DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

8TH JOINT MEETING OF THE BOARD OF SCIENTIFIC ADVISORS AND THE NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 6, 2016

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

BOARD OF SCIENTIFIC ADVISORS and
NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
December 6, 2016

The Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) convened for the 8th Joint Meeting on 6 December 2016, in Conference Room 10, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 6 December 2016, from 8:30 a.m. to 2:22 p.m., and closed to the public from 2:23 p.m. to 4:00 p.m. The NCAB Chair, Dr. Elizabeth M. Jaffee, Deputy Director, The Sidney Kimmel Comprehensive Cancer Center, Co-Director, Skip Viragh Center for Pancreas Cancer, The Dana and Albert "Cubby" Broccoli Professor of Oncology, Johns Hopkins University, and the BSA Chair, Dr. Chi V. Dang, Director, Abraham Cancer Center, Professor of Medicine, Perelman School of Medicine, University of Pennsylvania, presided during the open session. Dr. Jaffee presided during the closed session.

BSA Members
Dr. Chi V. Dang (Chair)
Dr. Kenneth C. Anderson (absent)
Dr. Dafna Bar-Sagi
Dr. Ethan M. Basch
Dr. Michael John Becich*
Dr. Sangeeta N. Bhatia (absent)
Dr. Melissa L. Bondy*
Dr. Arul M. Chinnaiyan (absent)
Dr. Graham A. Colditz (absent)
Dr. Christopher M. Counter*
Dr. Joseph M. DeSimone (absent)
Dr. Daniel C. DiMaio
Dr. Karen M. Emmons
Dr. Carol E. Ferrans
Dr. Chanita Hughes-Halbert
Dr. James V. Lacey
Dr. Maria Elena Martinez
Dr. Luis F. Parada
Dr. Sylvia Katina Plevritis*
Ms. Diane Zipursky Quale
Dr. Martine F. Roussel
Dr. Victoria L. Seewaldt
Dr. Kevin M. Shannon (absent)
Ms. Mary L. Smith (absent)
Dr. Ian M. Thompson*
Dr. David A. Tuveson*
Dr. Cheryl L. Walker (absent)
Dr. Eileen P. White
Dr. Kevin P. White
Dr. Cheryl L. Willman*

NCAB Members
Dr. Elizabeth M. Jaffee (Chair)
Dr. Peter C. Adamson
Dr. Francis Ali-Osman
Dr. Deborah Watkins Bruner
Dr. Yuan Chang
Dr. David C. Christiani
Dr. Judy E. Garber
Mr. Lawrence O. Gostin
Dr. Scott W. Hiebert
Dr. Beth Y. Karlan
Dr. Timothy J. Ley (absent)
Dr. Electra D. Paskett
Dr. Nancy J. Raab-Traub
Dr. Mack Roach III
Dr. Charles L. Sawyers (absent)
Dr. Margaret R. Spitz
Dr. Max S. Wicha

Alternate *Ex Officio* NCAB Members
Dr. Robert T. Anderson, DOE (absent)
Dr. Michael A. Babich, CPSC (absent)
Dr. Robbie Barbero, OSTP (absent)
Dr. Vincent J. Cogliano, EPA (absent)
Dr. Michael Kelley, VA (absent)
Dr. Aubrey Miller, NIEHS (absent)
Dr. Richard Pazdur, FDA (absent)
Dr. Craig D. Shriver, DoD (absent)
Dr. Kerry Souza, NIOSH (absent)
Dr. Lawrence A. Tabak, NIH (absent)
Dr. Richard J. Thomas, DOL

* pending appointment

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Douglas R. Lowy, Acting Director, National Cancer Institute
Dr. Jeff Abrams, Acting Director for Clinical Research, Division of Cancer Treatment and Diagnosis
Dr. L. Michelle Bennett, Director, Center for Research Strategy
Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics
Dr. Henry P. Ciolino, Acting Director, Office of Cancer Centers
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences
Dr. William Dahut, Acting Scientific Director for Clinical Research, Center for Cancer Research
Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research
Dr. Dan Gallahan, Acting Director, Division of Cancer Biology
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Ed Harlow, Special Advisor to the Acting Director
Dr. Toby T. Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis
Dr. Warren Kibbe, Acting Deputy Director and Director, Center for Bioinformatics and Information Technology
Dr. Kristin Komschlies, Acting Director, Office of Scientific Operations, NCI Campus at Frederick
Dr. Barry Kramer, Director, Division of Cancer Prevention
Dr. Jerry Lee, Deputy Director, Center for Strategic Scientific Initiatives
Dr. Glenn Merlino, Scientific Director for Basic Research, Center for Cancer Research
Dr. Tom Misteli, Director, Center for Cancer Research
Ms. Donna Siegle, Acting Executive Officer, Acting Deputy Director for Management
Dr. Dinah Singer, Acting Deputy Director and Director, Division of Cancer Biology
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis M. Staudt, Director, Center for Cancer Genomics
Dr. Ted Trimble, Director, Center for Global Health
Mr. Michael Weingarten, Director, Small Business Innovation Research and Small Business Technology Transfer Programs
Dr. Jonathan Wiest, Director, Center for Cancer Training
Dr. Robert Wiltrout, Special Advisor to the Acting Director
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Cancer Research and Prevention Foundation
Dr. Carolyn Best, American Urological Association
Ms. Paula Bowen, Kidney Cancer Association
Ms. Susan G. Braun, National Cancer Institute, Council of Research Advocates
Mr. William Bro, Kidney Cancer Association
Dr. Carol Brown, Society of Gynecologic Oncologists
Dr. Mythreyi Chatfield, American College of Radiology
Dr. Margaret Foti, American Association for Cancer Research
Dr. Francis Giardiello, American Gastroenterological Association
Ms. Shandi E. Hill, American Society of Therapeutic Radiology and Oncology
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Ms. Rebecca A. Kirch, American Cancer Society
Dr. Steven L. Klein, National Science Foundation

Ms. Laura Levit, American Society of Clinical Oncology
Dr. W. Marston Linehan, Society of Urologic Oncology
Ms. Margo Michaels, Education Network to Advance Cancer Clinical Trials
Dr. Patricia Mullan, American Association for Cancer Education
Ms. Nancy O'Reilly, American College of Obstetricians and Gynecologists
Ms. Leah Ralph, Association of Community Cancer Centers
Dr. Marlon Garzo Saria, Oncology Nursing Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Johannes Vieweg, American Urological Association
COL (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, 6 DECEMBER 2016

TUESDAY, DECEMBER 6, 2016

I. CALL TO ORDER AND OPENING REMARKS—DRS. CHI V. DANG AND ELIZABETH M. JAFFEE

Dr. Elizabeth Jaffee called to order the 8th Joint BSA and NCAB meeting and welcomed members of the Board, *ex officio* members, 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. Drs. Chi Dang and Jaffee reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to approve the minutes of the 7 September 2016 NCAB meeting was approved unanimously.

