DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
142nd NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 14-15, 2007

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

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BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 142nd regular meeting on Thursday, 14-15 June 2007, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Thursday, 14 June 2007, from 1:15 p.m. to 4:20 p.m. and closed to the public from 4:20 p.m. to 5:30 p.m. The meeting was open to the public on Friday, 15 June 2007 from 8:00 a.m. until adjournment at 11:45 a.m. NCAB Chair Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

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

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

Alternate *Ex Officio* NCAB Members
Dr. Irma E. Arispe, OSTP
Dr. Michael A. Babich, CPSC (absent)
Dr. Allen Dearry, NIEHS
Ms. Raye-Ann Dorn, VHA (absent)
Dr. Raynard S. Kington, NIH (absent)
Dr. Peter Kirchner, DOE
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Dori Reissman, NIOSH (absent)
Dr. Donald J.Wright, DOL (absent)

Members, Executive Committee, National Cancer Institute, NIH

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

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Eve I. Barak, National Science Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Paula K. Brown, Intercultural Cancer Council
Mr. Rodney Cotton, American Urological Association
Mr. George Dahlman, Leukemia and Lymphoma Society
Ms. Cindi Stephans, American Society of Clinical Oncology
Ms. Georgia M. Decker, Oncology Nursing Society
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Ms. Rebecca A. Kirch, American Cancer Society
Dr. W. Marston Linehan, Society of Urologic Oncology
Mr. David Lofye, Lance Armstrong Foundation
Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Dr. John Stevens, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Mr. Douglas Ulman, National Cancer Institute, Director's Consumer Liaison Group
Dr. Robyn Lynn Watson, American Society of Therapeutic Radiology and Oncology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists

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THURSDAY, JUNE 14, 2007

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 6 FEBRUARY 2007 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, called to order the 142nd NCAB meeting. She welcomed members of the Board, the President's Cancer Panel, *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 6 February 2007 NCAB meeting. The motion was seconded and the Board unanimously approved the minutes.

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

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2008.

III. DIRECTOR'S REPORT—DR. JOHN NIEDERHUBER

Status Report on Fiscal Year (FY) 2007 Appropriations. Dr. John Niederhuber reminded members that the period of growth in appropriations that the NCI experienced since FY 1999 ended and NCI appropriations have not grown over the past few years. The challenge since then has been to manage intramural NCI and extramural expectations with a budget that is less than inflation. The Basic Research and Development Price Index (BRDPI), which is based on an estimate of what it costs to perform research in the United States, is estimated at 3.8 percent for FY 2007. Members were reminded that the NCI strategy and mechanism for developing an operating budget in this fiscal climate has been to create a pool of about $60 M to $70 M, which can be reallocated to create new initiatives from a prioritized list or bring previously reduced programs back to an appropriate level. This process has been executed in an integrated fashion across the NCI and took place in FY 2007 over a prolonged period of time because of the delay in enacting the joint resolution. Dr. Niederhuber noted that the consensus of the Executive Committee (EC) is to continue this process absent any change in the level of appropriations. A 2-day EC retreat is scheduled for mid-July to begin the planning process for FY 2008.

Members were reminded that the revised continuing appropriations resolution (CR) for FY 2007, which became effective on February 15, provided a budget that was a continuation of the budget for FY 2006, with a few changes. NIH noncompeting grants (Type 5s) were to be reduced by 2.9 percent across the board; the NIH-wide target for awards to new investigators was set at 1,500; and Institutes and Centers (ICs) were required to use one-half of the money that they retain from the Roadmap initiative to fund additional competing Research Program Grants (RPGs). In regard to the latter, the NIH was required to fund 500 additional RPGs at an average cost of $324 K. Dr. Niederhuber informed members that the EC has worked since February on funding the large NCI programs. The Cancer Centers Program funding plan for FY 2007 has been put in place with a fairly minor cut in funds. With input from the Cancer Center directors, it was decided that the Cancer Centers Program would be funded on a sliding schedule to give added weight to the review scores received by the centers. Currently, 63 Cancer Centers are supported by the NCI, including two new centers: Dan L. Duncan Cancer Center, Baylor College of

Medicine, Dr. C. Kent Osborne, Director; and Stanford Comprehensive Cancer Center, Dr. Irving Weissman, Director.

Dr. Niederhuber reviewed the status of the FY 2007 budget allocations for the final quarter of the fiscal year, reflecting the movement of unused funds to programs where they can be used as programs evolve toward the end of the funding cycle on September 30. Estimates are that the end-of-year R01 payline will reach the 13th percentile for a success rate close to 20 percent, and the *R01 payline for new investigators will be at the 19th percentile. A total of 5,175 RPGs is estimated for FY 2007, including an estimated 1,314 competing grants and 205 *R01s for new investigators. Dr. Niederhuber announced that he is attempting to obtain governmental authorization for a pilot program for new investigators at the NCI. If the program is authorized, the parent institution would be required to have a mentoring committee in place to support new investigators from the time they enter the faculty until they reach the time for tenure decision 6-7 years later. Members were reminded also that the NCI reserves about 20 percent of its competing pool annually to fund exceptions above the payline toward the objective of achieving a balance in the NCI portfolio.

Continuing his status report for the final quarter, Dr. Niederhuber noted that, in addition to Type 5 grants targeted at 2.9 percent below commitment of record per NIH policy, Special Programs of Research Excellence (SPOREs) are about 3 percent below FY 2006; Cancer Centers were increased 2 percent from FY 2006; Cooperative Groups are flat with FY 2006; and Training is 2.6 percent below the FY 2006 level. In a recent meeting with Cooperative Group leadership, it was emphasized that difficult or flat budgets for the Groups result in a reduction in planning for new trials because of uncertainties faced regarding availability of funding in the second and third years of the trial.

Status of Legislation for FY 2008. Members were reminded that the FY 2008 President's Budget (FY08 PB) requests $28.849 B for the NIH, $232 M (0.8%) over the FY 2007 annualized CR. For the NCI, the PB figure is $4.782 B, 0.2 percent (!$9 M) lower than the FY 2007 annualized CR. In its markup on June 7 of the FY 2008 Labor/Health and Human Services (HHS) Appropriations Bill, the House Appropriations Subcommittee on Labor, HHS, and Education recommended appropriation of $29.650 B to the NIH—$750 M (or 2.6%) over the FY 2007 Joint Resolution (JR07) and $1.029 B (or 3.6%) over the FY 2008 PB. This bill would provide $4.870 B to the NCI, an approximately $73 M (or 1.5%) increase over JR07 and an $88 M (or 1.8%) increase over the FY08 PB. These figures include the $63.2 M that would have been programmed in past years for the NIH Roadmap Initiative or Common Fund. Action by the full Labor/HHS Committee is the next step in the Congressional budget process. In a statement by Representative Obey (D-WI), Subcommittee Chair, the increase recommended for the NIH was intended as an investment to: 1) increase the number of new and competing research grants by approximately 545 over FY 2007 to about 10,645; 2) lift the 2-year freeze on the average cost of new research grants; 3) help train the next generation of researchers; and 4) provide $110.9 M for the National Children's Study and $300 M for the global AIDS fund. The Subcommittee also recommended continuing to fund the NIH Common Fund from the NIH Office of the Director (OD) rather than as a tap on the ICs. The House Subcommittee bill markup would provide $495 M for the Common Fund, a $12 M (or 2.5%) increase over FY 2007.

NCI FY 2008 Operating Budget Development. Dr. Niederhuber discussed considerations and mandated expense increases to be taken into account in developing the FY 2008 operating budget based on the $4,797,639,000 recommended for the NCI in the House Subcommittee markup. This would be an increase of $72.743 M over the FY 2007 appropriation of $4,797,639,000. To begin with, an estimated $20 M would be set aside in consideration of the potential for the NIH Director and DHHS Secretary to exercise their transfer authority, reducing the subtotal of available funds to $52.743 M. NCI-wide requirements for competing RPG increases (estimated), rent/lease/utilities increases, a Small Business

Program increase, and mandated salary increases could reduce the available subtotal to !$13.657 M. The NCI Director's Reserve set aside would increase the deficit in available new funds to !$38,657 M. The FY 2008 budget development challenge, therefore, will be to identify revenue resources to cover those required expense increases and generate a pool of about $60 M for new initiatives that address emerging scientific opportunities, program expansions, and program restorations. He stated that the EC will begin in July to explore potential recoveries and redeployments to achieve that goal.

