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

8th VIRTUAL JOINT MEETING of the BOARD OF SCIENTIFIC ADVISORS AND NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
29–30 November 2023

Virtual Meeting
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
29–30 November 2023

The Board of Scientific Advisors (BSA) of the National Cancer Institute (NCI) and the National Cancer Advisory Board (NCAB) convened for their 8th Virtual Joint Meeting on 29–30 November 2023. The meeting was open to the public on Wednesday, 29 November 2023, from 1:00 p.m. to 3:00 p.m., and Thursday, 30 November 2023, from 1:00 p.m. to 5:06 p.m., and closed to the public on Thursday, 30 November 2023, from 12:00 p.m. to 1:06 p.m. The NCAB Chair, Dr. John D. Carpten, Director, Comprehensive Cancer Center, Director and Chief Science Officer, Beckman Research Institute of City of Hope, and BSA Chair, Dr. Keith T. Flaherty, Director of Clinical Research, Massachusetts General Hospital Cancer Center, Professor of Medicine, Harvard Medical School, presided during the open sessions. Dr. Carpten presided during the closed session. In the open sessions, the BSA considered new requests for applications (RFAs) and requests for proposals (RFPs) of new and re-issue concepts presented by NCI program staff

BSA Members

Dr. Keith T. Flaherty (Chair)
Dr. Chandrakanth Are
Mr. Timothy Babich
Dr. Suzanne J. Baker
Dr. Karen M. Basen-Engquist
Dr. Otis W. Brawley
Dr. Andrew T. Chan
Dr. Nelson J. Chao
Dr. Gloria D. Coronado
Dr. Mark P. Doescher
Dr. Chyke A. Doubeni
Dr. Shelton Earp
Dr. Jennifer R. Grandis (absent)
Dr. Dorothy K. Hatsukami
Dr. Trey Ideker
Dr. Karen E. Knudsen
Dr. Michelle M. Le Beau
Dr. Ana Maria Lopez
Dr. Karen M. Mustian
Dr. Lisa A. Newman
Dr. Raymond U. Osarogiagbon
Dr. Sylvia Katina Plevritis
Dr. W. Kimryn Rathmell
Dr. Erle S. Robertson (absent)
Dr. David Sidransky (absent)
Dr. Cornelia M. Ulrich
Dr. Samuel L. Volchenboum
Dr. Robert H. Vonderheide
Dr. Richard C. Zellars

NCAB Members

Dr. John D. Carpten (Chair)
Ms. Margaret Anne Anderson
Dr. Nilofer S. Azad
Dr. Anna D. Barker
Dr. Richard J. Boxer
Dr. Luis Alberto Diaz, Jr.
Dr. Andrea A. Hayes Dixon
Ms. Ysabel Duron
Dr. Howard J. Fingert
Dr. Christopher R. Friese
Ms. Julie Papanek Grant
Dr. Amy B. Heimberger
Dr. Nikan Khatibi (absent)
Dr. Ana Navas-Acien
Dr. Fred K. Tabung
Dr. Susan Thomas Vadaparampil
Dr. Ashani T. Weeraratna
Dr. Karen M. Winkfield

President's Cancer Panel

Dr. Elizabeth M. Jaffee (Chair) (absent)
Dr. Mitchel S. Berger (absent)
Dr. Carol L. Brown

Alternate *Ex Officio* NCAB Members

Dr. John Gordon, CPSC
Dr. Joseph R. Graber, DOE
Dr. Michelle Heacock, NIEHS (absent)
Dr. Michael Kelley, VA (absent)
Dr. Richard Pazdur, FDA (absent)
Dr. Tara A. Schwetz, NIH (absent)
Dr. Craig D. Shriver, DoD
Dr. Kerry Souza, NIOSH (absent)

Members, Scientific Program Leaders, National Cancer Institute, NIH

Dr. Douglas R. Lowy, Acting Director, National Cancer Institute
Dr. Oliver Bogler, Director, Center for Cancer Training
Dr. Philip E. Castle, Director, Division of Cancer Prevention
Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics
Dr. Henry P. Ciolino, Director, Office of Cancer Centers
Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research
Dr. Dan Gallahan, Director, Division of Cancer Biology
Mr. Peter Garrett, Director, Office of Communications and Public Liaison
Dr. Katrina A.B. Goddard, Director, Division of Cancer Control and Population Sciences
Dr. Satish Gopal, Director, Center for Global Health
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. Tony Kerlavage, Director, Center for Biomedical Informatics and Information Technology
Dr. Kristin Komschlies McConville, Acting Director, Office of Scientific Operations, NCI at Frederick
Dr. Glenn Merlino, Scientific Director for Basic Research, Center for Cancer Research
Dr. Tom Misteli, Director, Center for Cancer Research
Dr. Meg Mooney, Associate Director, Cancer Therapy Evaluation Program
Dr. Diane Palmieri, Director, Center for Research Strategy
Dr. Henry Rodriguez, Director, Office of Cancer Clinical Proteomics Research
Mr. Jeffrey Shilling, Chief Information Officer and Chief of Infrastructure and Information Technology Services Branch, Center for Biomedical Informatics and Information Technology
Ms. Donna Siegle, Executive Officer and Deputy Director for Management, Office of the Director
Dr. Dinah S. Singer, Deputy Director, Science Strategy and Development
Dr. Sanya A. 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. Robert Yarchoan, Director, Office of HIV and AIDS Malignancy
Dr. Maureen Johnson, Executive Secretary, Office of the Director

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THURSDAY, 30 NOVEMBER 2023

I. NATIONAL CANCER ADVISORY BOARD (NCAB) CLOSED SESSION—DR. JOHN D. CARPTEN

"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.C., and section 1009(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. §§ 1001-1014)."

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

Dr. John Carpten adjourned the NCAB Closed Session at 1:06 p.m.

II. CALL TO ORDER AND OPENING REMARKS—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Dr. Carpten called to order the 8th Virtual Joint Board of Scientific Advisors (BSA) and National Cancer Advisory Board (NCAB) meeting. He welcomed members of the Boards, *ex officio* members, President's Cancer Panel 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. Dr. Carpten reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Dr. Keith T. Flaherty noted that this will be his last meeting as he completes his tenure. Dr. Flaherty expressed appreciation to Dr. Gray for her work and support of these Boards. He noted that during the past 2 years, both he and Dr. Carpten witnessed Dr. Gray work behind the scenes to make these Boards function more effectively and for their intended purpose. Dr. Flaherty complimented her professionalism, commitment, and excellence in her position.

Dr. Carpten called Board members' attention to the future meeting dates listed on the agenda.

Motion. A motion to accept the minutes of the 6 September 2023 NCAB meeting was approved unanimously.

III. NCI ACTING DIRECTOR'S REPORT—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Acting Director, NCI, welcomed members of both the BSA and NCAB to the 8th Virtual Joint Meeting of these Boards. Dr. Lowy discussed recent news and updates, research and programmatic highlights, and the NCI budget outlook.

Recent News and Updates. Dr. Lowy remarked that this will be the third transition of the NCI Director since 2017. President Joseph R. Biden announced his plans to appoint Dr. W. Kimryn Rathmell, Hugh Jackson Morgan Professor of Medicine and Biochemistry, Chair, Department of Medicine, Physician-in-Chief, Vanderbilt University Medical Center, and BSA member, as the next NCI Director. Dr. Monica M. Bertagnolli, NCI Director from 2022 to 2023, is the new NIH Director.

Dr. Lowy informed the Boards of a recent NCI Memorial. Dr. Worta McCaskill-Stevens, Director of the NCI Community Oncology Research Program (NCORP) and Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), passed away on 15 November 2023. NCORP is a landmark visionary program for the NCI. In appreciation of Dr. McCaskill-Stevens for her leadership and exemplary work, Dr. Bertagnolli announced during the September NCAB meeting the establishment of the NCI Worta McCaskill-Stevens Career Development Award for Community

Oncology and Prevention Research. A notice of funding opportunity (NOFO) will be published in the near future.

Dr. Lowy highlighted several NCI updates. The reignited Cancer Moonshot℠ is a guiding light for the NCI because of its three principal goals (from least to most challenging to achieve): (1) reduce the U.S. cancer death rate by 50 percent in 25 years; (2) overcome cancer disparities; and (3) end cancer as we know it, for all people. The NCI is making progress in each of these areas. During her time as NCI Director, Dr. Bertagnolli and the Boards discussed energizing the reignited Cancer Moonshot in fiscal year (FY) 2023 with funds from the initial Cancer Moonshot. NCI's role is to ensure that these aspirational goals become feasible. The Biden Administration implemented an all-of-government approach to "ending cancer as we know it" and established the Cancer Cabinet in 2022. On 13 September 2023, the White House convened the Cancer Cabinet to advance the goals of the Cancer Moonshot. Dr. Lowy attended this meeting, and the Cabinet discussed several new initiatives, including the Advanced Research Projects Agency for Health (ARPA-H)–NCI Biomedical Data Fabric Toolbox; the U.S. Department of Veterans Affairs (VA)–NCI veterans for tobacco cessation programs; and two-way data exchange between the NCI Surveillance, Epidemiology, and End Results (SEER) program and the VA Central Cancer Registry. Further details can be found on the White House Briefing website.

