U.S. Department of Health and Human Services
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National Cancer Institute

11th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
October 12, 2022

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
11th Virtual Meeting of the Frederick National Laboratory Advisory Committee

12 October 2022

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 11th Virtual Meeting on 12 October 2022. The meeting was open to the public from 11:00 a.m. to 2:46 pm EDT. The FNLAC Chairperson, Dr. Candace. S. Johnson, President and CEO, M&T Bank Presidential Chair in Leadership, Roswell Park Comprehensive Cancer Center, presided.

FNLAC Members

Dr. Candace. S. Johnson (Chair)
Dr. Andrea H. Bild (absent)
Dr. Catherine M. Bollard
Dr. Carol J. Bult* (absent)
Dr. John H. Bushweller
Dr. Timothy A. Chan (absent)
Dr. Lisa M. Coussens
Dr. Angela M. Gronenborn* (absent)
Dr. Mary J.C. Hendrix*
Dr. Scott W. Hiebert
Dr. Rodney J.Y. Ho*
Dr. Allison Hubel
Dr. Dineo Khabele
Dr. Anant Madabhushi*
Dr. Denise J. Montell (absent)
Dr. Patrick Nana-Sinkam
Dr. Nilsa C. Ramirez Milan
Dr. Erle S. Robertson
Dr. Lincoln D. Stein (absent)
Dr. Linda F. van Dyk

*Pending Appointment

NCI Senior Leadership

Dr. Stephen J. Chanock (absent)
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage
Dr. Kristin L. Komschilies
Dr. Douglas R. Lowy
Dr. Tom Misteli (absent)
Ms. Donna Siegle
Dr. Dinah S. Singer

Executive Secretary

Dr. Wlodek Lopaczynski

TABLE OF CONTENTS

I. Opening Remarks—Dr. Candace S. Johnson 1
II. NCI Principal Deputy Director's Report—Dr. Douglas R. Lowy 1
III. NCI Director's Remarks—Dr. Monica M. Bertagnolli 3
IV. Recognition of Retiring FNLAC Members—Dr. Douglas R. Lowy 4
V. Cryo-Electron Microscopy (Cryo-EM) Training—Dr. Dwight Nissley 4
VI. Patient-Derived Models Repository (PDMR)—Drs. James H. Doroshow and Yvonne A. Evrard 5
VII Frederick Technology Showcase—Drs. Michael Salgaller and Vladimir Popov 7
VIII. RAS Working Group Report—Dr. David A. Tuveson 8
IX. Ongoing and New Business—Dr. Candace S. Johnson 10
Establishment of NCI RAS Initiative Evaluation Team *Ad Hoc* Working Group—Dr. Christopher D. Kane 10
Updated Mission Statements of the FNLAC *Ad Hoc* National Cryo-EM Program Oversight Subcommittee and FNLAC *Ad Hoc* National Cryo-EM Program Oversight Working Group—Dr. Candace. S. Johnson 10
X. Adjournment—Dr. Candace. S. Johnson 11

I. OPENING REMARKS—DR. CANDACE S. JOHNSON

Dr. Candace. S. Johnson, Chair, called to order the 11th Virtual Meeting of the Frederick National Laboratory Advisory Committee (FNLAC) and welcomed the Committee members, National Cancer Institute (NCI) staff, and guests. Dr. Johnson reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Wlodek Lopaczynski, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Motion. A motion to approve the minutes of the 27 June 2022 FNLAC meeting was approved unanimously.

Dr. Johnson called Committee members' attention to the confirmed future meeting dates listed on the agenda, noting that the next FNLAC meeting will be held on 27 February 2023 and will be virtual. The subsequent meeting will be held on 10–11 July 2023 and is planned as an in-person meeting.

II. NCI PRINCIPAL DEPUTY DIRECTOR'S REPORT—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Deputy Director, NCI, also welcomed the FNLAC members and attendees to the meeting. Dr. Lowy began by welcoming five new FNLAC Members: Dr. Carol J. Bult, Professor and Knowlton Family Chair, The Jackson Laboratory; Dr. Angela M. Gronenborn, UPMC Rosalind Franklin Professor and Chair, Department of Structural Biology, University of Pittsburgh School of Medicine; Dr. Mary J.C. Hendrix, President, Shepherd University; Dr. Rodney J.Y. Ho, Professor, Department of Pharmaceutics, School of Pharmacy, University of Washington; and Dr. Anant Madabhushi, Professor, Wallace H. Coulter Department of Biomedical Engineering, Radiology and Imaging Sciences, Biomedical Informatics, and Pathology, Georgia Institute of Technology and Emory University.

