DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
159TH NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 13, 2011

Building 31C, 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 159th regular meeting on 13 September 2011, in Conference Room 6, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 13 September 2011, from 9:00 a.m. to 1:00 p.m. and 2:15 p.m. to 3:55 p.m., and closed to the public on Tuesday, 13 September 2011, from 1:00 p.m. to 2:15 p.m. The NCAB Chair, Dr. Bruce A. Chabner, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Massachusetts General Hospital, Boston, MA, presided during both the open and closed sessions.

NCAB Members
Dr. Bruce A. Chabner (Chair)
Dr. Anthony Atala (absent)
Dr. Victoria L. Champion
Dr. Donald S. Coffey
Dr. Marcia R. Cruz-Correa
Dr. Kevin J. Cullen
Mr. William H. Goodwin, Jr. (absent)
Dr. Waun Ki Hong (absent)
Mr. Robert A. Ingram (absent)
Dr. Judith S. Kaur
Ms. Mary Vaughan Lester (absent)
Dr. H. Kim Lyerly
Dr. Karen M. Meneses (absent)
Dr. Olufunmilayo I. Olopade
Dr. Jennifer A. Pietenpol
Dr. Jonathan M. Samet
Dr. William R. Sellers

President's Cancer Panel
Dr. LaSalle D. Leffall (absent)
Dr. Margaret Kripke (absent)

Alternate *Ex Officio* NCAB Members
Dr. Michael A. Babich, CPSC (absent)
Dr. Patricia Bray, OSHA/DOL
Dr. Michael Kelley, VA
Dr. Aubrey Miller, NIEHS (absent)
Dr. Richard Pazdur, FDA (absent)
Dr. John F. Potter, DOD
Dr. R. Julian Preston, EPA (absent)
Dr. Michael Stebbins, OSTP
Dr. Marie Sweeney, NIOSH (absent)
Dr. Lawrence Tabak, NIH (absent)
Dr. Sharlene Weatherwax, DOE

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Harold Varmus, Director, National Cancer Institute
Dr. Jeff Abrams, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Kenneth Buetow, Associate Director, Center for Bioinformatics and Information Technology
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Mr. John Czajkowski, Deputy Director for Management and Executive Officer
Dr. James Doroshow, Deputy Director for Clinical and Translational Research
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Peter Greenwald, Associate Director for Prevention
Dr. Ed Harlow, Special Assistant for Science Planning
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research
Dr. Douglas R. Lowy, Deputy Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Joseph Tomaszewski, Co-Director, Division of Cancer Treatment and Diagnosis
Dr. Ted Trimble, Director, Center for Global Health
Mr. Michael Weingarten, Director, Small Business Innovation Research
Dr. Linda Weiss, Director, Office of Cancer Centers
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Director, Center for Cancer Research
Ms. Joy Wiszneauckas, Executive Secretary, Office of the Director
Dr. Barbara Wold, Director, Office of Cancer Genomics
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Ms. Paula Bowen, Kidney Cancer Association
Mr. William Bro, Kidney Cancer Association
Dr. Carlton Brown, Oncology Nursing Society
Dr. Carol Brown, Society of Gynecologic Oncologists
Ms. Pamela K. Brown, Intercultural Cancer Council
Ms. Suanna Bruinooge, American Society of Clinical Oncology
Mr. Adam Clark, Lance Armstrong Foundation
Dr. Yvette Colon, National Cancer Institute, Director's Consumer Liaison Group
Mr. George Dahlman, Leukemia and Lymphoma Society
Mr. Matthew Farber, Association of Community Cancer Centers
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambarresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological 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. Steven Klein, National Science Foundation
Dr. Hal C. Lawrence, III, The American College of Obstetricians and Gynecologists
Dr. W. Marston Linehan, Society of Urologic Oncology

Mr. Richard Martin, American Society of Therapeutic Radiology and Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Dr. Patricia Mullan, American Association for Cancer Education
Ms. Barbara Muth, American Society of Therapeutic Radiology and Oncology
Ms. Christy Schmidt, American Cancer Society
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Ms. Pamela Wilcox, American College of Radiology
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, SEPTEMBER 13, 2011

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF 28 JUNE 2011 MINUTES—DR. BRUCE A. CHABNER

Dr. Chabner called to order the 159th NCAB meeting. He welcomed members of the Board, *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. Chabner 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 28 June 2011 NCAB meeting. The motion was seconded, and the Board unanimously approved the minutes.

II. FUTURE BOARD MEETING DATES—DR. BRUCE A. CHABNER

Dr. Chabner called Board members' attention to future meeting dates.

