DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
147th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 8, 2008

Building 31 C, Conference Room 6
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 147th regular meeting on 8 September 2008, in Conference Room 6, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, 8 September 2008, from 8:00 a.m. to 3:30 p.m. The meeting was closed to the public on Monday, 8 September 2008, 3:45 p.m. to 5:00 p.m. The NCAB Chair, Dr. Carolyn D. Runowicz, Director, The Carole and Ray Neag Comprehensive Cancer Center, Farmington, CT, presided during both the open and closed sessions.

NCAB Members
Dr. Carolyn D. Runowicz (Chair)
Dr. Anthony Atala
Dr. Bruce A. Chabner
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Kenneth H. Cowan
Dr. Lloyd K. Everson (absent)
Ms. Kathryn E. Giusti
Mr. William H. Goodwin, Jr.
Dr. Waun Ki Hong
Mr. Robert A. Ingram (absent)
Dr. Judith S. Kaur
Mr. David H. Koch
Ms. Mary Vaughan Lester
Dr. Diana M. Lopez
Dr. H. Kim Lyerly
Dr. Karen Dow Meneses
Dr. Jennifer A. Pietenpol
Dr. Daniel D. Von Hoff (absent)

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

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

Members, Executive Committee, National Cancer Institute, NIH

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

Liaison Representatives

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

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MONDAY, SEPTEMBER 8, 2008

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 17–18 JUNE 2008 MINUTES—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz called to order the 147th NCAB meeting. She welcomed members of the Board, the President's Cancer Panel (PCP), *ex officio* members of the Board, liaison representatives, staff, and guests. Members of the public were welcomed and invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), in writing and within 10 days, any comments regarding items discussed during the meeting. Dr. Runowicz reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was made to approve the minutes of the 17–18 June 2008 NCAB meeting. The motion was seconded and the Board unanimously approved the minutes.

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

Dr. Runowicz called Board members' attention to future meeting dates, which have been confirmed through 2010.

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

Dr. John Niederhuber, Director, NCI, welcomed new NCAB members and expressed appreciation to Dr. Runowicz for her willingness to serve as NCAB Chair for another term. He recalled that the NCAB was established by the Nixon Cancer Act of 1971 to advise the Secretary of the Department of Health and Human Services (HHS) and the NCI Director; Board members are leaders in medical and scientific disciplines. NCI's mission is to preempt the development of cancer, drive science to new knowledge, ensure access to the latest science for all people, and ensure the best outcome for patients. Cancer presents a large human and economic burden: more than 500,000 people died of cancer in 2007, 47 million Americans lack health insurance, and there were nearly 12 million cancer survivors in 2007. NCI's challenge remains to meet these needs during a sustained period of a flat budget, not accounting for inflation.

The President's Budget for FY 2009 is $4.809 M, which reflects a +0.1 percent change from FY 2008. Research program grants (RPGs) were funded at the 14th percentile plus extensive exceptions, for a success rate of approximately 20 percent. New investigator grants were funded at the 19th percentile plus exceptions, totaling about 200 awards. It is estimated that the NCI will fund 1,250 competing RPGs in FY 2008. The NCI also funded the Greenebaum Cancer Center at the University of Maryland. In addition, the NCI received a $25.56 M supplement, which was part of a $150 M supplement given to the NIH in July/August 2008. It is likely that supplements are the way that the NIH will receive incremental budget increases in the near future; this raises concerns about future year impacts of supplemental funds. Another budgetary challenge is the uncertainty about the number of submitted applications, which were down in 2008 but appear to be rising for 2009. During the 2008 Executive Committee (EC) budget retreat, held in July, additional 2008 resources were examined, a list of priorities was generated for 2009, and input to the NIH and to the Office of Management and Budget (OMB) about 2010 funding was discussed. One tool that the NCI uses to manage communication and expectation is the professional judgment budget; for the 2010 Congressional justification, the NCI currently is preparing its progress report and professional judgment budget, as well as working on its submission to OMB.

The NCI has prepared a draft national proposal to accelerate cancer research that manifests the United States' commitment and investment in providing leadership in science and interest in attracting young people to work in the fields of science; it also proposes budgetary increases that account for inflation. Additionally, in preparation for the change in the Administration, the NCI's transition team has identified topics of importance to the NCI and the National Cancer Program, such as clinical research, heath informatics, pharmaceutical costs to society, cancer research as a model for other diseases, and quality of care/outcomes research.

The Cancer Centers Program includes 64 NCI-designated Cancer Centers, 41 of which are Comprehensive Cancer Centers, and it operated under a budget of $262 M in FY 2008. The Centers leverage their core cancer center grants for an estimated 14- to 38-fold return on investment. Cancer Center principal investigators (PIs) receive 60 percent of NCI's extramural funding. Members were told that updates would be given later in the day regarding the NCI Community Cancer Centers Program (NCCCP) Pilot and the Special Programs of Research Excellence (SPORE), which has been moved to the Division of Cancer Treatment and Diagnosis (DCTD).

The Cancer Genome Atlas (TCGA), which the NCI co-sponsors with the National Human Genome Research Institute (NHGRI), has received attention from the press: "Scientists have mapped the cascade of genetic changes that turn normal cells in the brain and pancreas into two of the most lethal cancers. The result points to a new approach for fighting tumors and maybe even catching them sooner." (Associated Press, September. 4, 2008). Pilot programs are focused on glioblastoma, ovarian, and lung cancers; glioblastoma studies have identified at least four genetic subtypes, and newer sequencing technology is being applied across the pilots.

The NCI serves an enabling platform of connectivity among the academic research university and the scientists in those laboratories, the private sector, and the public sector. The goal is also to become a connector of other public activities of the government, such as the Centers for Medicare and Medicaid Services (CMS), the U.S. Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC), particularly by providing a neutral ground where these organizations can come together to wrestle with policy issues. An important component of this is NCI's targeted drug development platform, which works across the spectrum from genome to patient and aims to speed the process of targeted drug translation.

The NCI remains concerned about working with budgets that continue to be lower than inflation, providing leadership and resources to academia and industry, attracting the brightest talent to biomedical research, and building translational research programs. It also remains focused on knowledge management at NIH, new approaches to cancer, and the transition to a new Administration.

Questions and Answers

Mr. David H. Koch, Executive Vice President, Koch Industries, encouraged the NCI to track the amount of private philanthropy that sponsors cancer research annually. Dr. Niederhuber responded that a precise amount has not been ascertained but 90 to 95 percent likely has been influenced by the NCI Cancer Centers program. He said that another story that needs to be told is what a dollar of NCI money put into a specific city means for that city's economy. Dr. Runowicz expressed appreciation to all members who have supported cancer research. Dr. Bruce Chabner, Clinical Director, Massachusetts General Hospital Cancer Center, Chief of Hematology/Oncology, Massachusetts General Hospital, said that a recent survey showed that Cancer Centers receive more than $1 B in philanthropy, and the number likely is $1.5-2 B; NCI's seed money for infrastructure is important, as industry support would not exist otherwise. He said that this raises the question about the place of science in the presidential campaign.

Dr. Donald S. Coffey, Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, Johns Hopkins University School of Medicine, expressed his agreement. Dr. Coffey also commended private donors but cautioned that money given to a committee rarely makes it to an individual investigator. Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, stated that at her university, discretionary dollars received from donors are used to enhance the careers of the young investigators.