Dr. Lowy reported on NCI news and updates, cancer research advances, the Cancer Moonshot℠, and the budget update and *NCI Annual Plan and Budget Proposal for Fiscal Year 2024*.

NCI News and Updates. Dr. Lowy announced that Dr. Monica M. Bertagnolli began as Director, NCI, on 3 October 2022 and would be providing remarks. He highlighted several other NCI updates. The Federally Funded Research and Development Center (FFRDC) re-competition is in progress and governs the operations of the Frederick National Laboratory for Cancer Research (FNLCR). The request for proposals was released on 23 June 2022; proposals are due by 20 February 2023, and the award date is scheduled for 2024. The NCI is planning a pre-proposal conference for late fall 2022. The NCI also is developing plans for in-person tour of FNLCR. On 17–19 October 2022, the FNLCR will sponsor the fourth RAS Initiative Symposium at the FNLCR campus, and it will be hybrid of in-person and virtual attendance. *RAS* is an oncogene mutated in more than 30 percent of human cancers.

Dr. Lowy reminded the FNLAC that the NCI Office of Communications and Public Liaison previously reported on the FNLCR awareness campaign. Upcoming activities include releasing a video marking 10 years of FNLCR as a national laboratory, planning a new *Cancer Currents* blog post in November 2022, and planning a survey of extramural researchers. Further updates will be provided later in this meeting.

In September 2022, the White House Office of Science and Technology Policy, in collaboration with the Alliance for Childhood Cancer and Coalition Against Childhood Cancer, hosted a forum on childhood cancer in recognition of Childhood Cancer Awareness Month. Prior to starting as NCI Director, Dr. Bertagnolli helped organize this forum, which was a community-driven event. Panelists representing

the NCI included Dr. Greg Reaman, incoming Scientific Director, NCI Childhood Cancer Data Initiative (CCDI), and Dr. Stephen J. Chanock, Director, Division of Cancer Epidemiology and Genetics (DCEG), NCI.

Cancer Research Advances. Dr. Lowy described recent cancer research findings. Significant advances have been made in the outcomes for patients with human epidermal growth factor receptor 2 (HER-2)–positive breast cancer. On 11 August 2022, a HER-2 inhibitor, trastuzumab deruxtecan (Enhertu), received U.S. Food and Drug Administration (FDA)–accelerated approval for use in adults with HER2-mutant non-small cell lung cancer (NSCLC). This marks the first time that patients with HER2-mutant NSCLC have an FDA-approved targeted therapy option. Trastuzumab adds to the long list of therapeutic options for these patients, which have contributed substantially to the decrease in mortality rates in lung cancer that extends beyond the results of smoking cessation alone. Two recent NCI-supported studies discovered a vulnerability in different forms of gliomas that have dependence on *de novo* pyrimidine nucleotide synthesis. NCI's Glioblastoma Therapeutics Network soon will sponsor a clinical trial to evaluate the promising drugs. In addition, new results from a clinical trial that tested an immunotherapy drug, teclistamab (Tecvayli), in people with relapsed or refractory multiple myeloma showed that nearly two-thirds of participants had at least a partial response. People with advanced multiple myeloma, the second most common blood cancer, soon could have another treatment option.

Dr. Lowy discussed the importance of the potential role of technology development in addressing health disparities, of which technology development is a major emphasis for the FNLCR. To increase the likelihood of a technological development decreasing cancer health disparities, the field needs to think about disparities from the beginning of the process rather than the end. The aim must be to develop technology with a focus on reducing disparities. In his keynote address at the 15th American Association for Cancer Research Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, Dr. Lowy noted his three main takeaways about health disparities. First, although significant progress has been made in reducing mortality rates for every racial and ethnic group in the United States, with the exception of American Indians/Alaskan Natives, there is still a long way to go to address this multifaceted problem. Second, it is important to be inclusive in research and developing the cancer research workforce. Third, the cancer research community has a role, whether it is in the United States or in low- and middle-income countries. These roles can span a wide range of research from technological development aimed at reducing disparities to research on the populations most affected.

Cancer Moonshot℠ Update. On 12 September 2022 (the 60th Anniversary of President John F. Kennedy's Moonshot Address made in 1962), President Joseph R. Biden detailed progress of the Cancer Moonshot℠ in "ending cancer as we know it for all." In his speech, the President emphasized that beating cancer is something "we can do together" and announced several NCI initiatives. Additionally, President Biden introduced Dr. Bertagnolli and spoke on how "we can usher in the same unwillingness to postpone the same national purpose to end cancer as we know it."

