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

13th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
July 10, 2023

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
13th Virtual Meeting of the Frederick National Laboratory Advisory Committee

10 July 2023

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 13th Virtual Meeting on 10 July 2023. The meeting was open to the public from 1:00 to 3:50 p.m. 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
Dr. Carol J. Bult
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 (absent)
Dr. Anant Madabhushi
Dr. Nilsa C. Ramirez Milan
Dr. Denise J. Montell
Dr. Patrick Nana-Sinkam
Dr. Erle S. Robertson
Dr. Linda F. van Dyk

NCI Senior Leadership
Dr. Monica M. Bertagnolli
Dr. Stephen J. Chanock
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage
Dr. Kristin L. Komschlies
Dr. Douglas R. Lowy
Dr. Tom Misteli (absent)
Ms. Donna Siegle (absent)
Dr. Dinah S. Singer

Executive Secretary
Dr. Wlodek Lopaczynski

TABLE OF CONTENTS

I. OPENING REMARKS—DR. CANDACE S. JOHNSON

Dr. Candace. S. Johnson, Chair, called to order the 13th 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 February 2023 FNLAC meeting was approved unanimously.

Dr. Johnson called Committee members' attention to the future meeting dates listed on the agenda, noting that the 2025 proposed meeting dates will need to be confirmed. The next FNLAC meeting will be held on 19–20 October 2023 and is planned as an in-person meeting.

Motion. A motion to confirm the 2025 FNLAC meeting dates was approved unanimously.

II. NCI DIRECTOR'S REPORT—DR. MONICA M. BERTAGNOLLI

Dr. Monica M. Bertagnolli, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. Dr. Bertagnolli reviewed the agenda and provided updates on the NCI budget, cancer drug shortages, the National Cancer Plan (NCP), and NCI program activities and personnel.

NCI Budget. Dr. Bertagnolli reported that debt limit and budget negotiations indicate flat funding for the government for the next 2 years. She highlighted the importance of being transparent about how public funding is spent and reviewed NCI's budget expenditures. The Research Project Grant (RPG) pool is the largest investment of NCI funding, at 44 percent of the total budget. Non-RPG activities include the NCI-Designated Cancer Centers (Cancer Centers) and Specialized Programs of Research Excellence (SPOREs) at 8 percent; other research grants (e.g., career development awards) at 9 percent; National Research Service Awards at 1 percent; and research and development contracts at 12 percent, which support the extramural community via the Frederick National Laboratory for Cancer Research (FNLCR). Research and management comprise only 7 percent of the NCI budget, and 18 percent supports intramural research.

From fiscal year (FY) 2016 to FY 2023, the NCI appropriations (base and total) steadily increased, amounting to $7 billion (B) in FY 2023 and including funding for the Cancer Moonshot℠ initiative, which is in its final year of 21st Century Cures Act funding; the Childhood Cancer Data Initiative (CCDI); and COVID-19 serology research, which began in April 2020. During this same period, the NCI increased paylines for early-stage investigators (ESIs) seeking R01s/R37s from the 12th to 17th percentile. For established investigators, the payline was at the 10th percentile in FY 2016, decreased to the 8th percentile in FY 2019, and reached the 12th percentile in FY 2023. Dr. Bertagnolli underscored the importance of raising paylines to maximize investments in cancer research.

NCI's budget has increased from $4.6 B to $7.1 B since FY 2003, but its adjusted purchasing power has decreased by 13 percent during this period as a result of inflation. Dr. Bertagnolli emphasized that this loss of purchasing power represents significant challenges in NCI's ability to fund researchers, invest in critical infrastructure, and support trainees. A flat budget would lead to additional challenges.

Cancer Drug Shortages. Dr. Bertagnolli explained that cancer drug shortages are making it increasingly difficult to care for cancer patients. The NCI also is concerned about how shortages could affect research. An estimated 170 government-sponsored cancer clinical trials (from active to trials in

review) are potentially affected by these shortages. Dr. Bertagnolli emphasized that it is critical that all people with a cancer diagnosis have access to the drugs that their doctors prescribe.

National Cancer Plan. Dr. Bertagnolli explained that societal-level changes are essential to achieving the goals of the Cancer Moonshot initiative. The NCP outlines eight goals: prevent cancer, detect cancers early, develop effective treatments, eliminate inequities, deliver optimal care, engage every person, maximize data utility, and optimize the workforce. These goals are accompanied by strategies, as well as the current state of science. Dr. Bertagnolli explained that the document will be revised as new opportunities and needs emerge over time.

The President's Cancer Panel will be assisting the NCI in monitoring the NCP. This process will involve two components: (1) engaging the community in public sessions to discuss contributions and demonstrate progress to the public and (2) tracking progress over time in annual reporting and in-depth reviews. Dr. Bertagnolli emphasized that the plan is intended to break down barriers to collaboration across the cancer research community. The NCP can be accessed on the NCI website, which includes an NCP Digital Toolkit.

NCI Program and Personnel Updates. Dr. Bertagnolli reported that the Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH) is open and enrolling patients and is a follow-up trial to NCI-MATCH. ComboMATCH is being coordinated through the ECOG-ACRIN Cancer Research Group and is the largest initiative of its kind to test combinations of cancer drugs; identify promising treatments; and advance them to larger, more definitive trials. ComboMATCH comprises numerous Phase 2 treatment trials, each evaluating a drug combination of either two targeted drugs or a targeted drug plus a chemotherapy agent. The combinations include U.S. Food and Drug Administration (FDA)–approved drugs and investigational agents contributed by pharmaceutical companies. Notably, ComboMATCH also includes children, whereas NCI-MATCH focused on adults.