In summary, Dr. Niederhuber expressed the view that the NCI budget will continue to be less than the inflation rate for the foreseeable future. He gave assurance that the NCI will work to find and fund the best science and the best scientists. The needs are to manage expectations, continue scientific growth and maintain a balance within the NCI portfolio, and seek to leverage additional resources.

NCI Community Cancer Centers Program (NCCCP) Pilot. Dr. Niederhuber reported that all pilot sites for this program have been named and leadership from the Centers will be meeting on the NIH campus soon to discuss implementation. This goal of this pilot project is to sponsor multiple pilot sites for 3 years to identify critical factors that define a state-of-the-art Community Cancer Center. Those factors will be incorporated into a future program and will provide guidance for addressing the many issues relating to access to care. Dr. Niederhuber acknowledged and commended the work of Dr. Maureen Johnson and all who worked on the design of this research project. The objective of the NCCCP is to make improvements across the continuum of cancer care from risk assessment to treatment and during types of care delivery. The ultimate measure of success will be that the NCCCP has made a significant impact on the quality of care in the community setting. Dr. Niederhuber noted that development of the pilot has encompassed the delivery site, community hospital, and private practice offices that surround the site. In addition, the NCI has worked with the local community and state governments, recognizing that the quality of care is affected by these multiple levels of influence. The pilot sites also have been connected with NCI's Cancer Centers and Academic Cancer Centers Programs. A major focus of the pilot program will be to identify the problems and difficulties associated with implementing an informatics infrastructure within this environment.

Research focus areas of the NCCCP pilot are: 1) clinical research to increase trial accrual and minority accrual and determine the feasibility of conducting early phase trials, as well as to promote participation in research networks; 2) disparities; 3) quality of care and the use of evidence-based guidelines; 3) survivorship; 4) biospecimen initiatives, and 5) information technology, including a Cancer Bioinformatics Grid (caBIG™) implementation assessment and a focus on privacy/data-sharing issues. Research focus areas for the overall program relate to appropriate program components, cancer medical staff credentialing, academic linkages, institutional commitment, knowledge exchange among sites, and federal and state program linkages. The intent of the NCCCP pilot is to gain information from these research questions about the components of an ideal community setting and how best to connect the NCCCP to the Cancer Centers program and the individual sites to each other. The goal is to deliver a higher quality of care and bring the latest discoveries more rapidly to people where they live.
Dr. Niederhuber described the evaluation plan for the pilot: a high-powered group of individuals, both internal and external, to serve on the evaluation committee for the 3 years; quantitative and qualitative metrics across the components to be applied throughout the 3 years; and an evaluation of the implementation, operations, and performance of the pilot sites, including process and impact assessments.

Dr. Niederhuber called attention to the 10 sites that had been selected from the more than 45 applications received from 22 states. He noted that the selection by the review committee of two not-for-profit groups, each operating multiple hospitals, could provide information on whether success in the few sites picked by the groups for participation in the pilot could be duplicated across the board in a rapid fashion. The hope 3 years from now is that, through research, the NCI will have determined the best

methods to enable the provision of state-of-the-art, multispecialty care and early phase clinical trials in community-based locations to meet the needs of the people.

Questions and Answers

A list of Evaluation Committee members was requested.

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

Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel, and Charles R. Drew Professor of Surgery, Howard University College of Medicine, introduced his colleague on the Panel, Dr. Margaret Kripke, Executive Vice President and Chief Academic Officer, The University of Texas M.D. Anderson Cancer Center. He reminded members that the Panel's 2006-2007 series of meetings entitled *Promoting Healthy Lifestyles to Reduce the Risk of Cancer* had been discussed at previous NCAB meetings. Throughout this series, the Panel gathered testimony on current research, knowledge gaps, and community programs relevant to promoting healthier behaviors and cancer risk reduction. At the Panel's final meeting in the series on February 12, the issues addressed related to the impact of tobacco and environmental tobacco smoke on cancer risk. In particular, the Panel heard that despite declines in U.S. smoking rates, the dangers of tobacco remain high and the problem is worsening in other parts of the world. For example, countries such as China and India are experiencing large increases in tobacco use. To address the global impact of tobacco, the World Health Organization (WHO) has negotiated an international treaty known as the Framework Convention on Tobacco Control (FCTC) aimed at reducing tobacco-related deaths worldwide. As of the previous week, 147 countries had ratified the FCTC; the United States is not on that list, however. Dr. Leffall noted that Panel meeting participants strongly advocated for followup on barriers related to FCTC ratification.

Also at the Panel's February meeting, the effectiveness of warning labels against tobacco use was revisited. Evidence was brought forth that suggests graphic labels depicting a broad range of associated health risks (e.g., impotence) can deter people from smoking. The last update of tobacco warning labels in the United States was in 1984. Dr. Leffall noted that meeting participants emphasized the need to promote widespread access to evidence-based tobacco cessation services. It was noted that although primary prevention is critical to long-term reductions in tobacco use, cessation provides rapid decreases in health care costs and reductions in morbidity and mortality.

The Panel heard that smoking prevention and cessation policies need to target subpopulations with a higher risk of smoking addiction. These subpopulations include patients in substance abuse and mental health treatment programs, as well as the 37 million Americans living in poverty. Moreover, additional smoking cessation research is needed among the 18- to 24-year-old age group to better understand the reason for high spontaneous quit rates among this group. This is an important research priority because this age range is viewed as the transition period between quitting versus dependence on tobacco products. The phenomenon of continued smoking by cancer patients also was presented as an understudied area, one that is critically important to cancer treatment outcomes and survival. A call was made to incorporate smoking cessation programs in all oncology settings.

Dr. Leffall reported that the Panel heard once again about the overarching need for political will to address the problem of tobacco use in the United States and abroad and that political leaders need to act to protect public health. He informed members that the Panel is in the process of preparing its final conclusions and recommendations from this series, and a report will be presented to the President later this summer. Preparations also have begun for the 2007-2008 series of Panel meetings on *Strategies for Maximizing the Nation's Investment in Cancer*. The meetings will focus on the overarching question of

what changes to the current system of research and care would have the largest impact on reducing mortality and morbidity from cancer. Specific issues that may be addressed include: alternative models of funding cancer research; government appropriations for cancer research and care; the balance of NCI's research portfolio; and the changing roles of key constituents in the continuum of research and cancer care. Dr. Leffall noted that a multidisciplinary group of experts representing a broad range of perspectives will be convened. Meeting dates are September 10, October 22, and December 3, 2007, and January 28, 2008. Additional information on the series can be obtained from Karen Parker, Special Assistant, President's Cancer Panel, by telephone at 301-451-9462 or e-mail at klparker@mail.nih.gov or through the Web site http://pcp.cancer.gov.

Questions and Answers

Dr. Runowicz commended the Panel for taking on a very challenging issue.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

FY 2008 Appropriations. Ms. Susan Erickson, Director, Office of Government and Congressional Relations (OGCR), briefly reviewed the appropriations process leading to the enactment of the FY 2008 budget. Following the announcement of the President's Budget on February 5, a Budget Resolution was passed to decide on the allocation of the overall discretionary budget to the 12 House Appropriations Subcommittees. NIH hearings were held in the House on March 6 and in the Senate on May 21. Allocations as set forth in the Budget Resolution were made to the Appropriations Subcommittees on June 5. On June 7, the House Labor/HHS Subcommittee held its markup of the FY 2008 appropriations. Action by the full Labor/HHS Committee is expected later in the month, to be followed by a vote in the House of Representatives. In the Senate, the Subcommittee markup is expected in July.