In support of the next phase of the Cancer Moonshot℠, the NCI has issued requests for applications (RFAs) for implementing three new programs: Cancer Moonshot℠ Scholars, Telehealth Research Centers of Excellence (TRACE), and multi-cancer detection. The first cohort of Scholars is anticipated to be announced in 2023. The NCI issued the first TRACE awards to four academic institutions in August 2022. The multi-cancer detection effort has been endorsed widely and is underway.

An important component of the reignited Cancer Moonshot℠, as well as a long-term commitment for the NCI, is to increase enrollment of underrepresented groups in NCI clinical trials. The goal is to mimic at-risk populations for the specific cancer studied, emphasizing a need for greater investment (e.g., community engagement) and more diversity among health care providers. The NCI is in the process of taking steps to ensure that this becomes a reality. The NCI Equity and Inclusion Program

will host the NCI Summit on Increasing Diversity, Equity and Inclusion in Early Phase Clinical Trials on 16 November 2022. The aim is to identify and discuss the implementation of best practices for increasing inclusion and equity in NCI cancer clinical trials. Dr. Lowy acknowledged Dr. Worta McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention (DCP), and her team, who have led this effort within the NCI Community Oncology Research Program (NCORP). Minority accruals in the NCI's National Clinical Trials Network (NCTN) increased from 14 percent during the effort's initial 3-year period (1999–2001) to 25 percent during the most recent 3-year period (2017–2019). The majority of the increase in enrollment has been in Black/African American and Hispanic populations. Minority enrollment data collected during the pandemic from 2020 and 2021 are pending.

Annual Plan and Fiscal Year (FY) 2023 Budget. The *NCI Annual Plan and Budget Proposal for Fiscal Year 2024* was published in September 2022. The Annual Plan (also called Bypass Budget or Professional Judgment Budget) highlights four areas of scientific opportunities: multi-cancer detection tests, undruggable targets, cell therapy, and persistent poverty. Dr. Lowy remarked that the number of undruggable cancer targets has diminished substantially during the past decades. Targeting tumor suppressor proteins directly remains a challenge; however, the positive factors that contribute to the induction and maintenance of cancer are coming into fruition in novel candidate interventions.

This year, the NCI Professional Judgment Budget for FY 2024 proposes $9.98 billion for the base appropriations, which supports investigator-initiated research, the FNLCR, and the Specialized Programs of Research Excellence (SPORE) program. The FY 2023 appropriations are pending, and the government is operating under a continuing resolution that expires on 16 December 2022. The House passed its bill out of committee and proposed a $466 million (M) increase for the NCI. The Senate's draft bill proposed a $290 M increase. The NCI anticipates that the FY 2023 enacted appropriations will continue the trend of being more than the President's budget proposal.

III. NCI DIRECTOR'S REMARKS—DR. MONICA M. BERTAGNOLLI

Dr. Monica M. Bertagnolli, NCI Director, also welcomed the FNLAC members and attendees to the meeting. She expressed appreciation to Dr. Lowy, Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, Director, Division of Cancer Treatment and Diagnosis (DCTD); Dr. Dinah S. Singer, Deputy Director, Scientific Strategy and Development; and Ms. Anne Lubenow, Chief of Staff, for making this transition seamless. She also expressed appreciation to Dr. Lowy for serving as Acting NCI Director for the third time and for moving the NCI through its mission without any loss of forward momentum. Dr. Bertagnolli noted her experience working with the Mitre Corporation, which manages FFRDCs. She has been a collaborator in many FFRDC activities, with the most significant being related to cancer. She is familiar with the FFRDC mechanism and understands that it brings an essential component to the NCI: infrastructure support for intramural investigators, which is crucial and would be difficult to achieve in other ways. Aside from this important service, the FFRDC provides the NCI the flexibility to bring in expertise as necessary to undertake special projects that have very highly defined scope and limited duration and to achieve goals that then can be disseminated to the entire world to the benefit of those who are tackling problems in health.

In the discussion, the following points were made:

- In the next phase of the Cancer Moonshot^{SM}, the NCI has proposed to increase the pipeline of new drugs anticipated to extend the range of undruggable targets that can be manipulated. New candidates can be submitted either via the NCI Experimental Therapeutics (NExT) program managed by the FNLCR or through other mechanisms of investigator-initiated research. The productivity of the NExT program has been significant.