The NCI has cancer research collaborations with many other U.S. government departments (i.e., U.S. Department of Defense, U.S. Department of Energy, and U.S. Department of Commerce and the VA) and U.S. Department of Health and Human Services (HHS) agencies (e.g., the U.S. Food and Drug Administration [FDA], the Centers for Disease Control and Prevention, the Health Resources and Services Administration, ARPA-H).

Dr. Lowy represented the NCI/NIH at the Cancer Survivorship Summit held 16 October 2023 at Nova Southeastern University in Davie, Florida, that was organized by Congresswoman Debbie Wasserman Schultz (D-Florida), a breast cancer survivor. First Lady Dr. Jill Biden delivered the keynote speech, and Dr. Lowy discussed cancer survivorship and its importance. The directors of the three Florida-based NCI-Designated Cancer Centers (Cancer Centers) participated in a panel discussion.

Research and Programmatic Highlights. Dr. Lowy highlighted the latest progress in cancer screening and treatment, including activities related to the Cancer Moonshot.

A recent report from the Cancer Intervention and Surveillance Modeling Network (CISNET) published in the November 2023 issue of *JAMA Network Open* revealed the number of cancer-specific deaths that could be averted per 100,000 people eligible for cancer screening. The report also called attention to the number of deaths that could be averted if there were a 10 percent increase in screening for lung, colorectal, breast, and cervical cancers, with the highest effect observed in lung cancers. Combining smoking cessation programs with screening increases the number of lung cancer deaths averted by 15 percent. Lung cancer screening rates tend to be low in underrepresented minorities. Women tend to be more represented with current lung cancer screening guidelines. Increasing screening of eligible people could help to narrow these health disparities. Dr. Lowy acknowledged Dr. Eric (Rocky) J. Feuer, Chief, Statistical Research and Applications Branch, Surveillance Research Program, Division of Cancer Control and Population Sciences (DCCPS), NCI, who is senior author of this report and conceived CISNET. This modeling network has significant impact on the NCI and all of cancer research and has informed United States Preventive Services Task Force (USPSTF) recommendations. Dr. Feuer will be retiring from the NCI in December 2023 with several noteworthy accomplishments, including co-developing the Joinpoint software for analyzing cancer rate trends and SEER*Stat for calculating incidence-based mortality. Dr. Feuer has been nominated for a Samuel J. Heyman Service to America Medal for his significant contributions to the NCI.

A systematic review published in the June 2023 issue of *Cancer Journal for Clinicians* examined social determinants of health and cancer screening intervention in the United States. The results showed

that social determinants of health–related interventions were associated with increased cancer screening rates, providing strong evidence for the importance of such interventions.

To the extent possible, the NCI is working to bring cancer care, screening, and prevention to the patient, rather than having the patient seek cancer control and treatment. The FDA has approved health care workers to perform the sampling for cervical cancer. Other countries have self-sampling as an approach to bring screening to the patient. Approximately 50 percent of patients with cervical cancer in the United States belong to under screened or underinsured populations, many of which are Hispanic. To address this health disparity, the NCI is working with the FDA and companies to conduct the Cervical Cancer "Last Mile" Initiative, which is a randomized controlled trial. The aim is to provide sufficient evidence for the FDA to approve self-sampling.

The NCI established the Cancer Screening Research Network (CSRN) to conduct trials and studies specifically related to cancer screening, and it anticipates funding multiple centers in the initial screening effort, which is the Vanguard Study for Multi-Cancer Detection.

DCCPS investigators and colleagues reported on cancer mortality rates at all cancer sites, including lung and bronchus cancer and colorectal cancer across nonpersistent and persistent poverty counties. The study groups consisted of Black/African American and White/Caucasian urban patients and Black/African American and White/Caucasian rural patients. The results, reported in the June 2022 issue of the *Journal of the National Cancer Institute*, showed higher mortality rates for Black/African American patients than for White/Caucasian patients at all cancer sites and within the rural counties, but to a lesser extent in the urban counties, regardless of poverty level. The mortality rates were higher for both groups than for the comparable (e.g., age-adjusted) urban population. For lung and bronchus, the rural mortality rates for both Black/African American and White/Caucasian patients were substantially higher than the mortality rates for comparable patients who were located in urban counties. This trend can be attributed to a combination of increased smoking in rural areas and less access to the advances in lung cancer treatment. The difference in rates was higher in the rural populations within the persistent poverty counties than within the nonpoverty counties. These trends were similar for colorectal cancer. Over the past decades, a progressive decrease of 2 percent annually in the incidence of lung cancer has been observed, primarily because of smoking cessation initiatives. The annual percentage change in mortality the last 6 years was 4.7 percent, which is twice as fast as the lung cancer incidence rates. The NCI largely attributes this to advances in cancer treatment. Several lung cancer drugs received FDA approval in the last 2 years. The speculation is that access to these drugs is lower in the rural areas than in the urban areas. Analyses are in progress to provide the needed evidence.

The My Pediatric and Adult Rare Tumor Network (MyPART), which was funded in the initial Cancer Moonshot, is an international collaboration led by the NCI Pediatric Oncology Branch (POB). More than 25 countries have enrolled more than 500 patients in the last 4 years. A detailed report on MyPART was presented by Dr. Brigitte C. Widemann, Chief, POB, Head, Pharmacological and Experimental Therapeutics Section, Senior Investigator, and Special Advisor to the NCI Director for Childhood Cancer, and Dr. Karlyne M. Reilly, Senior Associate Scientist, POB, NCI, during the September 2023 NCAB meeting and can be accessed from the NCAB website. Rare cancers represent 27 percent of cancers in the United States. More than 0.5 million (M) cancers per year in the United States are rare tumors, and 25 percent of cancer deaths can be attributed to rare cancers, which translates to 150,000 people dying annually in the United States. MyPART seeks to better catalogue patients with rare cancers to develop interventions.

Another important advancement in cancer treatment is FDA approval of the programmed death-1 receptor (PD-L1) checkpoint inhibitor atezolizumab for advanced alveolar soft part sarcoma, which was reported in the *New England Journal of Medicine*. The study is led by the NCI Intramural Research Program, and 40 percent of patients are treated at the NIH Clinical Center. Alveolar soft part

sarcoma is a rare cancer that affects mostly adolescents and young adults. This is the first time that this immune checkpoint inhibitor has been approved for use in children.

NCI Budget Outlook. Dr. Lowy reminded the BSA and NCAB members that the NCI received significant increases in its budget from FY 2017 to FY 2023, of which the initial Cancer Moonshot appropriation represented $300 M to $216 M annually. Also, during this time period, for experienced investigators, the payline was at the 10th percentile in FY 2017, which decreased to the 8th percentile in FY 2019, returned to the 11th percentile in FY 2021, and then remained stable. In addition, the NCI increased paylines for early stage investigators (ESIs) R01/R37 by 6 percent, resulting in an increase from the 12th to 17th percentile. Over the past 4 years, the NCI has increased the Research Project Grant (RPG) pool budget from 41 percent to 44 percent, but this increase has not kept pace with the number and rate of applications received.

Critical components of the interconnectedness of the NCI budget and programs include research funding, training and workforce development, resources for researchers, operating expenses, the Cancer Centers, and clinical trials. The overall goal is to improve health outcomes. Dr. Lowy emphasized that the NCI budget is not developed in a vacuum and not just within the context of the NIH, but rather is determined within the federal budget ecosystem along with many other national priorities, as defined by Congress. The FY 2024 budget is uncertain in terms of funding for the NIH and NCI. Two potential lapses in appropriation were averted. Continuing resolutions (CRs) were signed on 30 September 2023 and 17 November 2023. The current CR expires on 2 February 2024. The NCI has tentatively established interim paylines for FY 2024: 9th percentile for R01 grants to established and new investigators, 14th percentile for R01 grants to ESIs, and 9th percentile for exploratory grants (R21). Noncompeting grants (e.g., Type 2 grants) will be funded at the 90 percent level as recommended by the NIH.

The *Annual Plan and Budget Proposal for Fiscal Year 2024* (also called the Bypass Budget), released in September 2022, requested a budget of $10 billion (B), which represented a $700 M increase above the FY 2023 base budget and continued the $216 M for the Cancer Moonshot. The NCI actually received $500 M above the FY 2023 enacted budget. In September 2023, the NCI released its FY 2025 Professional Judgment Budget and proposed a budget of $11.5 B to maintain the FY 2023 paylines at the 12th percentile. To fund the noncompeting grants at 100 percent, the NCI would need to add about $250 M to the FY 2024 RPG pool. In addition, the NCI incurs $75 M to $100 M annually in increased mandatory expenses, such as costs for physical and cybersecurity, utilities, and the Center for Scientific Review.

