

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

**14th JOINT MEETING
of the
BOARD OF SCIENTIFIC ADVISORS AND
NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
December 3, 2019**

**Conference Room TE406, East Wing, Shady Grove Campus
National Cancer Institute
National Institutes of Health
Bethesda, Maryland**

**BOARD OF SCIENTIFIC ADVISORS and
NATIONAL CANCER ADVISORY BOARD JOINT MEETING
BETHESDA, MARYLAND
Summary of Meeting
3 December 2019**

The Board of Scientific Advisors (BSA) of the National Cancer Institute (NCI) and the National Cancer Advisory Board (NCAB) convened for the 14th Joint Meeting on 3 December 2019 in Conference Room TE406, East Wing, Shady Grove Campus, NCI, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, 3 December 2019, from 8:00 a.m. to 4:18 p.m. and closed to the public on Tuesday, 3 December 2019, from 4:30 p.m. to 5:14 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 BSA Chair, Dr. Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President and Chief Scientific Officer, Professor, Department of Biochemistry and Molecular Pharmacology and Medicine, New York University (NYU) Langone Health, NYU School of Medicine, presided during the open session. Dr. Jaffee presided during the closed session. In the open session, the BSA considered new requests for applications (RFAs), Cooperative Agreements (Coop. Agr.), requests for proposals (RFPs), and program announcements with special receipt, referral, and/or review (PARs) of new and re-issue concepts presented by NCI Program staff.

BSA Members

Dr. Dafna Bar-Sagi (Chair)
Dr. Kenneth C. Anderson
Dr. Michael John Becich (absent)
Dr. Mary C. Beckerle
Dr. Melissa L. Bondy
Dr. Otis W. Brawley
Dr. Graham A. Colditz
Dr. Christopher M. Counter
Dr. Carol E. Ferrans
Dr. Keith T. Flaherty (absent)
Dr. Karen E. Knudsen
Dr. James V. Lacey, Jr.
Dr. Michelle M. Le Beau
Dr. Sylvia Katina Plevritis
Dr. W. Kimryn Rathmell
Dr. Leslie L. Robison
Dr. Martine F. (Sheer) Roussel
Dr. Robert D. Schreiber (absent)
Dr. Victoria L. Seewaldt (absent)
Dr. Kevin M. Shannon (absent)
Dr. David Sidransky
Dr. Ian M. Thompson, Jr. (absent)
Dr. David A. Tuveson
Dr. Robert H. Vonderheide
Dr. Eileen P. White
Dr. Cheryl L. Willman

NCAB Members

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

*pending appointment

Alternate *Ex Officio* NCAB Members

Dr. Robert T. Anderson, DOE (absent)	Dr. Richard Pazdur, FDA (absent)
Dr. Michael A. Babich, CPSC (absent)	Dr. Craig D. Shriver, DoD
Dr. Vincent J. Cogliano, EPA (absent)	Dr. Kerry Souza, NIOSH (absent)
Dr. Michael Kelley, VA (absent)	Dr. Lawrence A. Tabak, NIH (absent)
Dr. Aubrey Miller, NIEHS	

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Norman E. Sharpless, Director, National Cancer Institute
Dr. L. Michelle Bennett, Director, Center for Research Strategy
Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics
Dr. Henry P. Ciolino, Director, Office of Cancer Centers
Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences, and Interim Director, Center for Global Health
Dr. William Dahut, 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
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
Dr. Paulette S. Gray, Director, Division of Extramural Activities
Dr. Ed Harlow, Special Advisor to the NCI Director
Dr. Toby T. Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis
Dr. Sara Hook, Director, Office of Scientific Operations, NCI Campus at Frederick
Dr. Tony Kerlavage, Director, Center for Biomedical Informatics and Information Technology
Dr. Douglas R. Lowy, Principal Deputy Director, National Cancer Institute
Dr. Glenn Merlino, Scientific Director for Basic Research, Center for Cancer Research
Dr. Tom Misteli, Director, Center for Cancer Research
Dr. Margaret Mooney, Acting Director, Cancer Therapy Evaluation Program
Dr. Henry Rodriguez, Acting Deputy Director, Center for Strategic Scientific Initiatives
Mr. Jeff Shilling, Chief Information Officer and Chief of Infrastructure and Information Technology Services Branch, Center for Bioinformatics and Information Technology
Ms. Donna Siegle, Executive Officer and Deputy Director for Management, Office of the Director
Dr. Dinah Singer, Deputy Director for Science Strategy and Development
Dr. Sanya Springfield, Director, Center to Reduce Cancer Health Disparities
Dr. Louis M. Staudt, Director, Center for Cancer Genomics
Mr. Michael Weingarten, Director, Small Business Innovation Research and Small Business Technology Transfer Programs
Dr. Deborah M. Winn, Acting Director, Division of Cancer Prevention
Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

Liaison Representatives

Ms. Carolyn Aldige, Prevent Cancer Foundation
Dr. Carol Brown, Society of Gynecologic Oncologists
Dr. Margaret Foti, American Association for Cancer Research
Dr. Leo Giambaresi, American Urological Association
Dr. Francis Giardiello, American Gastroenterological Association
Dr. Mary Gullatte, Oncology Nursing Society
Dr. Ruth Hoffman, American Childhood Cancer Organization
Dr. Steven L. Klein, National Science Foundation
Ms. Laura Levit, American Society of Clinical Oncology
Ms. Maria Lopez, Kidney Cancer Association

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, Inc.
Ms. Nancy O'Reilly, American College of Obstetricians and Gynecologists
Ms. Leah Ralph, Association of Community Cancer Centers
Ms. Susan Silver, National Coalition for Cancer Survivorship
Ms. Christy Schmidt, American Cancer Society
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Johannes Vieweg, American Urological Association
Dr. Pamela A. Wilcox, American College of Radiology
COL. (Ret.) James E. Williams, Jr., Intercultural Cancer Council

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TUESDAY, 3 DECEMBER 2019

I. CALL TO ORDER AND OPENING REMARKS—DRS. ELIZABETH M. JAFFEE AND DAFNA BAR-SAGI

Dr. Elizabeth Jaffee called to order the 14th Joint Board of Scientific Advisors (BSA) and National Cancer Advisory Board (NCAB) meeting and welcomed members of the Boards, *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. Jaffee and Dafna Bar-Sagi reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion to accept the minutes of the 4 September 2019 NCAB meeting was approved unanimously.

Dr. Jaffee reminded the Board members that the 10 June 2019 Joint BSA and NCAB meeting minutes were approved electronically and called members' attention to future meeting dates listed on the agenda and in the Board book.

II. NCI DIRECTOR'S REPORT—DR. NORMAN E. SHARPLESS

Dr. Norman E. Sharpless, Director, NCI, welcomed members of both the BSA and NCAB to the 14th joint meeting of these Boards. Dr. Sharpless provided an update on the U.S. Food and Drug Administration (FDA) cancer-related regulatory work, NCI fiscal year (FY) 2020 funding and appropriations, and NCI activities.

Dr. Sharpless informed members that the White House had announced appointment of new members to the President's Cancer Panel (PCP): Chairperson, Dr. John P. Williams, Breast Cancer Surgeon, Medical Director, Breast Cancer School for Patients, Clinical Professor, Institute for Biohealth Innovation, George Mason University; as well as, two members, Mr. Robert A. Ingram, General Partner, Hatteras Venture Partners; and Dr. Edith P. Mitchell, Clinical Professor of Medicine and Medical Oncology, Department of Medical Oncology, Director, Center to Eliminate Cancer Disparities, Associate Director, Diversity Affairs, Sidney Kimmel Cancer Center, Thomas Jefferson University.

Dr. Sharpless acknowledged pending members to the NCAB: Dr. Anna D. Barker, Chief Strategy Officer, Lawrence J. Ellison Institute for Transformative Medicine, University of Southern California; Dr. Howard J. Fingert, Consultant; Dr. Andrea A. Hayes-Jordan, Byah Thompson Doxey Distinguished Professor of Surgery, Division Chief, Pediatric Surgery, Surgeon-in-Chief, University of North Carolina Children's Hospital; and Dr. Susan Thomas Vadaparampil, Vice Chair, Health Outcomes and Behavior, Associate Center Director, Community Outreach, Engagement, and Equity, Moffitt Cancer Center.

FDA Cancer-Related Regulatory Updates. Dr. Sharpless reflected on his time as FDA Acting Commissioner and highlighted work related to the NCI and oncology. Of interest to the NCI are FDA's regulation of medical products, drugs, devices, and diagnostics; impact on U.S. clinical trials; preference for real-world evidence (i.e., multiple sources of health care information outside of the typical clinical research setting); and role in the regulation of tobacco and tobacco control in the implementation of the 2009 Family Smoking Prevention and Tobacco Control Act. From April 2019 to October 2019, the FDA approved seven therapeutic oncology drugs, 13 cancer treatment supplements, and 11 devices, including companion diagnostics for cancer (e.g., prostate-specific antigen point-of-care test). In addition, the FDA Oncology Center of Excellence initiative entitled Project Facilitate is assisting health care providers with submissions of compassionate use investigational new drugs, and the Project Orbis initiative supports concurrent oncology product submission and review in the United States and among international

partners, including Australia and Canada. Dr. Sharpless noted that during this time period, the progress in cancer exceeded progress in any other therapeutic area and that this success and the rate of approvals suggest that the engine producing new cancer therapies and diagnostics is effective and robust. He speculated that the increased interest in cancer research as evidenced by the increase in NCI R01 applications could be related to this success. Although complex, the regulatory decisions must be made with the available data, which the FDA relies on the Centers for Disease Control and Prevention (CDC), NIH, and the NCI to develop. In essence, the NCI has resources not found at other agencies; therefore, intergovernmental collaboration is critical.

NCI FY 2020 Funding and Appropriations. Dr. Sharpless informed the BSA and NCAB members that the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Labor-Department of Health and Human Services [HHS]) FY 2020 spending bill markup includes a \$300 million (M) increase for the NCI over the FY 2019 enacted budget, and the Senate Appropriations Labor-HHS Subcommittee spending bill markup includes \$208 M. Both bills include a \$50 M annual appropriation for the new Childhood Cancer Data Initiative (CCDI) in the base appropriation. Dr. Sharpless explained that Ms. M. K. Holohan, Director, Office of Government and Congressional Relations, will provide a detailed report on the NIH/NCI budget later in the meeting.

Cancer MoonshotSM Initiative Updates. Dr. Sharpless reported that the Cancer MoonshotSM annual allotment of \$195 M for FY 2020 will remain at this level until the funding ends in FY 2024. The Initiative has established several large networks (e.g., the Drug Resistance and Sensitivity Network) engaged in collaborative research and repositories of tissues and new models and systems, many of which will extend beyond the allocated funding. The NCI convened a meeting of the individual Cancer MoonshotSM networks on 17–19 November 2019 to discuss progress and a collaborative meeting of eight networks on 20 November 2019 to catalyze inter-network communication and encourage collaboration.