Motion. A motion to approve the minutes of the 31 October 2016 BSA meeting was approved unanimously.

II. FUTURE BOARD MEETING DATES—DRS. CHI V. DANG AND ELIZABETH M. JAFFEE

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

III. NCI ACTING DIRECTOR'S REPORT—DRS. DOUGLAS R. LOWY, JAMES H. DOROSHOW, AND DINAH SINGER

Dr. Douglas R. Lowy, Acting Director, welcomed members of both the NCAB and BSA to the eighth joint meeting of these Boards and noted the value they bring to the NCI. He expressed appreciation to the BSA for its continued efforts in giving advice on Requests for Applications (RFAs) and to the NCAB for its work supporting the 2016 Blue Ribbon Panel (BRP) Report of the Cancer Moonshot and advocating for sustained appropriations from Congress to support the Cancer Moonshot. Dr. Lowy extended appreciation to the NCI and the extramural community for their continued support.

He called members' attention to the fact that the meeting date—December 6, 2016—is the date that non-termed Presidential appointees, including the permanent position of NCI Director, must submit letters of resignation. As Acting Director of the NCI, he is exempt from this action. Dr. Lowy conveyed his strong commitment to serving the NCI and ensuring the continuity of operations during the transition of Administrations. He was joined by Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, who provided an update on NCI's Clinical Research Programs and Dr. Dinah Singer, Acting Deputy Director, NCI, who updated the attendees on the BRP and Cancer Moonshot.

Accomplishments in Advancing Cancer Research. Dr. Lowy reflected on his time as NCI's Acting Director and emphasized areas he initially focused on: cancer health disparities, Precision Medicine Initiative in Oncology (PMI-O), and investigator-initiated research. He told members that the NCI had sponsored several conferences on cancer health disparities and initiated the Early Onset Malignancy Initiative, a cohort study of underrepresented minorities who experience cancer disparities. The study will focus on the biology of cancer, health care access utilization, and lifestyle factors. In terms of biology, efforts will focus on detailed molecular analysis of early onset tumors to gain insight into the similarities and differences with different racial populations. He discussed data suggesting differences in the mutational landscapes of colorectal cancers (CRC) in African Americans and adverse outcomes for CRC associated with mutations that are more common in African Americans.

Dr. Lowy remarked on the strong bipartisan support that the NIH has had for biomedical research, including the strong support for cancer research as realized in the two White House Initiatives: PMI-O and Cancer Moonshot. He told members of an effort to bring precision medicine to American Indians and Alaska Natives and touched briefly on the National Meeting on Precision Medicine and Cancer in American Indian and Alaska Native Communities held on November 10, 2016, in Oklahoma City, Oklahoma, where he was an invited speaker.

Members also were reminded of the herculean effort of the BRP to generate recommendations for the Cancer Moonshot; Dr. Lowy thanked the co-chairs, Drs. Tyler Jacks, Massachusetts Institute of Technology, Elizabeth Jaffee, Johns Hopkins University, and Dinah Singer, NCI, for their leadership. Since the release of the BRP's report, the NCI has been able to emphasize the importance of pediatric cancer research. He has participated in meetings at the White House and on Capitol Hill with pediatric cancer advocates. The pediatric cancer community is energized by the recommendations. Since the report, more emphasis is being given to implementation research and dissemination of standard of care (SOC).

NCI-Designated Cancer Centers. Members were informed that funding was increased for the NCI-designated Cancer Centers Support Grants, and utilization of Administrative Supplements to existing Support Grants also was increased. As Acting Director, Dr. Lowy visited 15 NCI-designated Cancer Centers and was impressed with the level of commitment, quality of work, and dedication of the staff. He reported on some of the collective efforts of the Cancer Centers. In 2014, the NCI issued Administrative Supplements to support Human papillomavirus (HPV) vaccinations, and in 2016 the 69 NCI-designated Cancer Centers collectively promoted, in an announcement, the importance of these vaccinations. Several meetings, such as the 2016 HPV Summit, have been convened with the Cancer Centers and other Federal agencies, including the Centers for Disease Control and Prevention (CDC), to discuss strategies for improving HPV vaccine uptake. Also, the NCI will be placing more emphasis on smoking cessation and will engage the Cancer Centers in this next joint effort.

Investigator-Initiated Research. Dr. Lowy referred members to NCI's website for newly released data about the investigator-initiated research awards and conveyed that the NCI is continuing its strong support of investigator-initiated research. He reported a 17 percent increase in the number of awards, solicited and unsolicited, issued through the Research Project Grant (RPG) Pool program, R01, and the Outstanding Investigator Award, R35, funding mechanisms from fiscal year (FY) 2013 to FY 2016. There has been a 25 percent increase in Type 1 (new) and Type 2 (competing) awards, which has meant an increase in the amount of funding needed to maintain the RPG pool. In addition, the NCI has been successful in funding the Noncompeting Continuation (Type 5) awards at 100 percent. All of the funding successes described have been achieved in spite of fluctuations in the NCI budget.

NCI Budget. Members were informed that the NCI budget was level from FY 2005 to FY 2015 resulting in a decrease in purchasing power; beginning with FY 2016, however, an encouraging trend is noted. He reiterated the bipartisan support for the NIH and biomedical research and the prospect of the additional resources for the Cancer Moonshot to be funded in the 21st Century Cures Act. The NCI operates under discretionary funding, and this Act will be under mandatory funding. The Senate approved a $2 billion (B) increase and the House, a $1.25 B increase. In a yearlong continuing resolution (CR), these increases will not occur, so the case for the appropriations should be made. He pointed out that notable members of Congress are advocating for sustained increases to the NIH and NCI budgets as did U.S. Representative from Oklahoma and Chair of the House Subcommittee on Appropriations, Thomas Cole, when he attended the National Meeting on Precision Medicine held in Oklahoma that was mentioned earlier.