Dr. Lowy discussed the possible impact of the proposed FY 2024 "flat" budget on NCI activities. From FY 2003 to FY 2013, the NIH received fewer increases in its budget, marking the end of the so-called budget doubling. In FY 2013, NCI's purchasing power decreased by 24 percent. Although the NCI received budget increases for 9 of the 10 years between FY 2013 and FY 2023, it has 13 percent less research buying power in 2023 than in 2003. This presents a significant gap in research that can be supported and is part of the reason that the NCI is working to do more research with less. A flat budget is not truly flat, because research costs continue to increase, and the 21st Century Cures Act funding for the Cancer Moonshot is in its final year of appropriations. This outlook may require cuts across various NCI programs. Dr. Lowy noted that he and Mr. Weston Ricks, Director, Office of Budget and Finance, NCI, have discussed the NCI budget and appropriations in various forums, including at the September 2023 NCAB meeting and in the *NCI Bottom Line: A Blog About Grants and More*. Additional information can be found on the NCI website. Dr. Lowy noted that Ms. M.K. Holohan, Director, Office of Government and Congressional Relations, NCI, will discuss the NCI FY 2024 budget further.

Questions and Answers

Dr. Karen E. Knudsen, Chief Executive Officer, American Cancer Society, Inc. (ACS), American Cancer Society Cancer Action Network (CAN), suggested exploring ways that CISNET can be used in a

whole-of-cancer community approach to create calls to action for cancer screening. Leveraging updated cancer screening guidelines, such as the ACS Lung Cancer Screening Guidelines, would be one place to start. Dr. Lowy pointed out that the ACS guidelines on expanding the screening eligibility criteria for former heavy smokers, even if 15 years or more have passed since they stopped smoking, are similar but not identical to those of the USPSTF. Having more people eligible for lung cancer screening is one way to address this health disparity.

Dr. Chyke A. Doubeni, Professor, Department of Family and Community Medicine, Associate Director, Diversity, Equity, and Inclusion, The Ohio State University Comprehensive Cancer Center, Chief Health Equity Officer, Wexner Medical Center, Director, Center for Health Equity, The Ohio State University, commented that the reignited Cancer Moonshot goals can be achieved with coordinated long-term strategies and engagement of NCI's talent pool and brain-trust. He asked about NCI's efforts to meet these goals. Dr. Lowy noted that much of the research highlights presented in his report focused on ways the NCI can consider in addressing the Cancer Moonshot goals; equitably distributing a current standard of care is one important aspect. From his perspective, solutions will extend beyond research to policy changes, and efforts will need to be implemented at scale to have an impact.

Dr. Cornelia M. Ulrich, Chief Scientific Officer and Executive Director, Comprehensive Cancer Center, Huntsman Cancer Institute, The University of Utah, was struck by the data showing both racial and geographic (rural versus urban) disparities in cancer. She asked whether the NCI could expand further analyses to broadly understand the possibilities for interventions and ways to address health disparities. Dr. Lowy explained that the NCI is focusing on two types of analyses: lung cancer and total cancers. Dr. Neal D. Freedman, Chief, Tobacco Control Research Branch, DCCPS, NCI, and Dr. Meredith S. Shiels, Senior Investigator, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics (DCEG), NCI, are leading efforts to examine survival rates for different population groups.

Dr. Otis W. Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, commented that guidelines alone will not save lives, and he noted the effectiveness of lung cancer screening. He suggested including policy needs in any communications or messages about cancer screening. Policymakers should be made aware that establishing lung screening programs without providing hospitals the additional resources, including scanners and staff with expertise, can potentially increase the health disparities.

Dr. Mark P. Doescher, Professor, Department of Family and Preventive Medicine, College of Medicine, University of Oklahoma Health Sciences Center, suggested establishing an implementation science network through the Cancer Moonshot as a nationally coordinated research network to address cancer screening in high-needs and remote rural areas.

Dr. Karen M. Mustian, Dean's Professor of Oncology and Surgery, Departments of Surgery, Radiation Oncology, and Public Health Sciences, University of Rochester School of Medicine and Dentistry, called attention to the critical need to review efforts for retaining NCI investigators beyond the first and second R01 grants, especially with the current status of NCI paylines. The NCI can consider approaches that will enable team science such that a scientist is not penalized for serving as a multiple principal investigator (MPI) on a RPG during their career. Dr. Lowy highlighted that the NCI increased the duration of the R01s from 5 years to 7 years for ESIs who were funded by payline to become R37s, which are Method to Extend Research in Time (MERIT) awards. In closed session, the NCAB reviews the ESIs' progress in the fourth year of their R01 funding and makes recommendations for converting to the R37. Approximately 90 percent of ESIs up for review have been performing very well in their research. He noted that the NCI has had discussions within the NIH about not crediting the MPI the same as an individual award, but the NCI has no control over how this is addressed.

Ms. Ysabel Duron, Founder and Executive Director, The Latino Cancer Institute, suggested investing in community-based organizations that have been effective in encouraging cancer screening in their respective communities as an approach to lessening mortality rates in underserved communities.

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

Ms. Holohan reported on NCI's congressional updates, including a status update on the FY 2024 appropriations process, as well as recent hearings and visits. In June 2023, Congress agreed on and the President signed into law the Fiscal Responsibility Act of 2023 (FRA) to suspend the debt ceiling for 2 years (until 1 January 2025) and to set spending levels for FY 2024 and FY 2025. Ms Holohan commented that the period required debt limit increases are often paired with larger budget agreements, such as the FRA legislation. The FRA caps FY 2024 nondefense discretionary spending at FY 2023 levels; except for Defense funding, which is increased by 3% (as requested in the President's Budget request), and limits FY 2025 spending to a 1 percent increase. Notably, the FRA includes a penalty – a 1% reduction to all spending categories –triggered if Congress fails to pass all 12 appropriations bills by January 1. The reduction becomes permanent if the bills aren't done by April 30th. This will hurt all categories of spending but will particularly affect Defense spending, since they will be cut 1% and forego an agreed-upon 3% increase. It is unclear whether a full-year CR would be considered "completing" the appropriations bills, thereby avoiding the penalty. Shortly after Congress passed the FRA and it was signed into law, the GOP House Freedom Caucus balked at the legislation and insisted that Republican leaders pursue steeper budget cuts to return to FY 2022 funding levels. The House Republican leadership began talking about the FRA funding levels as "a ceiling, not a floor" and insisting that Congress could choose to appropriate lower funding levels than those stipulated in the FRA. This position was not supported by Senate Republicans and was rejected by House and Senate Democrats.

On 25 October 2023, Representative Mike Johnson (R-Louisiana), a member of Congress for 6 years, became the 56th Speaker of the House. The federal government is currently funded at FY 2023 levels by a "laddered" CR, the second stopgap measure of this fiscal year, with an unusual "ladder" in which there are two different durations of funding specified for the spending bills. The first CR funded all 12 spending bills from 1 October 2023 to 17 November 2023. The second CR was enacted on 16 November 2023 and divides the funded bills into two groups with different durations of funding Group 1, which will be funded through 19 January 2024, includes the bills for Military Construction and Veterans Affairs; Agriculture; and Transportation and Housing and Urban Development. Group 2—all funded through 2 February 2024—includes the Labor, Health and Human Services, Education, and Related Agencies (Labor-HHS) (which funds the NIH); Defense; State; Commerce-Science-Justice; and four other bills. No aid for Israel or Ukraine has been included, and no provisions for border security are provided. Neither CR contained policy riders.

Ms. Holohan noted that most of the federal budget supports programs such as such as Medicare, Medicaid, the Children's Health Insurance Program, and Social Security. For the discretionary funding controlled by the House and Senate Appropriations Committees, no agreement on topline spending levels has been reached. The Senate Labor-HHS Appropriations Subcommittee is writing its spending bills to FRA levels, whereas the House Labor-HHS Appropriations Subcommittee is writing its spending bills to much lower levels. The differences are significant. . One point to note, the requirement for keeping the FY 2024 spending bills at FY 2023 levels is about the top-level funding number for all accounts. This does not mean that every single agency or even every spending bill will be cut by the same percentage. Congress can pick and choose where to apply cuts, as long as they hit the required overall funding level. There continues to be strong bipartisan support for cancer research, and NCI is hopeful that appropriators will do their best to continue to support cancer research as they have done in the past.