Dr. Runowicz commented that even small donations help, and that programs such as "Stand Up To Cancer" have helped to increase awareness among the public to support research, even at small levels. Dr. Coffey agreed that the program's greatest impact is on public awareness. Dr. Pietenpol added that awareness is important regarding the numbers of individuals who die every day from cancer and the significant role of basic research and discovery. Ms. Kathryn Giusti, CEO and Founder, Multiple Myeloma Research Foundation, Inc., suggested that the NCI also should track investments by industry and pharmaceutical companies, and she asked Dr. Niederhuber to share his thoughts on the possible energy that "Stand Up To Cancer" might bring to the fight against cancer. Dr. Niederhuber said that he welcomed any program that raised the public's awareness to the disease and noted the need for honest communication and transparency. Ms. Giusti observed that the public is unaware of and often asks questions about the NCI's leadership, particularly in collaborative research. Dr. Niederhuber affirmed NCI's leadership role and mentioned its work in technology, including nanotechnology and proteomics, as an example of the NCI forging ahead in a new frontier.

Dr. Niederhuber stated that the investment in cancer is an investment in other diseases as well, including diabetes, macular degeneration, and particularly HIV/AIDS; the NCI's research encompasses immunology, immunology of infectious disease and virology, and potentials for vaccines against cancer problems, and this research yields a rich trove of data and findings for other disease research.

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

Dr. LaSalle Leffall, Jr., Chair, President's Cancer Panel (PCP) and Charles R. Drew Professor of Surgery, Howard University Hospital, reminded members that the PCP completed its 2007-2008 series of meetings on "Strategies for Maximizing the Nation's Investment in Cancer." This series encompassed themes: the role of the NCI in the Nation's cancer enterprise; patient-centered cancer research and care; coordination across the cancer enterprise; innovative scientific discovery; access to quality cancer care for all; smoking cessation and prevention; regulatory barriers; and the need for a unified message/vision within the cancer community. The Panel is in the process of preparing its conclusions and recommendations from this series, and a final report will be presented to the President in the upcoming weeks.

The 2008-2009 meeting series is entitled "Environmental Factors in Cancer". The meetings will be held in East Brunswick, NJ, on September 16, 2008 (industrial and manufacturing exposures); Indianapolis, IN, on October 21, 2008 (agricultural exposures); Charleston, SC, on December 4, 2008 (indoor/outdoor air pollution and water contamination); and Phoenix, AZ, on January 27, 2009 (nuclear fallout, electromagnetic fields, and radiation exposure). These meetings are intended to help determine the status and role of regulatory agencies responsible for monitoring environmental hazards, identify research needs and potential new areas of collaboration between Federal agencies, increase public awareness of environmental and occupational hazards, and develop recommendations for better regulation of toxic and other potentially hazardous chemicals and materials.

Questions and Answers

Dr. Chabner encouraged the PCP to include ultraviolet radiation in its agenda on radiation exposure, particularly because of the growth in the tanning industry. Dr. Leffall said that the issue would be taken into consideration.

Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, asked about the PCP's plans to address the disproportionate risk from environmental pollutants placed on vulnerable populations in urban and rural/agricultural communities. Dr. Leffall responded that he appreciated the question and affirmed the PCP's acute awareness of cancer health disparities.

Mr. Koch wondered whether the PCP has been able to extrapolate examples that show the direct effect of its reports. Dr. Leffall replied that the PCP discusses this issue frequently but recognizes that myriad factors all contribute in the fight against cancer; he said that the PCP continues to disseminate its reports to as many people as possible.

Ms. Giusti praised Dr. Leffall for the Panel's ability to educate the public, as demonstrated by the example of Mr. Lance Armstrong. She expressed hope that Mr. Joe Torre would be as successful in this area as Mr. Armstrong has been. Dr. Niederhuber thanked Dr. Leffall for agreeing to continue to serve as the Chair of the PCP.

V. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Director, NCI Office of Government and Congressional Relations (OGCR), reminded members that the President's Budget for FY 2009 included $29.3 B for the NIH and $4.809 B for the NCI. The House of Representatives and Senate put forward draft bills that were slightly higher: the House bill included $30.380 B for the NIH and $ 4.975 B for the NCI, and the Senate bill would provide $30.255 B for the NIH and $ 4.959 B for the NCI. House action included a hearing on March 5 and Subcommittee approval on June 19. Senate action involved Subcommittee approval on June 24, full Committee markup on June 26, reporting of the bill on July 8, and an NIH hearing on July 16. Impacting FY 2008 appropriations, a supplemental spending bill (H.R. 2462) was signed into law (P.L. 110-252) on June 30 that allocates $150 M to the NIH, of which the NCI receives $25 M.

Ms. Erickson next described several recently enacted laws. The Caroline Pryce Walker Conquer Childhood Cancer Act (H.R. 1553; P.L. 110-285) expands and intensifies pediatric cancer research to ensure early access to treatment and makes treatment available to underserved children; it also establishes a National Childhood Cancer Registry. The Medicare Improvements for Patients and Providers Act (H.R. 6331; P.L. 110-275), which was passed by the legislative bodies, vetoed by the President, and became public law through an override of the veto on July 15, prevented a 10.6 percent cut in Medicare physician payment that was scheduled to take effect on July 1, and it holds payment at the current rate for 18 months. The FY 2008 War Supplemental Appropriations also was enacted. Pending legislation includes the National Cancer Fund Act, NIH Emergency Supplemental Appropriations, Federal Advisory Committee Act Amendment, Lung Cancer Mortality Reduction Rate, Quit Smoking for Life Act, and Family Smoking Prevention and Tobacco Control Act.

Questions and Answers

Dr. Chabner asked whether any action had resulted from the NCAB's letter to the Administration regarding the World Health Organization (WHO) Framework Convention on Tobacco and if there were any changes regarding the treaty. Ms. Erickson said that the letter was transmitted, but no response was

received. Dr. Robert Croyle, Director, Division of Cancer Control and Population Services (DCCPS), added that several other countries have signed the treaty, but that the United States is not a signatory. Dr. Runowicz suggested that the NCAB should reissue the letter recommending U.S. ratification of the treaty to new administration officials following the inauguration.

VI. ANNUAL UPDATE: AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)— DR. RICHARD SCHILSKY

Dr. Richard Schilsky, President, ASCO, described ASCO's strategies and activities to improve cancer care and prevention, advance education and training, foster communication, advocate sound policy, and support professionals in all settings. The Presidential theme for this year is personalizing cancer care. ASCO has identified, analyzed, and developed plans to help more than 26,000 members from 121 countries address challenges surrounding workforce supply/demand, cost of cancer care, cancer care disparities, palliative care, clinical trials infrastructure, and administrative burden of health care delivery and research, among others.

Workforce Supply/Demand. Issues about the workforce include that 50 percent of oncologists are nearing retirement, there is a reduced interest in internal medicine, and funding for fellowship slots is limited. In addition, the demand for oncology visits is outstripping the availability, particularly because of increased survivorship and increasing cancer incidence in an aging population. This requires a coordinated, multifaceted approach. ASCO's strategic plan goals are to: identify ways to improve practice efficiency; adapt/expand training; and collect, assess, and report real-time data, as well as initiate a Physician Investigator Project. Other planned activities include: competitive grants to study innovative practice arrangements, pilot projects to test innovative practice models, partnerships with other health professionals, increases in number and funding for training slots, recommendations for increasing exposure to outpatient oncology during medical school training, and development of a workforce information database and health of the workforce report. A principle challenge is that increased clinical demands will jeopardize the time clinicians have to engage in research. The solution will require compensation for protected research time, increased reimbursement for added costs of patient recruitment and monitoring, and standardization and simplification of the research process. ASCO and NCI are working together to monitor oncology demand data.

Cost of Care. Health care spending is growing at an unsustainable rate, with oncology care comprising 5 percent (and growing rapidly) of the spending. Cancer agents are among the most expensive drugs, and patient testing is intensive. ASCO's plan is two-staged: Phase I involves the development of information and methods to integrate cost considerations into treatment decision making, and Phase II is the development of policy recommendations. ASCO is discussing cost drivers and strategies to reduce cost, such as efficacy and cost-effectiveness comparisons, evidence-based clinical care, improvements to the efficiency of drug development, better patient-physician communication, cost-benefit analysis and value in decision making, and biomarkers for treatment selection.

Cancer Care Disparities. Minority populations are increasing, many lack insurance, and they are not well represented in the medical community. Even with insurance, barriers of language, geography, and culture limit access to cancer care and affect outcomes. ASCO is considering activities related to: access to health insurance through legislative reform; access to cancer screening services; education to increase provider, patient, and public awareness; support for minority researchers; promotion of workforce diversity through loan repayment programs; and patient-centered care models.

Palliative Care. Palliative care should extend through the continuum of cancer care and requires an integrated approach to care management. It poses a global challenge, with 50 percent of new cases

occurring in the developing world and 80 percent of these diagnosed at advanced stages and dead within 1 year. At least 60 percent of advanced cancer patients experience moderate to severe pain combined with other complications. A significant range of new palliative care treatments have been introduced during the past 10 years. ASCO's plans in this area encompass: education (update and disseminate resources, support training programs, standardize palliative care terminology); policy (advocate for integration of palliative care and adequate coverage); patient access to a full range of palliative care drugs; and promotion of integrated palliative care models, quality care, and research.

Clinical Trials Infrastructure. Issues in clinical trials include the complexity of trial activation, limited physician participation and incentives, the threat of needed industry support to independence, and differing practices and demands among industry and the NCI. ASCO is considering activities that involve advocacy to increase NCI funds, education, resources and tools, and a Community Oncology Research Grant. Challenges remain to streamline protocol activation, increase trial reimbursement, facilitate industry collaborations, harmonize FDA expectations and NCI procedures, and develop partnerships with stakeholders.

Regulatory Complexities. Reducing burdens of regulatory complexities is paramount to increase participation in clinical trials. This can be accomplished through legislative and regulatory advocacy and existing partnerships (e.g., data collection and case report form standards, and the FDA Critical Path Initiative). Potential partnerships with ASCO could help prepare best practices for HIPAA and biospecimens, address NCI Central Institutional Review Board evaluation findings, integrate the Cancer Biomedical Informatics Grid (caBIG) and electronic health record efforts, and work with the FDA to refine "minimum necessary" data sets.

Dr. Schilsky stated that shared goals of research, education, and information bring the cancer community together in promoting quality cancer care. ASCO advocates for a strong federal cancer research program.

Questions and Answers

Dr. Victoria L. Champion, Associate Dean for Research, Indiana University School of Nursing, offered several considerations in terms of cancer care, including adding other professionals to clinical oncology care: health care teams should be conceptualized; underserved populations should be reached through interactive technology, such as computers; and the cancer care continuum, which begins with prevention, should start at birth or even prenatal times and cover the entire lifespan. Dr. Schilsky agreed and added that ASCO has launched a new Web site (www.cancer.net) targeting patients, as well as the ASCO University, to provide a series of Web-based, training modules in issues that are important to ASCO cancer patients and providers. He also shared his surprise in recently learning from representatives of the physician assistants' professional society that physician assistants do not receive specific training about oncology during their generic education. ASCO is considering creating educational modules for physician members to use to train the physician assistants and nurse practitioners they have recruited to work with them.

Mr. Koch observed that young people tend to move into fields where compensation is the greatest, and that a strong perception exists that the field of oncology is underpaid relative to other medical areas; he asked whether Medicare and Medicaid reimbursements to oncologists were a factor or if other causes were responsible. Dr. Schilsky commented that part of what is discouraging people is that oncology is hard, demanding, and emotionally compelling work. Dr. Runowicz added that medical students incur a tremendous financial debt; she recommended recruiting students when they are interested in science, alleviating or removing their financial burden of becoming a scientist or doctor, and looking at

compensation issues. Dr. Anthony Atala, Director, Wake Forest Institute for Regenerative Medicine, Professor and Chairman, Department of Urology, Wake Forest University School of Medicine, said that in addition to too few trainees coming from medical school, the increasingly larger aging population poses challenges. Dr. Schilsky agreed that it is a global problem and that interest in medicine and science as careers should be encouraged in high school and at younger ages. Dr. Waun Ki Hong, Head, Division of Cancer Medicine, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M.D. Anderson Cancer Center, expressed support for ASCO's leadership on workforce issues and encouraged ASCO to work with the Accreditation Council for Graduate Medical Education (ACGME) to expand the number of slots available for hematology/oncology fellows.

Ms. Giusti asked about ASCO's budget status and funding sources. Dr. Schilsky said that ASCO's annual operating budget is approximately $80 M; it is effectively a flat budget, and ASCO has developed a revenue diversification plan to raise funds from other sources.

Dr. Kaur asked Dr. Schilsky to share his perspective on the dramatic complexity of protocols and changes to the clinical trials structure to meet the needs of the protocols. Dr. Schilsky responded that although complicated protocols may take longer to enroll subjects and answer the clinical question, the ones that are successful yield an unmatched richness of data, such as well-annotated biospecimens from patients on clinical trials.

VII. STATUS REPORT: NCI COMMUNITY CANCER CENTERS PROGRAM (NCCCP)—DRS. MAUREEN JOHNSON, THOMAS PURCELL, MARK KRASNA, AND STEVEN CLAUSER

Dr. Niederhuber remarked that one of his initial goals as Director was to extend the NCI into the community and expand access to cancer care. The NCCCP, having completed the first year of its 3-year pilot, has surpassed early expectations. Dr. Maureen Johnson, Project Officer, NCCCP, provided an overview of the Program and introduced the speakers: Drs. Thomas Purcell, NCCCP PI and Director of the Billings Clinic Cancer Center, Division Chief, Service Lines; Dr. Mark Krasna, Medical Director, St. Joseph Medical Center Cancer Institute, PI, Catholic Health Initiative (CHI); and Dr. Steven Clauser, Chief, Outcomes Research Branch, NCI Project Officer, NCCCP Evaluation.

NCCCP Program Overview. Dr. Johnson stated that approximately 85 percent of cancer patients receive their care within their local communities but treatment often is fragmented. Addressing this fragmentation was one of the goals of NCCCP as well as to bring state-of-the-art cancer care to community settings. Baseline criteria for site participation are that the center must be hospital-based with innovative programs that incorporate surgery, radiation oncology, and medical oncology. The site must see 1,000 new cancer cases each year and have a minimum annual enrollment of 25 patients in clinical trials. The institutions commit to caring for the underserved and must agree to the policy that any patient who is screened for cancer is treated, regardless of insurance status. All sites agreed to implement the electronic medical record (EMR) by the end of the 3-year pilot.

The program chose six community hospitals in urban and semi-rural areas, two rural hospitals that serve Native Americans, and two multistate health systems with multiple program locations. NCI funds each Center at $500 M per year for a total of $15 M over 3 years. The program relies on strong private/ public partnerships, and top hospital management has demonstrated their commitment to the NCCCP. The sites have agreed to co-invest $47 M to support the goals of the program.

The major pillars that support the NCCCP pilot are clinical trials, advocacy, biospecimens, survivorship, quality of care, information technology, including caBIG and EMRs, and disparities.

Addressing health care disparities is an important component of the NCCCP pilot; each site must allocate 40 percent of NCI funding to this end. The sites see approximately 27,000 new cases per year, a substantial portion who could contribute to the research enterprise in clinical trials and biospecimen collection. The network also is enhancing the cancer research infrastructure, showing increases in patient accrual to clinical trials in just 1 year. All sites have surpassed the deliverable for biospecimens for the pilot and are adopting optimal processes for formalin-fixation, the first step necessary for high-quality biospecimens. Further, the sites have made many new connections to community organizations, with a focus on reaching the underserved. NCCCP staff has expanded linkages with oncologists to coordinate care and promote research and have reached out to primary care providers to improve screening.

Through collaborations created by the NCCCP network, hospitals are sharing data to improve adherence to evidence-based practices. As a result of the pilot, the NCI has signed a memorandum of understanding with ASCO's Electronic Health Records Initiative that will ensure that ASCO and the electronic record vendors incorporate the needs of community hospitals in developing EMRs and include NCI's caBIG compatibility. The NCCCP model addresses one of the major blocks in the cancer research continuum, the translation of clinical trials into everyday clinical practice and decision making. The community cancer center sites are well equipped to evaluate interventions in real-world settings and to reduce disparities.

Billings Clinic NCCCP Site. Dr. Purcell presented a progress report of his site via videoconference. He stated that much of what NCCCP has done for delivery of cancer care can be translated over into other areas of medicine associated with complicated service lines. The Billings Clinic Cancer Center, a multispecialty clinic with an academic-like structure, has a geographic catchment area the size of Indiana, Ohio, and Illinois combined. The past paucity of NCI-designated cancer centers in Montana forced patients to travel as far as Salt Lake City, Denver, or the Mayo Clinic in Rochester, MN, for their care. The Billings Clinic has nine oncology/hematology outreach clinic locations, some so remote that oncologists must travel by plane to reach them.

The impact of the NCCCP pilot on the growth of the Montana cancer program has been dramatic. In FY 2003, the Billings Clinic Cancer Center had 10 employees (3 physicians) and $24 M overall cancer services revenue. One year after the initiation of the NCCCP pilot, the Center has 70 employees (10 physicians and 3 mid-level practitioners) and $80 M in overall cancer services revenue. With more than 1,450 patients per year, the Billings Clinic Cancer Center enrolled more than 160 patients in clinical trials. The NCCCP has substantially expanded access to NCI-sponsored research programs, to the NCI Biospecimen Collection, and caBIG technology expertise, thereby leading to better care. Advances in telemedicine technology have allowed this NCCCP site to extend care to disparate populations (the uninsured and Native Americans). Native Americans, particularly the Crow Tribe, constitute an important patient population for the Billings Clinic Cancer Center.

The Billings Clinic Cancer Center is now a regional leader in cancer research, focusing on gene therapy, immunotherapy, and quality-of-life parameters. With the support of the NCCCP, patients have access to high-level, complicated clinical trials and novel therapies that have not been available before. By forging a better relationship internally, with the biospecimens laboratory and the radiology department, this NCCCP site has been able to provide state-of-the-art "best practices" cancer care. A high priority is to accrue to cooperative group studies, and researchers are now affiliated with the Gynecology Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG), among other cooperatives. One unique trial, available only at the Billings Clinic Cancer Center and a few academic institutions, involves injecting vaccinia virus encoded for granulocyte monocyte colony stimulating factor (GM-CSF) directly into the tumor in patients with melanoma and hepatocellular carcinoma. Researchers are intravesicularly injecting adenovirus encoded with GM-CSF in patients with refractory or recurrent early-

stage bladder cancer. Phase 1 data thus far have shown complete responses after a single dose. The Billings Clinic NCCCP plans to continue to recruit patients who would not otherwise have access to these types of studies and to form collaborations with other NCI-designated cancer centers.

The Center's access to the Native American population will allow further genetic studies. Staff recognizes the challenges of resolving disparities in cancer care within this population; many patients lack access to preventive/screening services and certain procedures and treatments because of inadequate Indian Health Service (IHS) funding. Understanding tribal cultural norms and gaining individuals' trust is critical to the Program's outreach.

Catholic Health Initiative (CHI) NCCCP System Site. Dr. Krasna commended the NCI's selection of CHI as a NCCCP site because it represents a microcosm of U.S. health care and because CHI had chosen cancer care as its highest priority for 2008-2009. Five hospitals are participating in the pilot: St. Joseph Medical Center, an urban Baltimore facility where 35 percent of patients are African American; Penrose-St. Francis Health Services in a low-income, medically underserved area of Colorado Springs; and a consortium of three hospitals in rural Nebraska. The limited number of available trials makes Nebraska a prime site for increasing both the number of trials and participant levels.

The strategic vision for CHI's recently launched Catholic Health Oncology Network was well aligned with the mission of the NCCCP pilot: "to be an integrated system-wide oncology research and multidisciplinary care initiative focused on delivering new standards of oncology care and quality." The CHI Research and Development (R&D) Board committed $5 M to cancer research and development to match the NCI NCCCP awards of $500,000 per year for 3 years, which was split between the two hospitals and the rural network of three hospitals.

The CHI NCCCP has expanded outreach and screening at all of its sites, implemented cancer information services, and created patient navigator programs to integrate the clinical aspects of multidisciplinary management and reduce disparities in health care. With the impetus from the NCCCP award, the CHI has established partnerships with other institutions, such as with University of Maryland's Regional Community Network, and received additional funding from American Cancer Society grants and common foundation grants.

Monthly conference calls between the CHI sites and quarterly retreats have allowed consistent sharing of best practices. Through the group cooperative mechanism, the CHI NCCCP has expanded access to clinical trials, becoming affiliated with RCOG, the Cancer and Leukemia Group B (CALGB) group, and the American College of Surgeons Oncology Group (ACOSOG). Improving biospecimen collections, one of NCCCP's core components, is a focus of the CHI site. An additional grant from CHI's R&D Board will fund a new center for translational research at St. Joseph's Cancer Institute. The Institute will collect tissues from the 250,000 cancer patients seen at CHI sites and store them in one unique facility, governed by the Office of Biorepositories and Biospecimen Research (OBBR) Best Practices.

Dr. Krasna asserted his belief that the NCI's pilot evaluation will show that patient-centered, multidisciplinary cancer care reduces time to diagnosis and treatment and ultimately influences quality of life and survival. Future challenges include demonstrating patient satisfaction and improved patient care, finding ways to meet physician needs, and developing a robust list of benefits for participating in clinical trials.

NCCCP Evaluation. Dr. Clauser described the components of the NCCCP evaluation process. The internal evaluation, which is specific to program development, is being led by the NCCCP Program Advisory Committee. NCI staff evaluates program deliverables and works with all sites to help them

implement components of the NCCCP pillars. The evaluation is concentrating on the pilot organizations' abilities to create, acquire, or leverage leadership, expertise, and resources. The researchers seek to measure how well the different sites have created the organizational structures necessary for the NCCCP to be effective. The evaluation considers the organizational context of the community cancer centers to assess their performance. The evaluative guiding principles are that: the measures of interest are grounded in theory and current understanding in the literature; multilevel and multimethod (quantitative and qualitative) approaches are used to increase the reliability of findings; and that triangulation of findings will help interpret program development and performance over time. An example of triangulation is conducting focus groups of patients and caregivers to help interpret the results of patient surveys.

Approaches from organizational theory and management science are needed to evaluate how NCCCP organizations implement change. Successful organizations transition from sense-making to operationalizing to learning. Built on this model of organizational change, evaluators created a conceptual framework to interpret the NCCCP sites' activities. Site visits are part of a longitudinal multiple case study design being used to understand NCCCP implementation, assess change in site performance over time, and determine which NCCCP structures and processes are associated with successful implementation and performance. All NCCCP sites were visited in the spring of 2008, and coding and analysis of Year 1 data are underway.

To better characterize the return on the investment and to identify average and/or incremental costs associated with NCCCP activities, a micro-cost analysis has been undertaken, which is a unique feature of the evaluation. An economic analysis of increasing clinical trials accrual is an example of this type of evaluation. A "business case"/"strategic case" analysis for participating sites will scrutinize the expected short- and long-run financial impacts and how they relate to other strategic goals of the project. The economic evaluation will be essential for predicting program sustainability.

Because patient-centeredness is at the heart of NCCCP activities, researchers are interested in the patient's perspective on access to clinical trials and psychosocial services and on coordination and continuity of care. NCCCP patients, 475 from each site, will be surveyed twice throughout the pilot to assess change over time. The survey is being cognitively tested and is undergoing final revision while awaiting IRB clearance. Years 2 and 3 activities include repeat site visits for 2009 and 2010, ongoing micro-cost data collection and analysis, and fielding the second round of patient surveys. The results of NCCCP's evaluation will be regularly disseminated to NCI leaders and advisory boards. A series of progress reports stemming from the evaluation will be distributed throughout the course of the pilot.

Questions and Answers

Dr. Chabner asked about specific endpoints that were being measured, such as accrual to clinical trials, changing mortality, and improved patient satisfaction and acknowledged the difficulty of establishing an evaluation process for diverse community cancer centers. Instead of complicated diagrams and complex evaluation analysis, he suggested simplifying the endpoints or deliverables. Dr. Niederhuber replied that the original goal of the program was to transform the fragmented care in communities lacking a university or major cancer center. Dr. Clauser replied that the disparities pillar was being evaluated by analyzing changes in the proportion of charity care delivered by NCCCP centers and the quality-of-care pillar was being evaluated by looking at clinical measures such as timing of treatment, provision of adjuvant chemotherapy to Stage 3 colorectal cancer patients, and availability of hormonal therapy to breast cancer patients.

Dr. Chabner asked about the measurable endpoints used at the Billings Clinic Cancer Center. Dr. Purcell responded that one parameter is increasing the number of people receiving appropriate screening for cancer; the Billings Clinic has gathered hard metrics on accrual of African Americans and Native Americans into clinical trials. Dr. Karen M. Meneses, Professor and Associate Dean for Research, University of Alabama at Birmingham School of Nursing, asked how rural and frontier patients were being included in the NCCCP patient surveys. Dr. Clauser said that they hoped to accrue rural patients from the Billings Clinic and that focus groups would provide additional information about how the pilot site had affected their experiences. Dr. Krasna added that each site prepares quarterly reports documenting progress with deliverables such as clinical trials accrual, accrual of minority patients, or accrual for biospecimens.

Dr. Kaur commented that data on comorbidities in disparate populations should be prospectively collected and included in the protocol screening information. Comorbid conditions significantly affect how patients respond to cancer treatment. Mr. Koch asked if a NCCCP site could change a protocol if it was performing poorly at that particular institution. Dr. Johnson said that the value of a pilot is that it discerns what works and what does not; that which is feasible in a research center may not be in the community setting.

VIII. CELLULAR TELEPHONES AND BRAIN TUMORS—DRS. JOSEPH FRAUMENI AND PETER D. INSKIP

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), informed the Board that the NCI's intramural research program has been asked in the past to investigate suspected links between certain environmental exposures and the risk of developing cancer. The NCI has studied a host of cancer risks associated with numerous exposures, including artificial sweeteners, fluoridation of water, breast implants, and a variety of chemicals in the workplace. The Radiation Epidemiology Branch has brought together dosimetrists and epidemiologists to clarify cancer risks associated with indoor radon, exposures around and within nuclear facilities, and exposures to radioactive fallout. A mounting interest in the health effects of exposures to non-ionizing radiation stimulated the Branch's case-control study of the association between cellular telephone use and brain tumors. Dr. Fraumeni next introduced Dr. Peter D. Inskip, Senior Investigator, Radiation Epidemiology Branch, DCEG, who presented the results of his study and summarized the current state-of-evidence revealed by subsequent research. In 1993, a televised anecdotal claim that a man's wife died of a brain glioma caused by frequent cell phone use attracted widespread media attention leading to Congressional hearings. As little was known about the cancer risks of radiofrequency radiation, the NCI added a cell-phone component to a previously planned comprehensive case-control study of brain tumors. Despite public health concerns, the utilization of the novel technology increased rapidly in the United States to an estimated 255 million wireless subscribers by December 2007.

The mechanism by which the radiofrequency radiation from cell phones could cause cancer is unknown and to date, entirely speculative. The radiofrequency energy waves are billions of times lower than the energy from an x-ray photon and have insufficient energy to break molecular bonds or ionize molecules. Animal studies have failed to show any evidence of carcinogenicity or genotoxicity from similar levels of non-ionizing, radiofrequency radiation. To test the association in humans, the NCI examined 489 newly diagnosed cases of glioma, 197 cases of meningioma, and 96 cases of acoustic neuroma from three different urban hospitals, matched with 799 control subjects. Between 1994 and 1998, researchers interviewed participants about their past cellular phone usage and found that there was no association between incidence of glioma and level of cell phone use. Further, in the glioma patient sample, laterality of tumor had no association with the side of the head the subject reported holding the cell phone. Similar findings were found for meningiomas and acoustic neuromas. A limitation of this

study, as in most case-control studies, is that results are dependent on subjects' accurate reporting past exposures—in this case, frequency, duration, and laterality of phone use. Additionally, since the NCI study was completed, there have been changes in cellular technology, including moving from mostly analog to digital systems and use of higher frequency bands. Two other early studies, a case-control study in the United States. and a Danish cohort study also failed to show an association between glioma and cell phone use.

In the next generation of research, the expanded Danish cohort study, which followed 420,095 persons through to 2002, found no increase in brain tumor incidence, even among long-term wireless subscribers. Pooled analyses of data from four Scandinavian countries and the United Kingdom, all of which are participating in the large-scale INTERPHONE study, did not show overall associations between the risk of glioma, meningioma, or acoustic neuroma and the cumulative hours of cell phone use or the number of calls.

Studies of occupational exposure to radiofrequency radiation and cancer have provided additional insight. Research on 195,000 Motorola workers engaged in manufacturing and testing cell phones failed to show an association between radiofrequency exposure and mortality due to brain cancer, as did a cohort study of more than 40,000 Korean War Navy veterans exposed to high-intensity radar. In other studies, researchers have not found an association between cell phone use and other cancers, such as non-Hodgkin lymphoma or parotid gland tumors. Studies have confirmed a well-established association between cell phone use and motor vehicle accidents, outcomes not related to radiofrequency radiation but to mental distraction. Further studies are needed to detect longer term risks of cell phone use and to determine the risks to children. The ongoing analyses of the INTERPHONE study and from a northern European case-control study of childhood cancer will likely yield more conclusive evidence.

Questions and Answers

Mr. Koch asked whether similar studies have been conducted on the effect of magnetic radiation from high power electric transmission lines and the incidence of brain cancer. Dr. Inskip explained that in his reading of the literature, there was no association between such exposure to low frequency radiation and brain cancer in adults. In a few pooled analyses of different studies investigating childhood brain cancer, the evidence is slightly less negative but inconclusive. Dr. Inskip referred to journal articles showing no association between adult brain cancer and electrical appliance use in the home or occupational exposure to extremely low frequency radiation.