Update on NCI's Clinical Research Programs. Dr. Doroshow reminded members that the NCI received a $70 million (M) increase for the PMI-O in 2016, and he described both the spending of those

funds in FY 2016 and the projected allocations for FY 2017. Twenty percent of the funds were used to develop a Genomic Data Commons (GDC), a large annotated database of cancer patient's samples, and to support other information technology initiatives related to precision medicine; 65 percent was used to award Administrative Supplements to NCI-designated Cancer Center's Support Grants for research in key areas of PMI-O: immunotherapy biomarkers, pancreatic cancer, cancer drug resistance, development of additional therapeutic models, and development of standard operating procedures for the development of T cell-mediated immunotherapy approaches. He expressed appreciation to the BSA members for their cooperation and support in reviewing and approving the PMI-O RFA concepts at the virtual BSA meeting. The NCI is in the process of finalizing and issuing these RFAs; funding will be available in September 2017.

Dr. Doroshow told members that a percentage of the PMI-O funds were used, first, to develop a NCI-Pediatric Molecular Analysis for Therapy Choice (MATCH) Trial and, second, to expand the Adult NCI-MATCH Trial to include an accrual of 6,000 patients and performance of detailed molecular characterizations of all patients' samples. As of December 1, 2016, 3,600 patients have been enrolled in the NCI-MATCH trial; the trial averaged 120 patient enrollments each week and will achieve its accrual goals by June 2017.

The remainder of the funds were used to develop the NCI Virtual Drug Formulary, whose goal is to streamline the process to enable Cancer Center investigators easier access to drugs for clinical trials. The NCI has received pledges for 40 therapy drugs from 20 different companies; the next steps will be to renegotiate the current Cooperative Research and Development Agreements (CRADAs) with those companies. Expectations are to launch in early January of 2017 with five companies and 10 therapy drugs.

BRP and Cancer Moonshot Recommendations. Dr. Singer provided an update on the implementation of the BRP's Cancer Moonshot recommendations and the interagency science activities of the Federal Task Force (Task Force). She reminded members that through its Working Groups, the BRP worked aggressively from April 2016 to August 2016 to develop 13 Moonshot recommendations. Three with cross-cutting themes were combined into single recommendations bringing the total recommendations for the Cancer Moonshot to 10, which were provided in the Cancer Moonshot Report to the NCAB in September 2016. Following comments from the NCAB, the NCI revised, finalized, and forwarded the report to the White House. The BRP Cancer Moonshot Report, along with the Report of the Cancer Moonshot Task Force, were made available to the public in October 2016.

The NCI has begun to develop implementation strategies centered on scalable initiatives considering the budgetary constraints. Strategies are divided into two categories: immediate implementation for FY 2017 and long-range planning for FY 2018. Implementation measures that leverage existing activities (e.g., PMI) have begun for seven of the 10 recommendation areas: immunotherapy, fusion proteins, therapeutic vulnerabilities, implementation science and screening, prevention and early detection, technology development, and the tumor atlas. The NCI intends these efforts to be starting points and anticipates sustainable funding from other initiatives and mechanisms, such as the 21st Century Cures Act. The three remaining recommendations—retrospective analysis, a data ecosystem, and patient engagement—will require more in-depth planning.

The NCI envisions establishing think tanks and organizing implementation teams of subject-matter experts (e.g., the BRP Working Groups) for each recommendation. These groups will be charged with making thorough investigations into the recommendations, seeking advice, and engaging the broader cancer research community to help develop initiatives. A Coordinating Committee will oversee all of the activities of the implementation teams, and NCI leadership will approve all initiatives. In addition, the NCI will be engaging in public and private partnership actions to advance the Cancer Moonshot goals

(recommendations). She briefly summarized three interagency Task Force science initiatives the NCI is engaged in: the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network, Department of Energy advanced computing capabilities to develop predictive models, and the Blood Profiling Atlas.

Questions and Answers

Dr. Francis Ali-Osman, Margaret Harris and David Silverman Distinguished Professor of Neuro-Oncology, Professor of Surgery, Professor of Pathology, Duke University Medical Center, asked about the measures and metrics for assessing the progress of the implementation teams. Dr. Singer replied that the role of the Coordinating Committee will be to monitor the progress and explained that the organizing structure also will include a steering committee, composed of the Division Directors and NCI Director, which will establish metrics and oversee evaluations.

In response to a query by Dr. Max S. Wicha, Deputy Director of the Taubman Institute, Distinguished Professor of Oncology, and Professor, Internal Medicine, Division of Hematology and Oncology, University of Michigan, on adjudication of NCAB's letter to Congress urging appropriations for implementing the BRP's Cancer Moonshot recommendations, Dr. Lowy responded that the NCI thinks that NCAB's appeal was effective and that the next step is to wait for a response from Congress.

Dr. Maria Elena Martinez, Professor, Department of Family Medicine and Public Health, Program Leader, Reducing Cancer Health Disparities, Moores Cancer Center, University of California at San Diego, asked about the process for soliciting applications. Dr. Singer explained that existing funding mechanisms (e.g., flexible and accelerated), contracts, and special Federal provisions (such as the Other Transaction Authority) are all possibilities that the NCI will use. Dr. Lowy added that several recommendations will be funded best as a team-based or network structure, as the Frederick National Laboratory for Cancer Research (FNLCR) is, and that heterogeneous funding mechanisms will be explored. The Frederick National Laboratory Advisory Committee is reviewing the role of FNLCR in the Moonshot recommendations.

Dr. Ethan M. Basch, Associate Professor of Medicine, Division of Hematology/Oncology, and Director, Cancer Outcomes Research Program, University of North Carolina at Chapel Hill, asked about support for the recommendations that involve interagency collaborations. Dr. Lowy replied that the NCI is engaged in discussions with interagency groups to chart paths to implementing those recommendations. For example, groups involved in the collaborative effort of the data ecosystem for sharing and analysis have had meetings to discuss resolving data sharing issues of existing and new data.

IV. LEGISLATIVE REPORT—MS. M. K. HOLOHAN

Ms. M. K. Holohan, Director, Office of Government and Congressional Relations (OGCR), reported on FY 2017 budget and appropriations, the 21st Century Cures Act, Executive Branch nominations, and other legislation of interest. The current CR expires on midnight December 9, 2016, and appropriators are hoping for an Omnibus spending bill for the remainder of FY 2017, which would allow increasing funding for the NIH by $1.25 B to $2 B. However, another CR is likely to be approved to fund the government through April 28, 2017. Budget increases are less likely during extended CRs, and agencies will continue to operate on FY 2016 funding levels. Appropriators are working to identify key priorities that can be accommodated as budget anomalies to the CR.