Key Focus Areas. Dr. Sharpless reminded the BSA and NCAB members of the NCI's four key focus areas, basic science, workforce development, big data, and clinical trials, and highlighted current efforts. NCI's support for the Research Project Grant (RPG) pool is a major effort in reaffirming its commitment to basic science, which is to facilitate development of significant biological insight of cancer biology. Significant new funding has been allocated to the RPG pool within the past 2 years. This trend is expected to continue in FY 2020.

In the area of workforce development, the NCI issued Method to Extend Research in Time (MERIT) Awards (R37) as a mechanism to extend funding for Early Stage Investigators (ESIs) who are R01 recipients for an additional 2 years. Data on how the MERIT Awards affect ESI success and out-year costs are expected to be reported soon. The Research Specialist Award (R50) launched in 2016 to encourage development of stable research career opportunities for exceptional non-tenure track scientists wanting to continue to pursue research in an existing NCI-funded research program, but not as independent investigators. The NCI remains committed to workforce diversity through the Center to Reduce Cancer Health Disparities (CRCHD) Partnerships to Advance Cancer Health Equity (PACHE) and Continuing Umbrella of Research Experiences (CURE) programs.

Regarding data aggregation and data usage, in the February 2019 State of the Union address, the White House announced a proposal to support a CCDI at \$50 M annually for 10 years beginning in FY 2020. In anticipation of the initiative's funding, the NCI has begun plans for implementing the CCDI both internally and externally. An *ad hoc* BSA Working Group supporting the CCDI was established and charged to advise the NCI on this effort. NCI's leading endeavor emphasizing how data should be used by large research organizations, the Cloud Pilots, was implemented in three sites and has been successful and used widely by both intra- and extramural investigators. Because of NCI cloud resources, which are equipped with popular data analysis tools, pipelines, and workspaces to save and share data, actual costs of using the cloud have decreased. The NCI cloud resources contain four proteomics data sets, 13 genomic data sets, and more than 24 reference data collections; 375 users access the resources

monthly. To date, 3,000 users are registered and nearly 900,000 analysis tasks have accumulated across the NCI cloud resources. In addition to the cloud resources, the NCI Surveillance, Epidemiology, and End Results (SEER) Program expanded to cover 35 percent of the U.S. population with 500,000 new cancer cases added annually. A new request for applications (RFA) was released for FY 2020 focusing on collecting data on disease recurrence. One ongoing data computing effort is the NCI–Department of Energy (DOE) collaboration on natural language processing, establishing a virtual tissue repository, and linking public and private payers.

In the area of clinical trials, Dr. Sharpless remarked that the NCI made large investments in the NCI Community Oncology Research Program (NCORP) in the past few years and in FY 2019 increased funding to \$20 M for the cooperative groups. NCORP covers 44 states, including Washington, D.C., Puerto Rico, and Guam; has seven Research Bases, 32 Community Sites, and 14 Minority/Underserved Sites; and supports 1,000 affiliates. NCORP helped to accrue patients for the Adult NCI-Molecular Analysis for Therapy Choice (MATCH) trial in 100 U.S. academic research institutions. A recent analysis of the impact of the NCI Clinical Trial Network (NCTN) on clinical cancer care generated by the Southwest Oncology Group (SWOG) was published in the September 2019 issue of *JAMA*. The report concluded that 45 percent of the Phase 3 clinical trials conducted from 1980 to 2017 influenced guideline care and/or new drug approvals. Dr. Sharpless emphasized that the SWOG report makes the argument that the NCTN, the major driver for modern cancer care, is a successful organizational structure to care for cancer patients in the United States. The NCI is actively reviewing ways to modernize the NCTN to improve its capabilities to support trials internationally.

Dr. Sharpless pointed out that the NCI Office of the Director receives numerous emails from investigators related to indirect costs in grants, paylines, and ESI status. To communicate to NCI-supported grantees, administrators, and applicants details on grants, funding policy updates, and research activities/priorities, the NCI launched a new blog, “NCI Bottom Line: A Blog About Grants & More”, on 10 September 2019.

Leadership Appointments and Vacancies. Dr. Sharpless called attention to recent appointments: Dr. Dinah Singer is Deputy Director for Science Strategy and Development; Dr. Margaret Mooney is Associate Director, Cancer Therapy Evaluation Program (CTEP); Ms. Joy Wiszneauckas has been named Director, Committee Management Office; and Dr. Satish Gopal is selected as Director, Center for Global Health (CGH), pending NIH approvals. He announced that Dr. Jonathan Wiest, Director, Cancer Center for Training (CCT) is retiring and that Dr. Oliver Bolger is selected as Director, CCT, also pending NIH approvals. Dr. Sharpless expressed appreciation to Dr. Wiest for his efforts in streamlining the NCI career development funding mechanisms (i.e., K awards), creating a new Predoctoral to Postdoctoral Fellow Transition Award (F99/K00), addressing salary and funding issues for new physician-scientist trainees, and pioneering educational and career development for NCI programs, including the Graduate Students Recruiting Program. Dr. Sharpless also noted the NCI’s ongoing recruitment efforts for directors of the Division of Cancer Prevention (DCP) and Division of Cancer Biology (DCB). He expressed appreciation to Dr. Deborah M. Winn, Acting Director, DCP, and Dr. Daniel Gallahan, Acting Director, DCB, for their continued support in filling these roles.

Dr. Sharpless expressed appreciation to Dr. Douglas R. Lowy, Principal Deputy Director, NCI, for serving as acting NCI director during his time at the FDA.

III. BUDGET OVERVIEW—DR. DOUGLAS R. LOWY

Dr. Lowy provided a closer look at the NCI budgeted regular appropriations and the RPG pool, with a focus on addressing how the NCI spends its money, specifically the FY 2019 regular appropriation estimates, and what has driven the increase in NCI grant applications; both queries emerged from prior discussions with the BSA and NCAB members. Primarily, the RPG pool is the largest investment of NCI funding. Specifically, 75 percent of the NCI budget in regular appropriations, excluding Cancer

MoonshotSM, supports extramural research, and the balance supports other funding, including intramural research. From FY 2014 to FY 2019, the NCI regular appropriations steadily increased, with more than 50 percent of that increase supporting the RPG pool, translating to a funding growth from 41 to 43 percent. Of the 43 percent of RPG pool funding, 57 percent supports traditional R01 grants, and the remainder supports other mechanisms, such as the R01 RFA, Program Project (P01), R21, and R35. Other research grants, including K awards, resource grants (U24 and R24), education (R25), and the Clinical Cooperative Groups (U10 and UG1), comprise 9 percent (\$550 M) of the RPG pool budget. The NCI-Designated Cancer Centers (Cancer Centers) and Specialized Programs of Research Excellence (SPORes) make up 10 percent (\$570 M) and support planning and administrative supplement grants and the Specialized Centers (U54s).

In addition, the NCI allocates 5 percent of its intramural budget to support the Frederick National Laboratory for Cancer Research (FNLCR), of which 59 percent is in direct support to the NCI Extramural Research Program and 41 percent is marked for indirect support for large-scale projects (e.g., RAS Initiative), laboratories, and core facilities. Examples of direct support include the NCI Experimental Therapeutics (NExT), Patient-Derived Models Repository (PDMR), and Genomic Data Commons (GDC). Aside from the RPG pool educational efforts, the NCI invests approximately \$260 M in training and developing a strong cancer research workforce. Dr. Lowy summarized the FY 2019 sources of funds and major budget increases. Congress increased the NCI budget by \$79 M over the FY 2018 enacted budget, and the NCI increased the RPG pool budget by \$86 M; invested \$46 M in the NCORP, NCTN, and Cancer Centers; and spent \$63 M on mandatory costs. The NCI also reduced internal operating costs by \$64 M and implemented a continuing grants policy cap at 97 percent from a decrease in funding for the Non-Competing Continuation (Type 5) awards in the RPG pool by 3 percent, resulting in a \$55 M source of funds.

Dr. Lowy informed the Boards that the number of competing (Type 2) R01 applications that NCI receives continues to be high in FY 2019. Even though the rate of increase is less than it was the previous 2 years, it is significantly higher than the rise in the NCI budget. Since FY 2001, the RPG pool application success rates have been lower than the rates at other NIH Institutes and Centers (ICs). From FY 2015 to FY 2018, the success rates for all other NIH ICs increased to 22 percent, but decreased for the NCI to 11 percent, a trend that is expected to continue in FY 2019. Since the June 2019 RPG report to the Boards, the NCI conducted an in-depth review into the contributing factors of the significant increase in the number of NCI RPG applications between FY 2013 and FY 2019 and found that the number of unique NCI R01/R37 applicants increased by 48 percent compared to a 9 percent increase in other NIH ICs. The major driver of this increase was: 1) the influx of principal investigators into the NCI applicant pool from other ICs and 2) investigators external to the NIH. The secondary drivers were the increases in multi-principal investigator applications, program announcements with special receipt, referral, and/or review (PARs) and applications to PARs, and increase in the number of applications submitted per principal investigator.

Dr. Lowy summarized that from FY 2013 to FY 2019, the NCI budget has emphasized the RPG pool, which has required increasing the pool's overall percentage, but the increase in submitted applications has outpaced NCI's investments in this area.

Questions and Answers

Dr. Michelle M. Le Beau, Arthur and Marian Edelstein Professor of Medicine, Director, University of Chicago Medicine Comprehensive Cancer Center, The University of Chicago, asked about the makeup of investigators in the category "not yet applying for an NCI grant." Dr. Lowy noted that senior investigators mostly comprise this category, but a combination of junior and senior investigators are often represented.

Dr. Timothy J. Ley, Professor of Medicine and Genetics, Division of Oncology, Department of Medicine, Washington University School of Medicine in St. Louis, asked whether plans are in progress to address the success rate and paylines given that the increase in applications from investigators outside of the NIH appears to be a continuing, sustainable trend. Dr. Lowy replied that it will take a concerted effort to return the grant success rates and paylines to levels the NCI would want; a FY 2020 budget that reflects the House and Senate markup bills would be one place to start. Dr. Sharpless added that NCI's efforts to mitigate the effects of the low paylines, such as cutting existing competing awards to fund new grants and considering co-funding cancer research with other ICs, can have a positive effect on paylines but are not sustainable. The NCI is in a unique position of having an intake of applications that exceeds the overall rates at the NIH. Congress is aware of these never-before-seen challenges and may have ways to alleviate them. In the long term, a larger NCI budget (i.e., regular appropriations) is the only way to address the robust increase in applications.

Dr. Christopher M. Counter, Professor, Department of Pharmacology and Cancer Biology, Duke University School of Medicine, inquired about the decision-making involved in allocating 43 percent of the NCI budget to the RPG pool and which funding mechanisms provide the highest return on investment. Dr. Lowy explained that because of inflation, the NCI budget was flat for 10 years, resulting in a 30 percent loss of purchasing power. Additionally, the cost of conducting research increased during this period, which affected all aspects of the NCI budget. The NCI used the budget increases to address the greatest need and opportunity, which has been the RPG pool. Because the NCI supports all areas of cancer research, identifying a funding mechanism with the highest return of investment obtainable is subject to perspective.