III. NCI DIRECTOR'S REPORT—DR. HAROLD VARMUS

Dr. Harold Varmus, Director, NCI, welcomed members and described recent news regarding personnel, budgetary, and programmatic changes occurring in the NCI and activities of interest across the NIH. Dr. Varmus welcomed Dr. William R. Sellers, Vice President/Global Head of Oncology, Novartis Institutes for BioMedical Research, Inc., as an official Board member. He announced several NCI appointments: Dr. Barry Kramer, Director, Division of Cancer Prevention, effective October 1; Dr. Barbara Wold, Interim Director, Center for Cancer Genomics; and Dr. Ted Trimble, Director, Center for Global Health (CGH). All three will present to the NCAB at future Board meetings.

NCI News. Advisory committees have been established to assist Dr. Varmus and the NCI leadership with the cancer Bioinformatics Grid (caBIG®) initiative and the NCI-Frederick enterprise. The BSA caBIG® Oversight Ad hoc Subcommittee was established in response to the BSA's recommendation and is chaired by Dr. Daniel Masys. The NCI-Frederick Advisory Committee (NFAC) had an introductory orientation in August, with the new members and presentations by Dr. David Heimbrook, CEO of SAIC-Frederick, and NCI leaders and scientific investigators. In response to the NFAC comments, the NCI will list the activities and services available at NCI-Frederick on its website, establish the Contractor Cooperative Research and Development Agreement (CRADA) to ease relationships with industrial partners, and develop a strategic plan for the NCI-Frederick enterprise. The first NFAC meeting will be held at Frederick to allow members to view the facilities, some of which currently operate at the margin of safety. NCAB's representative on the NFAC, Dr. Jennifer A. Pietenpol, Director, Vanderbilt-Ingram Cancer Center, and B.F. Byrd, Jr. Professor of Oncology, Vanderbilt University Medical Center, added that the NFAC oversight provides an opportunity to help the scientific community recognize NCI-Frederick as a strong extension of this campus, and for the NCI to understand what efficiencies can be realized by the shared resources and science occurring there as well as in Bethesda, MD. Dr. Varmus noted that the President's Cancer Panel was absent from today's meeting because its members had completed their terms, and he encouraged members to voice to the White House the importance of the Panel.

Dr. Varmus said that the NCI Center for Global Health, (CGH) is being established to better integrate cancer into the world of global health. The CGH's rationale, objectives, and mode of operation are outlined in an upcoming *Science Translational Medicine* article by Drs. Varmus and Trimble. An immediate goal is to integrate NCI's efforts in the international arena into a coherent structure that is organized by geographic domains and topics. Dr. Trimble provided an overview of the NCI's programs

established in China, Latin America, and Africa, including training and partnerships, to the NCAB Ad hoc Subcommittee on Global Cancer Research the preceding evening. Subcommittee Chair, Dr. Olufunmilayo F. Olopade, Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, Associate Dean for Global Health, and Director, Center for Clinical Cancer Genetics, University of Chicago Pritzker School of Medicine, told members that the Subcommittee had gained an understanding of the structure and funding of NCI's international efforts, and appreciated Dr. Trimble's leadership and the U.S. support of global health.

Dr. Varmus noted that noncommunicable diseases (e.g., cardiovascular, diabetes, mental disorders, and cancer) are rising in developing countries as life expectancy increases and behaviors that contribute to these diseases proliferate. The United Nations is holding a high-level meeting that will endorse a strong statement about care, prevention, and research on noncommunicable diseases, and Dr. Varmus will participate as part of a U.S. delegation led by Department of Health and Human Services (HHS) Secretary, Kathleen Sebelius. Other upcoming meetings on cancer in the international arena include: the African Organisation for Research and Training in Cancer's (AORTIC) 8th International Conference; and the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries' meeting on "Closing the Cancer Divide: The Global Equity Imperative of Expanding Access in Low and Middle Income Countries." In October, Dr. Varmus will join Ugandan President Yoweri Museveni at the opening of a new cancer research center in Kampala. Also, an upcoming meeting of the leaders of cancer research funding agencies from around the world will address cancer in the global health arena, including international policies and funding concerns, as well as issues about bringing genomics into clinical practice, improving prevention and screening efforts, and responding to the results of the National Lung Screening Trial (NLST).

Budget. Dr. Varmus reminded members that NCI's fiscal year (FY) 2011 budget was 1 percent lower than the FY 2010 level. Approximately 1,100 new grants were funded in FY 2011 with a success rate of 14 percent, which was accomplished through a 2–5 percent reduction from existing programs. The NIH has operated under a Continuing Resolution (CR) for FY 2011, and this likely will continue into FY 2012. The President's Budget for FY 2012 includes a 2 percent increase for the NIH, but the expectation for the budget is a reduction of 1–2 percent below the FY 2011 level. NIH Institutes and Centers (IC) Directors discussed long-term budgetary concerns during the NIH Leadership Retreat. In addition, during its July retreat, the NCI leadership focused on how to manage the financial decrements for the Institute, including the Divisions' programmatic priorities, in the face of a significant increase or decrease in the budget; Dr. Chabner attended as a representative of the Board. Dr. Varmus expressed the NCI's commitment to support research that makes scientific discoveries that advance public health, including programs such as The Cancer Genome Atlas (TCGA), and he encouraged members to share thoughts about NCI's management of its portfolio while dealing with a likely budget reduction during the next several years.