Members were informed that the House passed the 21st Century Cures Bill, H.R. 34, which includes appropriations of $1.8 B for 7 years for the Cancer Funding Initiative; the bill also is expected to pass the Senate. These funds will be subjected to appropriations every year and are designated for an NIH

Innovation Fund, which includes resources for cancer, PMI, and the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. The Cures Bill had not contained language that described the Cancer Moonshot until recently, when the Senate proposed renaming the Cancer Funding Initiative to the Beau Biden Cancer Moonshot Initiative.

Ms. Holohan pointed out that Presidential nominations for positions at the Department of Health and Human Services (HHS), NIH, and NCI is a very lengthy process that could range from a few months to years after a new President assumes office. The NCI is in a unique position with an Acting Director who is not subjected to this process early on.

Questions and Answers

Members were encouraged to contact their local legislators with comments on Congressional nominations. The OGCR is always available to discuss legislative issues.

V. TREATMENT OF LYMPHOMA INSPIRED BY FUNCTIONAL AND STRUCTURAL GENOMICS—DRS. LOUIS M. STAUDT AND WYNDHAM WILSON

Dr. Louis M. Staudt, Director, Center for Cancer Genomics, NCI, reported on the therapy of lymphoma, a common cancer, and the interplay of functional and structural genomics to interrogate essential cancer pathways. The Staudt laboratory used gene expression profiling (e.g., DNA Microarray) to dissect diffuse large B-lymphocyte (B cell) lymphoma (DLBCL) into two molecularly and clinically distinct subtypes: activated B-cell like (ABC) and germinal B-cell like (GBC). Each subtype has specific gene expression signatures and signaling pathways that confer different responses to therapy. Patients with GBC DLBCL showed increased survival compared to those with ABC DLBCL following chemotherapy treatment. He noted the collaborations with academic and industry partners to develop a specialized gene expression-based diagnostic test to predict lymphoma patient response to therapy.

The B-cell receptor (BCR) mediates the B-cell signal transduction pathways and has been shown to differentiate lymphoma subtypes. Active BCR signaling involves antigen activation, whereas tonic BCR signaling does not. A subset of ABC DLBCL tumors relies on active BCR signaling, and a subset of GBC DLBCL tumors relies on tonic BCR signaling; these findings convey therapeutic applications of this stratification. Dr. Staudt explained that multiple oncogenic mutations (e.g., BCR CD79 subunits A and B mutations) in ABC DLBCL tumors promote chronic active BCR signaling and provide a genetic basis for the response to therapy. Blocking these mutations with targeted therapy or precision medicine could be promising in lymphoma. Preliminary data showed that blocking Bruton's tyrosine kinase (BTK) with BCR signaling inhibitor, ibrutinib, in ABC DLBCL tumors with chronic active BCR signaling (activating mutations) decreased malignant cell survival. A 10-patient Phase I clinical trial conducted in collaboration with Dr. Wyndham Wilson, Senior Investigator, Lymphoid Malignancies Branch, Head, Lymphoma Therapeutics Section, Center for Cancer Research (CCR), NCI, to treat patients with mutated BCR and relapsed DLBCL showed complete response within 8 weeks of treatment with ibrutinib, with ongoing complete response more than 6 years after treatment. Due to the small size of this trial, it was not discernable whether these patients typified a normal response or were exceptional responders.

Drs. Staudt and Wilson co-led an NCI-sponsored multicenter Phase II trial of ibrutinib in relapsed/refractory ABC and GCB DLBCL cohorts. Findings demonstrated that ibrutinib was preferentially active in ABC DLBCL and extended the overall survival of the ABC DLBCL cohort. Mutational analysis of ABC DLBCL cohort tumors showed some association to *BCR* mutations and ibrutinib responders, but the relationship also was evident in *BCR*-negative ibrutinib responders. These data suggest that cancers can be strongly addicted to non-genetic signaling; for example, self-antigens, as reported by Dr. Staudt's laboratory, are capable of driving BCR signaling in ABC DLBCL.

Dr. Staudt explained that constitutive myeloid differentiation primary response gene 88 (MYD88) signaling is prevalent in ABC DLBCL and four of eight patients with both *BCR* and *MYD88* mutations responded better to ibrutinib than those possessing *MYD88* mutation alone, complementary to *in vitro* data and genetic evidence. To investigate these findings further, the Staudt laboratory used the proximity ligation assay to determine the interactions of BCR subunit CD79A and MYD88 in cells. They were able to show the colocalization of phosphorylated CD79A and MYD88 in the cytoplasm of ABC DLBCL cells. Use of whole genome clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 screening identified *MYD88* and toll-like receptor 9 (*TLR9*) as essential genes in ABC DLBCL cells. This led Dr. Staudt to formulate a working model of the BCR-MYD88 super pathway in ABC DLBCL and conclude that two pathogenic pathways lead to ABC DLBCL: BCR-dependent and ibrutinib-sensitive or MYD88-dependent, BCR-independent, and ibrutinib-resistant. He pointed out the high prevalence of the *MYD88* mutation, L265P, in extranodal lymphomas with an ABC DLBCL phenotype, such as cutaneous, testicular, and central nervous system (CNS) lymphomas. Drs. Staudt and Wilson hypothesize that extranodal DLBCLs are hyperaddicted to BCR signaling and will respond better to ibrutinib treatment.

Dr. Wilson reported on the NCI-sponsored Phase I study of ibrutinib combined with dose-adjusted temozolomide, etoposide, doxil, dexamethasone, ibrutinib, rituximab (DA-TEDDI-R) in non-HIV-related primary CNS lymphomas (PCNSL). He described the characteristics of immune-competent PCNSLs: ABC DLBCLs, an estimated 1,900 cases per year in the United States, occur on average in individuals 60 years of age, contain a high degree of CNS tropism, stay confined to the CNS throughout their natural history, and have poor prognosis of survival. The objectives of the study are to determine the ibrutinib response rate, the safe tolerated dose of ibrutinib plus DA-TEDDi-R, ibrutinib cerebral spinal fluid pharmacokinetics, and tumor mutations in *BCR* and *MYD88*. The trial design incudes a 14-day ibrutinib treatment window flowed by the DA-TEDDi-R chemotherapy. Patients enrolled were at a median age of 66 years, 77 percent were refractory to standard treatment, 23 percent had relapsed after treatments, and 83 percent were considered high risk with no chance of survival. Within the 14-day ibrutinib window, 94 percent of patients' tumors shrank in response to monotherapy regardless of their relapsed or refractory statuses from prior treatments. The TEDDi-R response revealed that 87 percent of patients were in complete remission, and outcomes data showed that refractory patients had a median progression-free survival of 8.2 months. Mutations in the *BCR* and *MYD88* genes were identified; however, the results were too limited to formulate any conclusions. He noted a patient who had a massive CNS tumor, was unable to speak, had failed radiation therapy, and was refractory to prior chemotherapy who saw remarkable tumor shrinkage after 14 days of ibrutinib monotherapy; this patient remains in complete remission 27 months after completing TEDDi-R treatment.