The FY 2024 Labor-HHS spending bills released by the House and Senate subcommittees differ in their approach to NCI funding in that the House declined to continue the $216 M appropriation for the

FY 2024 Cancer Moonshot, as it was not part of the NCI base appropriation and the mandatory funding stream authorized by the Cures Act concluded in FY 2023. In contrast, the Senate did continue this funding as part of NCI's FY 2024 budget, and also proposed an increase of $60 M to the NCI base budget.

The Senate and House appropriators will have a significant amount of work ahead of them upon return from the December recess. Congress has only a few weeks to reconcile conflicting spending levels on 12 different bills. The laddered CR creates two dates for possible government shutdowns: 19 January 2024 and 2 February 2024. In addition to different topline funding levels for FY 2024, other House and Senate conflicts include aid to Israel and Ukraine, reauthorization of foreign surveillance powers, border security, and stalled military promotions.

Congress has enacted one or more CRs in all but three of the last 46 fiscal years. The longer into the fiscal year that there is uncertainty about funding levels, the more difficult it is to plan biomedical research, both for the NCI and the grantees. Because the CR ends on 2 February 2024, that date would be the earliest that FY 2024 appropriations for NIH and NCI could possibly be settled.

Several senior members of Congress are retiring, which will result in a loss of institutional knowledge and, in many cases, members who have been longtime supporters of biomedical research. Approximately 31 House members (20 Democrats and 11 Republicans) and 6 Senators (5 Democrats and 1 Republican) have announced plans to leave office, either to retire or to seek another office. Ms. Holohan highlighted members familiar with the NCI who will be leaving office. Representative Anna Eshoo (D-CA) has been in Congress for decades and is a champion of biomedical research. Representatives Brian Higgins (D-NY) and Derek Kilmer (D-WA) both were chairs of the House Cancer Caucus, have been very supportive of cancer research, and worked closely with the NCI. Representative Kay Granger (R-TX), Chair of the full Appropriations Committee in the House is retiring. Senator Joe Manchin (D-WV) has also announced that he is not running for reelection.

Ms. Holohan highlighted some recent hearings and congressional visits to NCI, explaining that NCI hosts members of Congress and congressional staff for visits, and also collaborates with grantee institutions hosting congressional visits with NCI leadership participation. On 20 July 2023, Dr. Doug Lowy spoke at an event sponsored by One Voice Against Cancer (OVAC). The briefing at the Capitol Visitors Center well attended by congressional staff. On 7 November 2023, the Senate confirmed Dr. Bertagnolli as NIH Director.

Questions and Answers

NCAB Chair Dr. Carpten asked how HHS has managed with 365-day CRs and the various bills. Ms. Holohan explained that Labor-HHS is the largest nondefense discretionary bill and that it contains controversial policy riders, so it is almost always one of the last bills to be completed. Dr. Raymond U. Osarogiagbon, Adjunct Research Professor, Department of Medicine, Vanderbilt University, Chief Scientist, Baptist Memorial Health Care Corporation, asked what the Boards can do to help foster understanding and perhaps move dialogue on Capitol Hill regarding the NCI budget. Ms. Holohan first noted that federal agencies do not lobby. From her perspective, the most valuable thing for researchers to do is to work with their university colleagues to engage with their congressional delegations and to highlight cancer research and its impact on patients.

V. RECOGNITION OF RETIRING BSA MEMBERS—DR. DOUGLAS R. LOWY

On behalf of the NCI, Dr. Lowy recognized the contributions made by members of the NCAB whose terms of office have ended. He expressed appreciation for their service and dedication during the course of their terms. Those retiring BSA members are: **Dr. Otis W. Brawley,** Bloomberg Distinguished

Professor of Oncology and Epidemiology, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University; **Dr. Keith T. Flaherty,** Director of Clinical Research, Massachusetts General Hospital Cancer Center, Professor of Medicine, Harvard Medical School; **Dr. Karen E. Knudsen,** Chief Executive Officer, American Cancer Society, Inc. (ACS), American Cancer Society Cancer Action Network (CAN); and **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.

VI. INVESTIGATING THE ROLE OF CYCLIN-DEPENDENT KINASE (CDK)4/6 ACTIVITY DURING THE CELL CYCLE BY LIVE-CELL IMAGING—DR. STEVEN D. CAPPELL

Dr. Steven D. Cappell, Stadtman Investigator, Head, Single-Cell Dynamics Section, Center for Cancer Research (CCR), NCI, presented his research on understanding the fundamental principles of cell cycle regulation and began with some background. Proper cell cycle regulation is needed to maintain tissue homeostasis, repair wounds, and mount an effective immune response. When this process malfunctions, it can lead to cancer or degenerative diseases. The goals of the Cappell laboratory are to investigate fundamental molecular mechanisms that regulate cell cycle entry and exit, understand how these fundamental mechanisms malfunction and contribute to human disease, and translate findings to develop new or improved chemotherapies for cancer patients.

It is widely known that progression through the cell cycle is regulated by a series of checkpoints that control movement at each stage. Over the last 20 to 30 years, numerous biochemical and genetic approaches have been used to elucidate molecular mechanisms that appear to account for most of these observed checkpoints. Most of the chemotherapeutic and targeted agents that are used in cancer treatment are directing to these checkpoints. A major problem is that many of these agents, despite being successful in the clinic, often do not work as the models predict. For example, heterogenous responses from cells in a tumor in which only fractional killing occurs can lead to recurrence of the tumor. Unexpected compensatory mechanisms that arise can lead to resistance. This problem highlights that these molecular mechanisms that are enshrined in our textbooks and have been well studied do not present the complete picture for understanding how the cell cycle works. Dr. Cappell emphasized that the main challenge limiting a full understanding of these processes is that many molecular mechanisms were elucidated using biochemical techniques, but the checkpoints are often studied at the level of cell biology. One major challenge in research today is how to link these molecular mechanisms to the biological processes involved in the cell cycle.

Monitoring Cell Cycle Progression in Live Cells Using Fluorescent Biosensors. The Cappell laboratory is addressing these challenges by engineering new and using existing fluorescent biosensors for key enzymes in cell cycle signaling pathways that control progression through the cell cycle. Fluorescent biosensors enable monitoring the activities of these pathways in live single cells as they dynamically progress from each stage of the cell cycle. This approach allows measurement in thousands of cells simultaneously with the enzyme activities that are key for cell cycle control. The cells can then be treated with small-molecule inhibitors or chemotherapeutic agents to better understand how these enzyme activities are changing dynamically and in real time. Combining the biosensors with an automated time-lapse imaging and image analysis pipeline allows for converting these raw images from the microscope into single-cell time series data. This provides a quantitative and dynamic readout of these molecular mechanisms in cells.

Cyclin-dependent kinase (CDK)2 is a main regulator of cell cycle progression, and its known substrate is DNA helicase B. The C-terminus of DNA helicase B was fused to a fluorescent protein. The C-terminus has four potential CDK2 phosphorylation sites, a nuclear localization sequence, and a nuclear export sequence. When this peptide is unphosphorylated, the nuclear localization sequence dominates and the biosensor resides in the nucleus. When the kinase activates and phosphorylates the four sites, the

negative charges tip the balance in favor of nuclear export, and the biosensor is exported into the cytoplasm. This allows viewing the localization of this biosensor as it moves from the nucleus into the cytoplasm as a readout for CDK2 activity. This readout can then be quantified dynamically using the image analysis pipeline by measuring the fluorescence in the cytoplasm and in the nucleus. The ratio of these fluorescent values gives a quantitative readout of relative CDK2 activity. The cell starts in the G2 phase with high CDK2 activity; it then goes through mitosis and CDK2 activity rapidly drops. The CDK2 activity slowly increases over the course of the cell cycle, and then the cell goes through another mitosis, CDK2 activity falls again, and the cycle is repeated.

The Cappell laboratory's approach allows measurement of many cells simultaneously as they are asynchronously going through the cell cycle, revealing heterogeneous progression through the cell cycle. *In silico* synchronizing of these cells to mitosis results in two subpopulations of cells that behave differently. Some cells will immediately exit mitosis and turn on CDK2, indicating that they have entered the cell cycle. Some cells will immediately turn off CDK2, indicating that they have exited the cell cycle into a quiescent state, often referred to as G0 phase.

New Insights Into Cell Cycle Regulation Using Live-Cell Imaging. Since the Cappell laboratory opened in 2018, it has used live-cell imaging to study several different fundamental principles of cell cycle regulation. This research has revealed that cells take completely divergent paths after DNA damage rather than pausing at the G1/S checkpoint. Senescence is irreversible because transcription factor MYC is constantly degraded. Transient anaphase-promoting complex (APC) inactivation gives cells a metabolic boost during cell cycle entry. In addition to these question-based projects, the Cappell laboratory has also been interested in developing tools that can be used by the scientific community. The laboratory developed a new biosensor for the ubiquitin ligase, beta-transducin repeats-containing proteins (beta-TrCP), which is upregulated in many cancers and often is considered an oncogene. The Cappell laboratory is collaborating with the National Center for Advancing Translational Sciences, NIH, to use this biosensor in high-throughput small-molecule screens to identify inhibitors of beta-TrCP that could be used in the clinic.