Human Papillomavirus (HPV) Vaccine. Dr. Douglas Lowy, Deputy Director, provided a report on the status of the vaccine for HPV. Dr. Lowy informed members that the Centers for Disease Control and Prevention (CDC) recently reported that the rate of implementation for the HPV vaccine in the United States has stabilized; the current vaccine uptake likely is too low, however, to develop herd immunity against the HPV types targeted by the vaccine. The CDC Advisory Committee on Immunization Practices will vote soon on whether to upgrade its recommendation for male vaccination from permissive to routine, which would improve the likelihood of reimbursement by medical insurers and require medical caregivers to offer the vaccine to adolescent boys and their families. The current male vaccination rate is under 2 percent. The U.S. Food and Drug Administration (FDA) approved the vaccine Gardasil® for the prevention of genital warts and anal cancer in 2009 and 2010, respectively. HIV-positive patients with oral pharyngeal cancer primarily are males; incidence in this population is rising and is predicted soon to surpass the incidence of cervical cancer in the United States.

Dr. Lowy stated that recent findings from an NCI-supported HPV vaccine trial in Costa Rica, in which patients received one, two, or three doses, suggested that one dose of the vaccine Cervarix® was sufficient to confer 4 years of protection against HPV infection, specifically by HPV 16 and 18; it is unknown whether these results will be extrapolated for Gardasil®. In the developing world, the full three-dose schedule is expensive, even with tier pricing, and logistically complicated because of a lack of adolescent vaccine platform. Two doses could partially overcome both of these issues; however, the long-term duration of protection remains to be established. Dr. Lowy stated that Gardasil® is being provided in a two-dose schedule in parts of Canada and Mexico based on strong immune responses to two doses in young adolescents. In addition, the upcoming International Papillomavirus Conference will discuss alternate vaccine dosing schedules.

Drug Shortage Update. Dr. James Doroshow, Deputy Director, provided an update on the drug shortage situation. He informed members that approximately 80 percent of the 60–70 unique agents on the FDA's drug shortage list are injectable generic drugs, of which 20–25 percent are oncologic agents. Many of these unavailable drugs—such as doxorubicin, etoposide, and leucovorin—provide curative therapy for acute myeloid leukemia (AML), lymphoma, colorectal, and other cancers. The cost of the injectable oncologic drugs that are on the shortage list is $400 M, representing a fraction of the total cancer treatment drug cost of $125 B for 2010. In addition, the active pharmaceutical ingredient or bulk drugs comprise less than 5 percent of the shortage. The issue is finishing the material, putting it into a vial, and distributing it appropriately at a profitable cost. There also is a clear relationship between the time since a compound became generic and the number of generic makers involved in its production; the 12 or so makers of an agent with an expired patent dwindles to 2–3 manufacturers within 10 years. Dr. Doroshow told members that leadership throughout the HHS have recognized the issue and are working to coordinate a response, including the determination of whether a legislative or regulatory remedy is possible.

Questions and Answers

Dr. Chabner requested that Drs. Hall and Pietenpol provide a report on the NFAC at a future Board meeting.

Dr. Chabner expressed his support for NCI's commitment to basic research, noting that it is the foundation for therapeutic development, and he encouraged continued support for productive cancer centers, which serve as the engine for application both for industry and for NIH-derived basic research. Dr. Sellers seconded the notion of strategic programmatic cutting rather than small reductions across the NCI portfolio. Dr. Varmus related a lesson from a university that, when faced with a 25 percent reduction in its endowment income, identified its four highest priorities and reduced its operating budget dramatically; he noted that 85 percent of the NCI's budget supports extramural research, and that the contraction of funds while preserving the research enterprise is an issue that will need to be addressed by the overall federal science and technology apparatus. Dr. Chabner commented that the NCI mission of this institute is to cure cancer and to prevent cancer, and the Board will support the NCI's decisions. Dr. Varmus recognized that science is conducted by individuals at institutions, which need to provide the space and facilities for a strong research environment.

Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, and Professor of Medicine, University of Medicine, noted the steep rate of HPV incidence in African American patients in the United States, that U.S. vaccination rates are less than one-half of what they are in Canada and the United Kingdom, and the sentiments against forced vaccinations expressed during recent national political debates, and he asked about the NIH's and NCI's role in discovery of knowledge and promotion of implementation research to address vaccination issues. Dr. Varmus replied that the NIH's official role is to provide data from biomedical research, and the U.S. Preventive Services Task Force is mandated with providing public recommendations based on the data; the NCI can assist in the organization of public meetings. Dr. Chabner suggested that the NIH work with the FDA and the CDC to hold a high-level

meeting that shares current data with the public about the effectiveness of the HPV vaccine on preventing cervical and oropharyngeal cancers as well as adverse events and other risks. Dr. Varmus said that the NIH-FDA Council could consider this.