New Legislation. Ms. Erickson reported on recently introduced legislation of interest to the NCI. The National Cancer Act was introduced in the Senate on March 29 by Senator Dianne Feinstein (D-CA), cosponsored by Senator Sam Brownback (R-KS), and has been referred to the Senate Committee on Health, Education, Labor, and Pensions (HELP). Provisions with a specific NCI focus are: 1) grants for the development of targeted therapy; 2) establishment of a national childhood cancer registry; 3) expansion of cancer survivorship programs; 4) an educational program on clinical trials; 5) codification of biospecimen registry guidelines; and 6) other transactions authority for the NCI Director to carry out research in support of the development of advanced technologies leading to the delivery of clinical products to benefit cancer patients. Cancer-related provisions involving other agencies are: 1) colorectal cancer screening and lung cancer detection demonstrations for the Centers for Disease Control and Prevention (CDC); 2) expanded access to drugs for compassionate use and the development of surrogate endpoints and biomarkers for the U.S. Food and Drug Administration (FDA); and 3) cancer-related health insurance coverage for the Center for Medicare and Medicaid Services (CMS).

The Cancer Screening, Treatment, and Survivorship Act was introduced jointly in the House and Senate by Representative Janice Schakowsky (D-IL) and Senator Tom Harkin (D-IA). The bill includes screening research and survivorship research provisions for the NIH and NCI. Screening research mandates would include expanding research programs to identify and improve cancer screening and testing protocols; awarding grants to advocacy organizations to raise public awareness of screening; and emphasizing cancers with high mortality rates. Survivorship research mandates would include expanding survivorship research at the NCI Cancer Centers and evaluating models of survivorship care. The bill also would mandate a survivorship grant program to be administered by the CDC. Ms. Erickson noted that numerous other pieces of legislation were introduced focusing on specific cancers such as breast,

colon, lung, and prostate, many with a focus on screening coverage and awareness. These bills will be followed by the OGCR, and information on those that move will be provided to the NCAB at future meetings. Ms. Erickson reminded members that the Breast Cancer Stamp authority is due to expire before the end of the year. Bills have been introduced in both the House and Senate to extend the authority for another 2 years. A separate bill introduced in the House would make the stamp authority permanent.

Congressional Activities. Ms. Erickson reported on visits to the NIH and NCI by congress members and staff. On April 12, Representative Dave Weldon (R-FL), a member of the Labor/HHS Committee, was given an extensive tour of the Center for Cancer Research (CCR), in particular, the pediatric unit, where he was introduced to patients participating in clinical trials of new therapies. On May 31, a staff member in the office of Representative Brian Higgins (D-NY) spent much of a day learning about the NCI Intramural Program. He has requested a return visit for himself and colleagues. Ms. Erickson reported that Senator Barbara Mikulski (D-MD) conducted an informal hearing on May 24 to discuss the decline in mammography rates. The hearing was attended by 10 of the 16 female Senators. Presentations were made by Dr. Niederhuber; Dr. Nancy Breen, Division of Cancer Control and Population Sciences (DCCPS); and representatives from the American Cancer Society (ACS) and Susan G. Komen Foundation. Ms. Erickson commented that the level of interest in the topic has been manifest in the continuing communication of the Senators with NCI staff and the number of requests for additional information.

Ms. Erickson concluded by requesting feedback from NCAB members on services provided by the OGCR. These include the written report included in meeting materials, presentations at the Board meetings, and staff responsiveness to requests from Board members for information. She noted that a survey will be distributed by e-mail and that she looked forward to hearing from the members.

Questions and Answers

Mr. David Koch, Executive Vice President, Koch Industries, asked whether funding provisions were associated with the Feinstein/Brownback bill and whether there were any plans for a study of the costs of carrying out the mandates. Ms. Erickson replied in the negative.

VI. ANNUAL DELEGATIONS OF AUTHORITY (AMENDED)—DR. PAULETTE S. GRAY

Members were reminded that the annual delegations of authority by the NCAB to the NCI Director and statement of understanding with NCI staff on operating principles in extramural awards had been approved at the February meeting. Dr. Gray explained that the recently enacted NIH reauthorization legislation has mandated that grants of $50 K or less must now be presented *en bloc* to the NCAB for concurrence with the recommendations of the initial review group. Previously, the Board had been able to delegate authority for NCI staff to make those awards without bringing them to the Board during closed session. She asked for Board approval of an amendment to the statement of understanding to reflect the change mandated by the NIH reauthorization bill.

Motion. A motion was made to amend the Annual Delegations of Authority/Statement of Understanding as follows: **Concurrence of the NCAB with recommendations of the initial review group will be required except for: Training Grants and fellowships and other nonresearch grant applications** are not "proposals to conduct or support research," and thus are not subject to NCAB review and approval and without other concerns **may be awarded without presentation to the NCAB for concurrence, i.e., with the exception of the Ruth L. Kirschstein National Research Service Awards.** The motion was seconded and approved.

VII. P-4 CHEMOPREVENTION TRIALS ASSESSMENT WORKING GROUP REPORT—DRS. JOHN NIEDERHUBER AND BRUCE CHABNER

Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, summarized the P-4 Chemoprevention Trials Assessment Working Group Report. The P-4 trial is proposed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) to be performed in the Community Clinical Oncology Program (CCOP) through the Division of Cancer Prevention (DCP). The Working Group is chaired by Dr. Marty Abeloff, and NCAB members Drs. Chabner; Diana Lopez, Professor, University of Miami Miller School of Medicine; and Kenneth Cowan, Director, University of Nebraska Medical Center Eppley Cancer Center, were among its members. It met in March 2007, to discuss the current state of the science in breast cancer chemoprevention in the context of prior breast cancer prevention trials and advances in the molecular science that could impact the field in the future. The P-1 trial resulted in the approval of tamoxifen for prevention, but the agent has had modest clinical implementation; it involved nearly 14,000 women at a cost of $65 M. A second, ongoing trial (P-2) is comparing tamoxifen and raloxifene, focusing on the collection of toxicity information; the cost of this trial to date has been about $130 M. Because of fewer serious adverse effects, such as one-third fewer endometrial cancers and thrombotic episodes, raloxifene is seen as a safer agent than tamoxifen, although it is less effective at reducing ductal carcinoma *in situ* (DCIS). Furthermore, the offlabel use of raloxifene has been low. The proposed P-4 trial compares raloxifene with letrozole, an aromatase inhibitor (AI).

The Working Group had several concerns, including whether the study of an AI would change the practice of preventive oncology and that toxicity effects have discouraged the use of tamoxifen and raloxifene. Additionally, the lack of a placebo control in the P-4 trial would make it difficult to assess the toxicity of letrozole, which appears to have specific bone density and possible cardiac effects. Other on-going trials with exemestane, a bone-sparing AI, and anastrazole, are placebo controlled, and likely to provide more definitive information about toxicity of AIs in long term use. Other concerns were that SERMs have not proven effective on patient survival; and that the effects of the AIs, if positive, would take years to assess. The Working Group discussed whether the P-4 trial would lead to registration of letrozole for use in prevention. It was noted that letrozole would lose its patent before the trial is completed. The pharmaceutical company could file for a prevention indication if the study was positive, but it likely would not invest in marketing the agent because it would be available for generic marketing by that time. There also was concern about how the FDA views this trial design and the adequacy of toxicity evaluation. A careful look at the long-term toxicity of a new agent in a prevention setting is important because long-term negative effects might counterbalance the positive effects in terms of breast cancer prevention. It is unknown how long subjects would need to be monitored. The initial cost of the trial is estimated at $55 M for 5 years; followup costs likely would be $80 M or more for an additional 5 to 10 years. Finally, the expert panel agreed that the identification of biomarkers for high-risk patients is the greatest priority for future breast prevention trials to improve the risk/benefit ratio in using potentially toxic medication. The NSABP must assure the sharing of blood, tissues, and data (as necessary) with outside investigators through a transparent process.