- Robust, basic science initiatives focused on developing clinical treatment and prevention approaches remains at the core of what the NCI does regarding better understanding cancer and its diversity across populations.

- To address the diminishing role of surgeon scientists, who play a unique role in translating fundamental basic findings to the clinic, a program focused on NIH-funded grants would be needed to augment salaries and provide protected time for research.

- New NCI career development awards for surgeons in training are requiring 50 percent rather than 75 percent of time as a minimum commitment. The overall number of surgeon scientists receiving NCI awards has increased over the years, compared with physician scientists in general.

- The NCI-Designated Cancer Centers (Cancer Centers) could include, as an institutional commitment, a requirement that academic institutions help to support protected time for research.

- The Cancer Adoptive Cell Therapy Network (Can-ACT) is one of the NCI's recent approaches to addressing cell therapy as a priority in the budget and RFAs recently have been issued.

- The NCI is exploring ways to increase access to NCTN data. Approaches aimed at matching these data with the appropriate researchers will be essential.

- The greatest health disparity in gynecological cancers today is among Black/African American women diagnosed with endometrial cancer. The incidence is rising rapidly, and the mortality is significant. The hope is to find ways to bridge basic science findings of the high-grade, aggressive molecular types of endometrial cancer with what is observed in the clinic. Cancer Moonshot^{SM}-related activities have been helping to bridge this gap, and the NCI is planning a workshop in 2023 on this topic.

IV. RECOGNITION OF RETIRING FNLAC MEMBERS—DR. DOUGLAS R. LOWY

On behalf of the NCI, Dr. Lowy recognized the contributions made by members of the FNLAC whose terms of office have expired. He expressed appreciation for their service and dedication over the course of their terms. The following FNLAC members are retiring: 1) Dr. Catherine M. Bollard, Director, Center for Cancer and Immunology, Professor, Pediatrics and Immunology, Children's Research Institute, Children's National Hospital, The George Washington University and 2) Dr. Lincoln D. Stein, Director, Informatics and Biological Computing Platform, Ontario Institute for Cancer Research, Professor, Department of Molecular Genetics, University of Toronto, MaRS Centre.

V. CRYO-ELECTRON MICROSCOPY (CRYO-EM) TRAINING—DR. DWIGHT NISSLEY

Dr. Dwight Nissley, Director, Cancer Research Technology Program, FNLCR, and National Cryo-Electron Microscopy Facility (NCEF) organizational lead, introduced the NCEF Cryo-EM Training Program and began with a brief history. Launched in 2017 and housed at the Advanced Technology Research Facility (ATRF) on the FNLCR campus, the NCEF is an extramural user facility for cryo-EM data collection. In 2019, a Cryo-EM Research and Development component (renamed Advanced Cryo-EM Technology [ACT] Group), was established to explore new platforms, methods, and technology development for the cryo-EM field.

Dr. Nissley noted the three user communities that engage the extramural community in the NCEF. He informed members that Group 1 represents researchers with experience in cryo-EM technology who have some access to local screening microscopes but inadequate access to high-end

instrumentation; Group 2 represents structural biologists in adjacent disciplines (e.g., X-ray, nuclear magnetic resonance spectroscopy) who possess expertise in protein biochemistry but need training in cryo-EM specimen preparation, data collection, and processing; and Group 3 represents biologists with interests in important biomedical problems who are interested in adding cryo-EM methods to their toolkit but need training and collaboration in all aspects of the workflow (i.e., from protein purification to the final interpretation of the structures).

The NCEF began serving the Group 1 users by setting up the data collection capabilities and has had several accomplishments. During the past 5 years, the NCEF has provided data for, or supported, more than 125 extramural investigators in 50 academic/research institutions with 880 imaging sessions. During the past year, data on solving high-resolution structures were published in 29 peer-reviewed journals, with a total of 80 publications across the life of the facility. The NCEF houses two Titan™ Krios microscopes equipped with Gatan K3 cameras and Gatan BioQuantum K3 imaging filters at the ATRF. General imaging across the two microscopes collects 6,000–7,000 images concurrently for a 2-day session. Fringe-free imaging recently was added and increases the amount of data that can be acquired during a collection session. Software updates in the system workflow aims to double throughput.

For Group 2 users, efforts are focusing on providing grid preparation and screening services using a newer generation of grid-freezing technology. A VitroJet™ has been installed at the ATRF and is being validated currently. The technology component, the ACT Group, has a goal of pushing the cryo-EM resolution limits on lower cost and lower voltage microscopes. The Group is exploring 200 kiloelectron volt microscopes (e.g., JEOL Inc. CRYO ARM™ 200, Thermo Fisher Glacios).