Dr. Wilson called attention to an unintended consequence of the clinical trial, fungal toxicity. He reported that seven patients (i.e., 39 percent) developed invasive *Aspergillosis* involving the lungs in all cases, and the CNS in four out of seven patients; the lungs are the indicated entry point into the body. Two patients developed the condition in response to ibrutinib alone and two patients died from complications of fungal toxicity. He explained that patients had prior cancer treatments and were on chronic steroid regimens when they enrolled in this trial; this may have played a role in the fungal outbreak. Also, ibrutinib inhibits TLR signaling, including TLR9, via BTK in M1 macrophages and diminishes innate immunity surveillance of *Aspergillosis.* Upon speculation that steroid treatment/conditioning combined with ibrutinib may have caused the high rate of fungal toxicity, Dr. Wilson consulted with Dr. Michail Lionakis, Chief, Fungal Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH, who studies invasive pulmonary *Aspergillosis* infections in patients, about modeling this response in the laboratory. Preliminary results from Dr. Lionakis' laboratory showed that BTK knock-out mice had decreased survival following *Aspergillosis* inoculation compared to wild-type mice.

In summarizing the trial results thus far, Dr. Wilson concluded that ibrutinib has clinical activity in 90 percent of PCNSL patients, including refractory patients, and the PCNSL appears to be hyperaddicted to BCR signaling. In addition, DA-TEDDi-R produced complete remissions in 87 percent of patients, including those with refractory disease. However, ibrutinib increased the risk of invasive *Aspergillosis* when combined with steroids, which is likely due to the inhibition of macrophage function. The next step will be to add the antifungal agent voriconazole to the clinical trial design. Noting the possible interactions between ibrutinib and voriconazole clearance from the body, the plans are to reduce the dose of ibrutinib and perform additional pharmacokinetic studies.

Questions and Answers

In response to a participant's query on the identification of all the ways that the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway may be activated in lymphoma, Dr. Staudt stated that the NFκB pathway is activated in 50 percent of extranodal lymphomas, thus large-scale efforts are ongoing in his laboratory to identify subtypes of ABC DLBCL and additional regulators that also could activate this pathway.

Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President, Chief Scientific Officer, Professor, Department of Biochemistry and Molecular Pharmacology and Medicine, New York University Langone Medicine, New York University School of Medicine, asked about the mechanisms of TLR activations and the role of the inflammasome in these studies. Dr. Staudt noted the uncertainty as to whether a different ligand, aside from those currently known, is needed for activation of TLR9 in lymphomas and pointed out that interleukin 1 (IL-1) driven inflammsome activity did not appear to be involved.

In response to a query from Dr. Ali-Osman, Dr. Staudt answered that the mutations they have discussed were clonal heterozygotes, and they were not attempting to address the clonal nature of the disease. He acknowledged that although he and his colleagues hypothesized that *BCR* and *MDY88* mutations would confer an advantage to ibrutinib treatment, findings revealed that the double mutants provided a clue to unlocking cases in patients that were hyperaddicted to BCRs.

Dr. Dang lauded the NCI for its efforts to integrate intramural science with translational research and wondered about funding mechanisms to extend the lymphoma translational studies to the extramural community. Dr. Wilson stated that NCI's Division of Cancer Treatment and Diagnosis' (DCTD's) Cancer Therapy Evaluation Program (CTEP) had supported these types of studies. The plan is to conduct Phase II trials at multiple sites. Dr. Doroshow added that the NCI has prior examples of translating intramural clinical studies through its national networks via the U01 funding mechanism, and Dr. Lowy pointed out the unique resources and technologies of the CCR and noted the ongoing discussions with CCR's leadership about opportunities in this area.

Dr. James V. Lacey, Director and Associate Professor, Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, City of Hope, asked about the likelihood for having similar side effects to other targeted therapies like ibrutinib and the mechanistic approaches that could be developed to better understand and predict these types of adverse events. Dr. Staudt replied that the burden lies with basic science and clinical researchers to investigate targeted combinations safely at the preclinical and clinical levels and to do so at a slower pace. Dr. Wilson added that unfortunately, as in the case with ibrutinib, there is a steep learning curve with targeted agents, and not all toxicities (e.g., early versus late effects) are known until they are revealed during a clinical trial.

Dr. Wicha asked about the compassionate use of drugs that are approved for other indications and the existing methods to catalog side effects from targeted therapies. Dr. Staudt stated that efforts are underway in the extramural community to establish media and consortia where researchers and clinicians can collectively review clinical responses from trials involving off-label use of drugs; the hope is that the GDC will eventually house these data. Dr. Wilson encouraged adding warnings to product labels to state that specific adverse events have been observed for combinations of commonly used drugs that have been previously approved for single-use indications.

Dr. David A. Tuveson, Professor and Deputy Director, Cancer Center, Cold Spring Harbor Laboratory, wondered whether the invasive *Aspergillosis* cases could be related to patient's use of cannabis for pain and whether medical marijuana could be a risk factor in the study cohorts. Dr. Wilson stated that patients would have to be colonized with the fungus for it to be an issue and anything that increases colonization would be a factor.

Dr. Peter C. Adamson, Chair, Children's Oncology Group, Alan R. Cohen Endowed Chair in Pediatrics, The Children's Hospital in Philadelphia, commented that the perceived notion in the cancer community that targeted therapy is non-toxic had added to this problem.