Dr. Chabner concluded, and Drs. Lopez and Cowan concurred, that the P-4 trial is well-designed, interesting, and relevant, but unlikely to change the practice of preventive oncology. Dr. Lopez reaffirmed the Board's commitment to prevention but cautioned that chemoprevention can be toxic. Many of the people involved in this proposed trial may not really be at high risk for breast cancer and may suffer the effects of the intervention itself. Members were told that the study of the prevention of cancer has benefits and that the P-1 and P-2 trials likely are the most important NCI cancer prevention trials in demonstrating a reduction in risk of occurrence of any type of cancer. In view of the expiration of the patent, and the need for expanded research on biomarkers for risk, it was recommended that the

NCAB not endorse the trial as it was presented for current funding. Dr. Cowan suggested that the Board should be supporting the NCI to do more in prevention but to approach it in a way that furthers our ability to best identify those at risk for disease and therefore our parameters for inclusion in chemoprevention studies. The subcommittee agreed that the desire is to see research in prevention move forward in a manner in which we can identify cohorts most at risk and define agents which have a good safety profile and potential for long-term benefit.

Questions and Answers

Dr. Jean deKernion, Professor and Chairman, Department of Urology, David Geffen School of Medicine at the University of California-Los Angeles (UCLA), asked whether the study would be more feasible if it were confined to the high-risk group. Dr. Chabner replied that this would exclude minority women or other subgroups. Dr. Cowan said that the prevention field aims to make advances beyond the previous trials, which had used the Gail model and had identified a cutoff point of 1.67 percent fold increase risk.

Dr. Peter Greenwald, Director, DCP, expressed support for the P-4 trial and said that it holds the possibility for women who opt to take a pill for prevention of potentially preventing as much as 70 percent of breast cancer. He noted that the Women's Health Initiative, which cost eight times the estimate of the P-4 trial, was an important factor leading to the current decline of breast cancer and increased knowledge of heart disease.

Several Board members acknowledged the contributions made by prevention research to date but expressed their support for the NCAB panel's recommendation. Dr. Daniel Von Hoff, Senior Investigator, Translational Genomics Research Institute, Clinical Professor of Medicine, University of Arizona Department of Medicine, noted that the scientists who designed the trial are among the world's best in the breast cancer and prevention research fields and that he felt the trial should be supported.

Mr. Koch expressed concern about the affordability for the individual patient and coverage by average health insurance plans for letrozole. Dr. Chabner said that AIs currently are an expensive class of drugs; in addition, trials involving other AIs are ongoing and, if these are successful, letrazole likely would not be the drug of choice. Members were told that patient costs are not known at this time. Dr. deKernion asked about the relationship between the dollar value and the known risks of letrozole, in light of the other AI trials underway. Dr. Chabner noted that the AIs are not exactly alike, that exemestane has the significant advantage of sparing bone, but that the current evidence shows that AIs are more potent than tamoxifen. He said that the Working Group discussed the issue of sample availability from the P-4 and other AI trials.

Dr. Lloyd Everson, Vice Chairman and Member of the Board of Directors, US Oncology Incorporated, recognized the work of those who put the study concept together and the expertise of the members of the Subcommittee who reviewed it. He noted that there are clearly different views of the impact this trial would have on clinical practice and breast cancer prevention. Dr. Everson pointed out that ultimately this is the Director of NCI's decision and that he must make it based on the best advice the Board can provide and within the context of the fiduciary and scientific priorities of the Institute. He pledged his support to Dr. Niederhuber in making this difficult decision.

Dr. Don Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Johns Hopkins University School of Medicine, requested clarification on incidence and survival rates in breast cancer. Dr. Chabner said that a small percentage of women in these trials will get breast cancer

during a given time period. Because most of these women have their cancer discovered in an early stage and are cured by treatment, there is no survival endpoint for the trial.

Motion. A motion to accept the report of the P-4 Chemoprevention Working Group was approved unanimously.

This topic was discussed again during the presentation of the Translational Research Working Group (TRWG) final report. After the presentation, during the Question and Answer session, Dr. Coffey noted that one of the biggest challenges that we face in translational research is in the area of cancer prevention. He highlighted a recent presentation at the annual American Urological Association meeting titled, "Why Isn't Anyone Using Finasteride for Prevention?" as an example. In this case, Dr. Coffey pointed out that we have dedicated significant resources over the years to chemoprevention research using Finasteride and we have done so when we were aware that there were problems with the approach of raising the testosterone level within the prostate. He continued that this story was repeated at the Board meeting the previous day—the same story, the same argument. Dr. Coffey asked the TRWG presenters how their program might help address toxicology, prevention, and the interactions between the NCI and the community so that science rather than advocacy drives decisions.

Dr. William Nelson, co-chair of the TRWG, answered that the hope of translational research is to harness the products of the genome revolution to make go- no-go decisions more intelligently before large investments have been made. The intention is to use the capabilities of the whole system—modeling, basic biology, etc.—to prioritize our efforts and make decisions about specific approaches before they are very expensive.

Dr. Coffey followed up asking if the TRWG process had been in place if we would have had the discussions that took place the previous day about the P-4 study. Dr. Nelson explained that the TRWG plan does include two pathways which could address the needs of prevention research by focusing in developing risk assessment tools to correctly identify the right risk groups who would benefit from intervention.

VIII. UPDATE: TOBACCO LEGISLATION—DR. ROBERT CROYLE

Dr. Robert Croyle, Director, DCCPS, provided an overview of the Family Smoking Prevention and Tobacco Control Act (S. 625/H.R. 1108), which would provide to the FDA legal authority to regulate tobacco. The bill was introduced in Congress in February 2007 with bipartisan sponsorship. The lead sponsors were Senators Edward Kennedy (D-MA) and John Cornyn (R-TX) and Representatives Henry Waxman (D-CA) and Tom Davis (R-VA).

Dr. Croyle explained several important provisions of the bill. 1) The bill reinstates the FDA Final Rule restricting the sales and distribution of cigarettes and smokeless tobacco to children and adolescents. 2) The legislation provides restrictions on marketing and authorizes the FDA to restrict tobacco marketing when appropriate for the protection of public health, consistent with the First Amendment. Members were told that, in 2005, more than $13 B was spent in marketing tobacco; cigarette advertising has been shown empirically to increase young people's risk for smoking. 3) Extensive disclosure is required from the industry regarding ingredients, nicotine, design features, health, toxicology, and other information. 4) The bill bans all cigarette flavorings, other than tobacco or menthol, that are "characterizing flavors" of the product. 5) The FDA is granted the authority to establish and periodically re-evaluate tobacco "product standards." 6) Descriptors that imply that some cigarettes are less hazardous—such as "light," "low," and "mild"—are banned. 7) The FDA is granted the authority to regulate products having "modified risk" of tobacco-related disease based on the impact on both the individual and the population.

8) The bill provides to the FDA the authority to revise cigarette package warning labels. Other provisions include the establishment of a Tobacco Products Scientific Advisory Committee, the payment of user fees by manufacturers, and the "fast-tracking" of research on cessation products and approval by the FDA.

Some of the questions raised by the legislation include whether unintended consequences could result from regulation by the FDA, and how the FDA would regulate new and "modified risk" products in the absence of a complex science base. The Institute of Medicine's (IOM) report "Clearing the Smoke" and other reports provide a possible framework for evaluations. Members also were referred to the May 2007 IOM report on tobacco control "Ending the Tobacco Problem: A Blueprint for the Nation," as well as the Roswell Park Cancer Center's "Beliefs About Nicotine Delivery Survey," which reported that 46 percent of smokers surveyed believe that the FDA already regulates tobacco.