Dr. Atala asked how the correct facts could be disseminated to the public, given current misinformation in the media regarding cell phones and cancer. Dr. Inskip informed the Board that the NCI fact sheets had been recently updated to reflect the lack of association between cell phone use and brain cancer but questioned how regularly the public is informed about the fact sheets. Dr. Atala suggested that informational articles be written and distributed to the press.

IX. NEURO-ONCOLOGY OVERVIEW—DR. HOWARD FINE

Dr. Howard Fine, Chief, Neuro-Oncology Branch, Center for Cancer Research (CCR), emphasized that brain tumors are the leading cause of cancer-related deaths in children and the fourth leading cause of death in patients under 65 years of age in the United States. The category "primary brain tumor" represents more than 30 different tumors that range from fully curable to rapidly lethal. Although significant therapeutic advances in the treatment of some subtypes of brain tumors in children and adults have been made, median survival for most primary brain tumors is only approximately 14 months and long- term survivors often face significant long-term neurocognitive deficits.

The Neuro-Oncology Branch (NOB) is a joint effort by the NCI, the National Institute of Neurological Disorders and Stroke (NINDS), and the extramural community that serves as a national resource for central nervous system (CNS) malignancies and enhances translational science and pre-clinical and clinical development of experimental therapies for these tumors. The program sees 500 new patients and runs between 8 and 20 clinical trials for primary brain tumors each year. The NOB works with extramural investigators through the Cancer Therapy Evaluation Program (CTEP)-funded brain tumor consortia and through collaborative projects with the brain cancer SPOREs, as well with individual investigators and academic centers. The NOB also has been active in the planning of the new combined CTEP-sponsored brain tumor clinical trials consortia and has initiated translational research for oncogenomics and preclinical testing. The NOB also works with the private sector and regulatory agencies such as the FDA to facilitate screening of promising new therapeutic agents and to evaluate and establish new endpoints for testing these agents against primary brain tumors.

The NOB seeks to develop novel and innovative bench-to-bedside translational research efforts, with the goal of developing "personalized medicine" for every brain tumor patient. Three major groups represent NOB's efforts in this field: 1) Glioma Molecular Diagnostic Initiative (GMDI)/REpository of Molecular BRAin Neoplasm DaTaBase (REMBRANDT), the genomics computational biology effort; 2) work in molecular developmental biology, including efforts to identify glioma stem cells; and 3) the clinical science effort, currently focused on preclinical and clinical development of anti-vascular endothelial growth factor (VEGF) agents.

GMDI has developed a publicly accessible Web-based glioma database and informatics platform that houses pathologic, molecular, and genetic data with detailed clinical corollary data for more than 1,000 patients. This database will enable creation of a biologically significant pathologic classification system for gliomas, should lead to better prognostication and more informed therapeutic decisionmaking, and also will help in the search for new therapeutic targets. At present, 30 Centers participate in GMDI and have accrued nearly 900 patients prospectively. Gene expression arrays have been completed and genomic SNP analyses performed for more than two-thirds of these patients. REMBRANDT was created to serve as the data warehouse and bioinformatics system to manage these data. REMBRANDT also has a number of evaluation and informatics tools. For example, Kaplan-Meyer survival curves can be created based on gene expression and other clinical information.

The accumulation of such large amounts of data has allowed identification of common regions of genomic alterations in glioblastomas. SNP and RNA expression analyses have enabled closer evaluation of these alterations and identification of individual genes (such as *ATAD1*, *PTEN*, and *EGFR*) that may be of therapeutic interest. Epigenetic changes also affect cell biology and GMDI permits analysis of these changes through its cores that perform quantitative PCR and methylation studies. Epigenetic regulation of a gene may decrease mRNA levels more than would be expected based on DNA copy number analysis, and genes that appear to be epigenetically regulated may be new tumor suppressor genes. Analysis of the promoter region of an epigenetically regulated gene found hypermethylation, suggesting inappropriate inhibition of gene expression.

Analysis of gene expression profiles also has led to the development of classification schemas based on expression patterns and other biologic characteristics that differ from standard pathologic classification systems and may provide new insight on treatment. Analysis of approximately 800 glioma patients has found six new, distinct glioma subtypes. For example, a glioma that was not classifiable using previous designations was subjected to expression profiling and found to fall into subgroup GA2, which is characterized by highly deregulated cell cycle regulation and cell division genes. The patient was

treated as if he had a highly proliferative tumor, using drugs that are not traditionally used to treat gliomas. The patient had a nearly complete response and remained tumor-free a year after treatment.

TCGA has performed high-throughput DNA sequencing of more than 600 genes of interest in one type of glioma as well as analysis of epigenetic changes. GMDI activities synergize with those of TCGA through the GMDI's collection of samples from all glioma types and provision of extensive clinical data. GMDI also will generate genetic data from patients on trials of molecularly targeted agents, which will allow researchers to draw correlations between genetic profile and response to therapeutic agents. GMDI has initiated a program to produce glioma tissue arrays consisting of approximately 300 gliomas per slide; such slides are available to investigators throughout the United States. REMBRANDT has assisted in the testing and refinement of caBIG tools such as caARRAY and caINTEGRATOR, which have helped form the Cancer Molecular Analysis Portal, which houses TCGA data.

The NOB also has sponsored work on glioblastoma-initiating or glioblastoma stem cells. Traditional glioma cell lines may be poor representations of primary tumors, as they differ significantly with respect to morphology, genetic stability, gene expression profiles, and tumorigenicity. For example, the human glioblastoma U87 cell line forms a single mass without infiltrates within the brain of an immunodeficient animal, in contrast to the diffuse infiltrates observed in human glioma.

Evidence has suggested that cells with stem-cell-like characteristics might be more relevant for modeling glioma than differentiated cells that had become tumorigenic. Many features of glioma cells (migratory behavior, morphology, self-renewal, and proliferative capacity) are similar to those of normal neural stem cells. Therefore, glioma growth *in situ* may be driven by a small subpopulation of tumor-initiating cells with neural stem cell-like properties. To identify glioma stem cells, tumor cells from glioma patients were grown under either standard cell culture conditions with serum, which induces terminal differentiation of normal neural stem cells, or under conditions conducive to growth and nondifferentiation of stem cells (NBE conditions). Cells grown under NBE conditions formed neural spheres, which resemble structures formed by normal fetal neural stem cells grown in culture. In contrast, the cells grown under standard conditions developed epithelial-like cells that resembled commonly studied glioma cell lines. The NBE cells also gave rise to invasive tumors when implanted into the brains of immunodeficient animals.

Gene expression profiling of 24,000 genes found that the expression patterns of NBE cells were strikingly similar to those of the parental tumors and also bore a resemblance to patterns observed in normal neural stem cells, unlike the patterns observed for cells grown under standard conditions. The NBE cells had areas of loss of heterozygosity (LOH), amplification, and deletion similar to those seen in the parental tumor. The NBE cells also remained principally diploid even after multiple passages, in contrast to the matched serum-grown cells, which developed characteristics of genetic instability.

This work suggests that a primary glioblastoma contains a small subpopulation of cells with clonagenic potential and stem cell-like properties that give rise to nonclonagenic progeny. Growing these cells in the presence of serum induces terminal differentiation, creating a population of cells that no longer includes those with tumorigenic potential. In addition, cells grown in serum develop genomic instability, resulting in a population of cells that no longer resembles the primary tumor. These cells have been used for the past 30 years for studying glioblastoma, including the testing of potential new drugs. In contrast, culturing cells from glioblastomas under "stem cell conditions" maintains the stem cell population and thus the genotypes and phenotypes of the original tumors, thereby creating an improved model system for studying mechanisms of glioma pathogenesis and screening novel new anti-tumor agents.

Understanding why glioma stem cells do not appropriately differentiate *in situ* like normal stem cells may lead to new ideas for treatment. During normal embryonic neural stem cell development, neural stem cells undergo an early proliferative phase, promoted by cytokines such as bone morphogenic protein (BMP) and ciliary neurotrophic factor (CNTF). These same cytokines promote differentiation in later phases of embryonic neural stem cell development. The stem cell populations that give rise to glioblastomas may represent aberrations of the normal development process. Analysis of tumor stem cells generated from patients seen at the NIH found subgroups of tumor stem cells that did not undergo terminal differentiation in response to BMP and CNTF; instead, these cells responded by proliferating and increasing production of stem cell markers.

During normal embryonic neural stem cell development, the BMP receptor 1A allows proliferation of cells in response to BMP, but also induces expressions of the B1 BMP receptor. Expression of 1B in neural stem cells permits BMP to act as a differentiating or apoptotic agent. The B1 receptor was not expressed in a population of glioma stem cells, suggesting that these cells are similar to very early embryonic neural stem cells, do not spontaneously induce expression of the 1B receptor, and thus continue to proliferate in response to BMP.

Transfection of glioma stem cells with a 1B expression plasmid resulted in loss of expression of neural stem cell markers and increased expression of differentiation markers and development of a non-tumorigenic phenotype. The switch from 1A receptor expression to 1B expression was found to rely on demethylation of the 1B promoter, which was aberrantly methylated in the glioma stem cells. Treatment of these cells with 5-azacytidine resulted in demethylation of the promoter and upregulation of the 1B receptor and terminal differentiation of the cells in response to BMP.

Analysis using REMBRANDT determined that approximately 20 percent of the human gliomas in NOB's collection lacked 1B expression, and the 1B promoters in these cells were hypermethylated. This work shows that a functional differentiation pathway exists in most glioma stem cells and that a methylation-mediated block to BMP-induced differentiation in a subset of gliomas can be reversed using demethylating agents such as 5-azacytidine. A clinical trial is planned in which patients will be screened for downregulation of the 1B promoter and treated with 5-azacytidine.

Another approach to malignant glioma treatment features anti-VEGF therapy. Gene expression profiling has shown that high grade gliomas have a clear angiogenic profile stimulated predominantly by VEGF; thus, VEGF inhibition should inhibit malignant glioma growth. The Brain Tumor Therapeutics Screening Core has screened a number of anti-VEGF agents, including bevacizumab and vandetanib (Zactima), a dual VEGF/EGFR inhibitor and has treated more than 500 patients with high grade gliomas with these drugs. Dual VEGF/EGFR inhibitor therapy resulted in significant shrinkage of tumors after three cycles of generally well-tolerated treatment. Previous data had shown that combined bevacizumab/CPT11 therapy resulted in a significant response in cases of recurrent glioma, but CTP11 appeared to add toxicity. A trial of bevacizumab alone showed a dramatic radiographic response; more than 70 percent of patients had a significant response to treatment and approximately 30 percent were progression-free at 6 months, compared to historical data showing approximately 6 percent of patients progression-free at 6 months in other trials. Bevacizumab is currently under evaluation by the FDA for accelerated approval for treatment of recurrent gliomas.

The overarching goals of the NOB include promotion of clinical trials and genomic surveys of patients with glioma. Gene expression data and tumor stem cell lines also will be generated from each patient for further analysis. These efforts will lead to improved treatment and also better clinical trial stratification based on the genomics and the biology of each individual tumor.

Questions and Answers

Dr. Runowicz asked about the durability of the bevacizumab response. Dr. Fine explained that 6 months of progression-free survival is observed in approximately 30 percent of treated patients. In the field of neuro-oncology, 6 months has been agreed on as the endpoint for cytostatic agents. Of the patients who remained progression-free for 6 months, several had more than 2 years of bevacizumab treatment with no signs of tumor recurrence.

Dr. Hong asked if Dr. Fine had analyzed expression of EGF-R and VEGF in tumor tissues and whether use of a combination of angiogenesis inhibitors plus demethylating agents such as 5-azacyidine have been considered. Dr. Fine answered that efforts to develop effective drug combinations are under way, mostly in animal models. Other chromatin remodeling drugs such as histone deacteylase inhibitors also are being analyzed. EGF-R data are available for each patient; however, the response to Zactima does not appear to be correlated with EGF-R status.

Dr. Peter Kirchner, Senior Scientist, Office of Biological and Environmental Research, U.S. Department of Energy, asked if there were plans to image biomarkers for the tumor stem cells that are grown in non-serum media. Dr. Fine explained that he is working with Dr. Joe Frank to label patients' endothelial progenitor cells with iron compounds and use MRI to determine if these cells migrate to sites of angiogenesis. If so, this will represent a dynamic and real-time noninvasive imaging modality for biomarkers of angiogenesis. Dr. Kirchner asked if the iron compound markers remain with the stem cells as they proliferate or begin to disappear with progressive proliferation. Dr. Fine answered that the markers dilute with progressive proliferation.

Mr. Koch asked about efforts to obtain FDA approval for bevacizumab for glioma therapy. Dr. Fine answered that Genentech asked for accelerated approval based on their randomized Phase II trial in the spring of 2008. FDA asked Genentech to provide confirmatory data from the NCI trials. Genentech will present the combined data to the FDA in October 2008 for reconsideration of accelerated approval.

Dr. Chabner asked Dr. Fine to address whether using small molecules without irinotecan would be a more effective and less toxic treatment. Dr. Fine responded that Phase I and II trials of CPT11 alone have shown essentially negative responses, implying that irinotecan is not an active drug in glioma treatment.

X. UPDATE: SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORE)— DRS. JAMES DOROSHOW AND TOBY T. HECHT

Dr. James Doroshow, Director, Division of Cancer Treatment and Diagnosis (DCTD), and Dr. Toby T. Hecht, Acting Chief, Translational Research Program (TRP), DCTD, updated the Board on recent changes in the SPORE program, which were spurred by the Translational Research Working Group (TRWG) initiative to consolidate the various translational research groups across the Divisions, Centers, and Offices of the NCI. An upcoming conference in November, the NCI "Translational Science Meeting," will bring together trans-NCI translational investigators to fulfill the TRWG's vision of transforming translation and harnessing discovery for patient and public benefit. The goal is to identify and focus on the most promising projects that are ripe for translation.

The SPORE program, originally housed in the Organ Systems Branch in the Office of the Director, was moved administratively to DCTD. All NCI Divisions and the NCI Executive Committee are participating directly in the oversight of the SPORE program and working to enhance SPORE interactions across the programs and divisions, including the Cancer Imaging Program (CIP), the Cancer Diagnosis

Program (CDP), CTEP, Division of Cancer Prevention (DCP), and DCCPS. NCI staff is in the midst of recruiting a TRP director and are halfway through an information-gathering process of institutional visits and teleconferences to solicit suggestions from SPORE investigators about how the program can be improved. The current SPORE guidelines are under review, and recommendations for revision will be brought to the Board and to the Clinical Trials Advisory Committee (CTAC). NCI staff are assessing whether some of the guideline requirements might be fiscally onerous and are seeking ways to integrate and create incentives for collaboration across NCI-designated cancer centers, cooperative groups, and SPOREs with respect to clinical trials.

The first stage of SPORE guidelines' evaluation, which consisted of open discussions with the SPORE directors of M.D. Anderson Cancer Center, the Mayo Clinic, Johns Hopkins Oncology Center, and the Harvard Cancer Center (institutions that hold 50 percent of all active SPORE grants), has been completed. Directors were asked about the strengths of the program and their preferences for changing the guidelines. Teleconferences are being conducted during the second stage of the plan to receive suggestions and feedback from other SPORE programs across the country. The comments of the SPORE directors will then be given to the Clinical and Translational Research Operating Committee and CTAC to develop formal recommendations to be presented to the NCI Executive Committee for approval.
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A prominent issue that surfaced was the guidelines' requirement that research projects move from the laboratory into human studies within 5 years. Many clinical trials are very difficult to translate from the bench to the bedside within 5 years without outside sponsorship. Leaders suggested a milestone-driven approach that evaluated whether certain translational benchmarks were being met, such as GMP production of agents, toxicology, Recombinant DNA Advisory Committee approval, and investigational new drug application (IND) submission. The requirement that at least one project within a SPORE portfolio cover either early detection, screening, prevention, or population science was questioned. Leaders suggested making this stipulation optional or only requiring it for the most prevalent cancer types, such as breast, prostate, colorectal, and lung. The emphasis of SPORE research projects on an organ-site focus was discussed. While this approach allows for easier collaboration between SPOREs and for progression in understanding a particular disease, researchers suggested that broadening the organ site focus might permit non-traditional SPOREs to compete, such as research on AIDS-related and pediatric malignancies. SPOREs' research would be better guided by discerning the existing knowledge gaps.

Questions regarding the SPORE grant review process emerged as staff revisited the guidelines. Should first-time grants and competitive renewal grants be reviewed under different guidelines with different review criteria? In collaboration with the DEA's Research Program Review Branch, staff developed new review instructions and a new scoring tool for the FY 2009 SPOREs grants. Reviewers were asked to ignore past and present paylines and to recalibrate scores. Adjectival descriptors were eliminated, and every review element was rated with a numerical score. Reviewers were told to focus on the scientific project scores and to use the programmatic procedural elements to finesse the scores up or down. Upon analysis of the results of the first cycle, NCI staff found that the final scores were better spread across the range and were more aligned with the scientific project scores. Results will continue to be monitored through the next two grant cycles to determine if the guideline revisions were worthwhile.

Questions and Answers

Dr. Coffey asserted that the most effective NCI program for translation has been the SPORE program. The TRP should perform an analysis of past NCI research that has actually translated to effective treatments and examine the top six solid tumors to see whether new drugs had been developed that increased survival more than 4 months. Many investigators in translational research were initially funded by SPOREs, and ascertaining from what source the most promising young translational

researchers received their first three grants would guide the prioritization of the program. Dr. Coffey voiced concern about micromanagement of the program and about the cap on SPORE's total cost budget for the last 10 years.

Dr. Chabner applauded the NCI staff's work to reduce the number of restrictive SPORE guidelines and said that their efforts should not be viewed as micromanagement. Dr. Kim Lyerly, Director, Duke Comprehensive Cancer Center, provided his perspective as a SPORE director and reminded the Board of the situation several years ago when cancer centers were all maintaining their own tissue banks. SPORE leadership has since harmonized the communications, collaborations, and leveraging with respect to biorepositories.

Dr. Kaur asked whether SPORE would continue its disease-oriented/organ-specific focus or address other issues, such as molecular signatures, or if there were ways to encourage cross-fertilization across the disease-oriented groups. Dr. Doroshow replied that there are differing opinions about the categorization of SPORE research topics, including whether the program could focus on signaling pathways. With input from the extramural research community, novel solutions will likely emerge from the NCI's paradigm-changing "Translational Science Meeting."

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

Dr. Runowicz referred members to their notebooks for the minutes from the Subcommittees on Communication and Planning and Budget meetings, held in February 2008.

Subcommittee Report: Cancer Centers

Dr. Chabner reported on the NCAB *Ad hoc* Subcommittee on Cancer Centers meeting held on 7 September 2008. Dr. Linda Weiss, Chief, NCI's Cancer Centers Branch, provided a detailed analysis of patterns in funding for NCI-designated Center Centers between FY 2003-2007. Dr. Chabner requested that all NCAB members be given a copy of Dr. Weiss' slides. The Cancer Centers Support (CCSG) funding has increased at a higher level than the NCI appropriations overall. The Subcommittee examined the criteria used to determine funding levels. The current CCSG guidelines on budget requests created a $1 M cap (direct costs only) for new Centers and a benchmark ratio for recompeting Centers. The recommended benchmark is 15 percent of the eligible NCI grant funding base at the end of the most recent fiscal year.

Several factors influence the final funding decisions, including the amount of underlying NCI grant support that an institution is receiving at the time of application, the results of peer review, and the number and size of Centers competing. Centers are designated as small, medium, large, or extra large. Smaller centers often receive a bigger proportion of their overall funding base compared with larger centers. Because the original intent of the Cancer Centers program was to expand access to high-quality cancer care, geographic considerations can influence a Center's priority score.

The Subcommittee discussed the value of having a benchmark and concluded that some benchmark is needed to provide a guideline for funding. Instead of a strict ratio, an adjustable graduated scale might be an alternative. Subcommittee participants suggested that Cancer Center designation and CCSG funding could act as "seed money" for small, newer centers, to catalyze further development in underserved areas and facilitate an institution's ability to obtain funding from other sources. Following a full year of CCSG funding, Dr. Chabner suggested that the Subcommittee review the funding decisions and examine the funding formula.

Questions and Answers

Dr. Chabner asked whether the percent increase that a Cancer Center receives is dependent on its priority score. Dr. Niederhuber responded that staff had created a scale in which centers that did exceptionally well received an increase and those in the middle received funding at the same level, but the centers at the bottom end of the scale, towards 200, received decreases in funding. The score more often reflects an institution's support for the Center than the quality of the science conducted.

Dr. Kenneth Cowan, Director, University of Nebraska Medical Center Eppley Cancer Center, said that even though the ratio target value has been decreased from 20-25 to 15 percent, the NCAB could help the NCI deal with designated cancer centers' expectations for future funding. The outstanding ratings tend to be given to the larger centers just as 50 percent of SPORE awards go to only four centers, which are large ones. The peer review system takes into account the number of publications and quality of the discoveries that a Cancer Center produces. Dr. Cowan cautioned against changing cycle-to-cycle funding based simply on the overall score. Reviewers also should take into consideration the "value added" that centers bring to a community. Dr. Chabner emphasized that the most important determinant of funding increases should be the priority score and the quality of science. Dr. Runowicz concluded that there was a role for the NCAB to assist the NCI with Cancer Center funding issues and that a followup meeting of the subcommittee was advisable.

Miscellaneous

Dr. Runowicz requested that the new NCAB members review the list of subcommittees and indicate their preferences so that she can make assignments. Subcommittees usually meet the evening before the full NCAB meeting. Dr. Runowicz also requested that members submit additional topics of interest to Dr. Gray and herself for inclusion in future meetings.

XII. 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 1,964 applications were reviewed requesting support of $606,099,558.

XIII. ADJOURNMENT—DR. CAROLYN D. RUNOWICZ

Dr. Runowicz thanked all of the Board members for attending. There being no further business, the 147th regular meeting of the NCAB was adjourned at 5:00 p.m. on Monday, September 8, 2008.

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