Dr. James V. Lacey, Jr., Director and Professor, Division of Health Analytics, Department of Computational and Quantitative Medicine, Beckman Research Institute, City of Hope, remarked on the positive long-term developments of the increased R01 applications and multiple-principal investigator applications and PARs. He asked whether FY 2011 established a new normal with a 12 to 13 percent success rate, questioning whether this is more realistic given the current budget outlook in Congress. Dr. Lowy noted that the R01 success rates in FY 2011 were approximately 15 percent and have since decreased, translating to a reduced chance of receiving a grant from the NCI.

Dr. Karen E. Knudsen, Executive Vice President, Oncology Services, Jefferson Health, Enterprise Director, NCI-Designated Sidney Kimmel Cancer Center at Jefferson, Chair and Hilary Koprowski Endowed Professor, Department of Cancer Biology, Thomas Jefferson University, pointed out the increase in approved Cancer Centers emanating from the increase in R01 applications and asked about any accompanying increases to the Cancer Center program. Dr. Lowy shared his perspective that centers that have performed well should see increases in their budgets with a competitive renewal, which can be supported only by increases in the overall Cancer Center program budget.

Dr. Nancy J. Raab-Traub, Professor, Department of Microbiology and Immunology, School of Medicine, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, asked about the impact of the multiple-principal investigator applications in general and on the RPG budget. Dr. Lowy responded that although multiple-investigator applications assume a progressively larger percentage of the awards, the challenge is greater to receive a renewal grant compared to the individual investigator applications. Whether the multiple-investigator applications bring new skills to address a research question is to be determined.

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

Ms. Holohan reported on the Congressional rosters, appropriations and authorizations, FY 2020 appropriations process, and the Congressional calendar. Several members of the 116th Congress will be retiring or seeking other offices in 2020. Twenty Republican (R) House members, five of whom are from

Texas, and four Republican Senators are not seeking reelection. Among Democrats (D), eight in the House and one in the Senate are not seeking reelection. Rep. Nita M. Lowey of New York, Chair of the House Appropriations Committee, announced that she will be retiring in 2020, and several members on the existing roster, including chairs of each of the 12 Subcommittees, have expressed interest in filling this position. Rep. Lowey, the highest ranking Democratic appropriator in the House and a strong supporter of the NIH and NCI, also is chair of the House Subcommittee on State, Foreign Operations, and Related Programs and will be vacating this office, opening up another leadership position in the House. Two other House Appropriations Committee members are retiring: Peter J. Visclosky (D-IN) and José E. Serrano (D-NY). Recommendations on the next leading Democratic appropriator will come from a steering committee, and a decision will not be reached until the end of the 116th Congress.

Ms. Holohan provided an overview of appropriations, which outline how funds are spent on specific programs, and authorizations, which establish, continue, or modify federal agencies (e.g., the NCI) or programs. She first reminded the Board members that the 2016 21st Century Cures Act enabled the Cancer MoonshotSM and explained that Congressional leaders and sponsors of the 2016 bill, specifically Reps. Diana DeGette (D-CO) and Fred Upton (R-MI), are proposing a “Cures 2.0” legislation. On 26 November 2019, the legislators issued a Call to Action letter outlining some of their goals for digital innovation and caregiver training in this new iteration; input and feedback are being collected. The 21st Century Cures is a hybrid legislation, an authorizing bill that includes mandatory funding, and is structured differently from the regular NIH/NCI appropriation process. To be funded, a program must first be authorized; the NIH has broad authorization, but bills giving new authorities are rare. The Boards were reminded that certain types of research were exempted from the Paperwork Reduction Act, which benefited researchers and provided the NIH additional authority for enforcement, data sharing, and bill authorization. Unlike authorizations, which span multiple years, appropriations are yearly, and authorization within them is rare, especially for large programs. The 21st Century Cures Act was an exception.

Ms. Holohan echoed Dr. Sharpless on the House and Senate Appropriation Subcommittees on Labor-HHS spending bills and budget increases for the NCI and noted that the House base appropriation was derived from estimates based on the FY 2018 spending amounts prior to the August 2019 budget deal, whereas the Senate used the actual budgeted top-line dollar amounts, translating to different apportionment within the body of the two bills. To date, two budget continuing resolutions (CRs) have been approved: 1 October 2019 to 21 November 2019 (CR 1) and 22 November 2019 to 20 December 2019 (CR 2). The CR 2 includes additional funding for the Census Bureau in preparation for the 2020 Census. Congressional leaders agreed to a compromise on the topline for each of the 12 spending bills, which will be released following final bicameral settlements. Because of the challenges in funding the border wall, which affects two of the 12 bills, Homeland Security and Military Construction, Veterans Affairs, and Related Agencies, an omnibus encompassing all 12 bills, is unlikely. At 81 days into the fiscal year, a FY 2020 budget is still pending. The CR to fund the government expires in 17 calendar days and includes 8 legislative days. Congressional appropriators are working to settle the budget prior to recess.

Regarding the Congressional calendar, Ms. Holohan pointed out that the House could potentially vote on impeachment prior to the beginning of 2020 and the Senate will have to conduct a trial. This six-step process could conflict with or impede the budget appropriation progress. The House Judiciary Committee is expected to release its report on 3 December 2019, and the Intelligence Committee will begin hearings on 4 December 2019. When the House will vote on articles of impeachment is unknown, but the next step will be notification to the Senate, followed by commencement of the trial. The Senate rules dictate a 6-day-a-week work function for the impeachment trial, leaving little time for must-pass legislation (e.g., spending bills). In addition, the 2020 primary elections will begin in February in some states, and candidates who are senators will be challenged to be on the campaign trail.

V. COMPARATIVE ONCOLOGY PROGRAM: CLINICAL TRIALS IN DOGS WITH CANCER AND INSIGHT FOR HUMANS —DR. AMY LEBLANC

Dr. Amy LeBlanc, Director, Comparative Oncology Program (COP), Center for Cancer Research (CCR), provided an overview of COP's efforts in studying naturally occurring cancers in pet dogs and the translational relevance of those diseases to humans. The NCI has made a substantial investment in the intramural COP, and the COP investigators work closely with Division of Cancer Treatment and Diagnosis (DCTD) and other NCI Divisions on drug development activities and translational tumor biology. Within the broader comparative oncology community in North America, research focusing on comparative cancer genomics, gene-environment interactions, and cancer-associated risk factors is ongoing. The COP operates the NCI Comparative Oncology Trial Consortium (COTC), consisting of 24 members located within veterinary colleges across the United States and Canada. Ten of the associated veterinary colleges have formal membership and integration in the Cancer Centers. Clinical trial and drug development activities with other NCI cooperative groups, including CTEP, the Children's Oncology Group (COG), and such programs as NExT, are integrated into the COTC. In addition, the COTC receives support from philanthropic organizations and pharmaceutical companies interested in comparative oncology.

Dr. LeBlanc emphasized that spontaneous cancer in pet dogs is not uncommon. In fact, more than 1 million of the approximately 78 million dogs in U.S. households will develop cancer each year; many of these cancers are similar to those that occur in humans (e.g., non-Hodgkin's lymphoma, melanoma, osteosarcoma, soft tissue sarcoma, muscle-invasive bladder cancer, and brain tumors). Owners are increasingly interested in more advanced therapeutics and access to clinical trials for their pets. Dr. LeBlanc pointed out the advantages of a comparative oncology approach to cancer drug development. The pet dog model offers more synteny to humans compared to the rodent models with respect to similar druggable targets, tumor heterogeneity, imaging and treatment modalities, and valuable pre-investigational new drug (IND) work and early efficacy signals. The canine patient provides the researcher opportunities to obtain multiple biological samples and longitudinal observations collected through validated standard operating procedures (SOPs) during comparative oncology clinical trials and access to canine-specific assays and reagents through the COTC Pharmacodynamic (PD) Core virtual laboratory.

Dr. LeBlanc highlighted some of the COTC clinical trials and projects that have influenced cancer drug development and translational tumor biology. The COCT001 trial, conducted from 2007 to 2008, evaluated arginylglycylaspartic acid (RGD [Arg-Gly-Asp])-targeted delivery of phage-expressing tumor necrosis factor (TNF)-alpha in a cohort of tumor-bearing dogs that were enrolled at U.S. veterinary schools. The proof-of-concept study showed that the co-localization of RGD-TNF particles were present in tumor endothelium but not in the adjacent normal tissue. One patient from this trial lived another 4 years with its owners, and the data informed the follow-on Phase 1 trial in humans.

To address some of the challenges in the comparative oncology field, such as lack of data-driven research that bridges human and canine oncology, the COP began investigating osteosarcoma (OS) as one example of a comparative approach affecting human health. OS is a common canine cancer and a major medical problem for dogs in the United States and worldwide, particularly for large-breed dogs. Approximately 10,000 cases are reported annually in the United States, and the incidence in dogs outpaces human pediatric and AYA cases. Dogs who develop OS typically are not cured and progress to metastatic disease that mimics the human pediatric disease with similar clinical and molecular features, suggesting that the canine model is a key component for the discovery process for new treatments for children. Recent studies demonstrated that genome-informed therapy for OS could rationally assess new therapy and strategies. Biospecimens collected from prior canine clinical trials enabled the COP to engage in a comparative approach to OS drug development and translational studies of agents designed to improve outcomes for dogs and humans. The COP enrolled approximately 450 canine patients in three canine OS trials, including both early and late phase trials over the past 3 years. Multiple therapeutic

approaches, including novel biologics or vaccines, rapalog inhibition of mammalian target of rapamycin, and metabolic targeting of metastatic cells, are being evaluated. The outcome is a biorepository of clinically annotated, high-quality biospecimens, which is being used to ask new research questions and inform the next generation of trials.

Further efforts in the COP focus on deciphering the OS genome in dogs through the Dog² project. The goals are twofold: build a comprehensive comparative data set describing the molecular landscape of canine OS and leverage the existing COP canine OS biospecimen repository. The overarching aim is to leverage existing NCI tools and expertise to identify new approaches for pediatric OS by integrating canine OS data with human OS data (e.g., NCI Therapeutically Applicable Research to Generate Effective Treatments Initiative), identifying new druggable targets, interrogating preclinical models, and prioritizing therapeutic approaches to study in OS clinical trials.

Dr. LeBlanc described a DCTD-sponsored study on prioritizing a lead compound, one of three novel inhibitors of topoisomerase 1 (TOP 1), for activity in a naturally occurring canine model of non-Hodgkin's lymphoma. The study, COTC007b, evaluated whether this indenoisoquinoline class of TOP 1 inhibitors could be administered safely in tumor-bearing dogs and answered questions on the comparable toxicity profiles among the three agents, as well as comparable pharmacokinetic profiles and correlative PD markers for response. Nine COTC sites enrolled 84 dogs in the trial and completed dose escalation studies of the three agents. The results showed similar toxicity profiles with no unexpected adverse events. One agent exhibited 10 times higher tumor drug accumulation and an overall response rate that was twice that of the other two agents.