In 2004, the NCI and National Institute on Drug Abuse (NIDA) collaborated on an initiative concerned with "Testing Tobacco Products Promoted To Reduce Harm," which funds six R01 and R21 grants. The overall research issue has focused on whether potential reduced-exposure tobacco products provide a truly less-harmful alternative to conventional tobacco products, both on the individual and population levels. In addition, a research and development contract was awarded for a laboratory assessment of tobacco use behavior and exposure to toxins among users of new tobacco products promoted to reduce harm. The objectives are to assess how differences in individual smoking behaviors are influenced by different agents; to review, develop, and validate laboratory methods for assessing exposure and risk; and to create a public database of laboratory and clinical research methods.

Members were told that future research topics include: the impact of changes in ingredients and product design on tobacco use behaviors and emissions of nicotine and toxic chemicals, and methods and measures that could be used to assess the impact of changes in ingredients and product design. Other areas of research are: how the introduction and marketing of "reduced risk" tobacco products change consumers' perceptions of risk and tobacco use behavior; the effect of new tobacco products and marketing on population-level patterns of tobacco use, including initiation and cessation; and the changes in tobacco product warning labels that will have the greatest impact on consumers. Dr. Croyle cited a study by Strasser et al. (2007) involving Quest cigarettes, which are sold in three versions based on nicotine level. The study found that, in Quest products with the lowest nicotine level, there was evidence of compensation—that is, people smoked more to obtain a higher level of nicotine; in some instances, smoking a lower nicotine cigarette also increased a person's exposure to carbon monoxide.

Dr. Croyle concluded that many challenges and opportunities surround FDA implementation of this legislation, but research supported by the NCI, NIDA, and CDC has made a critical contribution to the underlying science. The proposed bill provides flexibility for regulations to evolve as scientific knowledge and experience increase. There likely will be an increased urgency to answer research questions if the proposed legislation is enacted.

Questions and Answers

Dr. Richard Pazdur, Director, Division of Oncology Drugs, FDA, said that regulating a substance that is not considered safe or effective, such as tobacco, will pose significant challenges. If the bill is enacted, the FDA will need to ramp up its staff capabilities to handle ensuing issues and work closely with ongoing tobacco programs.

Dr. Von Hoff said that the NCI should focus on the single message of "no smoking" and be careful not to adopt policies that shift the NCI's attention from that idea. Dr. Coffey noted that the bill's effectiveness might be limited because of the typical adolescent reaction against authority. Dr. Kripke

noted that some antismoking advocacy groups believe that the legislation should be more stringent, perhaps even eliminating nicotine from cigarettes.

Dr. Karen Meneses, Pegasus Professor and Beat M. and Jill L. Kahli Endowed Chair in Oncology, University of Central Florida, asked about the smoking behavior of young cancer survivors. Dr. Croyle said that some childhood cancer survivors are smoking, although at a lower rate than their peers of the same age.

Dr. Chabner said that, in addition to cancer, tobacco is responsible for other diseases or health-related problems, including heart disease, lung disease, and stroke. A concerted advertising campaign should be designed to present the whole picture of health problems that result from tobacco use. Dr. Runowicz added that human papillomavirus (HPV) and yellow teeth also are related to smoking. Dr. Croyle mentioned that the Truth Campaign, funded by the American Legacy Foundation, has been successful in using media to reduce the tobacco impact among teenagers.

IX. CLOSED SESSION—DR. CAROLYN D. RUNOWICZ

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4), 552b(c)(6), Title 5 U.S. code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

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

The *en bloc* vote for concurrence with IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,082 applications were reviewed requesting support of $558,420,526.

FRIDAY, JUNE 15, 2007

X. TRANSLATIONAL RESEARCH WORKING GROUP—DRS. ERNEST T. HAWK, LYNN MATRISIAN, AND WILLIAM NELSON

Dr. Ernest T. Hawk, Director, Office of Centers, Training and Resources (OCTR), presented the final report of the Translational Research Working Group (TRWG). He was joined by TRWG co-chairs Drs. Lynn Matrisian, Vanderbilt-Ingram Comprehensive Cancer Center, and William Nelson, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University. The TRWG was given the charge to evaluate the current status of NCI's investment in translational research and envision its future in an inclusive, representative, and transparent manner. The NCI's "bench to bedside and back" research infrastructure and programs include SPOREs, Cancer Centers, Cooperative Groups, CCOPs, and many other mechanisms. The TRWG focused on early translational research following from basic studies and extending into Phase 1 and Phase 2 trials to take advantage of advances in the knowledge of cancer biology and living systems, respond to a rapidly changing global environment, and make the most of opportunities while operating under flat or decreasing economic conditions.

TRWG activities included the recruitment of leadership and members; review of 11 foundational documents; analysis of the Clinical Trials Working Group (CTWG) process for ideas, challenges, and

lessons learned; and the development of a Web-based communication plan. Additionally, the Working Group gathered public input through several roundtables, analyzed NCI's current investments in translational research, and mapped six developmental pathways to clinical goals. Six subcommittees focused on organization and funding, core services, training/workforce, prioritization, project management, and external integration. The TRWG defined translational research as transforming scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality. It focused its efforts in early translation, looking at risk assessment and intervention pathways as a means to achieve clinical goals, with an aim to ensure that the most promising concepts entered the developmental pathways and advanced to the clinic or to "productive failure" and that progress was rapid, efficient, and effective. Members were told that NCI's translational research funding in FY 2004 was estimated at $1.3 B, or 30 percent of NCI's budget of $4.4 B.

The TRWG Report provided a summary vision to build a focused, collaborative, multidisciplinary enterprise, tailored to the distinctive requirements of early translational research, which transforms and strengthens this essential link from discovery to patient and public benefit. The key objectives include: improving coordination and collaboration and instilling a culture of goal-oriented management; improving the identification and entry of the most promising opportunities to tailor existing and new funding programs to promote participation by researchers; and enhancing the efficiency and effectiveness for individual projects and many supporting activities. The Report described TRWG initiatives that fell under three common themes: coordinated management, tailored funding programs, and operational effectiveness.

Four TRWG initiatives promoted **coordinated management**. One initiative established a coordinated NCI-wide organizational approach to manage the diverse early translation portfolio, reduce fragmentation and redundancy, and ensure that resources were focused on promising opportunities. Another activity identified part of the NCI's budget that was devoted to translational research. In addition, a set of award codes was developed to accurately capture the nature and scope of the early translational research portfolio. A fourth initiative worked to create a transparent, inclusive prioritization process. The proposed approach to prioritization includes broad public input, 10 ideas chosen for detailed analysis, and several concept packages that are reviewed for public comment and used to inform existing NCI initiatives as well as to develop special awards.

Recommendations to **tailored funding programs** included the modification of guidelines for multiproject, collaborative, early translational research awards and improvements to processes and mechanisms for the review and funding of investigator-initiated early translational research. Additionally, the TRWG recommended that Special Translational Research Acceleration Project (STRAP) awards be established to advance a select number of especially promising early translational research opportunities. Other initiatives were to establish a program for joint NCI/industry funding of collaborative early translational research projects that integrate the complementary strengths of all parties and to more effectively and efficiently provide access to and use of some of the translational research assets that the NCI already has constructed, such as the Rapid Access to Intervention Development (RAID), Rapid Access to Preventive Intervention Development (RAPID), and Development of Clinical Imaging Drugs and Enhancers (DCIDE) programs.

The last domain of the initiatives is in **operational effectiveness**. This included building a project-management system involving staff both at the NCI and at extramural institutions to facilitate coordination, communication, resource identification and access, and management of milestone-based progress for multidisciplinary, early translational research projects. Another initiative aimed to coordinate essential core services to reduce duplication and ensure high-quality services for projects and

investigators. A third recommendation for operational effectiveness was to improve standardization, quality control, and accessibility of annotated biospecimen repositories and their associated analytic methods. Three other initiatives focused on negotiating intellectual property agreements and agent access, increasing NCI interaction and collaboration with foundations and advocacy groups, and strengthening training programs and career incentives to maintain an early translational research workforce.