VI. BSA/NCAB SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORE) WORKING GROUP REPORT—DR. CHI V. DANG

Dr. Dang presented the report of the BSA/NCAB Specialized Programs of Research Excellence (SPORE) Evaluation Working Group (WG) and recognized the contributing members. The WG was charged in December 2014 by then-NCI Director, Dr. Harold Varmus to provide recommendations on the best support for translational science in the future and ways the SPORE program could enhance translation science; this charge was reaffirmed by Acting NCI Director Dr. Lowy. Dr. Dang summarized the overall broad recommendations for translational cancer research: support the highest quality of science (e.g., basic, translational, clinical, and population); maintain/sustain or increase the current level of NCI funding; develop incentives that will encourage collaborations between academic institutions and industry; and increase integration, leveraging, and interfacing of NCI's existing translational programs with the biopharmaceutical industry, advocacy groups, and other funding agencies.

Members were reminded that the SPORE program was established in 1992 to provide an integrated infrastructure for translational cancer research. Its goals and requirements included focusing on specific organ sites or common themes of biological mechanisms and required four projects with human endpoints; each project included a clinical and laboratory-based principal investigator. The flexibility to terminate projects early, support of career development and developmental research and core services, and requirements for collaboration with other SPOREs also were key features. Today, translational research remains a top priority for the NCI, and the SPORE program has successfully cemented NCI's national commitment to taking science into the clinic. Since the 1992 launch of the SPORE program, however, the knowledge base and technological advances have exploded, prompting a re-examination of the program to facilitate accelerating translational research. The WG therefore reviewed the characteristics of the SPORE program and was challenged to develop recommendations to increase the flexibility for advancing translational research.

As WG Chair, Dr. Dang ensured that all the views from the diverse team of experts were represented properly and focused on what is best for the NCI. The WG reviewed prior recommendations regarding the SPORE program and interviewed peers and colleagues. Two overarching themes resulted from those deliberations: establishing an oversight mechanism to act as an umbrella across the translational spectrum of the NCI and increasing flexibility in the SPORE program to allow more functionality in the translational research. Thus, the WG proposed development and implementation of a

SPORE successor program and development of a more integrated translational research effort that spans multiple NCI extramural programs. To address these needs and advance NCI translational cancer research with a vision for transitioning into the future, the WG recommends establishing an NCI Advanced Cancer Translational Research Program (ACTRP) to provide oversight, development, and implementation of a SPORE successor program named Translational Research Excellence (TREX), with flexibility as a central feature. The ACTRP will consist of an NCI Translational Research Strategy (NTRS) subcommittee that will be aligned with the BSA to direct the following components: portfolio management across NCI's spectrum of funding mechanisms and program development focusing on disease-specific provocative questions, setting goals and milestones. Regarding the mechanism to achieve a successful ACTRP, the NTRS subcommittee will use program announcements and RFA funding opportunities to intersect with PMI-O goals and the Cancer Moonshot recommendations.

The WG focused on and recommended key areas with increased flexibility that should result in significant outcomes from investment in TREX: involvement of research advocates, inter-institutional collaboration, clinical investigator involvement, clinical endpoint, TREX autonomy, consensus on metadata, data management, universal context, data commons, laboratory models, translational cores, and career development. Detailed descriptions of the TREX program-specific recommendations are provided in the BSA/NCAB SPORE Evaluation Working Group's Report.

In conclusion, the WG recognizes that translation research requires collaboration, flexibility, and input from multiple stakeholders and has, therefore, put forth recommendations that are intended to provide a framework that will allow increased flexibility from the NCI to support the translational research that is critical to patient outcomes across all cancer sites. In addition, the WG realizes that these recommendations have many far-reaching implications and anticipates engaging the extramural community in vigorous discussion to move these efforts forward.

Questions and Answers

Dr. Margaret R. Spitz, Professor, Dan L. Duncan Cancer Center, Baylor College of Medicine, congratulated the WG on a significant and forward-looking report, and she recommended including more explicit statements in the report that highlight the importance of population science as a translational science. Dr. Dang asked for such statements to be submitted for consideration.

Dr. Michael John Becich, Professor, Pathology Information Sciences/Telecommunications, Clinical/Translational, Department of Biomedical Informatics, University of Pittsburgh School of Medicine, lauded the WG for its report, but he noted that perspectives on data sharing were not clearly defined in the report. He also recommended that the NCI broadly consider revising the NCI Data Commons and GDC infrastructure to improve data sharing from SPORE programs and cautioned against flexibility. Dr. Dang clarified that the flexibility the report refers to is the formation and structure of the program. In response to comments by Dr. Ali-Osman, Dr. Dang agreed that the developmental research program should be preserved in the career development component of the program.

Dr. Adamson asked about the scope of the NTRS and the role of the Clinical Trials and Translational Research Advisory Committee in the oversight of the translational portfolio. Dr. Dang replied that the NCI will engineer and operationalize the WG recommendations after the report is finalized.

Dr. Deborah Watkins Bruner, Robert W. Woodruff Chair of Nursing, Nell Hodgson Woodruff School of Nursing, Associate Director for Outcomes Research, Winship Cancer Institute, Emory University, strongly recommended addressing toxicity assessment and symptom management in the

report, especially in regard to targeted therapies. Dr. Dang agreed and urged members to frame comments into realistic recommendations that the NCI could reasonably implement.

Dr. Electra D. Paskett, Marion N. Rowley Professor of Cancer Research, Director, Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University, expressed concerns that the universal consent process would discourage the requirement for sharing with the private sector and the inclusion of underrepresented minorities. Dr. Dang stated that the WG viewed universal consent as a project for which the NCI could address.

Dr. Gray clarified that the intent is for BSA and NCAB members to provide the key points and elements that could be incorporated into implementation plans that the NCI would develop. The points being raised by the members regarding specific issues identified today will be considered in those implementation plans.

Dr. Christopher M. Counter, Professor, Department of Pharmacology and Cancer Biology, Associate Professor, Radiation Oncology, Duke University School of Medicine, pointed out that the requirement for having a clinical investigator on each project would limit the participation of translational biologists and early-stage translational projects (e.g., drug development or structural biology) in the programs. Dr. Paskett cautioned against making changes that did not align with the definition of translational research. Dr. Lowy clarified that Dr. Counter is suggesting that a team of more than two researchers, which may not include a clinical investigator, would be focused on a common translational goal. He welcomes additional members' comments.

In response to a query by Dr. Martinez about the flexibility of the SPORE successor program, TREX, and incentives to include population science, Dr. Dang replied that the WG included flexibility in the program to ensure bringing forward the best ideas, rather than focusing on specific absolutes in the project requirements. All institutions and centers are not equipped the same and areas of expertise differ.