Dr. Victoria L. Champion, Associate Dean for Research, and Mary Margaret Walther Distinguished Professor of Nursing, Center for Research and Scholarship, Indiana University School of Nursing, commented that behavioral research should examine attitudes toward the HPV vaccine; knowledge is necessary but not sufficient for behavior change. Dr. Judith S. Kaur, Medical Director, Native American Programs, Mayo Comprehensive Cancer Center, and Professor of Oncology, Mayo Clinic, agreed and noted that some distribution issues have occurred in underserved communities, such as among the Native American Indian population. Dr. Lowy clarified that the vaccine is approved for use with the "Vaccine for Children's Money" Program and that people from poor families have been receiving the vaccine.

Dr. Sellers expressed enthusiasm for the vaccine, reflecting on this rare opportunity to eradicate three types of cancer. Dr. Chabner strongly encouraged an education campaign that helps the public understand the efficacy of the vaccine for males, addresses concerns about moral issues, and shares the latest information about alternate vaccine dose scheduling and vaccine efficacy with interested researchers, public health officials, and policymakers. Dr. Gray pointed out that this would be an excellent topic for the President's Cancer Panel to cover.

In response to a query by Dr. Sellers, Dr. Varmus stated that Secretary Sebelius held a recent meeting with generic drug manufacturers; the economic situation and issues surrounding profitability are contributing factors in the shortage of generic drugs.

Dr. Chabner reflected that the creation of a separate price category for generic drugs that are in short supply might encourage lower production of many more generic agents to increase prices. Dr. Varmus agreed and commented on the "grey market," in which certain drugs are accumulated shortly before they become in short supply and then are purchased by needy institutions at a much higher profit margin. He noted that the shortage list is growing despite the FDA's efforts to stop shortages.

Dr. Olopade encouraged more immediate action to assist cancer patients. Dr. Varmus said that short- and long-term solutions are being considered, including possible legislative and philanthropic activities. Dr. Doroshow added that a philanthropic effort is being considered to acquire bulk drugs, provide access to manufacturing facilities to fill unfinished vials, and import those vials under appropriate FDA guidelines.

Dr. Sellers commented that some manufacturing facilities were not meeting FDA standards, and he noted that a 6-month supply of drugs represents a significant amount of money that remains on a company's balance sheet until sold. Dr. Doroshow replied that supply-line issues account for approximately 40 percent of the problem, and prices allow only a small profit margin that creates a disincentive to develop a stockpile.

Dr. Varmus suggested that Board members could recommend solutions to handling the supply shortage in oncologic agents. Dr. Chabner agreed to solicit comments from NCAB members with therapeutic development expertise and discuss these ideas with Dr. Doroshow.

IV. NEW REGULATION ON MANAGING FINANCIAL CONFLICT OF INTEREST OF NIH SUPPORTED GRANTEES—DR. SALLY J. ROCKEY

Dr. Sally J. Rockey, Deputy Director for Extramural Research, NIH, described a revised rule on managing financial conflict of interests. Dr. Rockey told members that the rule, called "Responsibility of

Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors," is important to maintain the public's trust in research. This regulation has been in place since 1995. The NIH's increased promotion of translational research and the evolving landscape of biomedical research means that many more interactions are expected between NIH-funded investigators and the private sector. This rule should effectively manage, not inhibit, those relationships to ensure objectivity in the research. The revised final rule was published on 25 August 2011, and the ICs have 365 days to implement it.

Dr. Rockey described the framework of the rule and major changes to the regulations. In compliance with institutional policy, investigators who are awarded NIH grants or contracts must disclose significant financial interests to their academic institutions, which determines whether that interest constitutes a financial conflict of interest (FCOI) and are charged with managing that FCOI. The institutions, not the NIH, are in the best position to effectively manage the financial interests of their employees. Regarding significant financial interests, the rule has been revised from a $10,000 to $5,000 *de minimus* threshold for payments and equity interests, and a zero threshold for non-publicly traded entities.

The institutions must report additional information to the NIH when a conflict of interest has been identified, including the name of the entity, the value of the financial interest, the nature of the financial conflict, and key elements of how the conflict is being managed. Institutions must make information about certain financial interests that are determined to be FCOI publicly available, either through online publishing or upon request; Dr. Rockey said that some institutions already are posting on the web, and most others likely will follow suit. In addition, investigators must receive training in financial COI issues before engaging in public health service research and every 4 years thence. Members were encouraged to obtain further information at: http://grants.nih.gov/grants/policy/coi/.