The TRWG identified four principles to guide the timeline and budget: 1) organizational and administrative initiatives should be initiated as soon as possible; 2) a prioritization process must be in place before STRAPs can commence; 3) the budget for administration should be kept to a minimum by leveraging existing structures; and 4) the recommended extramural funding program is expected to require less than 1 percent of the NCI budget. These recommendations were developed within a specific context. The TRWG was given an unrestricted mission but was very aware of current realities in the development of these recommendations. There is no attempt to manage discovery science, which is different from translational science. There is, however, a firm commitment to the vision, and the Working Group strove to identify "responsible" implementation strategies that could be flexible to adjust to the environment. The TRWG intends to publish its six pathways to clinical goals and develop translational research award codes based on these pathways, implement a communications plan for the TRWG Report, and convene an internal working group to discuss implementation strategies.

Questions and Answers

Dr. Niederhuber thanked the TRWG leaders and members for their hard work. He said that it might be possible to accelerate the proposed timeline of the STRAP awards.

Dr. Coffey said that one of the challenges in translational research is to link translation to prevention. Dr. Nelson replied that the development of risk assessment tools is needed, as well as well-defined risk groups.

Dr. Coffey asked how the SPOREs fit into NCI's translational research schema. Dr. Hawk responded that the TRWG strongly advocates the SPOREs' organ-based approach. Dr. Nelson added that, in considering developmental pathways and activities, integrating and implementing well-thought out metrics can improve the effectiveness and efficiency of reviews and help improve the functioning of SPORE programs. Dr. Chabner suggested that the SPORE program could be reoriented totally toward translation.

Dr. deKernion asked for further information about the role of the Industry Relation Working Group. Dr. Niederhuber said that it will play an important role in NCI's partnerships with industry, particularly as the NCI continues developing its experimental therapeutics drug development base.

Dr. Peter Kirchner, Senior Scientist, Department of Energy, asked about the return on investment in terms of translational success for Small Business Innovation Research (SBIR) grants versus other types of grants, noting the role that Phase III grants could have in propelling new discoveries toward translational success. Dr. Hawk said that several SBIR grants were examined in the overall process. Dr. Matrisian added that overall there was a lack of metrics and evaluation procedures, such as for the Small Business Technology Transfer (STTR) or SBIR grants, but that the TRWG has worked to improve this through the pathways and coding system. Dr. Niederhuber said that an NIH pilot program is under development for grants that do not fall within the SBIR focus or that of other current grant vehicles.

Dr. Chabner suggested that the NCI could contribute to the development of diagnostics that refine

patient selection for appropriate therapy. Dr. Nelson agreed with the importance of integrating diagnostic tests and imaging in the drug development pathway.

Motion. A motion to accept the report of the Translational Research Working Group was seconded and approved unanimously.

XI. REPROGRAMMING METASTATIC TUMOR CELLS WITH EMBRYONIC MICROENVIRONMENT—DR. MARY HENDRIX

Dr. Mary Hendrix, President and Scientific Director, Children's Memorial Research Center, and Professor of Cancer Biology, Feinberg School of Medicine, Northwestern University, presented recent work on reprogramming metastatic melanoma cells using the embryonic microenvironment. Metastatic melanoma is a deadly disease, with less than a 20 percent cure rate and a median survival time of less than 1 year at the time of diagnosis. Currently, pathologists classify different stages of melanoma based on a classification scheme developed by Wallace Clark and colleagues in the 1960s. Recent molecular studies have identified subclasses of melanoma based on oncogenic mutations and differentiation status. Plastic, multipotent stem cell subpopulations also have been found within metastatic melanoma tumors, which confounds both the classification of tumors and the ability to target these cells in the most aggressive tumors. Dr. Hendrix described a subpopulation of tumor cells observed by members of her laboratory and colleagues that exhibited a phenotype called vasculogenic mimicry, which describes the ability of aggressive melanoma subpopulations to form perfusable, extracellular matrix-rich networks in three-dimensional tissue culture. These network structures closely resembled the primitive vasculogenic networks observed during embryonic development; and the tumor cells adopted a vascular phenotype, specifically an endothelial cell phenotype. Vasculogenic mimicry contributes to an extravascular perfusion pathway within the most aggressive tumors, and this collaborates with angiogenesis and vessel cooption, creating a rapid means for aggressive tumors to acquire a blood supply. Vasculogenic mimicry has been observed in many other forms of aggressive tumors. Dr. Hendrix's work aims to understand the cellular and molecular determinants underlying tumor cell plasticity to question the role of the microenvironment in contributing to the vasculogenic phenotype, and to try to understand the clinical implications of targeting melanoma tumor cell plasticity.

Dr. Hendrix described the molecular signature of plastic melanoma cells, determined through work performed in collaboration with Drs. Jeffrey Trent and Paul Meltzer. Highly aggressive melanoma cells were compared to poorly aggressive melanoma cells isolated from the same patient (isogenic cell types). The aggressive tumor cells expressed multiple cell-type specific markers, such as vascular endothelial cadherin (endothelial phenotype), keratins (epithelial phenotype), or hematopoietic markers. Metastatic melanoma cells were determined to express important embryonic stem cell markers. The highly plastic, aggressive cells also downregulated the melanocyte specific antigen MART-1 (Melan A). This led to the hypothesis that the most aggressive tumor cells have a deregulated genotype and a plastic phenotype that resembles that of multipotent stem cells. This information and the multipotent potential of aggressive melanoma cells led Dr. Hendrix to ask whether exposure of melanoma cells to a normal embryonic microenvironment could reverse the metastatic phenotype. Dr. Hendrix and colleagues developed three models to address this question: the chick embryo model, the zebrafish model, and human embryonic stem cell microenvironment (recently described in *Nature Reviews Cancer*).

Normal microenvironment deposited by human embryonic stem cells (HESCs) maintains the normal or pluripotent status of these cells and might be able to revert metastatic melanoma cells to a more normal phenotype through epigenetic influences. To explore this process, federally approved HESCs were placed on a three-dimensional matrigel matrix and allowed to condition the matrix over 3 to 4 days, leading to secretion of certain factors into their microenvironment. The stem cells then were removed and

metastatic melanoma cells placed on the matrix. After 3 to 4 days, changes in phenotype, behavior, or ability of the metastatic melanoma cells to form tumors in a nude mouse model were assessed.

HESCs form colonies and spheroid structures in three-dimensional culture. In the absence of the stem cell microenvironment, metastatic C8161 melanoma cells form an overconfluent layer. After contact with the microenvironment produced by the embryonic stem cells, the C8161 cells were induced to form spheroid structures. Media conditioned by the stem cells does not have the same effect, implying that the tumor cells must come into direct contact with factors deposited into the HESC microenvironment.

To determine if the tumor cells had reverted back to a normal melanocytic phenotype, Western blot analysis was used to examine expression of MelanA, which is expressed robustly by normal melanocytes. Metastatic melanoma cells placed on a control matrix do not express MelanA, a sign of their plasticity and dedifferentiated state. However, when metastatic melanoma cells are placed on a matrix conditioned by HESCs, they are induced epigenetically to re-express this normal melanocytic marker. If metastatic melanoma cells are placed in a microenvironment produced by normal human melanocytes, the cells do not re-express MelanA, suggesting that the HESCs secrete into their microenvironment a unique factor that induces metastatic melanoma cells to assume a more normal melanocytic phenotype. After exposure to the stem cell microenvironment, the ability of the metastatic melanoma cells to invade a basement membrane assay *in vitro* is decreased and they are less able to form tumors in an orthotopic nude mouse model compared to unexposed melanoma cells.