Restriction Point Model and CDK4/6 Inhibition. Dr. Cappell reported on his recent studies examining the irreversible cell cycle commitment, known as the restriction point. In the 1970s and 1980s, Pardee and Zetterberg described the point when cells appeared to be irreversibly committed to the cell cycle as the restriction point. If a cell is before the restriction point when mitogen signaling is lost, the cell will go quiescent. If a cell is after the restriction point where mitogen signaling is lost, the cell is thought to be irreversibly committed to the cell cycle and will complete the cell cycle and divide into two daughter cells. The daughter cells will go quiescent.

The molecular mechanism of the restriction point has been characterized and involves a feedback loop with the tumor suppressor retinoblastoma (Rb) protein, a family of transcription factors called E2F, and CDK2. CDK 4 and CDK6 are reversibly activated by upstream mitogen and kinase signaling, and once active, they inhibit Rb, which leads to the activation of a transcriptional program that activates CDK2. Importantly, CDK2 can phosphorylate and inhibit Rb, thus completing the feedback loop. Once this feedback loop is active, it is self-sustaining and irreversibly active. This occurs because in blocking upstream CDK4/6 or mitogen signaling, this pathway still remains active. This molecular mechanism is the clinical rationale for a wide variety of targeted agents that are used in the clinic, including CDK4/6 inhibitors, MEK inhibitors, and receptor tyrosine kinase inhibitors.

A postdoctoral fellow in the Cappell laboratory, Dr. James Cornwell, found that this pathway is not irreversible. Because CDK4/6 and mitogen signaling pathways are required for the entire cell cycle, treating with these inhibitors forces cells into quiescence from any point in the cell cycle. This observation was first made using the live-cell imaging platform. Dr. Cappell demonstrated two examples of cells that behave differently when treated with a CDK4/6 inhibitor. These cells are expressing the CDK2 biosensor and APC biosensor that allows monitoring the status of the feedback loop supposedly

underlying this restriction-point phenomenon. The cell starts in the G2 phase, goes through mitosis and G1/S transition, and then is hit with a CDK4/6 inhibitor. This cell will enter mitosis and divide into two daughter cells that can be tracked simultaneously. Because they have biomarkers for quiescence—high APC activity and low CDK2 activity—the daughter cells have entered into quiescence. This cell behaved as predicted based on the restriction-point model.

Many cells were observed taking a completely different and unexpected trajectory through the cell cycle. For example, a cell that starts similarly to the other cell in G2 phase, undergoes mitosis and the G1/S transition, and then is hit with a CDK4/6 inhibitor is seen doing something different from other cells. Rather than reach mitosis, it spontaneously loses its CDK2 activity and reactivates the APC, and this cell enters a G0-like state and is biochemically similar to the other two cells (high APC activity and low CDK2 activity). Fixing and staining these cells for a third marker of quiescence, phosphorylated Rb allows observing that both trajectories result in low phosphorylated-Rb. However, the cell that took the unexpected trajectory through the cell cycle possessed an extra copy of DNA because it skipped mitosis.

The next steps were to better understand what sets this 10 percent of cells apart from the other cells and why they take this different trajectory through the cell cycle and do not behave as expected by the restriction-point model. One clue that led Dr. Cappell and his laboratory to the answer to this question was examining the relative time it takes cells to either reach mitosis or exit the cell cycle. Using live-cell imaging experiments, they measured CDK2 activity and the time it takes cells to progress from S phase to the next mitosis, which is demonstrated by the rapid drop in CDK2 activity. The results revealed that, on average, it takes cells about 12 hours to reach mitosis. Subsequently treating cells with the CDK4/6 inhibitor showed that the time it took cells to exit the cell cycle significantly overlapped the time it took the other cells to reach mitosis. These two observed fates are mutually exclusive but were happening on very similar time scales. By definition, they were in competition with each other.

The Cappell laboratory hypothesized that blocking cells from undergoing mitosis would show all cells exiting into this G0-like state and not just a few outlier cells. To block mitosis, cells were treated with a CDK1 inhibitor and then with a CDK4/6 inhibitor. It was observed that all cells can exit the cell cycle into this G0-like state and take this alternate path through the cell cycle. These results suggest that there is nothing biochemical or genetically different about these few outlier cells, but the relative timing between either exiting the cell cycle or entering mitosis dictates their fate. Mechanistically, the reason this all-important feedback loop is reversible is that cyclin A mRNA is uniquely regulated by CDK4/6 throughout the entire cell cycle. Treating cells with a CDK4/6 inhibitor and measuring all the components of the signaling pathway revealed that cyclin A mRNA was rapidly lost upon treatment with the drug, while the rest of the signaling components appeared to be sustained for many hours. This was due to a new signaling component to this pathway. CDK4/6 regulates cyclin A mRNA through two Rb-like proteins, p107 and p130, and E2F4/5. Treating cells with the CDK4/6 inhibitor, cyclin A mRNA is rapidly lost, and the other signaling proteins can be maintained as long as those proteins are present because they can be relatively stable. This means that CDK2 will remain active as long as cyclin A protein is present. The Cappell laboratory was able to support this finding by showing a strong correlation between the half-life of cyclin A protein across different cell lines and the time it takes cells to exit the cell cycle. They experimentally manipulated this reaction by fusing cyclin A to an inducible degron system, thereby destabilizing it. When cyclin A is destabilized, cells exit the cell cycle faster upon treatment with the CDK4/6 inhibitor.

Instead of this restriction point phenomenon being regulated by a self-sustaining feedback loop, the restriction-point phenomenon is actually explained by the temporal competition between these two mutually exclusive fates of mitosis or cell cycle exit, because CDK4/6 and upstream mitogen signaling is needed for the entire cell cycle and not just early in G1 phase. The implications of this are that inhibiting CDK activity can send cells to this G0-like state where they have 4N DNA content or an extra copy of DNA. This study solves a long-standing, decades-old problem of the restriction-point phenomenon. These

findings go beyond our basic understanding of cell biology, given the clinical use of CDK inhibitors in the clinic and in clinical trials.

Summary. Dr. Cappell and his laboratory are beginning to understand how this new mechanism might be working in all animals and in the clinic. For example, CDK4/6 inhibitors are widely used in the clinic because of the frontline therapy for hormone receptor–positive breast cancer, and they are in clinical trials for a wide variety of other cancer types. In addition, a new generation of CDK2 inhibitors is in development by a number of pharmaceutical companies, either to be used alone or in combination with CDK4/6 inhibitors. Because these data have shown that these drugs can induce this alternative path through the cell cycle and into this G0-like state, it is critical to understand the long-term consequences of cells' being in this state. Preliminary studies are in progress to treat cells with CDK inhibitors and perform a washing step. These results will provide a clear answer to this question. When cells are washed and treated with these drugs, they enter this G0-like state. When the drugs are washed off, the cells reenter the cell cycle in G1 phase and go through another round of DNA synthesis in S phase. These cells will have 8N DNA content, indicating that they have gone through a whole genome duplication. Interestingly, these cells will undergo another mitosis and divide into four daughter cells. And if these cells are grown for long periods of time, this treatment, plus washing off the drugs, induces various types of aneuploidy, which could have drastic consequences for not only the cancer cells that are being treated but also for normal proliferative cells in different tissues in the body. Future studies will investigate this further. Dr. Cappell highlighted that this research demonstrates how a basic biological question can be translated and have important clinical implications.

Questions and Answers

Dr. Trey Ideker, Professor, Department of Medicine, University of California, San Diego, asked about the implications for development of palbociclib resistance, because it appears that there could now be another pathway, a G2-related or S/G2-related pathway, in which resistant mutations could be developed that are not Rb or MYC-related. Dr. Cappell explained that the drug wash-off experiment induces aneuploidy and that the shuffling of genes in these cells could lead to some small population where even MYC is upregulated or Rb is lost. This could be the genetic perturbation that leads to these resistance mechanisms.

Dr. Knudsen asked about collaborating with investigators conducting similar research on identifying the mechanisms of palbociclib resistance in clinically relevant model systems. Dr. Cappell noted ongoing efforts in reaching out to investigators to identify clinical samples or other laboratories that have patient data to further evaluate his findings.

NCAB Chair Dr. Carpten asked about the implications for or what the relation is to mitotic catastrophe and standard chemotherapy treatment and a potential mechanism of resistance. Dr. Cappell noted that this project started with experiments on inducing DNA damage and finding the exact same trajectory, which led them to think that it was related. They began investigating DNA damage pathways but were only triggering the G2/M checkpoint. NCAB Chair Dr. Carpten speculated that combining DNA damage with a CDK4/6 inhibitor, which is currently being conducted in clinical trials, could be inducing this alternate trajectory through the cell cycle.