Questions and Answers

Dr. H. Kim Lyerly, George Barth Geller Professor of Cancer Research, and Professor of Surgery, Duke University School of Medicine, asked whether a frame of reference for common FCOIs was available to help with institutional adjudication. Dr. Rockey answered that the regulations are as flexible as possible and include examples of FCOIs and possible ways to manage the issue. She added that several institutions are sharing best practices in FCOI management.

In response to Dr. Chabner's inquiries about specific financial disclosure requirements, Dr. Rockey confirmed that the exact amount of monies above $5,000 must be disclosed, and that institutions usually ask their investigators to report annually; although investigators must report the exact amount, institutions report ranges to the NIH. In addition, only financial FCOIs must be publicly available; investigators are not required to report other financial information on the website. Dr. Chabner recommended that "FCOI" be carefully defined, noting that institutions generally do not clarify this well and that their officials will be overwhelmed with questions. Dr. Rockey said that the revisions to the rule mean that institutions will have more information from their investigators.

Dr. Sellers commended the revisions and said that the public disclosure will be a positive influence on eliminating some of the issues that have arisen in the past. Dr. Chabner expressed his agreement.

Dr. Marcia R. Cruz-Correa, Associate Professor of Medicine and Biochemistry, University of Puerto Rico, and Basic and Translational Science Director, University of Puerto Rico Comprehensive Cancer Center, asked about requirements for the investigator to put disclosures in the IRB consent form. Dr. Rockey noted that most institutions include disclosure on the consent forms. She added that, per the Sunshine Act, which will be effective in 2013, the private sector will be required to report all payments of $10 *de minimus* to physicians on a publically accessible database. Payments to Ph.D. researchers, which include approximately 75 percent of NIH investigators, are exempt, and payments for clinical research are

not required to be made public for 4 years.

Dr. Olopade said that the rule was needed to prevent past behaviors, and that training for scientists and physicians about professionalism would help build the confidence of patients and the public. Dr. Rockey stated that reports about FCOI issues doubled when discussions commenced in 2008 about revising the rule. She noted that institutional FCOI is a much more complicated issue to be addressed, including what the federal role should be.

V. PROVOCATIVE QUESTIONS: STATUS AND FUTURE PLANS—DR. EDWARD E. HARLOW

Dr. Edward E. Harlow, Special Assistant for Science Planning, Office of the Director (OD), provided a report on the Provocative Questions Initiative. Dr. Harlow reminded members that Dr. Varmus had initiated the Provocative Questions Project as a way to focus on underappreciated and unde-identified research areas to advance the understanding of cancer and cancer control, address broad issues in cancer biology that have been difficult to solve, and develop research approaches that have a feasible chance of making significant progress within the near future. Nine workshops were held beginning in October 2011 to identify questions in the fields of population, clinical, and basic science, and a website allowed broader community participation in this activity.

NCI leadership selected 24 questions that resulted from these efforts for funding opportunities, with a budget of up to $15 M for the R01 and R21 mechanisms. Applications will undergo a 2-tier review process that first determines whether a project addresses the provocative question and then applies standard review criteria to vetted proposals. Proposals from principal investigators (PIs) new to the field are encouraged, preliminary data are not necessary, and the PI's past work in the field will not be weighed as heavily as in the standard review process.

Dr. Harlow presented examples of some of the provocative questions, including how obesity contributes to cancer risk, why some commonly used drugs decrease cancer incidence and mortality, if therapies aimed at keeping tumors static rather than killing them might extend survival, and why some disseminated cancers are cured by chemotherapy alone. The question of obesity and cancer risk exemplifies the multidisciplinary and innovative approach these questions require, spanning the fields of risk identification and cancer cell biology. Data and evidence about obesity and cancer risk prompted questions concerning risks of death for men and women from different forms of cancer increasing with body mass index (BMI), rising obesity trends in the United States, and decreased mortality rates from cancer for obese patients following gastric bypass surgery. Relevant to the effect of common drugs on cancer risk, Dr. Harlow showed that individuals taking aspirin have a lower risk of death due to cancer as they age; the mechanism behind this association is not known. Killing therapies might be a flawed approach to treating some cancers for the same reason that predation led to rapid changes in the coloration of peppered moths following the Industrial Revolution: cancer treatment might kill the most susceptible cancer cells, selecting for those that are most resistant. Finally, Lance Armstrong's treatment success is one well-known example of curing disseminated cancers with chemotherapy, and this phenomenon is not limited to a single cancer type or therapeutic agent.

The value of the Provocative Questions Initiative is that it highlights new research questions, engages the community, and advances research into new areas, which is particularly important in periods of restricted budgets. Dr. Harlow summarized how success of the project could be evaluated: in the short term, whether the RFAs generate exciting applications; in the intermediate term, whether the funded projects continue under traditional granting mechanisms; and in the long term, whether the questions themselves are answered. He acknowledged the assistance of NCI staff in administering the project and web design.