Dr. Melissa L. Bondy, Professor and Associate Director, Department of Pediatrics, Dan L. Duncan Cancer Center, Baylor College of Medicine, strongly recommended that population science and epidemiology be sufficiently detailed in the report to emphasize the strength they would bring to a project.

Dr. Bar-Sagi asked about the mechanism for deciding on credit for funding when multiple institutions are involved in one application. Dr. Gray stated that the NCI has various implementation plans that are made available to the SPORE program to address these issues, and Dr. Toby Hecht, Deputy Director, DCTD, added that credit is divided among all institutions that participate in the multi-institutional SPOREs for which principal investigators are from different institutions.

Dr. Luis F. Parada, Albert C. Foster Chair, Director, Brain Tumor Center, Member, Cancer Biology and Genetics Program, Attending Neuroscientist, Department of Neurology and Department of Neurosurgery, Memorial Sloan Kettering Cancer Center, lauded the NCI in establishing the multi-institutional SPOREs and expressed appreciation to the NCI staff for their support. He agrees with the importance of equal representation in different disciplines relating to translational science provided that the language in the report is nonexclusionary and not prescriptive. The emphasis should focus on the merit of the project.

Dr. Mack Roach III, Professor of Radiation Oncology and Urology, Director, Particle Therapy Research Program and Outreach, Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, asked about the rationale for changing the name of the program SPORE to TREX. Dr. Cheryl L. Willman, The Maurice and Marguerite Liberman

Distinguished Chair in Cancer Research, Director and Chief Executive Officer, University of New Mexico Comprehensive Cancer Center, University of New Mexico, replied that the original SPORE was mandated in a Congressional appropriation that was reflected in the language used. The parameters have changed to create flexibility in the program and changing the name to TREX to better emphasizes those changes.

Dr. Judy E. Garber, Director, Center for Cancer Genetics and Prevention, Dana Farber Cancer Institute, Professor of Medicine, Harvard Medical School, suggested that more clarity be provided in the report regarding flexibility of projects and how the new program would address cancer priorities. Dr. Adamson emphasized the importance of understanding how TREX will catalyze collaborations and such specific areas as population science and suggested that the report define them explicitly.

Dr. Gray clarified that the Boards' voting to accept the WG report with modifications does not mean that the NCI will implement the changes to the SPORE program. Funding opportunities and announcements developed from this report must be approved through the BSA.

Motion. A motion to accept the BSA/NCAB SPORE Working Group report with modifications was approved with 21 yeas, 0 nays, and 6 abstentions.

VII. TOMOSYNTHESIS MAMMOGRAPHY IMAGING AND SCREENING TRIAL RESEARCH—DR. WORTA MCCASKILL-STEVENS

Dr. Worta McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), NCI, reported on the Tomosynthesis Mammography Imaging and Screening Trial (TMIST), which is being led by the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG ACRIN) Cancer Research Group. She told members that from 1987 to 2013, 67 percent of women ages 40 and older had received a mammogram within the preceding 2 years as reported by the CDC. Tomosynthesis is an X-ray technique in which the detector follows an arch, reconstructing a series of high-resolution thin 3-dimensional (3D) images. This minimizes the overlap of 2-dimensional (2D) structures, a limitation of accuracy in imaging for younger women and women with denser breasts. Images of invasive breast cancer using single-slice tomosynthesis provides an enhanced view of the internal architecture compared to conventional 2D digital mammography. Hologic, Inc., the manufacturer of the first 3D system approved by the U.S. Food and Drug Administration (FDA) in 2011, has conducted clinical trials, but the preliminary evidence revealed that clinical trials involving tomosynthesis have been small, usually paired with 2D, and mostly conducted in Europe.

The NCI assessed the feasibility of conducting the TMIST. Ninety sites have agreed to randomize women to the intervention and 40 percent of the women who are expected to enroll will come from the community setting. The NCI has made significant efforts to engage primary care physicians and organizations that serve underserved populations to discuss ways to integrate radiologists with existing practices into the ECOG ACRIN. A pilot study funded by the Canadian Breast Cancer Foundation had enrolled more than 2,000 women as of October 2016. Participants will be analyzed for the TMIST and will reaffirm their consent for the long-term followup. Similar types of biospecimens will be collected as proposed for the TMIST, and 700 of the women currently enrolled will undergo their second round of screening.

Dr. McCaskill-Stevens pointed out that ACRIN had successfully completed high-impact screening trials, such as the Digital Mammographic Screening Trial (DMIST), and will build on this expertise. The primary aim of the TMIST is to determine whether the cumulative rate of advanced breast cancer in women undergoing screening with tomosynthesis plus digital mammography is reduced

compared to digital mammography alone. Secondary aims of the study will be to compare digital mammography with and without tomosynthesis and to perform subset analysis (e.g., age, density, and risk). Premenopausal women ages 45 or older will be screened annually for four rounds of screening; menopausal women without risk factors will be screened biannually for 2 rounds, and menopausal women with risk factors will be placed on annual screening intervals for four rounds. The TMIST study will enroll 165,000 women, complete accrual in 30 months, and achieve its primary endpoint by year 7. Patient-reported outcome and decision-making assessment data will be made available during the study. Enrollment will begin in the spring of 2017, and more than 90 sites have committed to participate. A steering committee, an independent data safety monitoring committee, and an advocacy committee are still being developed. The TMIST trial will establish a national biorepository of normal-to-invasive disease of a clinically annotated cohort using this new screening technology.

Questions and Answers

Dr. Garber asked about the timing of the TMIST trial and the fast uptake of the technology in the community. Dr. McCaskill-Stevens called attention to the FDA's account that only 23 percent of tomosynthesis systems were available in the United States. The distribution and utilization offered to women is not geographically uniform throughout the country, and sites that do have the systems are not prioritizing 3D over 2D screening.

Dr. Victoria L. Seewaldt, Ruth Zeigler Professor, Chair, Department of Population Sciences, Beckman Research Institute, City of Hope, pointed out that the standardizations for body mass index were not included and suggested that mammography density be factored in the screening interval, unless the schedule is annual for the entire cohort. Dr. Barry Kramer, Director, DCP, NCI, noted that the TMIST design is a compromise that leaders in the field agreed on: Annual screenings were excessive in some cases, and biannual assessments were insufficient to detect early disease.

Dr. Adamson asked about the differences in radiation exposure and the long-term effects. Dr. McCaskill-Stevens noted that the doses received in the study were within FDA's acceptable limits. Dr. Lowy added that participants will be tested over a 30-year period, and radiation exposure will be higher in women screened with tomosynthesis early on. Insight gained from the TMIST could change the SOC in the United States and move into the direction of other industrialized countries that screen biannually.

Dr. Lacey asked about including TMIST data in the GDC. Dr. Lowy explained that the intent is to use these biopsy samples for the Tumor Cell Atlas, a BRP Cancer Moonshot recommendation.

Dr. Paskett inquired about goals for underserved groups. Dr. McCaskill-Stevens noted that investigators have met with such organizations as the National Medical Association to address representation. This society and others have a large number of primary care physicians in their memberships who write prescriptions for mammography. The steering committee will lead the efforts to refine planning, recruitment, and retention for the TMIST.

Dr. Ian M. Thompson, Jr., Mays Family Foundation Distinguished University Professor Presidential Chair, Glenda and Gary Woods Distinguished Chair in Genitourinary Oncology, Director, Cancer Therapy and Research Center, The University of Texas Health Science Center, commented on the impressive ability of health services researchers to observe and monitor patients in clinical trials and engage in doing long-term outcomes after the followup period ends. He suggested building in cost for extended followup, either through the Centers for Medicare and Medicaid or the National Death Index. It would be a small investment to make for validating the intervention as well as for validating the surrogate endpoint as the ultimate endpoint.

VIII. RFA/COOPERATIVE AGREEMENT CONCEPTS—NCI STAFF

Division of Cancer Treatment and Diagnosis

A Data Resource for Analyzing Blood and Marrow Transplants—Dr. Vikram Devgan

Dr. Vikram Devgan, Branch Chief, Clinical Grants and Contracts Branch, Cancer Therapy Evaluation Program, DCTD, NCI, presented the concept for a RFA reissuance to continue funding the Center for International Blood and Marrow Transplant Research (CIBMTR or Registry). The CIBMTR is a data resource for analyzing blood and marrow transplants (BMT) and is the only data resource for BMT in the United States. Although there has been a dramatic increase in the worldwide utilization rate of hematopoietic stem cell transplantations (HSCT) for hematologic malignancies, major challenges still exist, such as graft versus host disease (GVHD) complications, infections, relapse, and secondary malignancy. In addition, the 1-year mortality rate among allogenic HSCT recipients remains high at 40 percent. To improve the outcome of HSCT, the NIH is utilizing two programs: Bone and Marrow Transplant Clinical Trials Network (BMT CTN) and the CIBMTR. The Registry collects baseline clinical data from donor and recipient, as well as post-transplant outcomes data, and conducts observational research studies. It has 425,000 registered patients from more than 500 transplant centers.

Dr. Devgan reported that the Registry is growing and is being used extensively with the addition of approximately 20,000 new cases each year. Data are shared with the broader community through standard annual reports, information request forms, and research study proposals. The infrastructure and processes that support CIBMTR's observational research studies, including 15 Scientific Working Committees and the Statistical Center was described. He also noted that the use of CIBMTR data through its observational research has contributed significantly to the scientific literature on hematologic malignancies and transplants.

The reissue concept would support the CIBMTR (U24), a data resource for analyzing blood and marrow transplants. Although the Registry has existed for some time and has been significant for transplant research, the 40 percent 1-year mortality rate for HSCT signifies the need for further research. Research proposals to conduct observational studies using CIBMTR data could provide answers to questions that are challenging to address in a clinical trial. Also, uninterrupted continuation of the CIBMTR will allow investigators to further define the usefulness of transplants in various clinical settings, identify prognostic factors, and compare transplant and non-transplant therapies. In addition, efforts will be made to link long-term outcomes for specifically defined patient subsets with genomic information. An FY 2016 portfolio analysis revealed that this is the only data resource for BMT in the United States, and it is the largest such resource in the world.

Subcommittee Review. Dr. Willman expressed the Subcommittee's strong support for the concept reissue. The CIBMTR is the Nation's only resource and registry for transplantation outcomes and data collection. Dr. Willman noted that the program staff had adequately responded to the Subcommittee's concerns about comprehensiveness and data quality reporting. The Subcommittee encouraged the Registry to expand the scope to include such correlative activities as genomic characterizations of patients with hematologic malignancies.

The first-year cost is estimated at $2.5 M for one U24 award, with a total cost of $12.5 M for 5 years.

Question and Answer

Dr. Becich asked about patient consent for collecting additional samples from the consolidated biorepository and the type of data that are shared. Dr. Devgan stated that the CIBMTR has more than 254 types of patient consent forms on file, including forms for independent studies from the collaborative efforts, but the U24 funding mechanism will not cover costs for additional analyses of these samples. Dr. Devgan noted that he would verify that only de-identified data are shared.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis re-issue Request for Application/Cooperative Agreement (RFA/Coop. Agr.) entitled "A Data Resource for Analyzing Blood and Marrow Transplants" was approved unanimously.

IX. ONGOING AND NEW BUSINESS—DR. ELIZABETH M. JAFFEE

NCAB *Ad Hoc* Clinical Investigations Subcommittee. Dr. Adamson provided a report of the 5 December 2016 meeting of the *Ad Hoc* Subcommittee on Clinical Investigations. The Subcommittee heard about implementation of new NIH-wide clinical trial reform and clinical trial reporting. There were discussions and concerns regarding implementation of the new NIH-wide initiatives and how they would impact therapeutic research, new investigators, and small-scaled clinical trials. The Subcommittee will be working to draft an NCAB-endorsed letter to NIH Director Dr. Francis Collins to address these concerns and suggest a phased implementation plan.

Motion. A motion to accept the report of the 5 December 2016 NCAB *Ad Hoc* Clinical Investigations Subcommittee meeting was approved unanimously.

Subcommittee Appointments. Dr. Jaffee stated that the subcommittees were reestablished and requested that members review their assignments.

Future Agenda Items. Dr. Basch suggested an update report on the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) at the next Joint BSA/NCAB meeting.

X. NCAB CLOSED SESSION—DR. ELIZABETH M. JAFFEE

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 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)."

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

XI. ADJOURNMENT—DRS. CHI V. DANG AND ELIZABETH M. JAFFEE

There being no further business, the 8th joint meeting of the BSA/NCAB was adjourned at 4:00 p.m. on Tuesday, 6 December 2016.

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Date Chi V. Dang, M.D., Chair, BSA

Date	Elizabeth M. Jaffee, M.D., Chair, NCAB
Date	Paulette S. Gray, Ph.D., Executive Secretary