As a starting point for determining the factor or factors responsible for reversion of the metastatic phenotype, microarray analysis revealed that Nodal, a stem cell marker, is overexpressed by 20-fold in aggressive melanoma cells compared with their poorly aggressive counterparts. Nodal is an embryonic morphogen that is a member of the transforming growth factor beta (TGFβ) superfamily and is responsible for maintaining the pluripotency of HESCs. Thus, aberrantly expressed Nodal could be responsible for the plasticity observed in metastatic melanoma cells. In humans, Nodal is expressed largely in embryonic tissues only, including the trophoblasts. Nodal expression also is observed in developing mammary glands but has not been found in other normal adult tissues. Two inhibitors of Nodal, Lefty A and Lefty B, have been identified. Both are strong inhibitors of Nodal and also are members of the TGFβ superfamily. The ratio of Nodal to its inhibitors is critical in cell fate determination events.

Nodal propagates its signal via a coreceptor complex composed of Cripto and activin-like kinase receptors (I, II). Nodal signaling leads to phosphorylation of SMAD 2 and 3, followed by association with SMAD 4 and translocation to the nucleus, which induces gene re-expression. Extracellularly produced Lefty inhibits the Nodal signaling pathway. Western blot analysis showed high levels of Nodal in two HESC lines and also in metastatic melanomas, but not in poorly aggressive melanoma cells. The co-receptor Cripto complex is expressed robustly by HESCs and barely by the melanoma cells; additionally, the Nodal inhibitor Lefty is expressed only by HESCs and not by either metastatic or nontumorigenic melanoma cells. Thus, although the pluripotency gene Nodal is expressed aberrantly in metastatic melanoma, these tumor cells do not express the Nodal inhibitor. More importantly, HESCs secrete Lefty into their microenvironment, which then inhibits aberrantly overexpressed Nodal in melanoma cells placed into this microenvironment.

The level of Nodal expression in metastatic tumor cells was measured during interaction with Lefty in the HESC microenvironment. PCR analysis showed high levels of Nodal expression in metastatic tumor cells, which were reduced by 87 percent after the tumor cells were placed on the HESC matrix. To determine whether Lefty produced by the stem cells was causing this response, Lefty was

isolated from the HESC matrix and metastatic tumor cells were exposed to the isolated Lefty. Western blot analysis showed that expression of Nodal also was dramatically reduced in these tumor cells. Exposure of the tumor cells to Lefty also resulted in reduced ability to form colonies in soft agar, which could be rescued by adding recombinant Nodal to the cells. To determine whether epigenetic mechanisms have a role in regulating this pathway, sequencing-based methylation analysis was performed. The metastatic melanoma cells exposed to the HESC microenvironment have a 32 percent increase in methylation of Nodal, suggesting that the Nodal gene is becoming silenced as a consequence of interacting with Lefty in the HESC matrix.

The importance of Nodal was tested in an *in vivo* zebrafish model. Green fluorescent protein (GFP)-labeled metastatic melanoma cells were introduced into zebrafish embryos in either the animal pole regions or into the blastoderm margin to determine if tumor cells expressing Nodal could communicate with the embryonic microenvironment via this morphogen. The embryos were examined 6 to 12 hours after transplantation. GFP-labeled tumor cells induced the formation of an ectopic cranial structure or outgrowth in the zebrafish embryos; nonaggressive tumor cells introduced into the same area of the embryo did not have the same capacity to communicate with zebrafish embryonic structures and form ectopic structures. Confocal microscopy was used to localize GFP-labeled tumor cells. The cells secrete Nodal and communicate with the zebrafish cells to induce formation of mesodermal and endodermal structures in a manner similar to that occurring during normal embryological development. Melanoma cells transplanted into the blastoderm margin induced formation of an entire secondary body axis. *In situ* hybridization showed localization of mesodermal and endodermal genes induced by Nodal. Further experiments showed that downregulation of Nodal in tumor cells using antisense morpholinos, followed by introduction into zebrafish embryos, resulted in loss of the ability of tumor cells to induce formation of an abnormal cranial outgrowth. Overexpression of the Nodal inhibitor Lefty in the entire zebrafish embryo was followed by introduction of metastatic tumor cells; these tumor cells no longer were able to induce formation of a secondary body axis.

Nodal and its associated pathway may represent a new biomarker(s) for the progression and aggressive phenotype of melanoma cells. To test this hypothesis, 50 clinical melanoma samples were analyzed for Nodal. Normal skin cells do not express Nodal. Very few melanoma cells express Nodal in the radial growth phase, and Nodal expression is increased in cells from the vertical growth phase. Analysis of metastatic lesions showed intense staining for Nodal. Thus, Nodal represents a promising new biomarker that should be developed further.

Dr. Hendrix's laboratory is working to investigate the signaling pathway of Nodal, an embryonic pathway that is re-expressed by highly aggressive melanoma cells. Several biotechnology companies have claimed patent rights to aspects of the Cripto coreceptor complex and for the ALK receptors. Therefore, public-private partnerships will be needed to develop this observation into a clinical approach for treating melanoma. One approach is to downregulate expression of Nodal using antisense morpholinos and small molecular inhibitors that inhibit a portion of the coreceptor complex. This work has led to the discovery that Nodal expression is regulated by a SMAD 2-dependent positive feedback loop that likely will have important consequences for developing a therapy based on this target. Also, if Nodal expression is downregulated in metastatic melanoma, the ability of the cells to express the plastic endothelial and epithelial phenotypes is diminished. The cells begin to express genes such as tyrosinase and MelanA that are associated with a normal melanocyte phenotype. These cells are less invasive *in vitro*, no longer exhibit vasculogenic mimicry, and cannot form extravascular perfusion pathways. A current focus is to achieve sustained downregulation of Nodal expression *in vivo*. Tumor cells with Nodal expression knocked-down by morpholinos and placed into an orthotopic nude mouse have a marked decrease in their ability to form tumors *in vivo*. However, within 15 to 17 days after inhibition of Nodal, Nodal is re-expressed in the cells, and tumor formation resumes.

In summary, aggressive melanoma cells are highly plastic, dedifferentiated, and have a multipotent phenotype similar to embryonic stem cells. Using an embryonic zebrafish model as a biosensor for tumor-derived signals showed that metastatic melanoma cells can secrete the embryonic morphogen Nodal and communicate with the developing embryo and induce embryonic structures. The Nodal pathway may represent a source of new biomarkers for metastatic melanoma and progression of melanoma and also may provide new therapeutic targets.

Questions and Answers

Dr. Runowicz thanked Dr. Hendrix and commented that this work provided an example of the need to partner with industry to develop clinical products from basic research.

Dr. deKernion asked Dr. Hendrix if she had performed any *in vivo* mouse model work with Lefty and whether any of the Nodal pathway proteins could be measured in serum. Dr. Hendrix answered that other investigators have shown that, in metastatic breast cancer, Cripto is released in patients with highly progressive disease; thus, there is a focus on using Cripto as a serum marker. Melanoma cells express Cripto at very low levels, if at all, indicating that epithelial tumors may be different in this regard than mesenchymal tumors. Concerning work on Lefty, experiments have been performed in which tumor cells are placed in contact with Lefty and then placed into a clonogenic assay. For approximately 2 weeks after the cells are transplanted, Lefty exerts an influence over the Nodal signaling pathway, and tumor colonies do not form. However, over time, as Lefty leaves the system and is degraded, colony formation can occur, which has led to efforts to develop sustainable Lefty expression in *in vitro* and animal models.

Dr. Coffey noted work by another group in which extracellular matrixes were constructed and reorganized and asked about the relation of this to Dr. Hendrix's work. Dr. Hendrix answered that they see similar events in a three-dimensional culture in which the matrix has been reorganized, but when the HESC colonies are removed physically, Lefty is found to have been deposited only where the colonies have interacted with the microenvironment. The adjacent matrix has no Lefty and no effect on tumor cells.

Dr. Chabner asked if monoclonal antibodies to Nodal had been used to try to inhibit its activity. Dr. Hendrix answered that there are few commercially available antibodies to Nodal (either monoclonal or polyclonal), and each recognizes a different Nodal isoform. Dr. Hendrix said that her laboratory may attempt to develop new antibodies to the different Nodal isoforms in collaboration with a biotechnology company.

XII. FOLLOW UP: NCI BEST PRACTICES FOR BIOSPECIMEN RESOURCES— DRS. ANNA BARKER AND CAROLYN COMPTON

Dr. Carolyn Compton, Director, Office of Biorepositories and Biospecimen Research (OBBR), presented the NCI Best Practices for Biospecimen Resources Report. Biospecimen resources are critical to accelerate the development of molecular-based diagnostics and therapeutics for personalized medicine. Key requirements that have been identified for biospecimen resources for postgenomic cancer research include: 1) best practice-based, data-driven technical and operational standards to ensure quality and enable reproducible molecular analysis; 2) high-quality specimen annotation, including both pathology and clinical data; 3) specimen access for investigators through a timely, centralized, peer-review process; 4) ethical and privacy compliance through a chain of trust; 5) state-of-the-art informatics systems to track specimens, associated data, and patient consents; and 6) communication and outreach efforts to ensure the greatest impact. The NCI undertook an indepth effort to address issues rising from heterogeneity in

practices among NCI-supported biospecimen resources that led to a lack of common procedures, standards, management principles, definitions, and computerized access systems, as well as to disparate approaches to ethical, legal, and policy issues. The NCI defines a biospecimen resource as a collection of human specimens and associated data for research purposes, the physical entity in which the collection is stored, and all relevant policies and procedures.

The First-Generation Guidelines for NCI-Supported Biorepositories were reviewed by numerous NIH and DHHS Offices and published in the *Federal Register* for public comment. They were revised based on many comments received and published in April 2007 as the current report. The report defines key terms to ensure that a common lexicon is available for biospecimen resource managers. It addresses two areas: 1) the physical aspects of handling specimens and handling data, including quality assurance/quality control and biosafety issues; and 2) indicators for the quality of the ethical, legal, and policy aspects that govern the use of specimens, particularly issues related to informed patient consent, access to biospecimens and data, privacy protection and custodianship, and intellectual property (IP).

Dr. Compton described the future plans for the Best Practices Guidelines. They will be made publicly available on the NCI OBBR Web site and distributed to managers of all NCI-supported intramural and extramural biospecimen resources. A national education and outreach program is planned, starting locally in June 2007, and extended through regional meetings throughout the United States in the fall of 2007. Additionally, a biospecimen resource self-evaluation checklist will be created based on the Guidelines. Periodic revisions of the Guidelines will occur with input from researchers, biospecimen resource managers, advocates, policymakers, and other stakeholders as new technologies and clinical practices emerge. Research will be conducted to establish the scientific basis for data-driven standards for specimen collection, processing, and storage. This includes a searchable Web-based tool to access biospecimen research data and a partnership with the College of American Pathologists.

Questions and Answers

Dr. Everson asked whether a tracking requirement for specimens existed. Dr. Compton said that, because this can be a complex issue for large resources, a caBIG™ silver-level type of information technology (IT) support—which would better pinpoint a specimen's location and the studies it has undergone—is recommended.

Dr. Von Hoff expressed support for a central repository and clearinghouse because of the lack of solid quality control of specimens in the past. He felt that it would be a better model to have a central bank in which investigators would deposit specimens. This would ensure that when the investigator retires, the specimens would not be left. Dr. Chabner noted that private tissue banks exist but provide only limited access to specimens and suggested that the NCI should consider including a requirement in its Cancer Center applications to indicate their operative tissue banks and their level of compliance with the guidelines of the biospecimen report.

Dr. deKernion agreed with the need to address blood supply occlusion to prevent additional stress or changes to tumors before they are handled or stored for research. He also suggested that the NCI consider developing a simple biospecimen manual that includes forms and other information for use by surgeons, pathologists, and all others who handle specimens.

Dr. Coffey asked about warm or rapid autopsy, as well as fresh tissue from normal patients. Dr. Compton said that because some specimens are not removed at surgery, the warm autopsy is the only way to collect them; difficulties are presented by banked normal, anatomical specimens, which are

required for epigenomic studies, and no collections currently exist that would be appropriate for large-scale epigenomic studies.

Motion. A motion was made to accept the NCI Best Practices for Biospecimen Resources Report. The motion was seconded and approved unanimously.

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

NCAB Tobacco Resolution. Dr. Runowicz read a draft tobacco resolution from the NCAB. She suggested that, if the Board approved it, a draft would be circulated among the Board, and the letter would be sent to the President on NCAB stationery and listing all NCAB members' names. Before being sent, the language would be modified to encompass all cancers, not just lung, and the draft would undergo a thorough proofreading.

Motion. A motion to approve the draft resolution of the NCAB applauding NCI and CDC efforts to develop improved strategies for discouraging tobacco use and urging federal and local governments to take all possible actions to curtail tobacco consumption in this country was approved unanimously.

Subcommittee Meetings. Dr. Runowicz suggested that one or more NCAB Subcommittees should meet during each regular NCAB meeting. NCAB currently has a number of subcommittees, including Planning and Budget (jointly with the Boards of Scientific Counselors (BSC) and the Board of Scientific Advisors (BSA)), Cancer Centers, Clinical Investigations, and others.

Experimental Therapeutics Subcommittee. Dr. Von Hoff provided an update of the NCAB Experimental Therapeutics Subcommittee's meeting on 14 June 2007. The Subcommittee provides advice to and oversight of the RAID Program and assists the NCI's Developmental Therapeutics Program (DTP) in the translation to the clinic of novel anticancer therapeutic interventions. The Subcommittee was informed about improvements made to the RAID Program in decision, management, and infrastructure support following a presentation by Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), to the NCAB in September 2006, on RAID's workshop report, action plan, and recommendations. The Subcommittee felt that the NCI's management of the Program was very good. The members wanted more information on the impact of the Program at the next report.

The Subcommittee advocated that greater marketing and communications about the RAID Program to the SPORE community would help maximize the NCI's return on investment, especially with work in rare cancers and pediatrics. It also commended the Program's progress made through its Oversight Committees and Special Emphasis Panel (SEP), which reviewed 35 active RAID projects, closed 7, put 5 on hold in review, and approved 121 out of 370 projects that were received. The Subcommittee was pleased to note that 32 agents developed through the RAID Program have been licensed. Moreover, approximately 1,600 patients are on RAID-generated agents; the Subcommittee felt that more effective followup is needed regarding those patients entering clinical trials, and that the NCI may need to assume a more active role in facilitating the investigative new drug (IND) process or continuing the agent development without changing the IP status.

The Subcommittee heard about RAID's Program and project management improvements, including the recruitment of two of four project managers. The RAID Principal Investigator (PI) training program, called "RAID Investigator 101" has been developed and includes a video, and resources exist to assist in the IND submission. Additionally, the RAID Program has enhanced its management support to facilitate movement from the bench to the bedside.

The Subcommittee raised the question of whether the drugs that get into the RAID Program are high priority or offer limited promise. It is important to follow up on what has happened to the RAID compounds once they reach the clinic; the Subcommittee felt that the reporting system warranted attention to ensure this follow up.

Miscellaneous. Dr. Runowicz confirmed that appropriate reports and other information would be provided to NCAB Members to answer questions raised during the Board's site visit to the Frederick Cancer Research and Development Center (FCRDC).

XIV. FUTURE AGENDA ITEMS—MEMBERS

NCAB Members offered suggestions for topics for future meetings. These included cancer health disparities and the progress of the clinical trials group, in particular the Clinical Trials Advisory Committee (CTAC). Other topics suggested for regular and periodic updates included the review process involving the new NCCCP program, the CCOP clinical trial mechanism, and the overall Cooperative Group clinical trials program. Dr. Runowicz requested that Members submit additional topics of interest to Dr. Gray and herself for inclusion in future meetings.

XV. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

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

There being no further business, the 142nd regular meeting of the NCAB was adjourned at 11:30 a.m. on Friday, June 15, 2007.

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Date Carolyn D. Runowicz, M.D., Chair

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