Questions and Answers

Dr. Cruz-Correa questioned the limited funds available and suggested that only the R21 mechanism be used. Dr. Champion added that it was unclear in the presentation whether funding for a given project could extend beyond 2 years. Dr. Harlow responded that both R01 and R21 funding mechanisms are needed, only R21 grants were limited to 2 years, and that the NCI may expand future funding for the Initiative, depending on its success.

Dr. Chabner asked for clarification about the review process and whether the reviewers would need special training. Dr. Harlow explained that the first review would be by an editorial board of senior investigators to determine a proposed project's potential to have a strong impact on the relevant provocative question, while the second round would be conducted by a study section, which will be educated about its mission. Dr. Gray clarified that the study sections will be NCI-constructed special emphasis panels with appropriate expertise.

Dr. Sellers expressed concern that $15 M would be insufficient to fund the exploration of 24 questions and asked whether the set of provocative questions should be limited or the intramural research program should become involved. NCI staff acknowledged that the NCI was concerned about balancing funding with the number of questions. The intramural program participated in formulating the Provocative Questions, but only will be involved in research under the Initiative through collaborations with grantees. Dr. Varmus added that there is an opportunity within the intramural program to make small awards so that researchers can become more engaged in the process.

Dr. Donald S. Coffey, The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, Professor of Urology/Oncology/Pathology/Pharmacology and Molecular Science, The Johns Hopkins University School of Medicine, suggested that identifying the most important questions in cancer research can be used to direct research as in the Provocative Questions Initiative, as an educational tool as was done in a contest at The Johns Hopkins University School of Medicine, or in a management context, which can be informed by investigating who was responsible for the most important breakthroughs in research on different cancers in the past 50 years and how they were funded. Dr. Harlow agreed that conducting such a history of past impacts of innovative thinking in the field of oncology likely would provide surprising and valuable answers.

Dr. Kaur commended the NCI for its multidisciplinary approach to formulating the Provocative Questions. Dr. Harlow replied that the NCI had tried to reach out to individuals that were not part of the traditional cancer research community in the workshops, but would like to make an even stronger effort to do so in the future.

Dr. Pietenpol suggested that the extent to which general R01 proposals begin to be shaped by the Provocative Questions might be an indicator of the Initiative's success and a benefit from the program. Dr. Varmus agreed that this would be a way by which the Initiative, even with limited funding, could influence the course of research in new directions and the ability to fund good grants.

Dr. Olopade asked whether the Provocative Questions might shape the future funding priorities of program leaders. Dr. Sellers added that this might be a step toward study sections becoming question- rather than discipline-based. Dr. Varmus responded that proposals under the Provocative Questions Initiative were likely to be more open-ended than under traditional RFAs, but that question-based study sections might be something to consider in the future.

VI. ONGOING AND NEW BUSINESS—DR. BRUCE A. CHABNER

***Ad hoc* Subcommittee on Global Cancer Research.** Dr. Olopade informed members that the Subcommittee met and reached consensus about the NCI's need to take a leadership role in global oncology research. The CGH should provide a lasting infrastructure that will serve this function and ameliorate the effects of past turnover among senior leadership. She added that the Subcommittee has agreed to meet before each NCAB meeting to help shape the CGH. In addition, the upcoming United Nations high-level meeting on noncommunicable diseases will help ensure that governments worldwide pay closer attention to cancer control in their countries; this is a great opportunity for the NCI to be a leader in global cancer research.

Dr. Chabner added his support for the CGH. He said that, in the past, the NIH has communicated and shared specific research ideas with scientists in developed countries, but the Center emphasizes how to improve global health through the treatment and prevention of cancer in the larger international community, including countries with less developed approaches. Interesting initiatives are underway, such as an activity that helps the media and press in Spanish-speaking countries better communicate to the public regarding cancer research topics.

Future Agenda Items. Dr. Chabner encouraged members to submit topics for discussion at future meetings to Dr. Gray and himself.

VII. CLOSED SESSION—DR. BRUCE A. CHABNER

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 the IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 3,989 NCI applications were reviewed requesting support of $1,097,723,563 and 82 FDA applications were reviewed.

VIII. OVERVIEW: NCI's SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM—MR. MICHAEL WEINGARTEN AND DR. ANDREW KURTZ

Mr. Michael Weingarten, Director, Small Business Innovation Research, presented an overview of the SBIR/Small Business Technology Transfer (STTR) Program at the NCI and introduced Dr. Andrew Kurtz, Program Director, SBIR Development Center, who spoke about the SBIR Phase IIB Bridge Award.

Bridging Science to the Market: The NCI SBIR Program. Mr. Weingarten explained that the SBIR/STTR Program is vital for commercializing high-impact technologies that can benefit patients, with the top three research areas being therapeutics, *in vitro* diagnostics, and imaging. The Program annually leverages approximately $110 M in funding from the NCI with $680 M from the NIH to offer two types of grants: Phase I feasibility studies and Phase II full research and development projects. Phase I applications have increased dramatically in recent years as access to venture capital has become more limited.