To engage the Group 3 users long-term, the FNLCR launched the inaugural NCEF Cryo-EM Training Program in September 2022. This 5-day training featured guest lecturers, including FNLCR experts and invited faculty in the morning sessions and moved into the NCEF for comprehensive hands-on training in a laboratory setting in the afternoons. The first cohort consisted of 12 participants selected from a pool of 60 applicants. Dr. Nissley reviewed the 5-day training agenda and acknowledged the NCEF and ACT teams, who organized the program. Future training sessions are being considered.

In the discussion, the following point was made:

- The NCI established the NCEF in 2017 to focus on cancer-related topics. In 2018, the NIH Common Fund launched an initiative to establish three regional centers for cryo-EM to provide services to the broader biomedical research community.

VI. Patient-Derived Models Repository (PDMR)—Drs. James H. Doroshow and Yvonne A. Evrard

Dr. James Doroshow provided an update on the PDMR model development, distributions, and preclinical studies. Dr. Doroshow stated that the PDMR, which launched in May 2017, serves as a resource for academic discovery efforts and public–private partnerships for drug discovery. The purpose is to collect and develop clinically annotated and molecularly characterized models with quality metrics. The main goal is to complement existing patient-derived model collections and focus on underrepresented models (e.g., rare cancers) and models representing racial and ethnic minorities. The NCI aims to provide models to the research community at a modest cost compared with other distributors. All related metadata, including deidentified patient clinical history and outcomes, model histology, and standard operating procedures, are made available through the PDMR website.

Members were informed that the PDMR has collected nearly 4,000 specimens from academic and research organizations across the United States; many are rare tumors. The patient-derived xenograft (PDX) tumor take-rates (i.e., ability to grow) from tissue implantations into host mice align with the

published data but vary across disease states and histologies. For example, head and neck cancers and malignant melanomas show higher tumor take-rates compared with hormone-responsive breast cancers. In response to FNLAC's prior recommendations on collaborating with institutions to collect specimens from warm autopsies, the PDMR team partnered with four Rapid Autopsy Programs (RAPs) to obtain autopsy specimens from primary tumors and metastatic disease. To date, 453 RAP specimens collected from 82 patients have been submitted to the PDMR. Another goal, whenever possible, is to develop all four models, PDX, patient-derived tumor cell cultures, cancer-associated fibroblasts, and patient-derived organoids, from matched specimens for comparative preclinical studies. These matched models can support mid- to high-throughput translational screening. The PDMR has distributed 2,500 total models among the academic, commercial, and intramural communities. Most of the Cancer Centers are accessing the repository. Major biotechnology and pharmaceutical companies have requested a large number of models to supplement their existing activities.

Dr. Doroshow described a revisit of a systematic study evaluating several drug combinations across NCI-60 Human Tumor Cell Lines Screen to identify unique anticancer drug pairs that would not necessarily have been predicted. The combination of nilotinib and paclitaxel was active in many cell lines in the screen, but the mechanism of action was not clear. Using 39 PDX models, Dr. Doroshow and his team showed an upregulation of cytokines, demonstrating the utility of the PDMR models for screening and mechanistic studies.

Dr. Yvonne A. Evrard, Operations and Program Manager, PDMR, FNLCR, provided an update on the efforts of PDX Development and Trial Centers (PDTCs) Research Network (PDXNet) in standardizing the reporting of preclinical tumor responses. The PDTCs and PDMR, coordinated through the PDX Data Commons and Coordinating Center, worked on a PDXNet tumor volume assessment project. No standard approach for *in vivo* tumor growth assessment is used across studies, making comparative responses challenging. The PDXNet team, led by Dr. Funda Meric-Bernstam at the MD Anderson Cancer Center, has developed a suite of tools tentatively named the PDX Volumetric Analyzer to address this challenge; it is in the final phase of development before making it available to the community in the public domain. Users will be able to upload tumor volume data with the provided template. Dr. Evrard demonstrated use of the tools and PDX volumetric analyzer, noting study data displays, summaries, and anti-tumor activities. Dr. Evrard highlighted more than 15 recommendations on reporting drug activity in the PDX models resulting from this project that also will be published with the suite of tools for community use. For example, conducting experiments using clinically relevant doses and schedules and assessing anti-tumor activity using a combination of two or more measurements.