VII. RFA AND RFP CONCEPTS—NEW AND RE-ISSUE—NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis

Microbiome-Targeted Intervention Cancer Network (MTCN) (New RFA/RFP)—Dr. Dan Xi

Dr. Dan Xi, Program Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, presented a new RFA/RFP concept on establishing the Microbiome-Targeted Intervention Cancer

Network (MTCN), which is co-sponsored with the Division of Cancer Biology (DCB). Preclinical research and human studies show that the microbiome can modulate cancer therapeutic outcomes, but challenges exist in translating microbiome research to cancer therapies. Phase 1/2 clinical trials of various designs evaluating fecal microbiota transplantation (FMT) and the defined-microbial consortia (i.e., group of diverse microorganisms acting in a community) for immunotherapy have been underway in the United States and internationally but lack coordination. Optimal donor selections for FMT, as well as a better understanding of long-term safety and patient stratification, are needed. For the defined-microbial consortia, the beneficial bacterial species that correlate with therapeutic outcomes vary across research laboratories and cohorts. Dr. Xi highlighted opportunities to address these challenges: conduct larger trials to confirm the pilot FMT trials that have shown encouraging results and improved immunotherapy response and toxicity; optimize the clinical trials; build a human fecal microbial profile for immunotherapy and a national FMT registry for the long-term safety follow-up; and research such variables as lifestyle and medications.

An FY 2022 portfolio analysis of NCI microbiome studies revealed only two microbiome-based cancer therapeutic clinical trials, one funded in FY 2018 and a second funded in FY 2022. The FY 2018–funded grant published encouraging results of the first-in-humans pilot trial of FMT to improve the anti-PD-1 response. Scientific gaps and clinical needs have been identified in the NCI microbiome portfolio. These include insufficient representation of clinical trials, lack of various assays and tools of microbiome measurement and data analysis, limited prospective studies examining multiple races and locations, overabundance of studies involving correlative analysis and preclinical projects, and limited translation of studies in mice to human studies. To address these gaps, the NCI needs to stimulate coordinated clinical testing of causal effects of the microbiome on cancer therapy and study the relevant mechanisms, ensure proper racial diversity in the human microbiome research, coordinate the standardization, and study the variables.

The purpose of this RFA/RFP is to accelerate the early-stage clinical testing of microbiome-targeted cancer interventions in a timely manner to improve the immunotherapy in the MTCN through the U19 Microbiome Research and Clinical Trial Centers (MTTC) and N01 Microbiome Clinical Network Coordinating Center (MTCNC). The goals of the U19 centers are to (1) develop optimal FMT or defined-microbial consortia for the early-phase clinical trials of safety and efficacy to overcome the immunotherapy resistance and reduce adverse events and (2) conduct the bidirectional human-relevant mechanistic studies. The N01 (research and development contract) will support two cores. The Administration Core will coordinate activities across the U19 centers. The Microbiome Core will harmonize and standardize the procedures and protocols for optimizing FMT and will define the microbial consortia and the clinical trial design, coordinate and standardize the bioinformatics and the data for the infrastructure, establish one MCTN Human Cancer Immunotherapy Fecal Microbiome Atlas and one FMT National Cancer Registry, and develop one fecal repository resource for distribution to the community. The priorities of the intervention are FMT or defined-microbial consortia for the immune checkpoint inhibitor or the chimeric antigen receptor (CAR) T-cell therapies.

The MCTN will consist of four U19 MTCCs, one MTCNC, and an MCTN Steering Committee. Each MTCC will manage two cores, have a basic cancer researcher and a clinical researcher as co-principal investigators (PIs), and will conduct a human study. Two of the four MTCCs must conduct a clinical trial. Examples of priority projects include developing fecal microbiota or defined-microbial consortia products and obtaining FDA Investigational New Drug Approval (IND) approval or conducting an FMT trial. Applicants must study the gut microbial composition and function using multi-omics, measure the immunological biomarkers associated with the therapy outcome, and investigate the variables to inform the optimal trial design. A pre- and probiotic project is encouraged. Multiple components and human relevance of the preclinical studies and a cohort composed of two or more racial groups are required.

Evaluation criteria for the MTCC RFA U19 include conducting a clinical trial and obtaining FDA IND approval for FMT and/or defined-microbial consortia, establishing new collaborative transdisciplinary teams for future clinical trials, and improving diversity and reducing disparity in cancer microbiome research. The MTCNC RFP N01 primarily will be evaluated on its effort (1) to advance cancer immunotherapy and microbiome research for a broad scientific community through sharing two comprehensive gut microbiome clinical databases and one biological fecal resource and (2) to advance technology and computation biology.

Subcommittee Review. Dr. Nelson J. Chao, Donald D. and Elizabeth G. Cooke Professor, Chief, Division of Hematologic Malignancies and Cellular Therapy/BMT, Director, Global Cancer, Duke University School of Medicine, expressed the Subcommittee's enthusiasm and support for the concept. Dr. Chao noted that the NCI microbiome portfolio is limited in these types of studies, which this concept is addressing. The Subcommittee appreciated NCI staff's responding to their concerns of optimizing this research, clarifying the research opportunities, and balancing the clinical and preclinical aspects of the projects.

The first-year cost for the one-time issuance is estimated at $7.5 M for four RFA U19 awards and one RFP N01 award, with a total cost of $37.5 M for 5 years.

Questions and Answers

Dr. Ideker commented on the relevance to and potential impact on this RFA/RFP of the controversy between two well-respected groups in the microbiome field regarding publications and the scientific disagreement about the accuracy of using microbes to identify cancers. The issue is whether microbiome sequence associations in tumors were mistakenly finding human DNA that were mislabeled in the microbiome or in microbial databases. Dr. Ideker asked about any resolution on this issue. Dr. Xi pointed out that NCI's concept encourages performing microbiome measurement with the tissue samples when available. She noted that the publications in question were discussing use of artificial intelligence (AI) and computation for batch correction, which is not standardized. This RFA/RFP also encourages proposals that use AI. Dr. Ideker attributes some of the disagreement to a database issue rather than mis-annotations.

Dr. Karen M. Basen-Engquist, Professor, Department of Behavioral Science, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, asked whether pre- and probiotic interventions include dietary interventions. Dr. Xi confirmed that the RFA would be responsive to dietary interventions.

Dr. Shelton Earp, Director, University of North Carolina Lineberger Comprehensive Cancer Center, Director, UNC Cancer Care, The University of North Carolina at Chapel Hill, commented that from the beginning, the three publications about microbes and cancer showed interesting effects but all had different problems, which has captured public attention. Dr. Earp emphasized ensuring that all data and biologic samples collected for this RFA/RFP be shareable and available for further analysis, including sequencing and computation.

Dr. Andrew T. Chan, Chief, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital (MGH), Director of Epidemiology, MGH Cancer Center, Daniel K. Podolsky Professor of Medicine, Harvard Medical School, agreed with Dr. Earp and noted that part of the reason for supporting this concept is to resolve some of the issues with clinical trial data in the field. Dr. Chan asked about FDA requirements for FMT, given the history of shifting standards on how this method is approved or considered as therapy, and whether there were efforts to coordinate with the FDA when proposals are funded. Dr. Xi explained that communications with the FDA about this research are ongoing and called attention to the September 2019 NCI-sponsored Strategic Workshop on Rigor and Reproducibility:

Precision Fecal Microbiota Transplant and Microbiome Cancer Therapeutics that she organized, which included the FDA in the panel discussions.

Dr. Ana Maria Lopez, Professor, Medical Oncology and Integrative Medicine (ABOIM) and Nutritional Sciences, Director, Integrative Oncology, Associate Director, Diversity, Equity, and Inclusion, Sidney Kimmel Cancer Center, Thomas Jefferson University, noted that she appreciates the perspective of bringing in multiple aspects of diversity and emphasized that access to food, geographic location, and processing of food, which can differ by age, all are components that may enhance understanding in this research.

Dr. Fred K. Tabung, Assistant Professor, Department of Internal Medicine, College of Medicine and Comprehensive Cancer Care, The Ohio State University, indicated that he thinks this issue of differences in annotation will continue to produce microbiome results that have no agreement with regard to which one is accurate and will continue to have questionable translatable findings. Dr. Tabung speculated on whether NCI could take a leadership role and organize a meeting with the two research groups involved—Salzberg Lab at Johns Hopkins University and Knight Lab at University of California, San Diego—to discuss any recent updates or resolutions. Dr. Xi noted that a microbiome workshop is being planned for February or March 2024 and that the NCI could invite these groups to participate.

Motion. A motion to approve DCTD's new RFA/RFP entitled "Microbiome-Targeted Intervention Cancer Network (MTCN)" was approved unanimously Small Business Innovation Research (SBIR) Development Center.

NCI SBIR Innovative Concept Award Program (Re-issue RFP)—Dr. William Bozza

Dr. William Bozza, Program Director, SBIR Development Center, NCI, presented a re-issue RFP concept for continuing the NCI SBIR Innovative Concept Award Program. The SBIR and Small Business Technology Transfer (STTR) program is one of the largest sources of early-stage seed funding for small business at the NIH. SBIR/STTR is a congressionally mandated program, with guaranteed set-asides each fiscal year. For FY 2023, $1.3 B was allotted to the NIH and $203 M to the NCI. The SBIR Innovative Concept Award was developed in response to recommendations of an external working group (*ad hoc* Working Group on SBIR/STTR) that was convened by the NCAB to evaluate the NCI SBIR program. The primary recommendation was to develop a high-risk, high-reward concept program that could help promote paradigm-shifting innovation.

In 2021, the NCI launched the Concept Award as a 3-year pilot to support early-stage high-risk, high-reward projects that focus on innovation. The solicitation focused on rare and pediatric cancer technologies. The Concept Award is a $300,000 contract funding opportunity for 1-year projects. No preliminary data are required. The aim is to fund companies to perform the experiments to obtain initial de-risking proof of concept data. Traditionally, the NCI SBIR program has been a three-phase program. This Concept Award is at the beginning of the SBIR pipeline.

The major objectives of the Concept Award are to increase early-stage innovation and high-risk, high-reward projects in the NCI SBIR portfolio; bridge rare and pediatric cancer portfolio gaps; achieve high responses; engage new small business customers and streamline the review/award process; and de-risk early-stage innovation and foster follow-on funding opportunities. Since the launch of the program, the NCI has issued 13 awards and invested $3.9 M in funding. Thirty-eight percent of the awards represent women and/or underrepresented minorities. The majority of projects funded were in the therapeutics category, followed by diagnostics, devices, and Clinical Laboratory Improvement Amendments laboratory tests. The cancer indications studied have been diverse and include rare cancers (e.g., rhabdomyosarcoma, pediatric glioma, juvenile myelomonocytic leukemia) and more common cancers (e.g., pancreatic, oral, esophageal) that have low survival rates and are in need of improvements of standard of care.

An external evaluation committee assessed the program with regard to portfolio innovation, rare and pediatric cancer focus, high response and new stakeholders, and project de-risking to determine whether the key objectives were met. The Concept Award uses a white paper process, consisting of the submission of a short 2- to 3-page summary of the technology, which is reviewed by internal experts at the NCI who provide feedback on whether the research being proposed is within the scope of the NOFO. From FY 2022 to FY 2024, the program received 70 to 100 white papers annually that led to full proposals and issuance of awards. Eighty percent of white papers and 69 percent of awards represented companies that were new to NCI SBIR funding, suggesting early-stage innovation. All concept awards were issued within 6 months of review. Eighty-five percent of the 13 awards investigated cancer indications that are deeply underrepresented in the NCI SBIR portfolio. Innovation included next-generation proteolysis targeting chimera, CAR T-cell technologies, first-in-class therapeutic targets, novel drug delivery methods, and innovative diagnostics. In terms of project de-risking, six funded companies were at the evaluation stage. Of the six, two have been successful. One—Coordination Pharmaceuticals, Inc.—is developing an X-ray activatable cancer vaccine for treatment of oral cancer. Through the Concept Award, the company generated a number of robust *in vivo* efficacy data sets for rare cancer murine models. After technology de-risking, the company completed IND-enabling studies and filed an IND with the FDA. First-in-human studies are scheduled to begin in the first quarter of 2024.

The external evaluation committee concluded that the Concept Award successfully met all evaluation metrics and highlighted the white paper review as a key feature of the program. Dr. Bozza explained that each year, the NCI recruits 70 reviewers from across NIH institutes and centers to participate in the white paper process. This process helps triage projects to advance the most innovative projects for full proposal submission. The external evaluation committee unanimously recommended that the Concept Award program continue. Two improvements they emphasized were to develop additional federal funding to further support de-risked technologies and to develop a pitch-day event. This concept re-issuance will continue the program and support follow-on Phase I NOFOs. ARPA-H is anticipated to co-fund the Phase II NOFOs during the later steps of the approval process.

Subcommittee Review. Dr. Osarogiagbon expressed the Subcommittee's support for the re-issue concept. He noted that the program had successfully achieved its objectives and that the response to the NOFO has been encouraging. The Subcommittee had some concerns about investigating non-rare cancers in the program, which NCI staff addressed. In addition, the Subcommittee emphasized including more projects that are evaluating devices.

The first-year cost for the one-time issuance is estimated at $3M for 5 to 10 Phase I awards and follow-on Phase II awards, with a total cost of $15M for 5 years.

Questions and Answers

Dr. Howard J. Fingert, Vice President, Medical-Oncology, ONO PHARMA USA, INC., asked about evaluation metrics and the potential of having a history of successful, sustained commercial access, especially with the failure rate in Phase 1 trials and INDs. Another metric for evaluation will be the actual number of patients in the United States who will have the opportunity to experience the benefit of the goal of the program and what the protocol entails. Dr. Bozza noted that the metrics for this concept align with the SBIR overall program evaluation. As the Concept Award grows over the next 5 years, achieving the metrics will be more obvious. A second company funded through the Concept Award program has commercial sales of $7 M within the 18-month post-award period.

Ms. Julie Papanek Grant, General Partner, Canaan, commended the NCI for the success of this concept after only 3 years of operation and emphasized the importance of highlighting the agility within the NCI to manage such a program.

Dr. Lopez suggested expanding the areas of interest to include investigations on pediatric cancer and the environment as a topic that small businesses can pursue.

Dr. Lisa A. Newman, Professor of Surgery, Chief, Division of Breast Surgery, Weill Cornell Medicine, suggested expanding funding to support surgical innovations.

Motion. A motion to concur on the Small Business Innovation Research Development Center (SBIR)'s re-issue RFP entitled "NCI SBIR Innovative Concept Award Program" was approved unanimously.

Small Business Transition Grant for Early-Stage Investigators (Re-issue RFA)—Dr. Jonathan Franca-Koh

Dr. Jonathan Franca-Koh, Program Director, SBIR Development Center, NCI, presented the re-issue RFA concept for the Small Business Transition Grant for Early-Stage Investigators. The small business programs include SBIR and STTR mechanisms. With the SBIR, the PI's primary employment is at the company, and partnering with universities is allowed, but not required. In contrast, the STTR mechanism allows flexibility in where the PI is employed and requires partnering with a university or nonprofit research institution. The goal of the STTR program is to assist technology transfer from academia to industry. The SBIR and STTR programs use a congressional set-aside and do not impact the RPG funding.

Dr. Franca-Koh explained that the motivation for the Small Business Transition Grant (SBTG) progrsm originated from an NCI-sponsored workshop that convened Cancer Center technology transfer and innovation offices. The workshop participants noted that in many cases, postdoctoral fellows and other early-career scientists are key for spinout university technologies but lack business experience. ESIs tend to have a lower success rate for SBIR funding mechanisms than experienced investigators. The NCI created an SBIR grant that specifically focuses on ESIs, which requires mentoring and provides entrepreneurial training, resources to spin out the technology, and flexibility to remain at the university initially.

A requirement of the SBTG program is that applicants must use the SBIR Fast Track Mechanism, in which they apply for both Phase I and Phase II funding simultaneously, and if successful, they transition to the Phase II project without having a second review. An ESI must be a PI who is within 10 years of their terminal degree, such as a Ph.D. or M.D. The ESI identifies two mentors (technical and business) who are committed to their project and are required to be either permanent residents or U.S. citizens. The SBTC will be structured into stages. The Phase I STTR supports the postdoctoral fellow as a PI training and preparing the technology, and the PI is required to complete the Innovation Corps (I-Corps) at NIH training. The Phase I STTR award provides up to $400,000 for 1 to 2 years. The next stage is Transition, a Fast Track during which the PI moves to the small business and updates the technology. The final stage is the Phase II SBIR, which is the business team phase, when the PI is nontransferable and provided with $2 M over 2 years.

Dr. Franca-Koh highlighted some accomplishments of the SBTG program. The I-Corps at NIH program is effective in providing entrepreneurial training. Participants completing the training gain key commercialization knowledge, on such topics as reimbursement, regulatory strategy, preclinical development, and clinical trials. Since the SBTC program launched in 2021, the interest from potential applicants has been strong, and feedback from the community of applicants and awardees has been positive. The increase in Phase II STTR applications after launching the SBTG program is potentially increasing the STTR pipeline. In the first round of funding, 15 proposals were received and 4 awards were made. The following year, 11 applications were received and 1 was funded. In this current round of funding, 15 applications have been received and are under review.

Two projects in the first cohort of SBTG awards successfully advanced to IND-enabling studies. PI and postdoctoral fellow Dr. Anne Reitz (Premier Physician Network) and Dr. Elliott Androphy (Kovina Therapeutics, Inc.) introduced technology capable of blocking human papillomavirus (HPV) infections before cancer develops and treating HPV-related cancers after detection. The project was successful in Phase I, moved to Phase II in summer 2023, and will be completing IND-enabling studies. The project also recently closed a $2 M seed funding round and is raising Series A funding. PI Dr. Robinson Reeder (Medical University of South Carolina) worked with Dr. Nathan Dollof (Leukogene Therapeutics, Inc.) to evaluate technology to develop a cancer vaccine to treat pancreatic ductal adenocarcinoma. The Phase I project was successful and transitioned to Phase II in summer 2023, and the team will further conduct efficacy and IND-enabling studies.

An external evaluation committee assessed the SBTG program and expressed strong enthusiasm for the program but recommended some changes: (1) expand the eligibility for foreign trainees; (2) allow a Phase I STTR option; and (3) improve outreach to multiple stakeholders. Dr. Franca-Koh noted that the SBTG program is part of the SBIR Development Center's broader strategy to help improve diversity and access to small business funding. The goal is to foster an ecosystem that encourages commercialization. Efforts will include building a pipeline, enhancing the SBIR Application Assistance Program, cultivating market research and customer discovery, and improving company creation and intellectual property evaluation.

The re-issue RFA will continue the SBTG program to enhance the spinout of technologies from NCI-funded projects and address the recommendations for improving the program. The SBTG program aligns with National Cancer Plan goals 3, 6, and 8 to develop effective treatments, engage every person, and optimize the work force, and it provides training and mentorship for ESIs.

Subcommittee Review. Dr. Brawley expressed the Subcommittee's strong support for the re-issue concept. The Subcommittee is impressed with the level of mentorship within this concept and appreciates the NCI staff responses to their concerns of underutilization of this program.

The first-year cost for the one-time re-issuance is estimated at $3.2M for 8 awards, with a total cost of $9.2M for 5 years.

Questions and Answers

Dr. Franca-Koh clarified that a formal white paper process is used with the Concept Award because of federal law governing contracts and the stricter rules about how to communicate with people who are interested in applying. Because the SBTG uses a grant mechanism, the SBIR Development Center encourages applicants to contact the center prior to applying to review their specific aims and discuss ways to strengthen their proposals.

In response to a follow-up question from Dr. Fingert on how the SBIR funds are spent and core training for applicants, Dr. Franca-Koh pointed out that the SBTG program uses the Fast Track, and to transition to the Phase II projects at the $2M level of funding, companies need to show that the original goals have been met and that Project I has been successfully completed. Any changes in scope to Phase I would need to be agreed to in writing prior to executing them. He noted that the NIH I-Corps training program has been a living process that is frequently updated. The goal of that training is to have the applicants conduct interviews, discover where the answers are, and move forward in the right direction.

Dr. Andrea Hayes Dixon, Dean, Howard University College of Medicine, Vice President of Clinical Affairs, Chair of Surgery, Howard University Hospital, suggested partnering with academic institutions that already have robust training for entrepreneurship and innovation (e.g., Stanford University, University of Michigan) and leveraging their experience and education on advancing a product to market. Dr. Franca-Koh noted that the SBIR Development Center has contacts in a number of

existing entrepreneurship programs but primarily provides I-Corps training. The SBTC application requires a detailed training plan but does not ascribe to any one model. .

Motion. A motion to concur on the SBIR's re-issue RFA entitled "Small Business Transition Grant for Early-Stage Investigators" was approved unanimously.

VIII. ONGOING AND NEW BUSINESS—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

NCAB Subcommittee on Cancer Centers. Dr. Susan Thomas Vadaparampil, Associate Center Director, Community Outreach, Engagement, and Equity, Professor, Department of Health Outcomes and Behavior, Moffitt Cancer Center, Chair of the NCAB Subcommittee on Cancer Centers, presented the report of the 29 November 2023 meeting. The Acting NCI Director, Dr. Lowy, attended the meeting. The Subcommittee heard a presentation from Dr. Henry P. Ciolino, Director, Office of Cancer Centers, NCI, and Executive Secretary, about the Cancer Centers program, including the funding history and increasing the number of new Cancer Centers. Dr. Ciolino also updated the Subcommittee on the Cancer Center Support Grant (CCSG) guidelines and key areas, including the Plan to Enhance Diversity (PED) and the intersection of Cancer Research Training and Education Coordination (CRTEC) and Community Outreach and Engagement (COE). Dr. Vadaparampil noted that the Subcommittee discussed quality and quantity and the importance of ensuring that the NCI designation reflects the high quality of NCI Cancer Centers' work and the review process, as well as what the tradeoff is for the intensity of this process versus making sure that Cancer Centers showcase their nature. The Subcommittee also discussed CRTEC and the underfunded status of COE, which is a crosscutting initiative; issues related to accepting Medicaid in the Cancer Centers; and the limitations of the CCSG as a research-focused grant. Dr. Vadaparampil conveyed that the NCAB offered support in whatever way is helpful and allowable and that Dr. Ciolino will explore a potential process in which new concepts are vetted in a broader setting for people who are stakeholders.

Motion. A motion to accept the report of the 29 November 2023 NCAB Subcommittee on Cancer Centers meeting was approved unanimously.

NCAB *Ad Hoc* Subcommittee on Experimental Therapeutics. Dr. Richard J. Boxer, Clinical Professor, David Geffen School of Medicine, University of California, Los Angeles, Chair of the NCAB *Ad Hoc* Subcommittee on Experimental Therapeutics, presented the report of the 29 November 2023 meeting. The Acting NCI Director, Dr. Lowy, attended the meeting. Dr. Boxer explained that this *ad hoc* Subcommittee was established in 2006 for a particular purpose and mission but did not meet periodically for its first 9 years. He noted that the Subcommittee began convening regularly in 2020 and that he had reviewed the last 4 years of minutes of the Subcommittee meetings to understand its activities. During the recent meeting, Dr. Rose Aurigemma, Associate Director, Developmental Therapeutics Program (DTP), DCTD, NCI, and Executive Secretary, provided a robust review of the DTP, outlining aspects of each program that answered the Subcommittee's questions over the last 4 years. Dr. Aurigemma highlighted the accomplishments across the Subcommittee's 2020–2022 priority topics: cell therapy, rational drug discovery, and supporting translational research training. The Subcommittee highlighted a common theme that the NCI should find a way to partner with the FDA regarding experimental therapeutics. Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, Director, DCTD, NCI, informed the Subcommittee that the NCI meets monthly with the FDA to review new clinical trial designs. The Subcommittee discussed whether the mission formulated in 2006 addresses NCI's needs today and will work over the next few months to update or craft a new mission statement. Any proposed changes will be presented to the NCAB for approval.

Motion. A motion to accept the report of the 29 November 2023 NCAB *Ad Hoc* Subcommittee on Experimental Therapeutics meeting was approved unanimously.

Other Business. Dr. Carpten noted that the annual BSA Concept Review Report is posted on the BSA members-only website. As requested, prior years of the report have been archived and can be accessed online.

Future Agenda Items. The BSA and NCAB members suggested reports on the following topics: cancer therapeutics and future directions, from Dr. Richard Padzur, Director, Oncology Center of Excellence, FDA; the progress of Cancer Moonshot studies on biomarkers, which could be disseminated to the immuno-oncology and cell therapy communities; the success of cancer-related policy initiatives and implementations; and the ARPA-H Biomedical Data Fabric Toolbox. Members also requested updates on the following topics: multi-cancer detection tests and the FDA's evaluation of these tests; strategies to address issues of workforce diversity within cancer programs; the Clinical Trials Innovation Unit; how new cancer models, such as organoids, can impact the success of FDA IND submissions; implementation of the proposals to simplify clinical trials and the eligibility criteria that were co-developed by the NCI, FDA, American Society of Clinical Oncology, and Friends of Cancer Research; and NCI's AI and data science strategies regarding basic, translational, and clinical research.

Dr. Knudsen volunteered to present a report from the ACS on policy changes (federal and state level) enabled by science generated within the Cancer Centers.

Members were asked to forward any additional suggestions for potential future agenda items to the respective Board chairs and Dr. Paulette Gray.

IX. ADJOURNMENT—DRS. JOHN D. CARPTEN AND KEITH T. FLAHERTY

Drs. Carpten and Flaherty thanked all the Board members, as well as the visitors and observers, for attending. There being no further business, the 8th Virtual Joint Meeting of the BSA and NCAB was adjourned at 5:06 p.m. on Thursday, 30 November 2023.

Date	Keith T. Flaherty, M.D., Chair, BSA
Date	John D. Carpten, Ph.D., Chair, NCAB
Date	Paulette S. Gray, Ph.D., Executive Secretary