The new SBIR Development Center has been established to enhance the commercialization success of SBIR-funded projects by reaching out to new applicants, developing new topics, and sponsoring forums to match awardees with investors. At the two forums that have been held, 4 of the 14 SBIR

awardees presenting closed deals, and another forum is scheduled for the spring of 2013. The SBIR/STTR also assists awardees with the FDA approval process.

Mr. Weingarten shared an SBIR success story about Guided Therapeutics, Inc, which received a Phase IIB Bridge Award in 2009; the company has more than doubled its employees and market capitalization, secured outside investment, and expects FDA approval for its first product in the fall.

SBIR Phase IIB Bridge Award. Dr. Kurtz described how the Phase IIB Bridge Award Program helps selected Phase II projects overcome commercialization hurdles to move from research to commercial development. As an example, an award can provide funding for drug development during the critical period before beginning clinical trials, but different products/technologies have their own barriers to commercialization. Successful Bridge Award applicants must have a third-party fundraising plan, which provides the NCI with an opportunity to leverage external resources, and are attractive to investors because the NCI shares the investment risk. The review process emphasizes commercialization potential, and since its inception the Program has funded 10 projects in therapeutics, imaging technologies, and diagnostics, with an overall application success rate of 14 percent. In total, awardees have leveraged more than twice their NCI funding from third-party investments, although a few very large agreements predominate.

A Bridge Award success story is Altor BioScience, which received Phase I and II SBIR grants to develop an antitumor drug, ALT-801, which had favorable safety and pharmacokinetics results in a Phase I clinical study. The company received a $3 M Phase II Bridge Award in 2009 and leveraged it with an $8 M third-party investment to finance further clinical trials, which will be used to establish treatment regimes for Phase II clinical studies. Bridge funding is complete and the company has successfully raised additional funds.

Questions and Answers

Drs. Chabner and Pietenpol asked whether any products sponsored by the SBIR/STTR Program were in widespread commercial use, had become the standard of care, or improved survival rates. Dr. Weingarten cited as an example TomoTherapy Inc., which developed a new type of radiation therapy and was acquired by AccuRay Incorporated.

Dr. Sellers noted that it would be interesting to determine whether any of the numerous drugs from small biotechnology firms that have been purchased by larger firms before FDA approval were developed under the SBIR/STTR Program and, in a more general way, to develop metrics to track systematically the success of SBIR/STTR companies. Mr. Weingarten agreed and referred to a 2005 study by the National Academy of Sciences, which determined that 40 percent of Phase II companies funded by the NIH over a 9-year period were able to produce a saleable product. The SBIR/STTR Program is planning to collect data from companies on various measures to evaluate their achievements, focusing on Phase II companies. Dr. Chabner thought that defining metrics (e.g., the 10-year survival rate, the number of products brought to market, and the success of products developed by grantees) would be valuable and that the metrics used should be quantified periodically.

Dr. Sellers recommended increasing the size of Phase I awards, which would allow funding of fewer companies but likely result in more receiving Phase II awards. In industry, the full-time equivalent (FTE) rate is $250,000. Mr. Weingarten noted that the NCI increased its Phase I award from $100,000 to $150,000, with a cap of $300,000. Dr. Chabner added that peer review from the granting process confers an advantage as well.

Dr. Kaur asked if the NCI collected statistics on how many women and minority-owned businesses were funded by the Program. Mr. Weingarten said that the NIH is beginning to collect these data.

Dr. Coffey inquired whether it was possible for the NCI to receive a portion of the profits from the sale products whose development it had funded, particularly now when funding is so limited. He pointed out that the NCI was formed to sponsor research, not development or delivery of medical care. Dr. Kurtz answered that the NCI does not acquire equity in companies it funds and that the government receives revenue from product sales in the form of taxes, which Dr. Chabner pointed out is legal under the Bayh-Dole Act, arguing as well that drug research is distinct from care delivery.

Dr. Sellers suggested that commercialization was being overemphasized and could bias funding toward commercial strategies with a large potential market, ignoring rare cancers; he suggested that a better metric of success might be proof-of-concept in humans. Dr. Chabner responded that ultimately SBIR/STTR is a small business program whose goal is to create jobs, although the focus of the Phase IIB grants could be changed to allow the achievement of proof-of-concept in humans prior to the expectation of commercialization. Mr. Weingarten added that size of market is one consideration; another could be whether a cancer has an accepted treatment.

Dr. Varmus asked what criteria the Bridge Program uses to judge commercialization potential and whether reviewers have a list of questions that are used to determine it. Dr. Kurtz replied that the Bridge Program has added criteria of whether a project addresses unmet needs, whether a market exists, whether the company understands the needs of customers, and as an interim milestone, whether the grantee has secured external funding. Dr. Chabner added that determining if the company had sufficient resources to develop the product for market is also important.