In closing, Dr. LeBlanc remarked on the future role of comparative oncology in cancer drug development in terms of continuing the scientific dialogue on the applicability and validity of the dog model of cancer for strategic advancement of novel agents.

Questions and Answers

Dr. Robert H. Vonderheide, John H. Glick MD Abramson Cancer Center's Professor, Professor of Medicine, Perelman School of Medicine, Director, Abramson Cancer Center, University of Pennsylvania, asked about details on the regulatory authority and resources on conducting clinical trials in dogs, particularly in gene therapy, which is becoming rate-limiting. Dr. LeBlanc replied that the comparative oncology community recognizes that the focus on biologics and immunotherapy is an emerging topic in the field. The goal is to integrate the dog model into those types of studies, which the COP advocates for at the NCI level. As extramural funding for these studies increases, support from the White House Office of Science and Technology Policy (OSTP) and other regulatory agencies that understand the value of this research will be critical. Data-driven policies to provide evidence that pets can be released back to their families after a study, as well as input from veterinary colleagues at the various federal agencies on this topic, also is needed.

Dr. David Sidransky, Director, Head and Neck Cancer Research, Professor of Otolaryngology-Head and Neck Surgery, Department of Otolaryngology, Head and Neck Surgery, Johns Hopkins University School of Medicine, commented on a macrophage activating factor for treating adenocarcinoma that was highly responsive in dog clinical trials but unresponsive in humans, suggesting that the emphasis should be on matching the trial results to the right patients. Dr. LeBlanc noted that the dog is a comparative biology model but will not be the answer to all research questions in cancer. Research focused on increasing understanding in the canine immune system and better ways to characterize the canine immune response are necessary to bring this model to performing at a desired level.

VI. NATURE AS A REMARKABLE CHEMIST: THE STORY OF TAXOL—DR. SUSAN BAND HORWITZ

Dr. Susan Band Horwitz, Distinguished Professor, Department of Molecular Pharmacology, Rose C. Falkenstein Chair in Cancer Research, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, presented her research on understanding the mechanism of action in the development of Taxol[®] (paclitaxel). Dr. Lowy prefaced the presentation by congratulating Dr. Horwitz on receiving the 2019 Canada Gairdner International Award for her achievements in cancer therapeutics.

Dr. Horwitz provided a brief history of Taxol. In the 1950s, the NCI and the U.S. Department of Agriculture (USDA) decided to collaborate on the discovery and development of new natural products for cancer treatment. In 1962, the bark and leaves of the Western yew, *Taxus brevifolia*, were isolated by college students studying in the state of Washington. Subsequently, these samples were sent to medicinal chemists Drs. Monroe E. Wall and Mansukh Wani at the Research Triangle Institute's Natural Product Laboratory in Research Triangle Park, NC. These investigators were able to isolate the paclitaxel molecule and determine its structure. In 1971, Drs. Wall and Wani published their findings in a landmark paper in the May 1971 issue of the *Journal of the American Chemical Society*. Dr. Horwitz's introduction to paclitaxel was not the published data, but a request from the NCI in 1977 to study the paclitaxel compound. After requesting and receiving a sufficient quantity of Taxol from the NCI, Dr. Horwitz and her graduate student at the time, Peter Schiff, began their studies.

Dr. Horwitz remarked on the architecturally complex structure of paclitaxel, which no medicinal chemist, only nature, could design. Paclitaxel is present naturally in the bark of the yew tree, but only comprises 0.1 percent by weight. Without the side chain of carbon 13, paclitaxel is inactive, but gives rise to the precursor baccatin III, which is in high yield in the needles of the tree. Dr. Robert Holton at Florida State University was the first to devise a method for the chemical synthesis of paclitaxel from baccatin III, a process that later became known as the Holton Taxol Total Synthesis. Today, 50 percent of paclitaxel is produced by the semi-synthetic method and 50 percent using plant tissue culture, which is prepared primarily in Germany. In addition to Taxol, the commercially available products and drugs with similar mechanisms of action are Abraxane[®], Taxotere[®] (docetaxel), and Jevtana[®] (cabazitaxel).

Dr. Horwitz detailed some of the biological and molecular properties of paclitaxel. In 1979, the Horwitz laboratory demonstrated that paclitaxel blocks HeLa cells (cervical cancer cell line) in the mitotic phase of the cell cycle and induces microtubule bundling. In another series of experiments, using purified tubulin, the laboratory showed that paclitaxel enhances tubulin polymerization and rapidly stabilizes microtubules *in vitro* independent of guanosine-5'-triphosphate or temperature. Other studies revealed that paclitaxel exerts its effects on microtubules by binding beta (β)-tubulin. To better understand the paclitaxel binding site on β -tubulin, Dr. Horwitz obtained radiolabeled Taxol from colleagues and, with her laboratory, developed a photoaffinity labeling method. They confirmed that paclitaxel binds critical amino acid residues in the β -tubulin N-terminus. Simultaneously, Dr. Eva Nogales, then a postdoctoral fellow at Lawrence Berkeley National Laboratory under the direction of Dr. Kenneth H. Downing, had generated a 3D model of paclitaxel and the alpha/ β -tubulin dimer that aligns with the photoaffinity labeling data.

Regarding the path to commercialization of paclitaxel, Dr. Horwitz explained that the 1979 findings on the unique mechanism of action were critical to moving the drug forward. Although the drug quantity was scarce for preclinical studies and toxicity problems were numerous, clinical pharmacologists and oncologists worked together over the course of 5 years and determined the best treatment regimen to reduce adverse events for patients, which involves pretreating with antihistamines and steroids, then infusing the drug continuously over a 24-hour period. The NCI completed successful clinical trials in humans and signed a Cooperative Research and Development Agreement with Bristol-Meyers Squibb, which subsequently brought the drug to market. Taxol was approved by the FDA in 1992 (20 years after the seminal publication) for refractory ovarian cancer, in 1994 for breast cancer, and in 1999 for non-

small cell lung carcinoma. In 2013, the Abraxane[®]-Gemcitabine combination was approved by the FDA for metastatic adenocarcinoma of the pancreas. Nearly 15 years after the first Taxol FDA approvals, other microtubule stabilizing agents derived from natural products were developed, including ixabepilone (Ixempra[™]), discodermolide, peloruside, and laulimalide.

Dr. Horwitz highlighted recent and ongoing studies in her laboratory on β -tubulin isotypes and their distribution in normal tissues comparatively to cancer. From these studies, she concludes that tumors from different origins express distinct tubulin isotypes and that paclitaxel binds differentially to distinct β -tubulin isotypes, suggesting a role for tubulin isotypes in the tumor response.

Questions and Answers

Dr. David A. Tuveson, Roy J. Zuckerman Professor, Director of the Cancer Center, Cold Spring Harbor Laboratory, asked about the biology of natural products in inducing cell cycle arrest affecting fungi growth. Dr. Horwitz explained that the exact mechanism is not well understood but research has shown that the endoplasm affects epothilone in the fungi interacting with the tree in a symbiotic relationship.

In response to a query by Dr. Lowy on synthesizing small molecules that would be active at the binding site, Dr. Horwitz noted that her laboratory is collaborating with Swiss researchers on X-ray crystallography of various drugs that could bind the active site.

Dr. W. Kimryn Rathmell, Cornelius A. Craig Professor, Department of Medicine, Director, Division of Hematology and Oncology, Vanderbilt University Medical Center, asked whether post-translational modifications could affect drug resistance regarding isotype-altering interactions. Dr. Horwitz pointed out that the post-translational modifications at the carboxyl end microtubules were strong and undoubtedly would affect drug interactions, conferring information on resistance.

VII. CANCER GRAND CHALLENGES COLLABORATION WITH CANCER RESEARCH UNITED KINGDOM—DR. ANDREW KURTZ

Dr. Andrew Kurtz, Program Director, Office of the Director, NIH, described the Cancer Grand Challenges (GC) Initiative, which is a new NCI program conducted in collaboration with Cancer Research United Kingdom (CRUK). Dr. Kurtz welcomed members of the CRUK team to the meeting. He explained that although the NCI has a large portfolio of investigator-initiated research, the Institute also encourages various approaches to address specific problems and research gaps and challenges the research community to investigate pre-identified questions. The Provocative Questions (PQ) Initiative, which was established in 2011 to stimulate perplexing, paradoxical, or less well-known research by engaging the cancer research community, is one such approach. Beginning in FY 2012, the NCI began issuing an annual PQ RFA to support R01 and R21 awards. Aside from the PQ, the NCI also supports a number of cancer research networks in which teams of investigators are needed to approach more complex problems through combined scientific efforts.

The opportunity exists to combine the PQ problem identification process with a multidisciplinary team-based approach to attack major problems from new perspectives. The CRUK, the world's largest independent cancer research charity, launched a cancer GC program with this type of model. The CRUK mission broadly overlaps with the NCI mission, and the research funding mechanisms are similar. In addition, the CRUK actively pursues partnerships with other international organizations to maximize funding. Given the similarities, Dr. Kurtz conveyed that there is an excellent opportunity for the two organizations to collaborate on a GC program. The prior CRUK GCs align with the NCI priorities. For example, the CRUK GC on developing innovative approaches to target mitogen-activated extracellular signal-regulated kinase as a drug target is similar to the NCI RAS Initiative, with the exception of having FNLCR coordinating activities rather than self-assembled research teams. One clear advantage of a

cancer GC is the ongoing opportunity to periodically identify new challenges through input and engagement with the cancer research community.

Dr. Kurtz informed the Boards that the NCI-CRUK GC process began with a series of international consultation workshops to solicit input from thought leaders around the world; two were held in Europe in late 2019, and one is scheduled to be held in the United States at the NCI on 4 December 2019. The BSA and NCAB members were invited to attend. A cancer GC Award Panel, composed of leading cancer researchers of international standing, will synthesize all the collective inputs from the workshops to identify the final set of seven to eight GCs and then announce the public launch. The selected GC teams will submit letters of interest/short applications, which will be evaluated by the Award Panel that will select a subset of applicants to submit a full application. Once applications are received, the Award Panel will conduct a final review and make funding recommendations to the CRUK. The process from start to end spans 2 years. Dr. Kurtz acknowledged the GC Award Panel's consists of 12 members, five representatives from the United Kingdom, four from the United States, and three from other countries.

The NCI will partner with the CRUK to co-fund approximately four GC awards per biennial funding round (i.e., 3 rounds). The NCI funding will be awarded using the NIH Other Transactions Authority (OTA) mechanism. Funded teams will sign a master Funding and Collaboration Agreement co-developed by the CRUK and the NCI. All partnership decisions will be approved by a Joint Steering Committee comprising CRUK and NCI leadership. The governance structure will consist of a Virtual Core Team that will include both CRUK and NCI staff who will be responsible for coordinating the activities across both organizations and providing recommendations to the Joint Steering Committee. The CRUK will serve as operational manager for the joint program and coordinate activities of the GC Award Panel. The NCI will have an opportunity to engage with the panel.

Operationally, the NCI envisions funding each of the successful teams and will co-fund every institution on each cancer GC team in a 50 percent match of direct costs with the CRUK. The NCI also agreed to support full indirect costs for its portion of the award to all U.S. institutions on a GC team but not for non-U.S. institutions. The CRUK has agreed to support 10 percent indirect costs in addition to its direct costs to U.S. institutions. The CRUK also does not plan to fund any indirect costs for non-U.S. institutions. The estimated total annual costs to the NCI for the four GC awards is \$15 million. To maintain the balance in funding the NCI portfolio with other NCI ideas from the community initiatives, the cancer GC awards and the PQ awards will be funded on alternating years beginning in FY 2022.

Questions and Answers

Dr. Max S. Wicha, Madeline and Sidney Forbes Professor of Oncology, Director, Forbes Institute for Cancer Discovery, Founding Director Emeritus, University of Michigan Rogel Cancer Center, Professor, Internal Medicine, Division of Hematology and Oncology, University of Michigan, remarked on how the cancer GC approach reflects the direction of scientific discovery and cancer research internationally. He asked how the funds would be leveraged to support the initiative given the budget constraints, particularly for investigator-initiated research grants, and whether the success of similar efforts, such as the Stand Up to Cancer (SU2C) Initiative and other large consortia, had been evaluated. Dr. Kurtz could not speak to the metrics of the SU2C at this meeting, and noted that although the evaluation metrics for the GC are being decided, the question-setting program and community engagement efforts are more robust compared to those of initiatives, such as SU2C. Reviewing the success of the NIH P01 funding mechanism in terms of publications that resulted from the research and citations might be useful.

Dr. Tuveson suggested supporting GC R01 grants that are similar to the PQ R01s that will provide opportunities to work on important cancer topics internationally and address the RPG pool

funding needs. Dr. Bar-Sagi, BSA Chair, suggested issuing GC awards higher than the principal investigator funding cap.

Dr. Howard J. Fingert commented on the NCI's strengths, investments, and research directions and the CRUK's experience in interventional studies, metrics, statistical approaches and refinement in such specialized methods as rank-preserving structural failure time models and inverse probability of censoring weighted analyses. He asked about efforts to review the CRUK lessons learned regarding long-term gains for the GC investments that would be separate from the discrete science experiments. Dr. Kurtz called attention to the ongoing negotiations with the CRUK subsidiary organization, Cancer Research Technologies, on coordinating commercialization and intellectual property outcomes expected to result from the GC awards. He acknowledged that opportunities exist for the NCI and CRUK to exchange learning experiences in this joint program.

In response to a query by Dr. Anna D. Barker, Dr. Kurtz confirmed that the NIH, not the NCI, OTA mechanism would fund the GC. Dr. Baker suggested reviewing and potentially leveraging similar organizations to the CRUK that are located in the United States for the GC.

Motion. A motion to concur with establishing the Cancer Grand Challenges Initiative, a new NCI program in collaboration with Cancer Research United Kingdom (CRUK), was approved unanimously

VIII. FOREIGN INFLUENCES ON RESEARCH INTEGRITY—DR. MICHAEL LAUER

Dr. Michael Lauer, Deputy Director for Extramural Research, Office of the Director, NIH, described three issues the NIH has been made aware of in the past few years pertaining to the impact of foreign influences on research integrity: shadow laboratories and undisclosed Chinese employment and grant research support; undisclosed financial conflicts of interest; and peer review breaches.

Shadow Laboratories/Undisclosed Chinese Employment/Grant Research Support. In the January of 2018 issue of *Nature*, a report on China's Thousand Talents Plan (TTP) suggested that this 10-year program was one in which promising scientists could obtain research funding and then discussed how out-migration (i.e., expatriate or expat) scientists were being lured back and how highly skilled foreign researchers were being recruited. The report indicates that to obtain funding from a foreign source, the scientist must secure employment in a foreign institution, particularly a Chinese institution. The NIH has since reviewed TTP applications, which ask questions about former and proposed employment status and are open to Chinese scientists younger than age 55 and foreign scientists younger than age 65. The focus is on scientists with an established research track record outside of China, most of whom have been highly successful in securing substantial NIH funding. All TTP applications are routed through the Chinese university employer.

An in-depth report titled "China's Influence on America's Talent" published by the Hoover Institution Press further describes the problem and refers to the TTP as a way of obtaining nontraditional collectors, referencing the recruitment of leading overseas scientists. Official websites identified hundreds of U.S. corporate employees, academics, and government officials who were employed through the TTP. In many cases, these individuals do not disclose receiving TTP funds to their employers. For the NIH, in nearly all cases, American employers became aware that their scientists were employed through the TTP only after they were quizzed. U.S. government employees are allowed to work only for the U.S. government; their employment by a foreign government is illegal. In a successful recruitment effort that is clean (e.g., fair and legal), a scientist working at an American university is recruited, accepts employment, leaves his or her current position, is no longer receiving a salary or being represented on grants to the NIH, and then relocates to the Chinese university. In the TTP recruitment efforts, a scientist is recruited from an American university to a Chinese university but without complete severance. Laboratories are maintained in both places and are similar in research focus (i.e., shadow laboratories).

The American university employer is unaware of the dual assignments and continues to pay the scientists who appear eligible for NIH funding.

Obtaining copies of signed contracts between scientists and Chinese institutions and reviewing the acknowledgement section of publications are two ways that the NIH was made aware of the violations. Within the copies of signed contracts, common features offered are time commitments (e.g., 1 to 3 months or fulltime), substantial research funding, laboratory space, equipment, personnel, signing bonuses, and deliverables, none of which are disclosed to the American university. These employment agreements undoubtedly create conflicts of commitment and conflicts of interest. Similar to American universities, scientists at Chinese universities are eligible to apply for grants. Undisclosed grants were discovered in the acknowledgement of U.S. publications. Investigators cited support from such entities as the TTP, National Natural Science Foundation of China, or the National Basic Research Program of China without any mention of an affiliation to a Chinese institution. The U.S. grant funded by the NIH and the foreign grant often are duplicates in scope and specific aims. The investigators are not disclosing a second grant. Some institutions have refunded the NIH for duplicate grants, and at least one guilty plea has led to an indictment for a similar incident involving a National Science Foundation (NSF) grant.

Undisclosed Financial Conflicts of Interest. Dr. Lauer presented one example now in the public press. A Chinese company, KangRui Biological Pharmaceutical Technology, founded by a University of California at San Diego (UCSD) ophthalmologist and geneticist develops tools for ophthalmological research. The company was worth \$11.7 M in 2017 and at the time that this report was released, the founder of the company had 49 percent equity interest in the company, and his wife had 27 percent. In published articles, the founder failed to list the company as an affiliation and declared no competing interests. An American philanthropist who was contributing funds to the company founder also to develop research tools was not aware of the Chinese company. The scientist resigned his position at UCSD. In addition to undisclosed business ties and academic affiliations, the scientist was having problems with the FDA regarding several human subjects research violations. The NIH has observed other cases of scientists who had significant equity interest in Chinese-based companies that were not disclosed to their American institution or the NIH. Some scientists obtained patents in China for work that likely was linked to NIH funding and research.

Peer Review Breaches. Dr. Lauer reported that an MD Anderson researcher was alleged to have emailed NIH grant applications to colleagues in China and instructed recipients to keep the information confidential. In another case, the researcher sent NIH grant applications to a department in the National Cancer Center/Chinese Academy of Medical Sciences. The American scientist obtained confidential NIH grant applications legitimately to support serving on a peer review committee. Law enforcement assisted the NIH in uncovering the breach. In another case, American scientists delivered data and samples to entities in China without any legal documentation (e.g., a material transfer agreement).

Dr. Lauer summarized that regardless of the problem, in all cases, the bottom line is theft, not collaboration, and pointed out that this theft encompasses many types of thievery, including: 1) employee theft when recruitment efforts are not clean and legitimate, 2) theft from the public in the distorted NIH funding, 3) theft of data in the illegal transfer of information, 4) theft of proprietary information from undisclosed conflicts of interest, and 5) theft of nascent ideas from peer review breaches.

Other NIH Preliminary Observations. Dr. Lauer informed the Boards that the NIH has contacted more than 70 institutions concerning 140 scientists across the United States, most of whom are involved in preclinical research. Roughly 75 to 80 percent of the cases reviewed showed discrepancies and indications of serious noncompliance. Despite documentation, denials of any wrongdoing persist. Dr. Lauer remarked on the growing institutional awareness about the issues, noting that many universities are posting comments governing international relationships and activities, as well as foreign influence and ethics, on their websites. Addressing foreign influences on research integrity has evolved into a government-wide effort. To date, the NIH has referred 24 cases to the HHS Office of Inspector General

for further investigation. The NIH is working closely with the Federal Bureau of Investigation (FBI), Department of Justice, and the Director of National Intelligence to resolve these problems. The NIH also is working with such non-federal organizations as the Council on Governmental Relations, Association of American Universities (AAU), Association of Public and Land-grant Universities (APLU), and the National Academy of Sciences on outreach.

Questions and Answers

Dr. Jaffee, NCAB Chair, asked whether other countries besides China were recruiting U.S. investigators to conduct research. Dr. Lauer replied that other foreign talent recruitment programs exist and participation by U.S. scientists is sparse, but influences from China are the most frequently observed by the NIH and appear to be a systemic effort.

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 whether scientists found in violation of the laws discussed were being prosecuted to the extent of the law. Dr. Lauer explained that prosecutions and imprisonments for violators have occurred at the NSF and the DOE for similar cases and encouraged attendees to continue paying attention to actions the NIH will take on future cases.

Dr. Barker remarked on the long-standing relationship between HHS and China, the fact that many members of the Chinese oncology community were trained in the Cancer Centers, and information freely passing between the two groups. She asked whether the TTP issues were affecting the science. On the NIH level, Dr. Lauer emphasized that the impact to the overall science ecosystem is not substantial given that only 140 of the 30,000 NIH-supported scientists are under investigation. Dr. Sharpless added that the NCI and other ICs have joint programs with international scientists that are working well, such as the U.S.-China Program for Biomedical Collaborative Research. He conveyed NCI's hope of continuing collaborations with all countries that are conducting good cancer research, but the not at the cost of research integrity.

Dr. Andrea A. Hayes-Jordan asked about methods of broadly disseminating this information to academic and research institutions. Dr. Lauer called attention to outreach efforts within the government in the OSTP and its National Science and Technology Council addressing this topic. Other organizations including the AAU, APLU, and the Association of American Medical Colleges also have engaged in outreach to the research community and are sharing best practices with institutions. The NIH and other agencies have met with key groups and presented this information. Dr. Lauer also noted that he testified at the Senate Homeland Security and Government Affairs Committee hearing on "Securing the U.S. Research Enterprise from China's Talent Recruitment Plans" and was joined by representatives from the FBI and the DOE. Dr. Sharpless added that Dr. Francis S. Collins, Director, NIH, sent letters in the spring of 2019 relaying the issues to each U.S. academic institution funded by the NIH.

Dr. Francis Ali-Osman, Margaret Harris and David Silverman Distinguished Professor of Neuro-Oncology Research, Professor Emeritus of Neurosurgery, Duke University Medical Center, inquired about the process to identify a violation given that concerns of targeting specific investigators and/or institutions have surfaced. Dr. Lauer explained that the FBI and whistleblowers have brought cases to the attention of the NIH. The most common way of identifying a violation is from NIH staff review of publications in which funding sources are cited. He pointed out that the NIH is aware of the concerns on profiling and targeting and noted some of the violations were reported by researchers. Not all scientists in question are Chinese; the NIH is observing that many outstanding foreign scientists being lured back are expat scientists.

In response to a query by Dr. Fingert on structured processes to disseminate this information (e.g., through a blog or newsletter) similar to the FDA Office of Scientific Investigations findings on

clinical trial conduct that would be proactive, Dr. Lauer commented that the NIH is coordinating with the OSTP on the messaging that would be representative of all areas of the government (e.g., computer science, defense, energy, and physics), not just biomedical research.

IX. ONGOING AND NEW BUSINESS—DRS. ELIZABETH M. JAFFEE AND DAFNA BAR-SAGI

NCAB *ad hoc* Subcommittee on Population Science, Epidemiology, and Disparities.

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, Chair of the NCAB *ad hoc* Population Science, Epidemiology, and Disparities Subcommittee, presented the report of the 2 December 2019 meeting. The NCI Director, Dr. Sharpless, and Principal Deputy Director, Dr. Lowy, attended the meeting. The Subcommittee was updated on the implementation of the recommendations from the *ad hoc* Working Group on Strategic Approaches and Opportunities in Population Science, Epidemiology, and Disparities detailed in the June 2019 final report to the NCI on the extramural cancer epidemiology cohort studies. This working group has completed its charge and will be inactive. A new working group will need to be established to address the new topic of disparities in the NCI. The Subcommittee heard presentations from Dr. Peter Ogunbiyi of the Center for Research on Cancer Health Disparities regarding diversity cancer training and from Dr. Emanuel Taylor regarding the annual Minority Health and Health Disparities report. The NIH/NCI definition of cancer-related disparities also was discussed. After a brainstorming session, the Subcommittee drafted a charge for a new NCAB *ad hoc* Cancer Disparities Working Group to 1) identify gaps in the NCI portfolio by populations across the cancer continuum and 2) provide recommendations to the NCI about ways to address those gaps. Drs. Paskett and Winn will contact Subcommittee members to assess their interest in serving on the new Working Group.

Motion. A motion to accept the report of the 2 December 2019 NCAB *ad hoc* Population Science, Epidemiology, and Disparities Subcommittee meeting and to concur on establishing an NCAB *ad hoc* Working Group on Cancer Disparities was approved unanimously.

NCAB Subcommittee on Clinical Investigations. Dr. Peter C. Adamson, Chair, COG, Alan R. Cohen Endowed Chair in Pediatrics, Children’s Hospital of Philadelphia, University of Pennsylvania, and Chair of the NCAB Clinical Investigations Subcommittee, presented the report of the 2 December 2019 meeting. The NCI Director, Dr. Sharpless, and Principal Deputy Director, Dr. Lowy, attended the meeting. The Subcommittee was updated by CTEP’s Associate Director, Dr. Margaret Mooney, on the Adult and Pediatric MATCH trials. Dr. Adamson noted the early lessons emerging from the Adult MATCH: the frequency of mutations of interest ranging from 0 to 3.5 percent is higher than projected, and the infrastructure of the NCI’s work with the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG ACRIN) and NCTN was well executed. He emphasized that the Subcommittee and other attendees agreed that the nearly 7,000 well-annotated biospecimens from the Adult MATCH trial, representing 15 percent of cancer patients, will be a valuable resource for the scientific research community. For the Pediatric MATCH trial, 10 percent of patients enrolled, and one early finding is that the hit rate is higher than projected for mutations of interest. The Subcommittee was also updated on the NCI’s continued investments and plans for future basket/umbrella trials in the NCTN, including the new precision medicine initiatives: Combination (Combo) MATCH Trial, AML/Myelodysplastic Syndromes (MDS) Basket Trial, and the ImmunoMATCH (iMATCH) Trial.

Questions and Answers

In response to a query on knowledge gained from the targeted therapy studies, the lack of efficacy, and the follow-up, Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, reminded the Boards that the initial intent with the available funds was to perform genomic sequencing of the Adult MATCH trial patient specimens using a small panel of genetic mutations. With

additional funds, the process has been expanded to perform whole-exome and RNA sequencing of these samples. Dr. Doroshov pointed out that the lessons learned about treatment and the spectrum of cancers studied have been significant and will be reported at a future meeting. A MATCH Trial ECOG ACRIN committee evaluates all requests for samples for correlative studies, and interested investigators are invited to contact Dr. Doroshov for further details.

Dr. Cheryl L. Willman, The Maurice and Margaret Liberman Distinguished Endowed Chair in Cancer Research, University of New Mexico (UNM) Distinguished Professor of Pathology, UNM School of Medicine, Director and CEO, UNM Comprehensive Cancer Center, UNM, inquired on the race/ethnicity of the MATCH specimens and the explanation for the differences in mutation frequency from the projected values. Dr. Doroshov explained that the specimens/patients matched the communities from which they were collected/recruited, but could not speak to the actual percentage of minority specimens in the biorepository. He noted that soon-to-be-published data show that the biopsy of metastatic disease revealed mutational profiles that are different from The Cancer Genome Atlas (TCGA), particularly for colorectal cancer and cholangiocarcinomas. Dr. Adamson added that the Pediatric MATCH did reasonably well with diversity in the specimens, but can stand to be improved.

Motion. A motion to accept the report of the 2 December 2019 NCAB Clinical Trials Subcommittee meeting was approved unanimously.

BSA *ad hoc* Subcommittee on HIV/AIDS Malignancy. Dr. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy (OHAM), Office of the Director, NCI, Executive Secretary, BSA *ad hoc* HIV/AIDS Malignancy Subcommittee, presented the report of the 24 May 2019 meeting. The Subcommittee reviewed the recommendations of the *ad hoc* Working Group on Immunology of Therapies & Vaccines and Research Structure, which were reported at the 10 June 2019 Joint Board meeting. Dr. Yarchoan referred members to the detailed meeting summary contained in the Boards book.

Motion. A motion to accept the report of the 24 May 2019 BSA *ad hoc* HIV/AIDS Malignancy Subcommittee meeting was approved unanimously.

Future Agenda Items/Other Business. The BSA and NCAB members were asked to forward any suggestions for potential future agenda items to Drs. Gray, Jaffee, or Bar-Sagi. Dr. Jaffee called attention to the annual BSA concept review report, including the archived reports of prior years and information on PARs and research and development contract concepts, all of which can be accessed from the members-only website. Printed copies are available upon request from Dr. Gray and DEA staff.

X. RFA/COOP. AGR./RFP AND PAR CONCEPTS—NEW AND RE-ISSUE—NCI STAFF

Division of Cancer Control and Population Sciences (DCCPS)

Research to Reduce Morbidity and Improve Care for Pediatric and Adolescent and Young Adult (AYA) Cancer Survivors (New RFA) (Clinical Trial Optional)—Dr. Danielle Dae

Dr. Danielle Dae, Program Director, DCCPS, presented an RFA concept on research to reduce morbidity and improve care for pediatric and AYA cancer survivors. Dr. Dae stated that treatment success in recent years for pediatric and AYA cancer patients has led to improved survival for these patients, resulting in a growing population of survivors. Dr. Dae emphasized that SEER data estimates that more than 630,000 cancer survivors in the United States are age 39 or younger. Consequently, this improved survival is accompanied by a lifetime of adverse events (AEs) to the extent that two-thirds of survivors of childhood cancer have reported at least one chronic health condition. These AEs, physical, psychosocial, and/or behavioral, can involve many of the body's organ systems. Observational studies reveal that childhood cancer survivors have health care delivery challenges, such as unmet needs for long-term follow-up; continuity of care across multiple providers, especially at the transition of care from

pediatric to adult; and follow-up care often delivered by a provider unfamiliar with the late effects of cancer.

Congress recognized this growing population and their needs and passed the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act in 2018 to strongly encourage research in this area. This RFA broadly aligns with the STAR Act's six priority areas, with consideration of health disparities, minorities, and other medically underserved populations. It also expands NCI's initial and rapid response to the STAR Act legislation, i.e., via RFA-CA-19-033, and in conjunction with the first RFA will build a network of R01/R21 researchers focused on childhood cancer morbidity and improving care for these patients.

Subcommittee Review. Dr. Martine F. Roussel, St. Jude Children's Research Endowed Chair in Molecular Oncogenesis, Full Professor, Department of Molecular Sciences, The University of Tennessee, Full Member, Department of Tumor Cell Biology, St. Jude Children's Research Hospital, expressed the Subcommittee's strong enthusiasm and support of the RFA concept. Dr. Roussel remarked on how this RFA demonstrates NCI's continuing efforts to implement the STAR Act. The Subcommittee lauded the NCI for identifying this need and prioritizing funding for pediatric and AYA cancer survivors research.

The first-year's cost of the one-time issuance is estimated at \$5 M for 12 to 14 R01/R21 awards in two receipt dates of \$25 M, with a total cost of \$50 M for 5 years.

Questions and Answers

In response to a query, Dr. Dae confirmed that secondary malignancies, which are serious concerns for these survivors, are one of the AEs that will be included in the scope of the RFA.

Dr. Lacey asked about the RFA's approach to addressing long-term effects in AYA patients as they transition the health care system into adulthood. Dr. Dae noted that the population of interest is patients diagnosed between the ages of 0 to 39 years, but the NCI is not operationally defining a cutoff age for proposals because patients are surviving longer. The RFA is responsive to proposals focusing on any aspect of post-treatment and persistent issues for these patients.

Motion. A motion to concur on the DCCPS's new RFA entitled "Research to Reduce Morbidity and Improve Care for Pediatric and Adolescent and Young Adults (AYA) Cancer Survivors (Clinical Trial Optional)" was approved unanimously.

Division of Cancer Biology (DCB)

Metastasis Research Network (New RFA/Coop. Agr.)—Dr. Joanna Watson

Dr. Joanna Watson, Program Director, DCB, presented an RFA concept to establish a Metastasis Research Network (MetNet). Dr. Watson informed members that metastasis accounts for the vast majority of deaths in patients with solid tumors; however, therapeutic strategies to manage metastatic disease are lacking. Although considered late, end-stage in the metastatic cascade, evidence suggests that metastasis can occur early and often and consists of two components: early dissemination and concurrent overlapping routes. Dr. Watson detailed the challenges in current metastasis research and noted the need and the gap in research: a new view of metastasis that accounts for the dynamic, nonlinear, multiscale physiological interactions required for tumor cell dissemination, colonization, growth, and drug resistance. In addition, opportunities exist to advance metastasis research to the extent that new viewpoints are permeating within the metastasis research community and new approaches and tools are emerging.

This RFA is proposing to establish a MetNet of multi- and interdisciplinary Research Centers (U54 funding mechanism) to focus on multiple metastatic cascade themes simultaneously. An administrative core and shared resource cores will support each MetNet Research Center. This RFA is positioned to enhance the NCI metastasis research portfolio, which has remained stagnant over the past 5 to 10 years, and encourage new researchers to enter the field.

Subcommittee Review. Dr. Mary C. Beckerle, Chief Executive Officer, Huntsman Cancer Institute, Jon M. Huntsman Presidential Endowed Chair, Distinguished Professor of Biology and Oncological Services, Associate Vice President of Cancer Affairs, The University of Utah, expressed the Subcommittee's strong support of the RFA concept, which addresses an unmet medical need. Dr. Beckerle commented on the fragmentation of metastasis research efforts to date and noted how this RFA provides an approach to coalesce some of these distinct areas into a concerted effort. The Subcommittee expressed that the RFA addresses a critical area in cancer research, fills a scientific and funding gap, leverages the efforts of the Cancer MoonshotSM, and provides an opportunity for significant intellectual gains. The NCI was encouraged to consider a long-term sustainability plan for the MetNet that extends beyond a second funding renewal.

The first-year's cost of the one-time issuance with two receipt dates in FY20 and FY21 is estimated at \$7.5 M for five U54 awards, with a total cost of \$37.5 M for 5 years.

Questions and Answers

Dr. Wicha commented on the overall clinical relevance and encouraged interrogating micro-metastasis in addition to the primary tumor, and Dr. Vonderheide suggested leveraging the MATCH Trial metastatic tumor specimens to answer research questions in the MetNet.

Dr. Roach suggested expanding the scope of the MetNet and the RFA to include other areas that could address the differences in therapeutic responses between patients, such as prophylactic radiation and stimulation of the immune response (i.e., abscopal effect).

Motion. A motion to concur on the Division of Cancer Biology new RFA/Coop. Agr. entitled "Metastasis Research Network" was approved unanimously.

Division of Cancer Control and Population Sciences (DCCPS)

Addressing Gaps in Knowledge Utilizing Cancer Survivor Cohort Studies (No Clinical Trial Options) (New RFA)—Dr. Joanne Watters Elena

Dr. Joanne Watters Elena, Program Director, DCCPS, presented an RFA concept on addressing knowledge gaps using cancer survivor cohort studies. Dr. Elena indicated that prospective cohort studies provide important information about key factors and cancer outcomes among survivors. The results from these studies can inform interventions, clinical guidelines, and patient management to mitigate adverse health outcomes. A DCCPS portfolio analysis of NCI-supported cancer survivor cohort studies identified three gap areas: less common cancer sites, racial/ethnic or otherwise diverse cancer survivors, and late effects of newer treatments. The purpose of this RFA is to support research to identify key factors that affect outcomes for cancer survivors in new prospective studies, and will use the bi-phasic UG3/UH3 funding mechanism. Dr. Elena noted that this RFA aligns with the recommendations of the *ad hoc* Working Group on Strategic Approaches and Opportunities in Population Science, Epidemiology, and Disparities outlined in its June 2019 final report to the NCI on the extramural cancer epidemiology cohort studies.

Subcommittee Review. Dr. Carol E. Ferrans, Harriet Werley Endowed Chair for Research, Professor, Department of Biobehavioral Health Sciences, College of Nursing, University of Illinois

Chicago, expressed the Subcommittee’s enthusiasm and support for the RFA concept. Dr. Ferrans stated that the Subcommittee appreciates NCI staff responses to their 12 recommendations, particularly on funding research that produces the most valuable cohort and requires detailed information on treatment exposure (e.g., specific agents and/or cumulative doses). In future budget requests, the NCI could consider a creative use of study biospecimens, linking to collaborative initiatives and expanding beyond U.S. populations to include low- to middle-income countries (LMICs).

The first-year cost of the one-time issuance is estimated at \$3.9 M for three UG3 awards for Years 1 and 2, \$7.5 M for three UH3 awards for Years 3–6, with a total cost of \$37.8 M for 6 years.

Questions and Answers

In response to queries on the potential RFA outcome to build a longitudinal cohort and its impact on similar RFAs and/or PARs, Dr. Elena explained that the intent of a 6-year funding cycle is to establish the necessary foundation to support all cohort studies. The NCI will continue to support current cohort-related RFAs and PARs.

Dr. Sylvia Katina Plevritis, Professor, Department of Radiology and Biomedical Data Science, Co-Chief, Integrative Biomedical Engineering Informatics at Stanford (IBIIS), Stanford University School of Medicine, suggested expanding the RFA scope to include disease recurrence studies.

Motion. A motion to concur on the DCCPS’s new RFA entitled “Addressing Gaps in Knowledge Utilizing Cancer Survivor Cohort Studies (No Clinical Trial Options)” with the inclusion of recurrence studies was approved unanimously.

Office of the Director (OD)

Strengthening Institutional Capacity to Conduct Global Cancer Research (new RFA)— Dr. Sudha Sivaram

Dr. Sudha Sivaram, Program Director, OD, presented an RFA concept on strengthening the institutional capacity to conduct global cancer research, which aligns with the recommendations of the NCAB *ad hoc* Working Group on Global Health as outlined in its August 2018 final report to the NCI. Dr. Sivaram explained that Low and Middle-Income Countries (LMICs) have a disproportionate cancer burden compared to high-income countries, which is likely to continue in the future decades, suggesting unique opportunities to advance cancer knowledge and research in these settings. Global cancer research also can help to inform or address cancer health disparities in the United States and other high-income settings.

Dr. Sivaram emphasized that these opportunities are not being pursued because of a lack of a trained global cancer research workforce and highlighted two recent reports on global oncology addressing this issue. The NCI CGH-American Society of Clinical Oncology (ASCO) “2018–2019 Global Oncology Survey of NCI-Designated Cancer Centers: Summary Report” revealed that of the 67 Cancer Centers responding to the survey, five reported having global training programs for more than 2 days annually. ASCO’s Academic Global Oncology Task Force in its September 2018 report “Global Oncology: Formalizing a Career Path in Building a Better World” recommended that training be central to advancing the global oncology field from informal and voluntary activity to a rigorous academic discipline.

This RFA is proposing an Institutional Research Training Grant (D43) that would be awarded to a U.S.-LMIC collaboration to support training global cancer researchers (both pre- and postdoctoral) and developing multidisciplinary global cancer research programs. The RFA also will address the gap in the NCI research portfolio and the demand from the cancer research community.

Subcommittee Review. Dr. LeBeau, Arthur and Marian Edelstein Professor of Medicine, and Director, University of Chicago Comprehensive Cancer Center, the University of Chicago, expressed the Subcommittee's strong support for the RFA concept. Referencing the NCI CGH-ASCO report, Dr. LeBeau noted that the Subcommittee was overwhelmed by the data indicating the need for a global cancer research training program. In fact, 47 percent of Cancer Centers have formal global oncology training programs, of which, only 15 percent have capacity-building and training applicable to LMICs. The Subcommittee recognizes that Cancer Center funding and philanthropic efforts are not adequate to support building a global oncology workforce and was impressed with NCI's innovative approach in the use of the D43 mechanism.

The first-year cost for the one-time issuance with two receipt dates in FY21 and FY22 is estimated at \$1.08 M in Year 1 and \$1.89 M in Years 2–5 for seven D43 awards, and \$810 K in Year 6, with a total cost of \$9.45 M for 6 years.

Questions and Answers

Dr. Fingert suggested exploring opportunities with nonprofit organizations to partner in training initiatives to support global cancer research, particularly related to technologies.

Dr. Plevritis suggested highlighting computational data science in the RFA as one area of training for new investigators supporting cancer research in LMICs and leveraging data available in the public domain as part of the training.

Motion. A motion to concur on the Office of the Director's new RFA entitled "Strengthening Institutional Capacity to Conduct Global Cancer Research" was approved unanimously.

Division of Cancer Prevention (DCP)

Addressing a "Last Mile" Problem in Cervical Cancer Screening (New RFP)— Dr. Vikrant Sahasrabudhe

Dr. Vikrant Sahasrabudhe, Program Director, DCP, presented an RFP concept to address a problem in cervical cancer screening, i.e., bridging the gap in health care and delivery. Dr. Sahasrabudhe informed members that although cervical cancer is one example of a success in cancer prevention, it still is not completely prevented. In the United States, more than 13,000 women are newly diagnosed each year, and more than 4,000 die annually. Prophylactic human papillomavirus (HPV) vaccines are highly effective against cervical cancer, but the full public health impact of national vaccination programs will not be realized for at least another generation. Roughly 50 percent of all incidences of U.S. cervical cancer occurs in women who have not been screened, have been infrequently screened, or do not participate in routine screening, which can be considered a "last mile" problem and a significant cancer health disparity. Concerted efforts are needed to address this problem and to reduce, and eventually eliminate, cervical cancer as a public health problem in the United States.

Regarding current U.S. guidelines for cervical cancer screening in average-risk asymptomatic women, the U.S. Preventive Services Task Force recommends primary HPV testing or the Papanicolaou test (Pap test) as preferred options for women between ages 30 and 65 but not co-testing (e.g., HPV plus Pap test). Despite the availability of these screening options, CDC reports that the utilization of cervical cancer screening remains suboptimal for nearly 3 out of every 10 women, regardless of insurance coverage. Women who were less likely to be screened include those of lower socioeconomic status and lower education attainment; racial/ethnic minorities and foreign-born women; and residents of rural counties with geographic inaccessibility to adequate screening services (e.g., the Appalachia, deep South, U.S.-Mexico border regions, Native American reservations, and Pacific/outlying islands).

A solution to improving cervical cancer screening is self-collection of samples by women (i.e., self-sampling) for HPV testing, which provides the opportunity and ease of collection. Self-sampling, which is not a new concept, has been implemented in organized cervical cancer screening programs throughout Europe, and several studies have shown clear advantages and high patient acceptability of using this approach. Currently, in the United States, the self-sampling strategy for HPV testing has not been incorporated into clinical guidelines primarily because of a lack of an FDA-approved method establishing a standard.

The goal of this RFP is to expand the current FDA-approved indication of use for HPV tests to include prescription-based self-sampling of cervicovaginal specimens for HPV testing. The aim is to develop a public-private partnership among federal/HHS agencies, industry stakeholders, and academic institutions, as well as professional societies and clinical practice guideline organizations, to plan, design, and conduct an FDA registrational screening trial. Participants—5,000 women ages 25 to 64, from diverse clinical settings, with varying HPV detection rates—will be enrolled in the trial. This RFP is proposing to conduct the trial through a Research and Development (R&D) contract and to fund two distinct components: a data management, auditing, and coordinating center (DMACC); and clinical sites for participant enrollment. The NCI will have the role of conducting, monitoring, and analyzing results of this trial and for maintaining the data master file to be submitted to the FDA.

Subcommittee Review. Dr. Kenneth C. Anderson, Kraft Family Professor of Medicine, Harvard Medical School, Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, expressed the Subcommittee’s enthusiasm and strong support for the RFP concept, which aims to merge the science and medicine of this issue to improve health. Dr. Anderson commended Dr. Lowy for his pioneering, seminal work that has enabled improved methods for cervical cancer screening and now vaccinations and prevention. He emphasized that the need for this RFP is obvious and that the NCI is the appropriate body to oversee the solutions to this “last mile” problem and engage major stakeholders noncompetitively toward a common goal. A collaboratively designed clinical trial is key, and having clinical sites that recruit participants representative of the cancer disparity is critical. The Subcommittee further emphasized requesting in the RFP that the clinical sites emphasize follow-up methods for navigating care for patients in fragmented health care systems after initial cervical cancer screening and encouraging partnerships that address engagement and access.

The R&D contract cost is estimated at \$1.5 M for a DMACC and \$4.5 M for five to six clinical sites, with a total cost of \$6 M for 3 years.

Questions and Answers

In response to a query, Dr. Sahasrabuddhe confirmed that patient instruction materials, particularly for HPV sampling kits, have been translated into languages other than English.

Dr. Rathmell asked about examples of successful NCI partnerships with industry of self-sampling models that could be leveraged. Dr. Sahasrabuddhe noted that the FDA Center for Devices and Radiological Health is partnering with National Institute of Allergy and Infectious Diseases to conduct a trial evaluating a nontraditional sampling approach for sexually transmitted diseases, which is one model the NCI could review. Dr. Mark C. Schiffman, Senior Investigator, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics (DCEG), added that self-sampling kits are being evaluated in a trial in Brazil. Two industry partners are supporting the DCEG and this trial and have worked out many of the legal issues.

Dr. Susan Thomas Vadaparampil commented on the missed opportunity if health care delivery is not systematically addressed and included in the RFP.

Motion. A motion to concur on the Division of Cancer Prevention’s (DCP) new Request for Proposal (RFP) entitled “Addressing a ‘Last Mile’ Problem in Cervical Cancer Screening” was approved unanimously.

Division of Cancer Treatment and Diagnosis (DCTD)

Towards Translation of Cancer Nanotechnology Interventions (R01) (Clinical Trial Not Allowed) (new PAR)—Dr. Piotr Grodzinski

Dr. Piotr Grodzinski, Chief, Cancer Nanotechnology Research Branch, Program Director, DCTD, presented a new PAR concept on translating cancer nanotechnology interventions. Dr. Grodzinski noted that interest in nanotechnology has seen tremendous growth. In FY 2018 alone, the DCTD/NCI received more than 700 R01 applications and funded 49. Nanotechnology-based formulations require a unique optimization process that involves testing several nanoparticle and active pharmaceutical ingredient combinations and warrants a separate funding opportunity announcement.

Several liposomal nanomedicines of known active pharmaceutical ingredients have been approved by the FDA in the past 10 years and have been evaluated in clinical trials. The results show a significant reduction of side effects, but only modest improvement in survival. Recent studies suggest that nanotechnology-based formulations relying on next-generation non-liposomal particles can enhance the efficacy of nanotherapeutics. Clinical trials evaluating non-liposomal formulations are limited. Efforts in the preclinical stage on maturing formulations will further expand the nanotherapeutics pipeline. Dr. Grodzinski highlighted two examples of nanotechnologies that are ready for clinical trials: radiodynamic therapy using nanoscale metal-organic frameworks for head and neck and prostate cancers and intraoperative imaging with ultra-small Cornell Dots (commonly called C Dots) also for head and neck, melanoma, breast, and cervical cancers.

The purpose of this PAR is to support preclinical research on maturing nanomedicine formulations of next-generation nanoparticles with strong potential to be effective in the clinic. The goal is to prepare these nanomedicines from R01, U01, and U54 technology demonstration projects for a successful entry into the NExT Program, NCI Experimental Therapeutics Clinical Trials Network (ETCTN), and other DCTD translational efforts. Dr. Grodzinski informed the Boards that the NCI Alliance for Nanotechnology in Cancer will discontinue the U54 Centers of Cancer Nanotechnology Excellence (CCNE) program in FY 2020 and that this PAR will specially support stabilizing nanomedicine synthesis, testing (*in vivo*) in multiple animal models, and evaluating new cancer indications and drugs for mature particle concepts. The research plan will leverage the services of the FNLCR Nanotechnology Characterization Laboratory (NCL) and the Laboratory of Animal Sciences Program (LASP).

Subcommittee Review. Dr. Tuveson expressed the Subcommittee’s support of the PAR concept, which aims to develop improved medicines and diagnostic methods for cancer patients by building on the success of the liposomal formulations. He noted nanomedicines have been approved in other countries, particularly chlorophyll derivatives in Europe for prostate cancer with similar mechanisms of action as those currently in the NCI path to nanomedicine translation. Although the CCNE program is being discontinued, Dr. Tuveson noted that this PAR mechanism is one way to link senior investigators with nanotechnology programs that, with the right support and link to NCI investigators, could be advanced in the DCTD’s translation programs, such as NExT and ETCTN. Applicants will have the benefit of the FNLCR NCL and LASP services and community involvement with NCI scientists. The Subcommittee sees the PAR also as a mechanism to assist researchers in crossing the funding gap (so-called “valley of death”) necessary for advancing promising cancer therapies and technologies toward commercialization. The RFP should clarify that all researchers proposing new ideas can apply, not just U54-funded investigators who already have achieved product milestones.

Questions and Answers

Given that a critique of the U54 CCNE program was that it focused heavily on technology and engineering without adequate consideration to the biology involved, Dr. Wicha asked about plans to engage more biologists in R01 hypothesis-driven research projects for nanotechnology development. Dr. Grodzinski explained that the CCNE program, which has a 15-year history, has achieved much of what the NCI had envisioned and that the program's initial focus on engineering and technology development in Phase 1 of the research/funding was primarily in response to the demands of the nanotechnology field at that time. Subsequent phases of funding solicited proposals focused specifically on the application of these technologies to address cancer biology questions. Many of the CCNE centers with engineering leads have dual technological/oncology leadership with Cancer Center directors, and research publications have evolved over time. The NCI recognizes that future proposals should originate from a biological problem or disease rather than the nanotechnology alone, which will be emphasized in the RFP review criteria.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' (DCTD) new PAR entitled "Towards Translation of Cancer Nanotechnology Intervention (R01) (Clinical Trial Not Allowed)" was approved unanimously.

Academic–Industrial Partnerships (AIP) to Translate and Validate *In Vivo* Imaging Systems (R01 Clinical Trial Optional) (Re-Issue PAR)—Dr. Christopher Hartshorn

Dr. Christopher Hartshorn, Program Director, DCTD, presented a re-issue PAR concept for continuing the AIP to Translate and Validate *In Vivo* Imaging Systems program. Dr. Hartshorn stated that the primary requirement is the formation of a collaboration consisting of at least one academic and one industrial or private-sector company partner to identify and translate an imaging solution. The AIP program offers a unique translational funding mechanism not offered elsewhere at the NIH. In addition, the AIP, which is a 5-year partnership serves as a translational channel for other NCI programs, including the Quantitative Imaging Network, National Center for Image-Guided Therapy, and Small Business Innovation Research/Small Business Technology Transfer programs, as well as the parent R01.

Dr. Hartshorn detailed the progress, success, and accomplishments of the AIP program. Since 2013, the AIP averaged 67 applications annually; of these, 71 percent focused on human subjects research, 37 percent involved software development, and 7 percent focused on machine learning and artificial intelligence projects. Nine applications were funded each year, and the award research categories mirrored the application percentages, with the predominate focus being human subjects research. Approximately 75 percent of NCI funds were allotted to AIP academic partners and 25 percent to industry partners, with some exceptions. The amount of funds contributed from large versus medium to small companies was relatively equal. Funded imaging systems included several different modalities (e.g., positron emission topography, magnetic resonance imaging, and optical) applicable across multiple tumor types. The AIP investigators completed 28 clinical trials, were granted 82 patents, received regulatory approvals for 25 products, commercialized 29 products, and generated 350 peer-reviewed publications. Dr. Hartshorn highlighted two examples of AIP success stories: a novel imaging agent, Peptide Receptor Radionuclide Therapy (PRRT), a University of Iowa–Molecular Insight Pharmaceuticals collaboration; and a novel imaging device Quantitative Three-Dimensional (3D) Ultrasound Breast Scanner, a UCSD/University of Texas at Southwestern–Techniscan Medical Systems/Quantitative Transmission Ultrasound collaboration. A version of the PRRT, Lutathera[®], was approved by the FDA in 2018, and the 3D Breast Scanner received the 2018 FDA Breakthrough Device designation.

This PAR re-issuance will support the integration of modern computational or informatics methods (e.g., machine learning and/or predictive analytics) into preclinical and clinical imaging methods to enhance or optimize utility for detection, diagnosis, or treatment monitoring.

Subcommittee Review. Dr. Plevritis expressed the Subcommittee’s strong support for the re-issued PAR concept, which is filling a critical gap between academia and industry to enhance the translation of *in vivo* imaging technologies. She stated that the Subcommittee was impressed with the success of the AIP program and the depth of applications, and that the members were also pleased with the future research direction to incorporate machine learning.

Motion. A motion to concur on the DCTD’s re-issue PAR entitled “Academic–Industrial Partnerships (AIP) to Translate and Validate *In Vivo* Imaging Systems (R01) (Clinical Trial Optional)” was approved unanimously.

XI. ADJOURNMENT OF THE OPEN SESSION—DRS. ELIZABETH M. JAFFEE AND DAFNA BAR-SAGI

XII. NATIONAL CANCER ADVISORY BOARD (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 discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussions for which there was A potential conflict of interest, real or apparent.

XIII. ADJOURNMENT OF THE CLOSED SESSION—DR. ELIZABETH M. JAFFEE

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

There being no further business, the 14th joint meeting of the BSA/NCAB was adjourned at 5:14 p.m. on Tuesday, 3 December 2019.

Date Dafna Bar-Sagi, Ph.D., Chair, BSA

Date Elizabeth M. Jaffee, M.D., Chair, NCAB

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