In the discussion, the following points were made:

- The National Center for Advancing Translational Sciences maintains the Assay Guidance Manual; this would be a good platform to incorporate information on assays developed in support of the PDMR.

- A mechanism is in place to connect the PDMR resources with major data centers and the PDXNet also provides models to the repository.

- Many of the activities of the PDMR resonate with biobanking; a presentation to the International Society for Biological and Environmental Repositories and the Society for Cryobiology on these efforts might be valuable.

VII. FREDERICK TECHNOLOGY SHOWCASE—DRS. MICHAEL SALGALLER AND VLADIMIR POPOV

Dr. Michael Salgaller, Supervisor, Technology Analysis and Marketing Unit, Technology Transfer Center (TTC), NCI, explained that the NCI and FNLCR Annual Technology Showcase (Showcase) began after a meeting in late 2016 with representatives from Frederick County, Maryland, and the City of Frederick, Maryland, who were interested in creating a better understanding and awareness of the cancer research being performed at the FNLCR and NCI. Dr. Salgaller informed members that the inaugural year, 2017, was a half-day event, expanded to a full-day event in 2018 with keynote addresses, participation of the Technology Transfer Ambassadors Program (TTAP), and poster pitches added. In 2019, based on feedback from participants, the event returned to a half-day format and included panels on various topics. In 2020, the platform transitioned to a virtual showcase, with outreach to 13 states and 6 countries. The TTC/FNLCR team received the NCI Director's Award. The Showcase added the patient's voice in 2021, included a fully virtual event, and was the recipient of the Federal Laboratory Consortium's State and Local Economic Development Award. In 2022, the Showcase was a hybrid event, with in-person and virtual attendance. Nearly 300 people attended, and programmatic presentations were added.

Dr. Vladimir Popov, Chief Innovation Officer, Center for Innovation and Strategic Partnership (CISP), FNLCR, noted that the Showcase is the only NIH conference with potential licensees and collaborators as primary audience, with an agenda that addresses their interests. The event has a co-sponsorship agreement with economic development offices of Frederick City/County, Maryland Technology Development Corporation (TEDCO), and the Federal Lab Consortium (FLC) to leverage resources, relationships, and expertise. The Showcase provides Principal Investigators opportunities to develop a business case presentation and provides postdoctoral scientists opportunities with the TTAP. Within the missions of the NCI and FNLCR, the Showcase addresses the gap in activities found in federal laboratories and provides a venue to display unique capabilities and expertise while promoting intellectual property developed therein. Commercialization and further development of these technologies is crucial to advance cancer research and treatments. The Showcase promotes best ideas available for collaboration and licensing, attracts new research and development resources and unique collaborators, represents the return on public investment, and stimulates and strengthens the economic development, thus benefiting public health. Dr. Popov highlighted reasons why this Showcase is a good for hosting in Frederick County, including the FNLCR and more than 100 life science companies.

Dr. Salgaller noted the target audience was expanded to include potential partners, such as national and international companies, and entrepreneurs' referral sources, such as trade associations and foundations. In 2022, 51 percent of Showcase attendees were from the NIH, NCI, or FNLCR; 26 percent represented companies; 10 percent represented other groups; 6 percent represented universities, and the balance represented foundations, accelerators, and investors. This Showcase addresses common myths about the NIH by focusing on translational and clinical research, working with hundreds of partners locally and internationally, and soliciting ideas externally.

Dr. Popov reviewed the 2022 Showcase agenda, highlighting the keynote speakers and benefits of the event specific to the FNLCR. The event educates the public on ways to partner with the FNLCR and NCI; highlights programs and laboratories; and reports unique services available to the external research community. The FNLCR and NCI scientists are educated on the industry innovations through 10-minute presentations including a business case and market analysis prepared by those representatives. Successful outcomes of the Showcase include a timeline of connecting technology to licensing, as well as establishment of partnerships and collaborations. In terms of outreach, the CISP has hosted 30 external events in 2022 and served as panelists, keynote speaker, or exhibitor at 20 events.

In the discussion, the following points were made:

- The Technology Showcase and the activities of Leidos, Inc., which owns Leidos Biomedical Research, Inc. that operates the FNLCR, are mutually exclusive.

- In terms of return on NCI investments, a technology transfer representative assists companies interested in a particular technology following a Showcase with next steps, including intellectual property, agreements, and licensing.

- The CISP and Showcase organizers could consider connecting with other groups about their approaches to technological translation and company start-ups.

- The NCI Technology Transfer Center sponsors Advancing Innovations through Mentorship (AIM), which is inspired by the I-Corps at NIH™ program.

VIII. RAS WORKING GROUP REPORT—DR. DAVID A. TUVESON

Dr. David A. Tuveson, Roy J. Zuckerberg Professor, Director of the Cancer Center, Cold Spring Harbor Laboratory and Chair of the FNLAC RAS *ad hoc* Working Group, gave the report from the Working Group on the NCI RAS Initiative. Dr. Tuveson informed members that the RAS Initiative was established in 2013, with the overarching goal to mobilize the cancer research community to develop ways to understand and target cancers driven by mutant *KRAS* (one of three human *RAS* genes involved in cell growth, cell maturation, and cell death) in an open research model of collaborations among government, academic, and industrial researchers. This aim is to leverage the state-of-the-art facilities at FNLCR, which now serves as a hub for the RAS Initiative and collaborating laboratories.

The initial 5-year funding cycle addressed critical knowledge gaps that had impeded the pursuit of RAS as a drug target. The program was reviewed and renewed in 2017, with a recommended increased focus on identifying and advancing RAS therapeutic compounds and developing a biophysical model of RAS activation and signaling in the membrane. Dr. Tuveson highlighted that the past 4 years have shown that with serious concentrated attention, all of the aspirational goals translated into accomplishments, resulting from structural biology, biochemistry, biophysics, and medicinal chemistry efforts.

The mission of the 12-member Working Group is to advise strategic, technical, and scientific aspects of the NCI RAS Initiative and present findings and recommendations to the FNLAC. The goals are to provide oversight to the program leaders and the FNLCR team, conduct regular and candid assessments of progress and suggestions for improvements or pivots, and ensure optimal connectivity between the FNLCR RAS Initiative and the extramural community. The Working Group convened nine meetings from September 2018 to August 2022. Today's objectives are to review progress during the current program cycle and provide recommendations for future directions. Dr. Tuveson summarized the accomplishments across key thematic areas of advancement, all aiming to provide new therapeutic opportunities.

RAS Dependencies and Membrane Biology. The RAS Team developed cell culture systems to identify distinguishing properties of RAS mutants, for example, glutamine and oxidation and reduction metabolism, which correlates with resistance to existing treatments used in the clinic. Top-down mass spectroscopy methods enabled unprecedented analyses of intact KRAS4b proteoforms in cancer cells, revealing distinct post-translational modifications on KRAS oncoprotein subpopulations. The synthetic membrane systems developed were used to test hypotheses about KRAS signaling.

Targeting RAS and RAS-Effector Interactions. Structural biology efforts targeting two effectors, rapidly accelerated fibrosarcoma 1 (RAF1) kinase and phosphoinositide 3-kinase (PI3K), has led to new discoveries. The RAS Team was the first in the field to solve the crystal structure of the KRAS RAS binding domain in a complex with the RAF1 cysteine-rich domain, suggesting a larger footprint in this region of RAS than described previously. The RAS Initiative is the first to solve the structure of KRAS-PI3K alpha (a) and to demonstrate that neurofibromin 1 (NF-1) forms high-affinity dimers.

RAS Biophysics, Molecular Dynamics, and Computational Biology. The RAS Team identified a major subpopulation of KRAS conformers that are displaced from the membrane and available to promote RAF activation. Molecular dynamics and surface plasmon resonance approaches were used to measure and predict the behavior of the RAS-RAF complex with lipid bilayer constituents. A multi-year collaboration with the U.S. Department of Energy Lawrence Livermore National Laboratory matched supercomputing and machine learning approaches to develop a multiscale computational model that allows simulations of hundreds of RAS and RAF molecules on a realistic 8-lipid membrane at time scales. The RAS drug discovery and development efforts resulted in the development of a KRAS mutant G12C inhibitor that was accelerated in the pipeline through strategic partnership. The RAS Team discovered a first-in-class RAS/PI3Ka complex small-molecule disruptor with an improved safety profile.

Fostering Interactions Between the RAS Initiative and the Scientific Community. Efforts continued to promote and mediate the sharing of knowledge and resources among RAS researchers in the academic, government, and private sectors. During this funding cycle, RAS Initiative investigators had 66 publications in peer-reviewed, high-impact journals. The RAS Reagent Group serves as a major hub and distributor of cell lines, protocols, and reference reagents. The RAS Team and FNLCR have sponsored RAS symposia and manages the RAS Lab Discussion forum.

Dr. Tuveson concluded that the RAS Initiative has exceeded its objectives since its inception, despite COVID-19 challenges. Two clinical candidates, KRAS G12C covalent binding inhibitor and KRAS/PI3Ka complex breaker, show promise in advancing to FDA investigational new drug approvals and clinical evaluation in 2023. The capabilities in structural, biochemical, and biophysical approaches have enabled targeting of the more common KRAS-G12D and KRAS-G12V oncoproteins and broadened the target landscape to include RAS effector and regulator proteins. The studies related to RAS biochemistry and regulation of NF-1 have been impactful. Biophysical and modeling revealed that RAS exists in dynamic states on the plasma membrane, with implications in signaling and drug development.

The RAS *ad hoc* Working Group offers the following recommendations for consideration during the next stage of the RAS Initiative:

- Continue efforts to translate in-house NCI RAS Initiative compounds to the clinic.
- Continue the pursuit of secondary targets, such as the PI3Ka-RAS “complex breaker” compound, for use as salvage or combination therapy.
- Continue to catalyze the renaissance in RAS targeting approaches on a global scale.
- Expand community engagement to further the impact of the NCI RAS Initiative.

In the discussion, the following points were made:

- At this phase of the RAS Initiative, it will be critical to know whether the promising drug candidates are “best in class” and likely will require evaluations in combination therapies. The NCI can consider conducting such studies.

- Developing unique RAS-specific PDX models is achievable, but the immune response, which is relevant in on-target therapies, would need to be considered.

Motion: A motion to accept the report of the RAS *ad hoc* Working Group was approved unanimously.

IX. ONGOING AND NEW BUSINESS—DR. CANDACE S. JOHNSON

Establishment of NCI RAS Initiative Evaluation Team *ad hoc* Working Group. Dr. Christopher D. Kane, Program Officer, Office of Scientific Operations, NCI at Frederick, explained that the NCI RAS Initiative Research Team is seeking an additional 5-year renewal. Dr. Kane stated that the renewal was needed to advance new preclinical and clinical drug candidates into clinical trials; broaden the RAS-directed therapeutics to additional RAS alleles and regulatory/effector proteins; and pursue other innovative strategies and technologies.

To facilitate this process, Dr. Kane noted that the NCI is seeking to establish a RAS Initiative Evaluation Team (RIET) Working Group (WG). Specifically, the WG will evaluate the scientific merit, productivity, and innovation of the RAS Initiative. The FNLAC RIET Working Group will conduct a review of the Renewal Package, which will include a report and recommendations of the FNLAC RAS *ad hoc* Working Group, a full written proposal provided by the RAS Initiative Research Team, and an in-person session report provided by the RAS Initiative Research Team.

The RIET Working Group will advise the FNLAC and NCI Director. The RIET Working Group will also conduct the technical review of the RAS Initiative Renewal Package and will generate a written report and recommendation which will be presented at the 27 February 2023 FNLAC meeting.

The RIET Working Group shall be composed of highly regarded scientists recruited from the academic research community and the private sector. Scientific excellence and domain expertise will be drawn from academic RAS and cancer biology researchers, biopharmaceutical/research institute experts, and structural biologists with relevant drug discovery and development experience, all balanced for gender, racial, and ethnic demographics.

Motion: A motion to concur on the establishment of the FNLAC NCI RAS Initiative Evaluation Team *ad hoc* Working Group was approved unanimously.

Updated Mission Statements of the FNLAC *Ad Hoc* National Cryo-Electron Microscopy Program Oversight Subcommittee and the *Ad Hoc* National Cryo-Electron Microscopy Program Oversight Working Group.

Dr. Johnson noted that the FNLAC needed to approve the updated mission statements of the ad hoc Cryo-EM Program Oversight Subcommittee and the related ad hoc Cryo-EM Working Group.

Motion: A motion to approve the updated mission statements of the FNLAC *ad hoc* National Cryo-Electron Microscopy Program Oversight Working Group and FNLAC *ad hoc* National Cryo-Electron Microscopy Program Oversight Subcommittee was approved unanimously.

X. ADJOURNMENT—DR. CANDACE S. JOHNSON

Dr. Johnson expressed appreciation to the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lopaczynski. There being no further business, the 11th Virtual Meeting of the FNLAC was adjourned at 2:46 p.m. EDT on Wednesday, 12 October 2022.

Date	Candace S. Johnson, Ph.D., Chair
Date	Wlodek Lopaczynski, M.D., Ph.D., Executive Secretary