Dr. Sellers noted that venture capital has become much less readily available. Dr. Chabner agreed that securing adequate funding to reach the proof-of-concept stage was difficult.

IX. NCI INTRAMURAL CLINICAL RESEARCH PROGRAM: UTILIZATION OF THE CLINICAL CENTER—DR. LEE HELMAN

Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research (CCR), NCI, reviewed the achievements and goals of the NCI Intramural Clinical Research Program. Dr. Helman reminded members that the CCR engages researchers in translational research, supports high-impact and innovative projects, and fosters collaborations with extramural and intramural NIH researchers. Its activities focus on advancing translational and molecularly based medicine, training researchers, conducting clinical trials, developing technology, and studying rare cancers. Many of CCR's clinical fellowship program alumni have had highly successful research careers.

The CCR is striving to improve its efficiency and efficacy as funds become more limited. The Center recently has developed a Strategic Alignment and Resource Planning Checklist (SARP) by which all protocols must be reviewed to ensure that they further CCR's mission. The SARP for each protocol is reviewed and approved by the CCR Branch Chief and the Scientific Director. Formalizing CCR's resource allocation process ensures that decisions are more transparent and focus on impact and outcomes.

CCR's research priorities include a molecular imaging clinic, standardized biospecimen collection, genome-wide and microRNA profiling of tumor and normal tissue, genetic background profiling of patients, and developing biomarkers to monitor targeted therapies. Imaging is a top CCR priority as the lines between imaging and pathology continue to blur, leading to a need for new techniques and technologies. Clinical characterization by the Clinical Molecular Profiling Core (CMPC) is part of all CCR clinical protocols and provides CCR clinical investigators with ready access to genome technologies, allowing characterization of patients and their tumors, as well as the ability to correlate imaging with sequencing data. The CCR Sequencing Facility provides next generation sequencing technologies to the intramural program and has led to publications in top journals. The CCR is identifying major opportunities for research, which like the Provocative Questions Initiative, will be high risk, bring together broad

groups, and have milestones that are achievable during the short term. The vast majority of CCR research encompasses Phase I or II studies.

CCR's ongoing collaborations involve its neighboring institutions, Suburban Hospital Johns Hopkins and the new Walter Reed National Military Medical Center (WRNMMC). Current efforts include patient referrals and a longstanding joint fellowship program. A snapshot of current CCR research reveals that of all protocols, approximately one-half are in the branches of medical oncology, pediatric oncology, and surgery; lymphatic/hematologic cancer represents the largest number by disease site; and a vast majority are Phase I and II studies.

Dr. Helman provided an example of the innovative application of genomics and imaging data that uses the genomic profiles of individual tumors to understand how mutations in cancer disrupt cell function. In the case of extremely rare pediatric gastrointestinal stromal tumors (GIST), genomic profiling uncovered a novel mechanism by which tumors can disrupt cell function. Tumor tissue with an essentially normal genome had widespread epigenetic changes that were uncovered using gene mapping DNA methylation. The metabolic effects of the genetic mutation that caused these changes are homologous to other rare forms of cancer and perhaps subsets of common cancers, and understanding the mechanisms could lead to potential treatments. Researchers are developing a form of imaging, hyperpolarized MRI that will use new types of biomarkers as diagnostic and real-time treatment assessment tools. These types of biomarkers have been tested on animal models and in human prostate tissue. New imaging capabilities at the CCR should allow researchers to extend these types of studies to the clinical setting.

Questions and Answers

Dr. Chabner asked about the competitiveness of the CCR's fellowship programs in terms of recruitment in medical and pediatric oncology and suggested that the NCI should seek additional opportunities to form affiliations in the medical oncology program, such as the NCI has with The Johns Hopkins University School of Medicine and the WRNMMC, to offer better training in subspecialties. Dr. Helman responded that attracting fellows was not difficult in pediatric oncology, surgery, or pathology, but the breadth and depth of the medical oncology program could be strengthened by forming affiliations with other institutions. The Center currently is collecting data about its alumni to evaluate their postgraduate careers.

Dr. Cullen inquired about the number of analytic cancer cases seen per year at the clinical center. Dr. Helman answered that the Center does not see newly diagnosed patients with common cancers, and therefore the numbers are low; forming affiliations with other centers would allow fellows in medical oncology to have more encounters with newly diagnosed patients.

Dr. Cullen asked about the percentage of intramural clinical trials that meet their accrual rates. Dr. Helman responded that the proposed trials are evaluated for their ability to accrue patients, and the CCR is following many of the rigorous evaluation processes established for NCI's extramural clinical trial system. Ongoing protocols are being monitored regularly and are closed if they fail to meet their accrual numbers.

X. ADJOURNMENTCDR. BRUCE A. CHABNER

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

There being no further business, the 159th regular meeting of the NCAB was adjourned at 3:55 p.m. on Tuesday, 13 September 2011.

Date	Bruce A. Chabner, M.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary