted to about \$54 M or 12 percent of the \$416 M increase. Actual disbursement of NCI's total FY 2003 budget of \$4.59 B for major line items was: (1) RPGs (predominantly R01s and P01s)—about \$2 B; (2) Cancer Centers and Specialized Programs of Research Excellence (SPOREs)—about \$380 M; (3) intramural research—about \$700 M, of which about one-third went for NIH assessments, management fund, and taxes; and (4) cancer prevention and control—more than \$530 M.

Mr. Hartinger then reviewed funding trends—shifts in percentages of the NCI budget for various mechanisms since the doubling of the NIH budget, reminding Board members that the NCI budget grew about 81.7 percent over that 5-year period. All mechanisms, except for RPGs, intramural research, and Clinical Cooperative Groups, have experienced percentage increases greater than the total NCI growth. Intramural research has expanded at the lowest percentage of all mechanisms. Board members were reminded that the omnibus bill, which includes NCI's FY 2004 appropriations, has not been enacted. Therefore, the NCI is operating under a Continuing Resolution until January 31, 2004, which allows for the same dollar amount as FY 2003. The omnibus bill under consideration includes a budget for the NCI of \$4.7 B, a 4 percent or \$178 M increase. However, an across-the-board reduction is being considered for the NIH, with unknown ramifications for the NCI budget. The challenge for the NCI is that FY 2004 funding decisions for grants and other programs must be made soon.

Mr. Hartinger reviewed other resource issues, including an update on full-time equivalents (FTEs) of staffing. The NCI used 3,166 FTEs in FY 2003, which is 0.8 percent over the ceiling of 3,088. However, changes to NCI's FTE ceiling are underway in several areas: (1) the NCI will be a contributor to the NIH Director's reserve to staff the Roadmap initiatives, and (2) the contracting-out initiative that was won by the NIH means that there will be a central NIH staff to support all grant awards, requiring a contribution by the Institutes of additional FTEs.

Mr. Stephen Hazen, Chief, Extramural Financial Data Branch (EFDB), NCI, presented a report of the RPG Working Group's November 12 meeting to discuss issues associated with FY 2004. He began by reminding Board members that the NCI Executive Committee (EC) has adopted a new policy to protect against the possibility that an influx of large percentiled R01s will create budget problems in FY 2004 and beyond. A separate payline will be established by the EC for percentiled R01s with direct costs of \$700 K or more (approximately \$1 M in total costs). The intent is to apply the common R01 payline whenever possible, but to reserve the right to reduce the payline based on budgetary constraints.

As background, members were reminded that challenges in FY 2004 include expectations in the

grantee community that the 20th percentile payline will be maintained; the increase in numbers of R01, P01 (program project grant), and R21 (exploratory developmental grant) applications; the increase in average cost requested; and the limited dollars available if the proposed 3.9 percent increase (\$179 M) in the NCI budget is enacted. Mr. Hazen illustrated that current FY 2004 estimates for T5s, administrative supplements, Requests for Applications (RFAs), competing grants, and Small Business Innovative Research (SBIR) and Small Technical Transfer Research (STTR) grants would require about \$141 M of the projected \$179 M increase to support RPGs. He noted that to address the challenge to fund more R01s, the NCI would need to take a greater than 11 percent average policy reduction of competing grants and limit the number of R21s, P01s, and others to maintain the FY 2003 payline, even as R01 numbers increase.

Using R21s as a surrogate for R01 success rates and challenges, Mr. Hazen showed that with the large increase of new R21 applications (921 in FY 2003, 1,411 in FY 2004), an NCI funding policy to pay the same number of R21s in FY 2004 (210) as FY 2003 (207) would have a significant impact on the success rate of R21 applications (22.5 percent in FY 2003, 14.9 percent in FY 2004). He noted that the very large increase in the number of R21 applications would require a 50 percent increase in the budget to keep the success rate level. He further explained that the increase in P01 applications is not as dramatic as the R21 increase, but the P01 success rate also will decline in FY 2004.

To put the FY 2004 budget challenge in perspective, Mr. Hazen noted that although the R01 mechanism is not experiencing the same growth as R21s, 30–35 R01s per point was the former estimate used to project the amount of funding needed at different points in the payline. In FY 2004, the funding estimate is based on 60 R01s per point, or \$20–22 M of costs per point on the payline. Mr. Hazen concluded with a review of RPG application numbers since the signing of the National Cancer Act in 1972. He pointed out that the steep increase during the past 5 years represents both an opportunity for funding good research and a challenge as the budget flattens in FY 2004 and beyond.

Dr. von Eschenbach reminded members that NCI's budget increase was about 80 percent over the time the NIH budget doubled, and NIH Institutes overall did not see the same increase in number of applications received as the NCI. This suggests that investigators are gravitating towards the opportunities that exist in cancer research. He expressed the view that the curve would not change dramatically based on dollars alone, but by virtue of scientific opportunities. Therefore, the challenges for the NCI will increase with regard to requests. He emphasized the importance of understanding that the payline of 20 percent was much different in 1980 than in 2004, because the number of investigators in cancer research is greater now than ever before in the history of the cancer research enterprise. Board members and the cancer research community were asked to be aware of the critical mass of intellectual capital that has been the result of the increasing number of grants funded as well as the success rate. The upcoming BSA/BSC meeting will be an opportunity to discuss what the future may look like, based on EFDB budget modeling and scenarios.

Questions and Answers

Dr. Jean deKernion, Professor and Chairman, Department of Urology, University of California School of Medicine, agreed that cancer research opportunities are increasing. He expressed the view, however, that unless budgets continue to keep pace, paylines will fall and the message to the community will be that there is a ceiling on the opportunity for cancer investigators. Dr. von Eschenbach replied that an 11 percent negotiated reduction in grant costs, the new large R01 policy, and the search for collaboration and partnership opportunities are strategies to begin to address the challenge. Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, suggested that the increase in R21 and large R01 applications may be related to the construction

of RFAs and Program Announcements (PAs) and the effort to ensure that all major advances are being addressed in the NCI research portfolio. He suggested the need to focus on the more key aspects of the portfolio.

V. PRESIDENT’S CANCER PANEL REPORT—DR. LaSALLE LEFFALL, JR.

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Department of Surgery, Howard University College of Medicine, reminded Board members that the President’s Cancer Panel (PCP or Panel) continued its examination during 2003 of issues and challenges associated with cancer survivorship begun at a meeting held in Lisbon, Portugal, in May. The second meeting held in Denver, CO, on September 5 focused on issues and challenges among pediatric cancer survivors. The third meeting was held in Austin, TX, on September 22 to examine issues and challenges among adolescents and young adults, and the fourth in Birmingham, AL, to focus on meeting the challenges of adult survivors. The last meeting in the series will be held in Philadelphia, PA, on January 5, 2004, to examine challenges to older adult cancer survivors—those diagnosed after age 60.

Dr. Leffall briefly summarized the proceedings of the Austin meeting. Disturbing trends among adolescent and young adult survivors—defined as those between ages 15 and 29 years—were portrayed as: lower participation in clinical trials, lower rates of post-treatment followup, higher rates of medical uninsurance or underinsurance, and lower overall improvement in cancer mortality rates. Adolescent and young adult survivors were referred to during testimony as the “lost cohort” due to the scarcity of age-targeted research, data, and applicable health education information. With this in mind, the Panel heard directly from the survivors about their post-treatment challenges and possible ways to address them. Loss of budding independence as a result of diagnosis was identified as a major social and emotional setback. Speakers emphasized that familial overprotectiveness and dependence on caregivers can become disabling. One speaker described the time during and immediately following treatment as a “psychosocial stalling” that made reintegration into the college and work settings especially difficult. To temper this, it was suggested that adolescents and young adults be included fully in their treatment processes and discussions of treatment effects.

Dr. Leffall noted that testimony pointed to a critical need for peer-based support among this group because peers are qualified to understand fears of recurrence, uncertainty, and social issues specific to adolescents and young adults. It was suggested that strong peer support relationships also might encourage compliance with recommended followup care. However, a significant challenge to fostering peer support is the difficulty survivors face in locating one another. The number of survivors in a given community is small, and information exchange among treatment facilities often is prohibited or discouraged.

Employment and insurance are other significant issues for this population. Studies document that young adults are at high risk of being uninsured. Participants shared examples of employment-related barriers, including feeling “job locked” to maintain insurability, being passed over for promotion, and overcoming perceptions that they are taking unnecessary leave time once their treatment is complete. Uncertainty about the future also seems to impact cancer-related choices among this group. Another issue adolescent and young adult survivors face is permanent infertility caused by treatment at a time in life when bearing children and raising a family often is a high priority. Although fertility-preservation options exist, they may not be available to or affordable for all patients.

Dr. Leffall then summarized the testimony of adult survivors—those diagnosed between the ages of 30 and 59—heard at the Birmingham meeting. Unlike younger survivors who struggle with fertility issues, adult survivors focus more on restoring sexuality and intimacy following treatment. The Panel

heard how important ancillary services, such as reconstructive surgery, physical rehabilitation, and counseling, are to reestablishing quality of life in these areas. Another issue identified by survivors was the lack of adequate pain management. An appeal was made to train more specialists in this area, better educate medical providers about pain, and conduct more research on pain pathways and effective pain treatments.

Because adults are generation “sandwiched” between raising children and caring for older adult family members, the Panel took note of how the long-term chronic effects of cancer and its treatment encumber more than the adult survivor. Participants asked for ways to support the entire family unit. Similar to the experience of younger adults, workplace discrimination continues to be an issue for adults whose cancer treatment or followup is perceived by employers as requiring excessive or prolonged absences. At this meeting, the Panel heard for the first time from cancer care providers and health system specialists about barriers to providing followup cancer care services. Managing long-term followup or coordinating care in community settings versus academic or Comprehensive Cancer Centers was addressed with agreement that more complex late effects often are better managed at Centers. It also was noted that an unintended consequence of the Health Insurance Portability and Accountability Act (HIPAA) may be the limitations placed on the ability of cancer specialists to provide former patients with updated information on long-term effects of cancer treatment.

Dr. Leffall noted that a representative of the American Society of Clinical Oncology (ASCO) described its guidelines for followup of colon and breast cancer survivors. Although useful in detecting recurrence of a primary cancer, according to Dr. Leffall, the guidelines appear focused on surveillance rather than survivorship. The hope was expressed that the upcoming annual review of the ASCO guidelines will address the need to incorporate other post-treatment followup, such as screening for secondary cancers, osteoporosis screening and management, and family counseling and risk assessment.

At this meeting, the Panel heard again about the substantial difficulties of uninsured and underinsured citizens for whom there are no easy solutions for obtaining cancer treatment, let alone post-treatment care. It was found that even for the insured, cancer exacts an enormous financial and emotional toll on patients and families, expressed as “the cost of survival.”

Finally, Dr. Leffall noted that universal concerns have continued to be raised across age groups at all of the meetings held so far: (1) developing a better system for coordinating post-treatment care, (2) providing improved access to relevant post-treatment information and supportive services, (3) creating a manageable process for documenting and transferring cancer-related medical information, and (4) developing guidelines covering possible long-term effects. Dr. Leffall noted that town hall meetings have been held in conjunction with each in the series of meetings to give the Panel an opportunity to hear from members of the community as well as invited speakers.

Following his report of the two latest Panel meetings on survivorship, Dr. Leffall proposed that the NCAB and the PCP entertain a resolution honoring Dr. Paul Calabresi for his extraordinary contributions to the National Cancer Program.

Motion. A motion was made to endorse the proposed resolution on behalf of the NCAB and the PCP recognizing and honoring Dr. Paul Calabresi for his leadership, vision, and extraordinary contributions to the National Cancer Program. The motion was seconded and approved. A formal presentation will be made at the February NCAB meeting.

VI. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Acting Director, Office of Policy Analysis and Response, NCI, began the legislative update with a report on the status of FY 2004 appropriations in Congress. The last seven pending appropriations bills, which included the Labor, HHS, Education Bill, were incorporated in an omnibus bill that was reported by the Conference Committee on November 25. Budget figures in the omnibus bill were \$27.99 B for the NIH and \$4.77 B for the NCI. Ms. Erickson noted that Congress will take up the omnibus bill when it reconvenes on January 20 if there is no action before the first session adjourns. A continuing resolution provides funding at FY 2003 levels through January 31, 2004.

Ms. Erickson reported that staff from the Division of Cancer Epidemiology and Genetics (DCEG) and DCB provided NCI testimony before a congressional hearing entitled “Preventing Another SV40 Tragedy: Are Today’s Vaccine Safety Protocols Effective?” The hearing was conducted by the House Government Reform Subcommittee on Human Rights and Wellness. Finally, Ms. Erickson presented highlights of recently introduced legislation: (1) the Pediatric Palliative Care Act introduced jointly on September 17 in the House and Senate to improve the palliative and end-of-life care provided to children with life-threatening conditions; and (2) the National Cancer Act of 2003 introduced by Senator Brownbeck for himself and Senator Gregg on November 21 to improve data collection and dissemination, treatment, and research relating to cancer. Following the update, Ms. Erickson was asked to keep the NCAB informed, between now and the February meeting, of any movement toward setting a definite date for hearings on the IOM report.

VII. SPECIAL RECOGNITION—DRS. ANDREW von ESCHENBACH, ALAN RABSON, AND JOHN NIEDERHUBER

Dr. Alan Rabson, Deputy Director, NCI, and Niederhuber joined Dr. von Eschenbach at the podium to recognize the contributions of Dr. Brian Kimes, Director, Office of Centers, Training, and Resources, who is retiring from the NCI after 27 years of service. On behalf of the NCI and the NCAB, Dr. von Eschenbach recognized Dr. Kimes for his leadership since 1976 in creating programs that have changed the face of cancer research within the United States and beyond. Dr. Kimes was cited for his major contributions as a leader in the development and implementation of the NCI-Designated Cancer Centers Program, co-founder of the SPOREs, a leader in building training and career development programs, and co-founder of NCI’s Minority Institution and Cancer Center Partnership Program.

VIII. OVERVIEW: CENTER FOR STRATEGIC DISSEMINATION—DR. EDWARD MAIBACH

Dr. Edward Maibach, Director, Center for Strategic Dissemination (CSD), NCI, began by defining dissemination in the words of Dr. Jon Kerner, Assistant Deputy Director for Research Dissemination and Diffusion, DCCPS, NCI, as “An active process through which target groups are made aware of, receive, accept, and use information and other interventions.” Dr. Maibach reviewed NCI’s longstanding focus on dissemination, and reminded members that the goal of dissemination is to turn knowledge into applications that benefit people—to achieve NCI’s 2015 challenge goal. In the absence of metrics to indicate the success of NCI’s dissemination efforts, Dr. Maibach referred to a study of the primary care practice, which concluded that it takes 17 years to turn 14 percent of original research to the benefit of patient care. He noted that Dr. Kerner and the DCCPS team have been engaged in work to improve those averages using three different models: knowledge synthesis (e.g., knowledge transfer teams); grant support (e.g., administrative supplements); and partnership (e.g., State cancer plans, Cancer Control PLANET, Body and Soul Program).

Dr. Maibach stated that he has been engaged for the past 3 months in a collaborative process throughout the NCI. Internal partners are various OD components, the DCCPS in the Translating

Research into Improved Outcomes Program (TRIO) and Health Communication and Informatics Research Branch, the Center to Reduce Cancer Health Disparities (CRCHD), and other Divisions and Centers. The collaborative team framed five objectives for dissemination at the NCI: (1) harmonize and better integrate the many NCI dissemination initiatives; (2) better understand the perceived needs of people and organizations and use these insights in shaping the way programs are developed and disseminated, a customer-centric mindset; (3) make people and organizations aware of NCI's information and applications that are of value to them; (4) enable people in organizations to make informed cancer-related decisions; and (5) persuade and enable people and organizations to adopt evidence-based approaches that will help reduce the risk and burden of cancer. An overarching consideration in all dissemination activities is that they must reduce cancer disparities.

Board members were informed of five trans-NCI dissemination strategies that have been articulated: (1) inform all efforts with extramural and in-house research; (2) plan for dissemination proactively through program design in collaboration with program development staff; (3) identify evidence-based applications or, as necessary, develop "best practice" applications and distribute them as appropriate; (4) cultivate partnerships to expand distribution channels and leverage impact; and (5) promote applications aggressively through mass media and targeted channels. Dr. Maibach described a synergistic model for getting evidence-based interventions into practice that was developed at the Robert Wood Johnson Foundation. Elements of the model are the push of ideas from science and technology into the marketplace, the pull exercised by demand characteristics of the market, and the capacity of the systems into which applications are introduced to adopt and deliver those applications. He expressed the view that the NCI is world class in terms of the science and technology push, but requires work in the area of building delivery capacity and creating applications that are predicated on the market demand today and into the future.

Turning next to the CSD organization and objectives, Dr. Maibach stated that the aim will be to assist Divisions and Centers in enhancing the dissemination potential of their applications. The proposed initial structure includes an Operations Research Office, an Office of Education and Special Initiatives, and the Office of the Director. He gave three examples of where the CSD can add value with the dissemination process. First, the strides made in transferring information from the bench to the bedside will be enhanced by returning clinical information back to the bench to ensure that the scientific effort is targeted on market demand. A second opportunity will be to expedite the process of creating transdisciplinary research. Finally, Dr. Maibach noted, as 2015 approaches, the work of the cancer community at large will produce many more prevention, early detection, treatment, and modulation interventions. The better the abilities, constraints, and demands of health care providers are understood, the better the NCI will be able to tailor those interventions to the unique operating characteristics of those service delivery environments. The CSD is engaging in direct research and a series of planning activities in meetings with health care professional organizations to inform that effort.

Questions and Answers

Dr. Amelie Ramirez, Associate Professor, Department of Medicine, Baylor College of Medicine, asked for particulars on the cancer disparities component. Dr. Maibach replied that disparities will be a collective commitment on the part of all who are engaged in dissemination planning as they begin to work collaboratively with program development staff. Dr. von Eschenbach added that it is important to understand, from the long-range strategic planning perspective, that as discovery and development moves more toward the era of genomics and proteomics, the delivery process will be technologically dependent and therefore more likely to be center focused. The problem of delivering interventions to minority and underserved communities that do not automatically have that linkage will require a longer range strategic planning and implementation process. The CSD will complement the work being done in all other

programs. The Board requested periodic updates on CSD planning and initiatives.

IX. OVERVIEW: OFFICE OF COMMUNICATIONS—MS. NELVIS CASTRO AND MS. MARY ANNE BRIGHT

Ms. Nelvis Castro, Acting Director, Office of Communications (OC), NCI, stated that all of the OC's current activities strategically support its mission, and a number of new initiatives have been planned to further enhance OC effectiveness for 2004. The OC represents the NCI on press-related, public information, and communication planning matters by managing information flow to and from the media. Press operations and media relations include handling media inquiries, issuing press releases and fact sheets, coordinating press conferences and media events as necessary, and coordinating training sessions to prepare scientists to speak with the media and effectively translate science for the public. Web sites include NewsCenter, a resource for the media to access scientific information, and BenchMarks, a resource for information on specific cancer topics.

Proactively, the OC is engaged in three major media outreach efforts. Hollywood Health and Society is an innovative pilot to reach consumers through entertainment media. Telemundo and Univision are channels for reaching Spanish-speaking audiences throughout their programming. Important scientific perspectives on cancer and cancer research are presented through editorials and letters to the editor. The OC also works closely with the trans-NCI scientific staff to support their communication needs for clinical trials, Institute initiatives and priorities, and special events.

Ms. Castro noted that OC's mission also includes working with internal and external groups to communicate NCI's research findings. Internal communications are facilitated through weekly meetings with representatives from NCI Divisions, Centers, and Offices, and emerging issues are proactively addressed. The OC engages collaboratively with external groups at the NIH, DHHS, and other government agencies and organizations. A new, expanded exhibit will continue to serve as a tool at more than 12 national meetings per year to highlight NCI's research priorities and showcase NCI's critical role in the cancer community. The Cancer Information Service (CIS) at local and regional meetings uses smaller exhibits and panels.

Ms. Mary Anne Bright, Acting Deputy Director, OC, NCI, continued the presentation with a review on the OC's use of technology to ensure rapid and accurate communication with all NCI stakeholders. A key effort is NCI's Web Site, cancer.gov, which currently is being redesigned to enhance the ability to search for and locate clinical trials. In addition, the OC is capitalizing on technologic innovations and collaborating with other organizations to enhance the PDQ Clinical Trials Database. For example, the OC is working with the National Library of Medicine to add clinical trials that currently are not in PDQ and to obtain additional trials from the clinicaltrials.gov Web Site. Other collaborations are with the Coalition of National Cancer Cooperative Groups to pilot TrialsCheck as a means for offering expanded search capabilities, and with the NCI Center for Bioinformatics to implement terminology in PDQ for improved precision of trial search and retrieval. To help users manage and streamline access to important sources of information, the OC has several ongoing projects that use technology to consolidate resources. LION (Library Online) contains a Web-based catalogue of more than 60,000 items about the NCI and cancer. Technologic advances also are being used to simplify the use of electronic databases such as the Publication Locator, Visuals Online, and the NCI Calendar of Events. The OC has developed and maintains an Intranet to enhance OC staff capability for rapidly accessing communication and information tools.

Throughout all of its activities, the OC ensures that the NCI speaks with a consistent and wide-reaching voice. In specific initiatives to fulfill this part of its mission, the OC offers numerous points of

access to the public for getting information including the CIS (1-800-4-CANCER), LiveHelp, and NCI's Smoking Quitline; distributes publications designed and printed in Spanish and English; and operates the CIS Partnership Program. The Partnership Program focuses on cancer control and reducing cancer health disparities through partnerships with national, state, and local organizations dedicated to serving minority and medically underserved audiences. Technical assistance is provided to strengthen their capacity to communicate about cancer using outcome-based data and evidence-based planning tools like the Consumer Health Profiles (CHPs). CHPs combine demographics, health, and lifestyle information to cluster profiles in different communities to enable CIS partners to reach those communities.

Ms. Bright noted that the OC is in the process of strengthening its national relationships and collaborations with the CDC, the American Cancer Society, and the Intercultural Cancer Council. In addition, the Director's Corner allows the NCI to conduct ongoing dialog with the cancer community through the weekly Director's Updates and listings of funding opportunities. Among the many OC priorities for 2004 are the NCI Cancer Bulletin (electronic newsletter) debut early in the year, cancer.gov redesign, NCI Annual Report, Director's Lecture Series, Director's All-Hands Meeting, and VisualsOnline enhancement.

Questions and Answers

Dr. Susan Love, Clinical Professor of Surgery, David Geffen School of Medicine, University of California (UC) at Los Angeles, asked about the status of the branding initiative for communications and the NCI in general since the death of the former OC Director. Ms. Castro noted that the project is on hold, and resources have been directed to communication activities planned for the near future. Dr. Love expressed the view that the initiative should be revisited to make the public, including members of Congress, more aware that the NCI is the source of much of the information. In response to a question from Dr. Moon Chen, Professor, Department of Epidemiology and Preventive Medicine, UC Davis Cancer Center, Ms. Bright outlined outreach initiatives that will take place in 2004 as a result of the letter of agreement signed with Univision. Cancer topics will be the focus during three of the months in Univision's year-long campaign to be aired on TV, radio, online, and in print, with information on healthy lifestyles, disease specifics, and available resources. In addition, the CIS worked with Telemundo's Executive Producer and a writer on a breast cancer program that was broadcast nationally and internationally, with the 1-800-4-CANCER number. Ms. Bright noted that the CIS marketing promotion plan will be submitted to the NCAB *Ad Hoc* Subcommittee on Communications for discussion prior to the next meeting.

In response to a question from Dr. Niederhuber, Ms. Bright outlined market research and evaluation activities that already have been conducted and noted that some of those activities will be housed in the CSD. Dr. Robert Croyle, Director, DCCPS, reminded members that the Centers Program for Excellence in Cancer Communication Research recently was funded to provide information for building linkages between extramural investigators and other NCI programs. Dr. Niederhuber asked that the Board be kept informed of progress in these areas.

X. NANOTECHNOLOGY STRATEGIC INITIATIVES—DR. MAURO FERRARI

Dr. Mauro Ferrari, Edgar Hendrickson Professor of Biomedical Engineering and Professor of Internal Medicine, The Ohio State University, described medical applications of nanotechnology as they relate to cancer at the NCI, highlighting NCI's strategic plans for employing nanotechnology towards meeting the 2015 goals. The Institute sponsors several nanotechnology-related programs, one of which is a collaboration with the National Aeronautics and Space Administration (NASA) that involves employing carbon nanotubes as molecular sensors on surfaces. Another collaboration with NASA involves utilizing

nanotechnology to assist in monitoring the health of astronauts during future extended (e.g., 2-year) space voyages.

The University of Michigan houses one of the premier nanotechnology programs and has developed self-assembling, polymer-type nanoparticulates known as dendritic polymers. These can be used as particulates for injection in the general circulation and can serve as platforms for performing a number of different functions, such as targeting. Dendritic polymers can be used outside of a cell as well as intracellularly as carriers for contrast agents. They also can be used as carriers for a therapeutic payload. In similar fashion, the NCI is developing nano-based particles, or liposomes, synthetically made to carry drugs with a targeting capability.

NCI's nanotechnology plan was developed over the past 6 months with input from a large number of experts from both the intramural and extramural communities. Major areas identified as challenges where it is believed that nanotechnology can enable significant breakthroughs in the fight against cancer include prevention and control, early detection in association with proteomics, imaging diagnostics, and multifunctional therapeutics. Nanotechnology applications relative to prevention and control include bioengineered vaccines and smart delivery systems to deliver agents that can prevent disease or neutraceuticals directed against premalignant lesions. Smart delivery systems can release therapies through a number of different mechanisms, including hydration and diffusion and remote induction with radiation. The nanoparticle could release the drug as well as a toxin that inactivates tight junctions and opens passages between the cells. Dr. Ferrari elaborated on the advantages of nanotechnology in terms of interfacing with biology at multiple scales for molecular targeting to allow for multiple functionalities in a small volume or on a single platform.

Nanotechnology can improve mass spectroscopy in a number of different ways, including limiting and focusing the range of free mass spectroscopy, providing enablements that are a pre-fractionation type of mass spectroscopy, or creating substrates to separate and identify molecular signatures on the surface prior to the absorption and mass spectroscopy analysis. Nanotechnology also could lead to the development of implantable biosensors. One challenge that should be issued is attempting to engineer protein resistance and avoid biofouling by using nanostructured materials at the surface level.

Key to imaging diagnostics is developing contrast agents that yield selected contrast anatomically as well as information on biological evolutionary diversity of neoplasms in varied populations and down the longitudinal axis of time. It may be possible to develop injectable particulates that can localize and signify disease, possibly at the stage of development, and add therapeutics. This concept gives rise to the notion of multifunctional therapeutics as a smart delivery system, which Dr. Ferrari noted should be a dominate focus of NCI's nanotechnology efforts.

In terms of NCI's strategic plan for nanotechnology, the Institute is attempting to integrate advances in the fundamental life sciences that are being recorded in the fight against cancer and in the corresponding clinical processes with nanotechnology. New and innovative funding modes in addition to the existing time-honored successful funding modes at the NCI may need to be developed, and training will be a crucial issue. The NCI has established a Cancer Nanotechnology Working Group, and in an effort to expand its contacts in the broader research community, road shows featuring nanotechnology and its applications to fighting cancer are planned. In addition, a number of workshops will be held that will focus on themes such as nanotechnology and imaging, nanotechnology in early detection via proteomics, and multifunctional therapeutic systems. In addition, intramural programs are being planned and developed with the objectives of achieving breakthrough validation in terms of basic science and transition to the clinic through rapid, high-visibility, high-impact operations that can best be translated from the laboratory into the clinic.

At present, it is difficult to compare advances in nanotechnology in clinical trials because of differences in vectors, targeting agents, disease indications, etc. Standardization and regulatory efforts are needed to allow for these comparisons and to move the field forward. One worthwhile effort in this regard would be the establishment of a cascade of assays that all nanoparticulate technology has to go through to become comparable. This effort could be accomplished through the Nanotechnology Standardization Laboratory that is being established and would allow for the opportunity to channel together resources from different sectors and fields of research. Additional future activities include developing nanoparticulates that function as carriers/vectors to better deliver anticancer drugs that have proven efficacy, and biologically modifying these nanoparticles so that they have the capability to target, avoid particular endothelial system uptake, and/or remain in the circulation for a specified period of time. Advances such as these carry the potential for better release profiles, better targeting, reduction in collateral damage, and dramatically accelerating the pathway to deployment in the clinical setting, as well as the opportunity for engaging synergistically with the private sector.

Questions and Answers

Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital, asked about private-sector involvement and how it might occur in the context of NCI's desire to have an open process of research evolution. Dr. Ferrari responded that a team has been assembled to address this complex issue. He added that the system, as it currently is set up, is not prepared to glean the results of emerging technologies, and it behooves the cancer community find the right paradigms to achieve these goals. Without deviating from the paradigm of the biotechnology type of development to the private sector, it is doubtful that advances from nanotechnology will help many cancer patients; the NCI should take an active role in trying to resolve this issue. Dr. Niederhuber asked where support from nanotechnology research originates. Dr. Ferrari explained that almost every major university and materials company have nanotechnology programs. Historically, most funding for nanotechnology research has been provided by the National Science Foundation, Department of Defense, and Department of Energy. The NCI should not compete with these entities in terms of promoting and developing key technologies; however, the transition of those technologies into the medical community and the cancer community in particular is a task only the NCI can accomplish. Developing synergistic relationships with these other agencies will help in this endeavor.

Dr. Niederhuber commented that the NCI could try to find an innovative approach to educating and exposing some of its leading scientists in physics, for example, to what it means to have colon cancer, breast cancer, and what the natural history of that disease is from beginning to end to generate more interest and crossover into nanotechnology efforts at the Institute. Dr. Ferrari agreed, and noted that at the NCI and in the academic community, it is difficult for established researchers to move into a completely different field. It is hoped that the Nanotechnology Standardization Laboratory can be used to facilitate these types of career moves in some way and improve training in this field. It is planned for the Laboratory also to assist researchers with applying nanotechnology to medicine. Dr. Eric Lander, Director, Whitehead Institute/Massachusetts Institute for Technology Center for Genome Research, asked whether there is a set of clear biological challenges that the Laboratory can assist researchers in examining. Dr. Freedman commented that because this is such an important technology, the NCI should be strongly behind it, and the Board should receive regular updates on the progress of NCI's nanotechnology activities.

Dr. McKinnon noted that the Nanotechnology R&D Act, signed the week before this NCAB meeting, allots \$50 M to the NIH out of an \$850 M national nanotechnology initiative for FY 04. Dr. Barker mentioned that the NIH has a Nanotechnology Roadmap, and the NCI will play a large role in these activities.

Dr. von Eschenbach concluded the discussion session by noting that, in anticipating an explosion in nanotechnology and its ultimate application to cancer, it is incumbent upon the NCI to position itself in front of this field as an unbiased broker to establish the platform and the standards. In creating a reference

point to which the research community can relate, it will allow for investigators to interchange and integrate information and progress as nanotechnology applications proliferate.

XI. WORKING LUNCH

Update: Task Force on Advanced Biomedical Technology Initiative—Dr. Eric Lander

Dr. Eric Lander reported on the progress to date in organizing the Task Force on Advanced Biomedical Technology, which he chairs. The four-part charge to the Task Force is to: (1) perform a technologic needs analysis with respect to cancer; (2) perform an opportunities analysis to identify technologies that are available and possible uses; (3) consider possible models for technology and how they can be integrated within the national program; and (4) consider how NCI's efforts in this area can relate to other diseases, other NIH Institutes and Centers, and other agencies. Dr. Lander noted that the Task Force roster includes a diversity of expertise and is strong with respect to science, technology, academia, and industry. Although the structure and processes have not been finalized, subgroups will be proposed to address issues related to profiles of cells, profiles of cancer and the organism, therapeutics, public health, and technology development. The initial meeting is scheduled for December 15.

Dr. Lander previewed the questions that have emerged in preliminary discussions:

- Where is the NCI in terms of technology, and what sorts of questions have yet to be addressed?
- What is meant by new technologies (e.g., the ability to take comprehensive profiles of cells and organisms and what that means)?
- What chemical, molecular, and nanotechnological tools are needed for detection, modulation, and delivery?
- What information technologies are needed to analyze, integrate, and turn data into information?

Dr. Lander noted that the potential goals for the use of the new technologies apply to both basic scientific and clinical research. There is a need to get the new technologies into the hands of the basic science research community to address basic biological challenges, such as the definition of better mechanisms, and into the hands of clinical scientists to address clinical challenges, such as the correct classification of cancers based on underlying molecular patterns or the deployment of proteomic tools for early detection in serum and by imaging. The Task Force will address the question of whether the limitation to taking full advantage of the new technologies is at the stage of invention, development, integration of multiple technologies to solve problems, or access. They will try to identify those needs that the NCI, in particular, can and should address. The final question for the Task Force is how to ensure that the promise of technology in cancer is fulfilled through funding mechanisms and challenges to the research community, which translate into a powerful program that will be the catalyst for achieving NCI's 2015 challenge goal. Board members were asked to submit their perspectives on the sorts of questions that should be addressed by the Task Force.

Questions and Answers

Dr. Love expressed the view that the emphasis of the new technologies should be on finding solutions to clinical problems relevant to the physiological totality of human cancer versus technologies in search of a use that appears to have resulted in reductionism. She pointed out that the Task Force roster should include clinicians. Dr. deKernion noted that it will be important to define clearly what the grand questions are and then promote the integration of geneticists, immunologists, and molecular biologists to answer those questions (i.e., to mine the technologic development that exists and focus it back towards basic discovery by posing the challenge). Dr. Larry Norton, Deputy Physician-in-Chief for Breast Cancer Program, Memorial Sloan-Kettering Cancer Center, commented that intermediate endpoints, such as response rate and response duration, have become the goals of therapeutics development over the years. He suggested that the new technologies present an opportunity to redefine the goals as stopping suffering or preventing disease progression because of the dramatic shift they have effected in biological research capabilities. Dr. Freedman suggested that the important focus should be on technologies that address the problem of how to change the public's behavior practices to make a major contribution to eliminating suffering and death from cancer. Dr. Lander asked that each NCAB member submit a suggestion in the coming week for a particular ability that would in his or her opinion drive progress on cancer forward.

XII. PROGRAM REVIEW OF CENTER FOR CANCER RESEARCH

Overview—Dr. Carl Barrett

Dr. Carl Barrett, Director, CCR, NCI, reminded members that the CCR was established in March 2001, by merging the Division of Basic Sciences and the Division of Clinical Sciences, and together with the DCEG, it constitutes the NCI's intramural program. Dr. Barrett noted that this biannual review of the CCR features six presentations by CCR scientists to indicate the basic, translational, and clinical research ongoing in the Center, with discussions to continue later in the meeting on reengineering the intramural program.

Fundamental Discoveries in Cancer

Role of DNA Breaks in Genomic Instability and Cancer—Dr. Andre Nussenzweig

Dr. Andre Nussenzweig, Senior Investigator, Experimental Immunology Branch, CCR, described research in his laboratory to show that not only the integrity of the DNA molecule itself, but also the proteins involved in packaging DNA in the nucleus are important for maintaining genomic stability and preventing cancer. The research has built on solid evidence that DNA double-strand breaks (DSBs) pose a considerable threat to genomic integrity because they are known to induce chromosomal aberrations that can lead to mutations and eventually cancer. These chromosomal imbalances are thought to promote tumorigenesis either by underexpression of tumor suppressor genes or by deregulated oncogene expression. Dr. Nussenzweig noted that DNA DSBs can be generated not only by ionizing radiation, but also during normal physiological events such as DNA replication, antigen receptor rearrangement in lymphocytes, meiotic recombination, and telomere dysfunction. His laboratory is attempting to understand the mechanisms by which bad outcomes from DSBs can be prevented. He demonstrated how histone proteins make up the nucleosome, which is double-wrapped with DNA, and how nucleosomes package the DNA into the small volume of the nucleus. He referred to the histone code proposed by Drs. Allis and Jenuwein based on the observation that the tails in the C terminus of histones actually undergo post-translational modifications, which form docking sites for different proteins that result in different biological outcomes.

Dr. Nussenzweig noted that his laboratory has been studying a histone variant called H2AX to understand the DNA damage response. A discovery in the laboratory of NCI's Dr. William Bonner showed that the induction of a single DSB results in the massive phosphorylation of histone H2AX molecules in the chromatin region surrounding the DSB. This results in signal amplification so large that DNA DSBs *in vivo* can be visualized using an antibody specific to the phosphorylated form of H2AX. This showed that phosphorylated H2AX forms large clumps of foci when cells are irradiated and DNA DSBs are induced. Further investigation with immunofluorescence and the fluorescence *in situ* hybridization technique by the Nussenzweig laboratory showed that phosphorylated H2AX (or gamma H2AX) marks the sites of DNA breaks during the normal physiological events. Dr. Nussenzweig explained that his laboratory next addressed the actual role of H2AX and its associated foci in the DNA gamma response, using a mouse model generated with H2AX deficiency. It was found that H2AX is essential for maintaining genomic stability. The H2AX knockout mice had chromosomal instability syndrome and exhibited many different phenotypes, including growth defects, hypersensitivity to radiation, male sterility, altered telomere topology, defective antigen receptor rearrangements, and enhanced tumorigenesis. Dr. Nussenzweig noted that, like some other DNA repair factors, the loss of H2AX did not directly lead to tumorigenesis because the mice lived quite long. However, when H2AX knockout mice were crossed with p53 knockout mice, and the highly abnormal cells were no longer eliminated by apoptosis, the double knockout mice die rapidly. In addition, it was found that having only one copy of H2AX promoted tumorigenesis in the p53 knockout mice, indicating that having only one copy of this histone is not sufficient to maintain genomic stability. In detailed analysis of the B cell lymphomas, consistent translocations were found in amplifications of the c-myc oncogene together with the IgH locus; notably the IgH locus was the site where the H2AX phosphorylation was seen in normal cells.

Dr. Nussenzweig concluded that these studies show that histone H2AX protects the genome from spontaneous irradiation, as well as V(D)J and class-switch recombination-induced DSBs, consistent with its phosphorylation at these sites. Relating these findings to H2AX and human cancers, he pointed out that the human H2AX gene maps to 11q23, which is the 11 megabase 3' of the ataxia telangiectasia mutant (ATM) kinase and is involved in signaling DNA breaks. H2AX resides within a minimal region hypothesized to contain a human tumor suppressor gene. A large number of human lymphomas and solid tumors contain deletions of 11q23 on a single allele (not necessarily involving ATM). Thus, H2AX deficiency or haploinsufficiency may contribute to tumorigenesis in humans.

Future directions for this research include seeking a better understanding of the chromatin changes that occur at the sites of DSBs because of the compromised genomic stability and multiplicity of phenotypes that occur in the absence of histone H2AX phosphorylation. One possibility that has been considered is the essential role of H2AX in forming the foci. In this respect, the hypothesis formulated in Dr. Nussenzweig's laboratory is that the chromosomal fragility, radiation hypersensitivity, growth defects, dysfunctional antigen receptor rearrangements, and male sterility all could be due to defective chromatin compaction in the absence of H2AX. Dr. Nussenzweig noted that there is additional, recent evidence for chromatin modifications at DNA DSBs and these actually may form a DNA damage-specific histone code, which may be critical for the maintenance of genomic stability.

TGF- β s in Cancer Progression: Complex Roles and Therapeutic Opportunities— Dr. Lalage Wakefield

Dr. Lalage Wakefield, Head, Tumor Suppressor Group (TSG), Laboratory of Cell Regulation and Carcinogenesis, CCR, presented a review of TSG research in two areas: (1) evidence for the dual role of transforming growth factor (TGF)- β as a tumor suppressor and pro-metastatic factor using breast cancer

as the paradigm, and (2) the attempt to antagonize TGF- β as a novel approach to suppressing metastasis. As background, Dr. Wakefield noted that TGF- β s are multifunctional polypeptide growth factors with widely expressed ligands and receptors. They play key roles in the development and maintenance of adult homeostasis and in response to injury, and they are the most potent known inhibitors of epithelial and immune cell proliferation. Experimentally, TGF- β s have biological activities that could either suppress or promote tumorigenesis, and the clinical data in the breast cancer paradigm are similarly conflicting. The unifying hypothesis is that TGF- β switches from tumor suppressor to pro-oncogenic factor during cancer progression. Dr. Wakefield's laboratory has formally addressed this hypothesis, asking whether TGF- β can switch from tumor suppressor to pro-oncogenic factor during cancer progression within a given cell lineage. The experimental system used was a staged series of human breast-derived cell lines, which represented normal, premalignant, well-differentiated tumors, and poorly differentiated metastatic tumors when xenografted into nude mice. To ask what role TGF- β s play in the different stages, a dominant negative TGF- β receptor was introduced into the four cell lines to block the TGF- β response and determine what effect this has when the cells are put *in vivo*. The findings were that TGF- β is a tumor suppressor in early pre-neoplasia and for low-grade breast cancer. However, in high-grade breast cancer, its tumor suppressor activities are lost and pro-metastatic activities are uncovered. In the absence of the TGF- β response, very little metastasis is seen. The conclusions from this study were that: (1) TGF- β can switch from tumor suppressor to pro-metastatic factor during carcinogenic progression within a given cell lineage; and (2) this switch occurs late in progression for breast cancer. Further research is attempting to decipher what happens at the metastatic switch stage.

Dr. Wakefield noted that these findings have implications for cancer therapy. Because the perturbation in the TGF- β system seen in late-stage disease is an increase in TGF- β ligand, the antagonizing TGF- β may be a viable therapeutic strategy. This strategy potentially would be applicable to a number of other tumor types, because TGF- β expression is increased in many advanced human cancers and correlates with enhanced invasion, metastases, and poor prognosis. Dr. Wakefield then described her group's "proof of principle" approach for showing that antagonizing TGF- β can suppress metastases. An antibody-like TGF- β antagonist (SR2F) was used consisting of the soluble extracellular domain of the type II TGF- β receptor, which binds the ligand, fused to the Fc domain of human IgG1. To control costs, a transgenic mouse was made that secreted SR2F from the mammary gland into the circulation, with distribution to all organs except the brain. This mouse was used to answer the questions "Does the SR2F antagonist protect the mouse against metastasis?" In an initial, simple experiment, metastatic melanoma cells were injected into the tail vein of control and transgenic mice to test metastatic efficiency. A site-independent suppression of metastases was found in all target organs for this cell line, and the suppression by SR2F appeared to be dose-dependent. Further study suggests that SR2F may suppress the transition from micrometastasis to clinically detectable macrometastasis.

Dr. Wakefield noted that the next step was to determine whether SR2F TGF- β antagonist could suppress metastasis without stimulating primary tumorigenesis or inducing new spontaneous tumors. A more realistic model of metastatic breast cancer (MMTV-Neu) was crossed with the antagonist mice to generate cohorts with (Neu/SR2F) and without antagonist (Neu). The findings suggest that SR2F suppresses metastasis in this breast cancer model without enhancing primary tumorigenesis. Further study to identify possible toxicities showed that prolonged (lifetime) exposure to SR2F is not associated with any of the expected adverse side effects. The conclusions from the second level of studies were: (1) a high-molecular-weight TGF- β antagonist can suppress metastasis without enhancing primary tumorigenesis in a metastatic breast cancer model, and (2) prolonged exposure to this type of TGF- β antagonist is not associated with any of the expected toxicities. To expedite this approach through preclinical development, Dr. Wakefield reported that the NCI and Genzyme Corporation signed a Cooperative Research and Development Agreement (CRADA) Partnership was signed in June 2003. To

further explore the hypothesis that TGF- β antagonists may have multiple uses in cancer therapy, the NCI component of the CRADA consists of a cooperative group of several independent NCI Principal Investigators (PIs) representing three different laboratories and branches. The studies are focusing on: (1) the use of TGF- β antagonists for the suppression of metastases; (2) use of these agents to improve hematopoietic recovery after myelotoxic chemotherapy; (3) relief from some of the fibrotic complications of radiation therapy, which can be dose-limiting; and (4) use of these agents to enhance various immunotherapy approaches such as vaccination.

Novel Approaches in Cancer Detection and Diagnosis

Mapping Molecular Network Interconnections Using Protein Microarrays for Patient-Tailored Therapy—Dr. Emmanuel Petricoin

Dr. Emmanuel Petricoin, Co-Director, NCI-FDA Clinical Proteomics Program, Senior Principal Investigator, Center for Biologics Evaluation and Research, FDA, reminded members that in a previous presentation, pattern technology developed by the NCI-FDA program was discussed. He stated that this discussion would focus on new types of protein microarray technology that the proteomics program has developed and is using in clinical indications. Future plans are to test the feasibility of a protein microarray-based technology for signal pathway analysis and for studying the circuitry or phosphoproteome of the cell. Dr. Petricoin noted that the heterogeneity among individuals holds true at a signaling level in the cell and for the circuitry in a wiring diagram of a cell. Therefore, the recent *U.S. News and World Report* article reporting the promise of breakthrough cures with new targeted medicines will become a reality only if patient and targeted medicine can be matched. The prospect from the FDA perspective is for increased efficacy and reduced toxicity for therapeutics in Phase III trials, if the new technologies are successful in matching the new targeted medicines with the right patient stratification.

Dr. Petricoin stated that NCI-FDA proteomic technologies focus on using molecular circuit images to choose the optimal therapy tailored to the individual patient, and monitoring the success of that therapy within the patient, coupling diagnostics with therapeutics. Because cancer is a product of the tissue microenvironment in which each cell type has a unique molecular portrait even within the same patient, understanding the signaling circuitry in all cells provides clues to the reason for changes that are occurring and to selecting the most effective medicine. The signaling circuitry is both intra- and extracellular, so these proteomic technologies are a systems biology-based approach looking at protein-protein interactions. They use laser capture microdissection (LCM) to orient around the problem of tissue heterogeneity, and even patient heterogeneity, by looking at cell populations from tissue biopsies in human tissue samples. The microdissected cells procured from a patient's tissue sample can be lysed, and the genomic and proteomic information can be analyzed.

Dr. Petricoin noted that to address the analysis challenge posed by the dynamic range of the proteome, a new protein array technology—reverse phase protein array—was developed, which coupled LCM with high throughput protein arrays. This technology enabled scientists to detect subtle differences in phosphorylation events that can occur between patients. Patient biopsy tissue samples are microdissected; each patient sample is arrayed in a miniature dilution curve, always in linear dynamic range of any antibody/analyte pair. The arrays then are probed with labeled, amplified antibody. Dr. Petricoin noted that this technology was used in a prostate cancer progression study that was reported in *Oncogene*. AKT and ERK activation was monitored to determine whether there was a build up of cells in premalignant lesions due to the prosurvival pathway increase, as measured by AKT phosphorylation as a surrogate, or whether the cells were dividing more rapidly, as measured by a mitogenic pathway surrogate. The microarrays gave very linear and reproducible results in both inter- and intra-assay analysis—linear with a correlation coefficient of 0.93. The study also showed very low coefficients of

variance in both an intra- and inter-slide comparison on microdissected material looking at prostate-specific antigen (PSA) from prostate cancer patients. Dr. Petricoin noted that many antibodies have been validated on a single-band Western blot, and the goal is to look at signaling circuitry to identify many events, not just one analyte or one event at a time. He described a study in colon cancer cells, which proved that the protein array technology can sense a cascade of events.

Dr. Petricoin stated that one use of the protein array technology is to study signal pathway profiling in human breast cancer biopsy specimens. One ongoing study involves a cluster analysis with several hundred phospho-specific endpoints, all normalized to the self protein for true signal pathway profiling. The antibody validation is ongoing as a preliminary step to the analysis. Dr. Petricoin described the different types of information that can be derived from the analysis. He noted that it has been possible to multiplex this technology to see both total Stat1 and phosphorylated Stat1 in the same array, using a dual-colored dye analysis. More importantly, this type of analysis has been extended to discreetly small numbers of cells, such as would be available in a tissue needle biopsy from a clinical trial. He described a study in a metastatic ovarian cancer population before and after treatment with Gleevec and demonstrated how the number of cells needed for protein array analysis can be calculated. In another study set of patients with metastatic breast and ovarian cancer treated with Herceptin followed by Taxol, the investigators were able to analyze tissue biopsies taken before and after treatment and longitudinally through recurrence. This is being done to look for clues to explain the patients' relapses after their initial response to Herceptin/Taxol. One of the findings was that phosphorylation of AKT is higher in the recurrence samples than in the initial sample, and although Herceptin knocked down the prosurvival pathway in the initial event, the rebound of that pathway was higher. It is hoped that this finding will allow the investigators to determine what is causing AKT levels to increase.

Dr. Petricoin noted that the analysis of this breast cancer array is underway using a heat map, and he described the findings from that analysis. Principle component analysis of human breast cancer phosphoproteome now can be performed, and the data now can be analyzed by phosphorylation levels. It was possible to discriminate a high percentage of normal tissue from cancer by a combination of phospho PKC α and phospho STAT1 levels. Extending this observation in the work of Dr. Laura Esserman's group, the question was asked as to how PKC α was affected in patients who had the better outcomes in a neoadjuvant setting on Adriamycin/Cytosin therapy where nodal involvement was a good prognostic factor. It was found that patients with fewer than three nodes involved had very high levels of PKC α when compared with those with four or more nodes. Dr. Petricoin noted that the same type of analysis can be done with other types of epithelial cancer such as ovarian. It is possible to build relationships by pathway phosphorylation levels, which is important because the drug target itself and the pathway around it can be studied.

Dr. Petricoin stated that the NCI-FDA program is working to address roadblocks to the successful completion of this protein microarray technology. The need for novel inhibitors is being addressed in relationships at CRADA and pre-CRADA levels with eight pharmaceutical companies to gain early access to their kinase inhibitors. Antibodies are being sought in collaborations with BD Transduction Laboratories. Reference standards are being developed with both the National Institute of Standards and Technology and BD. Platform development also is being pursued through CRADAs with eight other companies.

Future directions for this research are to use the information built around the interdependent interconnections that exist in a patient to conduct clinical studies that use combinatorial therapeutics in a rational and tailored way and at lower levels, then to take advantage of the lower level concentration for targeted therapy and therapeutic index scoring. Dr. Petricoin stated that this was proved in a study using

carboxy amido imidazole (CAI) with a COX-2 inhibitor in colon cells. Profound inhibition of growth was seen in the CAI/COX-2 inhibitor treated cells, but not in the cells treated with either compound alone. The same dramatic result was seen in CAI/COX-2 study in pancreatic cell lines as well as in arrays in the phosphorylation of the EGF receptor itself. Dr. Petricoin stated that the plan proposed by the NCI-FDA Clinical Proteomics Program is to incorporate kinase substrate profiling using reverse-phase protein microarrays into all CCR-based targeted therapy trials. At this time, a variety of Phase I and Phase II trials

are open to accrual, and the utility of protein microarrays is being evaluated. The hope for the future is to be able to target and tailor therapy based on the outcome from protein microarrays.

Oncologic Imaging: Structure, Function, and Molecular Biology—Dr. Peter Choyke

Dr. Peter Choyke, Chief, Magnetic Resonance Imaging, Diagnostic Radiology Department, NIH, began his discussion of the CCR Molecular Imaging Program by pointing out that current clinical imaging modalities have become very good at detecting small anatomic abnormalities. However, pure anatomic imaging is nonspecific. This is particularly problematic for cancer screening programs such as computed tomography (CT) for lung and colon cancer, magnetic resonance imaging (MRI) and mammography for breast cancer, and colonography, which take advantage of high-resolution imaging but suffer from nonspecificity and exposure of patients to radiation and expense. Dr. Choyke stated that a goal of current screening research is to utilize the new technology of serum proteomics to select for patients who should undergo imaging on the premise that the serum proteome will reveal those patients at high risk and imaging then will localize the tumor. Whether the proteomic study should lead to an imaging study, or vice versa, remains an open question. Moreover, imaging must advance beyond simply depicting anatomy. The new challenge is to combine powerful anatomic techniques with functional and molecular techniques, such as enhancement kinetics, to further refine the diagnostic accuracy of imaging. The menu of imaging modalities that currently can be brought to bear on the issues of tumor physiology and metabolism include CT, ultrasound, MRI, MR spectroscopic imaging, positron emission tomography (PET), nuclear medicine and optical techniques, and nanotechnology.

Dr. Choyke described research at the NCI focused on angiogenesis as a critical step in the progression of cancer. Angiogenic vessels are highly permeable—this property then becomes a possible marker for cancer. He demonstrated how it is possible to obtain an indication of the heterogeneous distribution of angiogenesis within a tumor by using a two-compartment pharmacokinetic (PK) model to analyze dynamic contrast enhanced MRI images through tumors. The rate at which contrast-enhanced blood enters the vascular space and exchanges with the tumor extravascular space is indicative of the vessel permeability. This easily performed test has been useful in the characterization and monitoring of tumors and is being used specifically as an indicator of success in angiogenic inhibitor clinical trials. In one trial conducted at the NCI, an anti-VEGF antibody was administered prior to conventional chemotherapy in advanced breast cancer. Dynamic contrast enhanced MRI showed an early and significant effect on the vascularity of the tumor with the anti-VEGF antibody alone but also showed that the combined effect of the antibody and chemotherapy was more profound. Dr. Choyke pointed out that this method may help in deciding early in a trial whether an angiogenic inhibitor merits continued evaluation. A similar concept is being explored in prostate cancer in NCI trials. Conventional imaging techniques have been disappointing in their ability to localize prostate cancer. Endorectal coil MRI of the prostate, which includes a dynamic contrast enhancement, is used to direct a transrectal-guided biopsy under MR to obtain a more accurate tumor localization. This information then can be used to direct minimally invasive targeted therapies such as high-dose rate brachytherapy or laparoscopic prostatectomies.

Dr. Choyke noted that hypoxia inducible factors, HIF1- α and HIF2- α , also are potential targets for angiogenesis imaging. Because HIF upregulates the glucose transporter gene family, GLUT, imaging methods that depend on glucose metabolism may reflect HIF activation. The imaging modality best suited to this research is fluorodeoxyglucose (FDG) PET, and this modality now is used in clinical trials to better understand the effects of angiogenic inhibitors. Dr. Choyke stated that, in addition to conventional FDG, the CCR Molecular Imaging Program has access to a number of novel PET agents. For example, C11-labeled carbon monoxide is used to quantitate blood volume and O15 water is used to quantitate flow in tumors during angiogenic-inhibitor therapy. In addition, a number of other PET agents are emerging from the Development of Clinical Imaging Drugs and Enhancers Program. These include fluoro-L-thymidine, which will soon be taken to the clinic, and a number of other agents that are not yet widely available clinically.

Dr. Choyke commented that the CCR Molecular Imaging program also can develop novel imaging probes. A variety of animal imaging units mirroring those available in the clinic are available for research including “micro” MRI, PET, Optical, and CT. Dr. Choyke stated that molecular targeting of imaging agents is a future direction for the CCR Molecular Imaging Program, which currently is recruiting chemists with the goal of developing highly specific imaging agents for early detection and treatment monitoring. Nanotechnology promises to enable the investigators to load the nanoparticles with both the appropriate target and sufficient quantities of an imaging beacon to be detected by imaging. This will be a platform technology that heavily depends on the nanotechnology initiative.

In summary, Dr. Choyke stated that the Molecular Imaging Program is a many-faceted program with clinical trial, pre-clinical evaluations, and developmental synthetic chemistry components that will enable building and testing probes for the future. This new initiative builds on an already rich array of resources that will be translated to the clinic in coming years both at the Frederick Cancer Research and Development Center and the Bethesda Campus. The program is committed to the concept of developing highly specific imaging probes that are relevant to the diagnosis and treatment of human cancers.

Questions and Answers

Dr. Love expressed the view that in imaging to detect angiogenesis, one presumes that micrometastases already exist; therefore, the clinical outcome will not be changed. Dr. Choyke pointed out that the modality is being used to differentiate lesions to see whether they have a benign versus malignant angiogenic profile. Dr. Freedman commented that the NCI can play an important leadership role in this research area and asked about plans for clinical testing in the cancer community. Dr. Choyke noted that funding is available for trials in this area for candidate probes, but additional evidence of efficacy is needed before the investment can be made in large trials. The NCI has a role to play in preliminary data gathering and pilot trials leading to cost-benefit analyses. Dr. Barrett noted that this is seen as an opportunity for the CCR program to work with the extramural Divisions. Dr. Ellen Feigal, Director, Division of Cancer Treatment and Diagnosis (DCTD), noted that DCTD has extramural cancer imaging investments that range across the entire spectrum from basic science to clinical trials. Dr. Niederhuber commented that the American Association of Cancer Institutes has an initiative whereby radiology Chairs from major research universities and Cancer Center Directors meet for a dialog on the organization and function of Cancer Centers. He noted that a problem in the academic community is that classic radiology departments are service oriented, and the training of young faculty does not include the same research opportunities as other disciplines.

Immunotherapy

Integrating Immunotherapy Into Cytotoxic Regimens: Pediatric Sarcomas as a Model—Dr. Crystal Mackall

Dr. Crystal Mackall, Head, Immunology Section, Pediatric Oncology Branch (POB), CCR, briefly reviewed the Branch's early leadership in the institution of chemotherapy for pediatric cancers. She cited the POB-sponsored clinical trial 86-C-169, which incorporated VP-16 and ifosfamide into the treatment of pediatric sarcomas, as having ushered in the state-of-the-art for this disease at the current time. Survival rates for patients with localized disease improved from 40 percent to between 50 and 60 percent. Dr. Mackall noted, however, that there have been no new chemotherapeutics since then that promise substantial improved survival for patients with nonmetastatic disease, and survival for patients with metastatic disease remains dismal. Patients who present with large, bulky tumors undergo multimodality therapy and experience a dramatic response but often sustain a metastatic recurrence followed by local recurrence at somewhere between 6 and 12 months. Dr. Mackall noted that the goal of POB scientists is to develop new consolidation therapies for use during the period of minimal residual disease to impact survival. Immunologic study of the host-tumor interface has shown that the intensive therapy induces profound T cell depletion in the patient and often the tumor recovers prior to immune system recovery. POB studies have focused at the discovery level on understanding the biology of T cell depletion and how to improve immune reconstitution and thus be able to incorporate immune-based therapies in that setting of minimal residual disease. Based on a multitude of evidence from their laboratory and from several others that interleukin-7 (IL-7) plays a critical role in recovery of T cells, either after bone marrow transplant (BMT) or intensive chemotherapy, POB investigators are interested in the development of IL-7 as an immunorestorative agent.

Dr. Mackall reviewed the history of recombinant human IL-7 (rhIL-7) since it was cloned in 1989, which culminated in 2000 in an NCI CRADA with Cytheris Corporation to co-develop a manufacturing process. A Phase I clinical trial is scheduled to begin immediately in the Clinical Center. She presented preclinical data, showing that IL-7 therapy in normal nonhuman primates had dramatic reversible increases in T cell numbers. The Phase I clinical trial is anxiously awaited so that work can begin on studies aimed at improving either tumor vaccines or immune reconstitution after chemotherapy or BMT. In the meantime, the POB has maintained an active clinical program by integrating immunotherapy into standard therapy for children and young adults with pediatric sarcomas. Close liaisons with centers across the country have been forged, and patients are referred to the NIH Clinical Center at the time of clinical presentation. T cells and monocytes are harvested at that time and cryopreserved in a close collaboration with the Department of Transfusion Medicine at the Clinical Center. Patients return home to receive multimodality therapy, which consists of multi-agent chemotherapy or surgery and/or radiotherapy. At 6-10 weeks, the patients return to the Clinical Center to receive immune reconstitution with autologous T cells and IL-2, which will be the platform for IL-7 in the future as well. An attempt is made at that time to immunize patients toward tumor-specific translocation-based peptides by pulsing this peptide on dendritic cells. Dr. Mackall pointed out that the POB is able to undertake innovative studies in rare diseases by recruiting patients from all over the country and abroad. The preferred method for developing these studies is to work with small cohorts of patients and make iterative changes. In this study, immature dendritic cells are administered in the first cohort and CD40 ligand mature dendritic cells in the second. Varying doses of IL-2 were used.

Finally, Dr. Mackall noted that no information on immune responses in patients was available when she began research to develop immune-based therapy for pediatric sarcomas, and no reagents were available. By undertaking the early-phase trials, the POB has been able to acquire tissue samples from patients, which enables researchers to work from bedside to bench to undertake the first-generation studies on the immunobiology of Ewing's sarcoma. These studies identified 4-1BB:1BBL interactions as a critical costimulatory pathway, which led to tumor-specific T cell activation in patients with Ewing's sarcoma. In an adoptive immunotherapy study using autologous CD8 T cells in a xenograft mouse

model, it was observed that the growth of primary tumors could be significantly diminished and, in some cases, metastatic disease could be prevented when T cells were generated using 4-1BB-based costimulation. These findings have led to further work on immunotherapy-based trials to find ways beyond autologous lymphocyte infusion to use adoptive immunotherapy administered to lymphopenic hosts in the hope of improving the outcome for patients with metastatic disease.

Design, Development, and Delivery of Recombinant Vaccines for the Therapy of Human Carcinomas—Dr. Jeffrey Schlom

Dr. Jeffrey Schlom, Chief, Laboratory of Tumor Immunology and Biology (LTIB), CCR, began by reminding Board Members that this is a programmatic effort in which the LTIB is responsible for the discovery phase, collaborates in the development phase with Therion Biologics Corporation through a CRADA, and collaborates with the Clinical Cooperative Groups in the delivery phase through a series of clinical trials. The program is based on the hypothesis that tumor-associated antigens (TAA) are, by definition, either weakly immunogenic or functionally nonimmunogenic. Cancer vaccine targets are proteins or peptides that are overexpressed in tumors versus normal tissues such as carcinoembryonic antigen (CEA) and MUC-1 or overexpressed in tumors and nonvital organs such as PSA.

Dr. Schlom noted that, on the basis of CEA characteristics, the hypothesis for CEA vaccine strategies is that they must be developed such that the presentation of these TAAs to the immune system results in far greater activation of T cells than is being achieved naturally in the host. These strategies have been placing the tumor antigen gene into a viral vector, diversifying prime and boost strategy, using T cell co-stimulation, altering the amino acid sequence of the tumor antigen to make an antigen more immunogenic (epitope enhancement), and using cytokines as biologic adjuvants. Pox vectors used were vaccinia for priming and avipox for boosting. These large viruses also are important because multiple transgenes can be inserted, they do not integrate into host DNA, and they efficiently infect the antigen-presenting cells. Phase I studies of a recombinant vaccinia-CEA (rV-CEA) conducted in the CCR demonstrated that it was safe and possible to induce T cell responses specific for CEA. A second Phase I study at Georgetown University of avipox-CEA confirmed its safety and ability to induce CEA-specific T cell responses and demonstrated that CEA-specific T cells can kill tumors expressing CEA. Preclinical studies conducted concurrently showed that the diversified prime and boost is more efficacious than the continued use of one vaccine. In another collaboration with Georgetown, these results were confirmed in a randomized Phase I/II study of vaccination in heavily pretreated patients with metastatic CEA-expressing carcinomas. Subsets of patients in the rV-CEA prime and avipox-CEA boost arm have survived to 5 years now, some having received between 25 and 30 vaccinations. Statistical analysis of the results showed also that the increasing survival correlated statistically with the generation of the CEA-specific T cell responses, suggesting that a more potent vaccine could be tried. Another finding from this study is that T cell responses are being generated to other TAAs like MUC-1, p53, and Her2/Neu, providing evidence of potential antitumor activity.

Next, Dr. Schlom discussed research to examine T cell co-stimulation as a modality, recognizing that these molecules are essential for vigorous T cell responses, especially with a weak antigen. Genes for the co-stimulatory molecules were introduced into the vaccine vectors. In the study, three co-stimulatory molecules, chosen for their apparent ability to work synergistically, were placed into a vector along with the tumor antigen. High levels of T cell activation were seen with the triad of co-stimulatory molecules (TRICOM), and the level of co-stimulation was found to be synergistic, not additive. All three molecules are in clinical trials (in the CCR and at Georgetown) of intra-tumoral vaccinations in melanoma, bladder cancer, and prostate cancer.

With the background of findings from preclinical studies and studies in CEA transgenic mouse,

CEA-TRICOM Phase I trials have been initiated at Fox Chase Cancer Center, Duke University, and Georgetown. Preliminary results in the heavily pretreated patients with life expectancy of between 6 and 12 months indicate no dose-limiting toxicity. Forty percent of the patients had stable disease at 4 months, 11 patients had stable or decreasing serum markers, and 1 had a complete response. Patients who remained stable after 6 monthly vaccinations went on to receive vaccinations every 3 months. Six of the latter group who progressed restabilized after returning to monthly vaccinations. Survival for some patients now is at 2 years. Very good CEA-specific T cell responses are being observed, and they have been found to correlate with progressive-free and overall survival.

Dr. Schlom briefly described a soon-to-begin trial at Dana-Farber Cancer Center and the CCR with another antigen found on gastroenterologic, ovarian, and breast cancers that has been combined to a vector

with two antigens and the TRICOM. Another PSA vaccine trial is producing dramatic decreases in CEA and PSA responses with just one co-stimulatory molecule; antigen cascade also is being seen.

Future studies will use TRICOM vaccines in combination with conventional therapies such as radiation and selected drugs. In that regard, two preclinical studies in the CEA transgenic mouse model are gathering data on the use of CEA-TRICOM vaccine and Celecoxib. Mice on the combination regimen are surviving at 2 years, and there is discussion about a possible clinical trial in familial polyposis with Celecoxib and vaccine. Other research in collaboration with the CCR Radiation Oncology Branch is studying radiation-enhanced antigen-specific lysis of tumor cells, and dramatic antitumor effects in large tumors are being seen.

Dr. Schlom explained that the strategic plan for clinical trial development of combinatorial vaccine therapy includes a lung cancer trial at stage III with standard care plus or minus vaccine, a metastatic breast cancer trial of Docetaxel plus or minus vaccine, a stage IV colorectal cancer trial of vaccine with and without radiation and vaccine with and without COX-2 inhibition, and a Phase I/II/III pancreatic cancer trial with a CRADA partner. In response to a question from Dr. Niederhuber, Dr. Schlom noted that the LTIB has an active proteomics program, and interesting patterns have been identified in a prognosis study in breast cancer patients. All of the serum has been banked for these studies.

XIII. CLOSED SESSION

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

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

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

DAY TWO: WEDNESDAY, DECEMBER 3, 2003

XIV. INTRAMURAL REENGINEERING INITIATIVE—DR. CARL BARRETT

Dr. Barrett discussed reengineering the intramural program, a process that has been ongoing since last spring, as well as the ways in which the intramural program can add to the overall mission of the NCI and contribute to its other strategic initiatives. Dr. Barrett emphasized that this process is not a reorganization, and the term “reengineering” was chosen to highlight that fact. He noted that one overarching goal during the reengineering has been to maintain the independent investigator-initiated component of NCI’s intramural research program and encourage translational and clinical activities in interdisciplinary research. Another overarching principle has been to recognize the existing strengths of the program and build upon those through development of crosscutting organizational structures, working groups, initiatives, and partnerships both with other Institutes as well as with academic centers and industrial partners.

Dr. Barrett reminded Board members that NCI’s intramural program is composed of the DCEG and the Center for Cancer Research. Together, these two entities are well positioned to serve as a premier center for cancer research. The intramural program has a strong foundation in basic science coupled with innovative technology development as well as outstanding clinical investigators within the NIH Clinical Center and the population scientists in the DCEG. This offers a unique opportunity to conduct both training as well as multi- and interdisciplinary research. The intramural research program also stands poised to provide leadership for a number of other opportunities in a variety of different arenas that will impact on the elimination of suffering and death due to cancer. Some of these opportunities include the opening of the new NIH Clinical Center in approximately 1 year, the establishment of a number of new consortia with extramural investigators and the intramural program, and the development of new technologies being driven in part through intramural program research. The intramural program also will play a significant role in meeting the goals of the NIH Roadmap by fostering new approaches to science, building new pathways to discovery, and reengineering the clinical enterprise.

Dr. Barrett noted some of the unique qualities of NCI’s intramural program, including: (1) a close link between the basic clinical and population research in a comprehensive and interactive environment, (2) a centralized and collaborative program of epidemiology with access to relevant populations and the ability to investigate “natural experiments” whenever and wherever they occur, and (3) access to the NIH Clinical Center. In terms of cancer interventions, the program’s research emphasizes the development and discovery of new agents and the origination of clinical studies that are new, rather than simply evaluating the effects of known drugs. As a result, there has been an increased focus on understudied diseases, cancers with increasing incidence, or cancers involving special populations. Dr. Barrett also noted that the IRP program has an environment that is conducive to the recruitment, training, and retention of fellows who are interested in transdisciplinary research.

At the onset of the reengineering effort, which originated from a challenge to the intramural program from Dr. von Eschenbach, a meeting for all intramural investigators was held at both the Frederick and Bethesda Campuses. Feedback was obtained through an anonymous Web-based system, and a series of focus groups were convened to address some of the specific reengineering objectives. The BSC also was asked to provide input.

Dr. Barrett elaborated on the five objectives of the intramural reengineering process. The first objective is to define and enhance the value added of the intramural research program to the NCI. Encompassed within this objective is the goal of preserving and enhancing the environment conducive to innovative, high-risk, long-term basic research while at the same time fostering translational, clinical, and population-based research. Functional structures within the intramural program were identified to

facilitate interactions and collaborations across disciplines and to create ways in which they could communicate in a common language. To help meet this first objective, efforts are underway to increase the interactions and collaborations between the intramural program with the extramural investigators and expand the interactions with the public and private sectors. Faculties and working groups have been organized to:

(1) provide a forum to engage scientists across administrative structures to promote interactions and communications; (2) promote translational and interdisciplinary research to afford opportunities to develop new technologies and resources beyond the scope of an individual investigator's abilities; and (3) enhance mentoring, recruitment, and training of fellows. At present, there are 24 faculties and working groups that are disease-, discipline-, or approach-based. Dr. Barrett estimated that there are more than 1,500 members in these faculties, and the majority of PIs are involved in multiple faculties. The intramural program also has established the NCI Eminent Scholar position, which involves a long-term relationship with extramural investigators who are expected to participate on a routine basis within the activity of the intramural program.

The second objective of the intramural reengineering process is to develop innovative new technologies and approaches for use in both cancer discovery, prevention, detection, diagnosis, and treatment. Four Centers of Excellence were established—in the areas of advanced biomedical technology, epidemiology, immunology, and molecular oncology—to dedicate the intramural program to high-risk, innovative, basic clinical and epidemiologic research. These Centers of Excellence serve as a focal point for resources and infrastructure for the purpose of accelerating research. They also facilitate interactions and new initiatives as well as provide leadership in these areas.

The third objective is to facilitate the development of a unique clinical research program within the intramural program for the delivery of novel cancer interventions for therapy as well as prevention. This objective involves the development of unique capacities as well as priority setting for the intramural program's clinical activities. A Centralized Medical Oncology Clinical Research Unit (MOCRUC) was created; this structure serves as a clinical partner to all intramural PIs. The MOCRUC helps facilitate the delivery of laboratory-based discoveries into the clinical setting and establish standards of excellence for clinical research and patient care. The MOCRUC is divided into different clinical research sections, each headed by a specialist in a particular type of cancer or approach.

The fourth objective of the intramural reengineering process is to foster training to ensure excellence within the program and reflect the need for new transdisciplinary approaches to cancer research. NCI's intramural program includes a vigorous and broad training program. Dr. Barrett explained that the intramural program provides a number of unique opportunities to conduct the type of training that is needed today in terms of engaging investigators in interdisciplinary research and fostering multidisciplinary collaborations.

The fifth and final objective is to implement a review and reward structure that will continue to encourage and reward innovative research while at the same time fostering collaboration and maintaining a premium on scientific excellence. Intramural program staff have had numerous discussions with members of the BSC regarding how to evaluate investigators conducting interdisciplinary team-based research.

Dr. Barrett noted that these discussions are leading to a good, mutual understanding of how this can be accomplished.

Dr. Barrett closed his presentation by describing some of the immediate impacts of the reengineering process, including better coordination of interactions between researchers. Within the intramural program, there has been an acceleration of development and implementation of new

technologies. The program has been facilitating translational research and has made improvements in its clinical programs. More connections have been made with extramural colleagues, new partnerships have been formed with industry, and training programs have been improved.

Questions and Answers

In response to a question from Dr. deKernion, Dr. Barrett explained that the MOCRU is a dedicated clinical infrastructure. Investigators who are part of the MOCRU are focused on clinical research, clinical training, and clinical care, but they form partnerships with a variety of laboratory structures that exist in other organizational structures. The centralized clinical trials infrastructure is a different entity that serves all clinical trials conducted at the NCI. Dr. Joseph Fraumeni, Director, DCEG, noted that the intramural program has been working to develop the Molecular Epidemiology Center as well as case-control and family-based consortia, which bring together intramural and extramural investigators in unique partnerships. In addition to studying cancers that are high in prevalence, incidence, and mortality, the program is examining some of the more lethal cancers, such as pancreas, liver, and esophageal adenocarcinoma, particularly those that are rising in incidence. There also is consideration given to international opportunities in which there are significant geographic variations in cancer. The program also is concentrating on the development of technology, particularly at the Frederick Campus, for biospecimen processing and storage as well as high throughput technologies and metabolomics.

Dr. Freedman asked about mentorships, noting that because of the program's unique resources, there is a good opportunity for graduate students around the country to share mentorship at the NCI. Dr. Barrett commented that the NIH has developed a highly successful Graduate Partnership Program, which is an infrastructure that enables joint programs between academic centers and the intramural program, both at the NCI as well as at other Institutes. There also exists a newly announced cross-training program between the FDA and the NCI to bring in a completely new group of first-rate scientists who are engaged in the regulatory process. It also was noted that with respect to the fellowship program, NCI's intramural program accepts 10 fellows per year. The program has partnered with the National Heart, Lung, and Blood Institute to create a joint program in hematology/oncology.

Dr. Norton expressed concern that the intramural program might not be doing enough in the areas of molecular diagnostics and molecular profiling, noting that the Cooperative Groups all are trying to construct these technologies. Instead of reconstructing these at Cancer Centers, it might be more beneficial to centralize these efforts through the intramural program, utilizing and leveraging the power of bioinformatics. Dr. Barrett agreed, noting that this is a significant challenge. Dr. Barker noted that part of the National Biomedical Technology Initiative involves optimally leveraging advanced intramural resources. There are opportunities for creating unique teams of scientists in the intramural and extramural communities to solve problems and leverage resources. Similar partnerships have been formed between the NCI and FDA.

Dr. Ramirez asked about intramural efforts to recruit minorities into training programs. Dr. Barrett explained that the intramural program is trying build up opportunities to access underserved populations in concert with the CRCHD. The program also is working with the CRCHD and Tulane University in an effort to train and recruit minority investigators. Dr. Fraumeni added that there also are ongoing efforts to target cancers that are excessive in certain ethnic populations, as well as certain geographic areas of the country where the rates are unusually high.

Dr. Barrett commented that the intramural program should not have preference in terms of clinical trials just because they are part of another government agency. Dr. Feigel discussed the

connection of the intramural program with the national extramural priorities in clinical trials. It is not an issue of preferential treatment, but rather how value is added to the national enterprise. There is an opportunity to increase the integration of intramural investigator activities with the national extramural program. Dr. von Eschenbach explained that unique strengths and unique opportunities exist within the intramural program. These need to be viewed from the perspective of capitalizing on the strengths in a manner that adds value to the entire enterprise occurring within the rest of the cancer community. Dr. Elmer noted that with regard to improving the numbers of underrepresented populations represented in clinical trials, the Washington, DC, Metropolitan Area includes almost 2 million Asian Americans and almost 1 million Latinos.

XV. THINK TANK TASK FORCES AND LONG-RANGE SCIENTIFIC PLANNING—DR. DINAH SINGER

Dr. Dinah Singer, Director, DCB, provided highlights of a series of think tanks on cancer biology being organized by the scientific staff in the Division. This series is focused on basic cancer biology research, the discovery aspect of the discovery, development, and delivery continuum. The goal is to identify emerging concepts and promising areas of investigation and to receive input from the research community regarding gaps and opportunities in basic research that the NCI might help to address. The DCB is organizing a series of nine think tanks with three purposes in mind to: (1) assess the status of cancer biology along the cancer initiation/progression/metastasis continuum, (2) determine the state-of-the-science and where it is heading in specific areas, and (3) determine what the NCI can or should do to facilitate progress in cancer biology. A driving force behind the series is the knowledge that advances in the development and delivery phases of the continuum are driven by advances in cancer biology.

The think tank series is organized around the continuum of cancer initiation, progression, and metastases. The subjects to be addressed by the think tank sessions include: initiation of cancer, with emphasis on genetic factors such as modifier and susceptibility genes and the epigenetics of cancer; nongenetic and external factors, including biological and chemical carcinogens, nutrients, and hormones; tumor immunology; cell decisionmaking mechanisms; tumor stem cells and tumor progression; the role of the tumor microenvironment; and integrative cancer biology. The topics are designed to overlap so that, ultimately, the information and knowledge gained from the think tanks will provide a broad perspective on current understanding of cancer biology. The format for each of the nine sessions will be the same. A maximum of 15–20 participants will be involved in each session. Participants will be selected to represent a broad range of subfields and related fields, and will represent various stages in their career development. The agenda for each session will be established in advance by the two invited Co-Chairs and DCB organizers. It will emphasize discussion rather than formal presentations, and will highlight areas of new information and greatest need. Participants will receive the agenda prior to each session and will be assigned an area to think about and perhaps to take the lead in discussing.

Questions to be addressed in each session include: (1) Where does the field stand today? (2) What knowledge is needed to advance the field? (3) What are the gaps/roadblocks to progress? (4) Are there areas of expertise that should, but have not, been brought to bear on problems in this field, and can this be remedied? and (5) What crosscutting tool(s), enabling technology, or infrastructure needs to be developed to facilitate development of the field?

Dr. Singer noted that three of the nine think tank sessions already have been held, and the format worked successfully to elicit creative and thoughtful discussion and facilitate the identification of specific issues and broader themes. The series is expected to be completed by June 2004. Expected outcomes include generating reports to summarize the scientific discussions. These reports will be published in journals when appropriate and posted on the DCB Web Site. Separate documents will summarize think

tank recommendations and provide a basis for the NCI to collate recommendations, develop plans, and construct global initiatives to address identified needs.

As a result of the three think tank sessions already held, the DCB has issued an RFA to develop integrative cancer biology programs to promote the analysis of cancer as a complex biological system, with an ultimate goal of developing reliably predictive *in silico* or computational models of cancer initiation and progression and for developing cancer interventions. The intent is to integrate experimental and computational approaches to understanding cancer biology and to encourage the emergence of integrative cancer biology as a distinct field. The P50 programs developed under this initiative will include a training component.

Questions and Answers

Dr. Peter Kirchner, Program Manager, Office of Biological and Environmental Research, U.S. Department of Energy, asked about the interaction between the nine think tanks, whether they would meet together, and how they would interrelate. Dr. Singer responded that the sessions will be conducted separately over a period of 6–8 months. Continuity is provided through the DCB scientific staff who will attend all of the sessions and by inviting some participants to attend more than one session. Dr. Neiderhuber noted that the Board might want to follow the progress of these sessions and may provide space on future agendas for updates on the process. He also expressed an interest in promoting coordination between the think tank effort and the efforts of the *Ad Hoc* Subcommittee on Biomedical Technology. Dr. Singer noted that Drs. Lander and Hartwell, who are involved in the *Ad Hoc* Subcommittee on Biomedical Technology, have been invited to all think tank sessions and participate as observers during conference calls and focus groups.

XVI. NATIONAL BIO-SPECIMEN NETWORK INITIATIVES—DR. ANNA BARKER

Dr. Barker called the Board’s attention to two documents in their possession, the National Biospecimen Network Blueprint and the Human Tissue Repositories Report prepared by the RAND Corporation. She urged attendees to read both documents. Dr. Barker noted that biomedical science, and especially cancer research, has reached a “watershed point” with regard to the convergence of science and technology. This is a point at which progress cannot be predicted because the extent to which technology integrates, informs, and actually accelerates the progress of science becomes unpredictable. In his book, Dr. Andy Grove called this point the “inflection point.” The National Biorepository Initiative (NBI) in particular, and “repository science” in general, exemplify this convergence of science and technology.

A key question is how to most effectively provide the resources to support the development of new interventions for cancer, especially new diagnostics and new therapeutics. An important barrier to achieving this goal is the lack of availability of uniformly collected, stored, and annotated tissue that is associated with a national resource that will allow progress toward the goal of using *in silico* resources to discover and develop new agents. A second issue for the NCI is not just to provide these systems, but to provide them in partnership with the community. The NCI must play a leadership role in this endeavor, but should not pursue it in isolation. In fact, the NCI is pursuing the NBI in collaboration with the National Dialogue on Cancer (NDC). The NDC held a meeting in 2002, at which the absence of a national strategy for biorepositories was identified as a major barrier to the development of new cancer interventions.

Dr. Barker remarked on the complexity of the issue of repositories. Tissues have been collected for more than 100 years in the United States. Currently, there are more than 300 million samples from about 150 million cases, with approximately 20 million new specimens being collected each year. Most

biorepositories were formed for specific reasons and have specific objectives. They may range from very large activities to very small ones, and are conducted in such settings as academic medical centers, Cancer Centers, and individual laboratories.

Dr. Barker noted that the international community has made more progress toward the centralization of a specific kind of repository that would support genomics- and proteomics-based research than has the United States. She mentioned ongoing efforts in Iceland (where 90 percent of those asked to sign up for the biorepository have complied), the United Kingdom (where the U.K. Biobank expects to collect 500,000 samples from individuals of ages 45–69 and to accumulate longitudinal data over approximately 10 years to examine diseases related to environmental exposure, including cancer; and the National Cancer Centre Tissue Repository is a new resource with which the NCI has collaborated), and Japan (where Biobank Japan is a 5-year initiative to collect 300,000 patient samples linked across cancer, diabetes, rheumatoid arthritis, and other diseases). She emphasized that genomics and proteomics research has reached the point where the internationalization of research no longer can be considered a matter of choice. The ability to compare data internationally is vital.

Dr. Barker provided an overview of the National Biospecimen Network Blueprint (the Blueprint) and urged Board members to read the document for themselves. The Blueprint was developed by a group consisting of more than 100 representatives of the public sector, private sector, survivors, and various disciplines. She stressed the importance of engaging pathologists in the biospecimen repository effort because of their role in controlling the acquisition and distribution of tissues. Dr. Barker explained that the NBI is a new effort and will be in addition to and overarching of all NCI current initiatives. The plan is to connect current resources in new ways and pilot the new initiative.

Dr. Barker emphasized that the Blueprint has not yet been finalized and encouraged Board members and others to submit their comments. Additional copies of both the Blueprint and the RAND Corporation report are available from Dr. Barker and from Dr. Julie Schneider, American Association for the Advancement of Science. Both reports also are posted on the NDC Web Site. In developing the Blueprint, the group considered a series of barriers, including comparability of data, the absolute protection of patients' genetic privacy, and issues concerning the ownership of tissues and investigator access. Several private companies are involved in repository efforts and sell tissues primarily to the private sector. Many Cancer Centers are engaged in this process to generate revenue and also as a source of tissues. Once data are sold and involved in experiments conducted within these companies, however, the data cease to be available in the public domain. This is a major concern because of its implications for limiting the amount and availability of data. The NCI has a specific interest in this area, and NCI progress review groups and others have asked that specific repositories be created to examine specific cancers and other diseases.

Dr. Barker noted that recent collaborative efforts with other countries are enabling the NCI to catch up in the repository effort. The NCI controls some of the major biospecimen network resources (approximately \$40 M to \$50 M worth) as well as many smaller resources. Some of these resources represent the type of state-of-the-art standards of practice that would be applicable to a national biospecimen network. Bringing consistency to the collection, storage, annotation of and support through bioinformatics, and provision of access to these data on a national basis, however, must be advanced in a more strategic manner.

Dr. Barker noted that private-sector companies have been supportive of the NBI. She expressed the opinion that such companies would be satisfied with having precompetitive data for use in developing cancer interventions and building intellectual property rather than having to address the issue of buying tissues and creating the database.

In providing highlights of the RAND Corporation report, Dr. Barker noted that RAND had conducted a pivotal study of biorepositories several years ago. For the current report, the NCI asked RAND personnel to revisit repositories thought to be potential best practices. The current report is based on visits to 12 resources, including some NCI resources. These ranged from being very centralized to being very distributed, served a broad range of purposes, and had few common standards.

The proposed NBI is to be a standardized resource. Goals include standardization of data (specifically, longitudinal data) and preservation of tissue to the maximum extent possible. Bioethical reviews will be conducted in addition to Institutional Review Board reviews. A state-of-the-art informatics system will be developed, along with a bioinformatics grid into which data can be input. Open peer-reviewed access is another goal of the proposed initiative. With regard to intellectual property concerns, it was decided to reduce focus on the intellectual property content of the resource itself. Data obtained from the resource may be used to develop intellectual property, however. With regard to the collection and distribution of data, the proposed initiative envisions a distributed resource with centralization of rare biospecimens and data. In summarizing what is envisioned under this initiative, Dr. Barker cited a scenario in which a researcher at perhaps the Memorial Sloan-Kettering Cancer Center, the M.D. Anderson Cancer Center, or the NCI would be able to go online, find a needed tissue, have the tissue sent if the study qualifies, access the database to see how many other similar tissues have been examined and to ascertain longitudinal data, and so forth.

Dr. Barker distributed copies of a study that had been published recently in the *New England Journal of Medicine (NEJM)* on biorepositories and the need for a chain of trust. The group that developed the Blueprint also saw the chain of trust issue as a primary concern. The Blueprint proposes that the national repository be run by a nonprofit organization to be overseen and managed by a board of governors. There would be an operating center and business units. This model is similar to that used to conduct organ donor programs. Funding would be multisector. Dr. Barker noted that all of the basic components of the proposal must be piloted to ascertain the feasibility of the project.

Dr. Barker noted that the Board has a committee that is concerned with tissue biorepositories. Perhaps this committee should be reactivated to enable the NCI to take the lead in this area. Dr. Ellen Feigal, Acting Director, Division of Cancer Treatment and Diagnosis, NCI, and her group presented a proposal for a potential pilot with cooperative groups at the last BSA meeting. Dr. Richard L. Schilsky, Professor of Medicine, and Associate Dean for Clinical Research, Biological Sciences Division, University of Chicago, has indicated that the leukemia group is very interested in piloting this concept. Prostate cancer funders also have expressed interest in piloting a prostate cancer endeavor. Dr. Barker suggested that this topic be revisited at the next NCAB meeting.

Questions and Answers

Dr. deKernion noted that significant progress has been made in areas such as specimen annotation and collection and noted the difficulty involved in addressing these areas. He suggested that a critical point to be decided is who will preside over the distribution of the samples. As this is an area in which significant conflict arises, this decision should be made early in the process of developing the NBI. He expressed his support for the idea of piloting concepts with specific diseases such as prostate cancer and then applying what is learned from such pilot programs as appropriate to a broad, international effort. Dr. deKernion posed the question of how for-profit companies that already have contracts to store tissues would be integrated into the larger NBI. Dr. Barker responded that a number of companies appear interested in becoming broader service providers and in cooperating with the NBI. She cited the potential for unprecedented partnerships. What will develop in the longer term is not yet certain.

Dr. Norton asked why the initiative should be governed by a 501(C)(3) rather than by the NCI. Dr. Barker referred to the *NEJM* article that had been distributed and cited survivor concerns about ensuring patient privacy based on the fact that the biorepository ultimately will be a source of genetic information on a patient-by-patient basis. The data must be accessible, but the genetic privacy of patients also must be protected completely. Thus, the chain of trust concept discussed earlier must be emphasized throughout the development and implementation of the NBI.

Dr. James Armitage, Dean, University of Nebraska College of Medicine, acknowledged that the NBI must be a prospective effort in terms of collecting specimens. He asked, however, about the thousands of specimens that currently exist and whether the biorepository might serve as a source of information about where such specimens are located so that researchers could seek referral information when looking for specific types of specimens. Dr. Barker agreed that thousands of repositories exist and noted that they have been identified by the RAND Corporation. She noted the need to integrate information on these legacy systems into the NBI in such a way as to be useful to researchers. Dr. Barker also noted that the group that developed the Blueprint was impressed with the possibility of eventually enlarging the effort to include public health information and to support public health research.

Dr. Niederhuber raised the question of whether a subcommittee or perhaps an *ad hoc* subcommittee on biorepositories should be appointed. Dr. Gray noted that a BSA subcommittee already was established to work with staff in this area. She suggested that, rather than appointing a separate NCAB subcommittee, an NCAB member or members could be appointed to work with the BSA subcommittee and to report back to the NCAB as a whole. Dr. Niederhuber said that he will watch his e-mail for a volunteer to serve on the BSA subcommittee and report back to the NCAB on this issue. He suggested that, initially, it might be appropriate for a Board member who serves on the *Ad Hoc* Subcommittee on Confidentiality of Patient Data to take on this task.

XVII. SUBCOMMITTEE REPORTS

Cancer Centers

There was no update on the Subcommittee on Cancer Centers.

Clinical Investigations

There was no update on the Subcommittee on Clinical Investigations.

Planning and Budget

The Subcommittee on Planning and Budget is planning to meet on January 26, 2004, to continue discussion of the budget.

***Ad Hoc* Subcommittee on Confidentiality of Patient Data**

Dr. Ramirez reported that the Subcommittee sent a letter to DHHS Secretary Thompson outlining the major findings of its public assessment regarding the HIPAA Privacy Rule. The Subcommittee's final report also was included in this letter. Both the letter and the report were included in Board members' meeting materials.

***Ad Hoc* Subcommittee on Bioinformatics and Vocabulary**

Dr. Chen reported that to date, CaBIG has engaged 49 of 60 Cancer Centers, and much progress has been made.

XVIII. IOM AND NCAB RETREAT REPORTS—DR. JOHN NIEDERHUBER

IOM Report

Dr. Niederhuber briefly described highlights from the IOM report on NIH reorganization, which was included in Board members' meeting materials. He noted the need for the Board to continue to monitor the impact of this report closely. Dr. Niederhuber explained that the NIH has been productive and successful in part because it is been a federation of highly specialized and somewhat independent units. Therefore, it is critical to maintain the strength of the individual Institutes. Although a matrix or decentralized structure presents difficult management and programmatic challenges, the IOM committee that drafted the report concluded that widespread consolidation or restructuring would not necessarily be the most effective approach to resolving those challenges. The committee did note opportunities for organizational, rather than structural, change; these administrative modifications could improve the strength, responsiveness, vitality, and accountability of the NIH. Dr. Niederhuber cautioned, however, that measures aimed at transcending a decentralized structure to optimize trans-NIH decisionmaking do not negatively impact the NCI in a financial manner. The NCAB, BSA, and other advisory groups will continue to work in concert to be supportive of the NCI and the IOM report.

NCAB Retreat Report

The NCAB Retreat was held in June 2003, and was aimed at addressing the following objectives: (1) review the current and future activities, roles, and responsibilities of the NCAB; (2) describe and agree on how the NCAB could make a more significant contribution to NCI's strategic direction; (3) be supportive of the Office of the Director and the Division Chiefs; and (4) address issues of communication and coordination among NCI advisory boards. Participants at the Retreat identified three major strategic goals for the NCAB (in addition to the grant-approval activities that are required by Congress): (1) vetting NCI's vision and plans, (2) monitoring the execution of NCI's strategic plans and the Director's progress in implementing those activities, and (3) asking probing questions about issues confronting the NCI and its vision and plans. A smaller working group was convened in August 2003, to examine these issues in more detail and advise the Board on how best to accomplish these goals.

The working group made the following recommendations:

- The Communications, Confidentiality of Patient Data, and Bioinformatics and Vocabulary *Ad Hoc* Subcommittees should be elevated to permanent Subcommittees of the Board.
- A draft of the NCI Bypass Budget should be made available at the February NCAB meeting to assist Board members in vetting NCI's vision and plans. At the subsequent June NCAB meeting, there should be a review of the progress towards finalizing the Bypass Budget. The annual report from the Chair of the DCLG advisory committee also will be given at this meeting. Then, at the September meeting, the working group recommended that a final draft of the Bypass Budget and annual reports from the Chairs of the BSA and the BSC be presented. The December NCAB meeting then would include the annual report from the NCI Director, intramural reports as appropriate, extramural program updates, and a review of the NCAB Subcommittees.
- A process should be established to report the NCI Director's progress in implementing the NCI

strategic plan and other activities. This could be accomplished at the time of the annual NCI Director's Report, and the NCAB could review and comment on the NCI goals, the 2015 plan and Bypass Budget, milestones, and the progress towards each of those.

- Periodic tours of selected NCI facilities should be planned to provide Board members with a better sense of the facilities where some of the activities that the NCAB reviews take place.
- Information provided to the NCAB by the Divisions and the Director's Office should be summarized or completed and provided to Board members in advance of the meeting rather than at the meeting when possible, so that members can become more familiar with the material. To that end, minutes from BSA, BSC, and DCLG meetings should be included in the NCAB meeting books to increase the communication between the various advisory boards.
- The NCAB should develop closer ties to NCI's Office of Communication and Office of Strategic Dissemination. It was recommended that these Offices be represented regularly on future NCAB

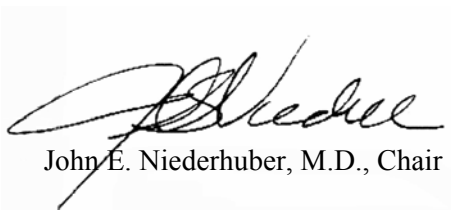
agendas, and that consideration be given to forming a Communications and Strategic Dissemination Committee from the *Ad Hoc* Subcommittee on Communication.

- Reports from each NCI Division should be given at each NCAB meeting.

XIX. ADJOURNMENT—DR. JOHN NIEDERHUBER

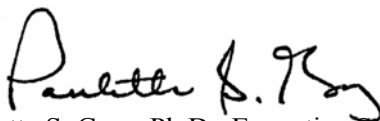
There being no further business, the 128th meeting of the National Cancer Advisory Board was adjourned at 11:40 a.m., on Wednesday, December 3, 2003.

2/18/04
Date



John E. Niederhuber, M.D., Chair

2/18/04
Date



Paulette S. Gray, Ph.D., Executive Secretary