The Pragmatica-Lung Cancer Treatment Trial is designed to eliminate potential barriers to enrollment, increase diversity and enrollment, streamline processes, and use focused endpoints and efficient data collection. The goal of the Pragmatica-Lung trial is to determine whether a combination of drugs can help those with advanced lung cancer live longer than with standard chemotherapy. The trial is being performed in collaboration with the FDA, NCI's National Clinical Trials Network (NCTN), NCI's Cancer Therapy Evaluation Program (CTEP), and two drug companies. The first concept presentation was shared in August 2022, and the first patient accrual occurred in March 2023. Dr. Bertagnolli underscored the importance of this effort in bringing trials to patients more quickly.

Dr. Bertagnolli remarked that the RAS Initiative has been renewed for 5 years and noted that Dr. Frank McCormick would provide an update later in the meeting. Dr. Bertagnolli also underscored the value of core FNLCR resources and programs for the research community and spoke on the importance of increasing awareness of the resource. She shared recent updates from the FNLCR, which include the consensus on RAS dimerization and new trials for a next-generation SARS-CoV-2 vaccine. The contract for operating the FNLCR, which is a Federally Funded Research and Development Center, is up for recompetition, and proposals are being evaluated currently. The award date is planned tentatively for 2024.

Dr. James L. Gulley has been selected as the Clinical Director of NCI's Center for Cancer Research (CCR), pending formal NIH approval. In his new role, Dr. Gulley will oversee the day-to-day operations of more than 350 active clinical trials in the NCI Intramural Research Program. Dr. Bertagnolli outlined unique features of the CCR, which include stable investigator resources, access to and development of cutting-edge technologies through the FNLCR, and access to the NIH Clinical Center. She briefly highlighted CCR scientific breakthroughs and recent FDA approvals.

A search for NCI's first Deputy Director for Data Science is underway. Dr. Bertagnolli spoke on the critical importance of addressing questions related to data usage, innovation, sharing, and access for intramural and extramural research. The new Deputy Director for Data Science will guide key data science initiatives; lead the NCI in efforts to collect, store, analyze, and share data; and build strategic partnerships to develop and disseminate advanced technologies and methods.

In the discussion, the following points were made:

- The Advanced Research Projects Agency for Health (ARPA-H) is still in early development, and its relationships with federal partners are being strengthened as the ARPA-H continues to mature. Numerous opportunities exist for collaboration in the areas of tools, technologies, approaches, and research directions. The NCI will be an active partner in future efforts.

- The NCI is committed to understanding the underlying biology of computational findings, and the endpoints for ComboMATCH reflect this principle. ComboMATCH is focused on molecularly targeted agents. A separate entity, iMATCH, is focused on immunotherapy combinations. Partnerships with pharmaceutical companies are essential for obtaining access agents for such trials. The NCI also recognizes the need for tools and resources to provide infrastructure for imaging data repositories.

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

Ms. M.K. Holohan, Director, Office of Government and Congressional Relations (OGCR), reported on the Fiscal Responsibility Act of 2023 (FRA) and the FY 2024 appropriations process to date.

The new federal debt ceiling agreement (the Fiscal Responsibility Act, or FRA) suspended the debt ceiling until January 2025 and set limits on discretionary federal spending for FY 2024 and FY 2025. For FY 2024, the FRA includes a 3.3% increase in defense spending (the amount requested in the President's Budget Request) but caps total overall non-defense discretionary spending at the 2023 level. For FY 2025, the FRA allows a 1% increase to total non-defense discretionary spending.

Congress included penalties in the FRA to ensure that all twelve appropriations bills are completed for FY 2024. The law imposes a 1% penalty on total discretionary spending (defense and non-defense) if all twelve bills are not enacted by 1 January 2024, and the cut will become permanent on April 30th if the bills are still not completed.

Ms. Holohan remarked that many unknowns remain regarding future appropriations for FY 2024. The disparity between the House and Senate budgets is projected to total over $119 billion, and House Appropriations Chair Kay Granger (R-Texas) has announced that she plans to rescind $115 billion from unspent funds (including some funds provided as part of COVID-19 relief efforts) in the process of finalizing the FY 2024 funding bills. The ultra-conservative House Freedom Caucus is opposed to many of the legislative strategies proposed by the Republican majority, which will add to the difficulty in finalizing the spending bills.

Ms. Holohan explained that the President's budget requested $716 M for the reinvigorated Cancer Moonshot (a $500 million increase from FY 2023) and $2.5 B for the Advanced Research Projects Agency for Health (ARPA-H, a $1 billion increase from FY 2023). On 4 May 2023, the Senate Labor–HHS Subcommittee convened an appropriations hearing on the President's FY 2024 budget for the NIH, which was attended by NCI Principal Deputy Director, Dr. Douglas R. Lowy.

Ms. Holohan presented a list of "must-pass" legislation, in addition to FY 2024 funding bills, that must be enacted before the current fiscal year ends on 30 September 2023. These bills include the FDA Animal Drug User Fee Act and Animal Generic Drug User Fee Act, as well as the Pandemic and All-

Hazards Preparedness Act; a new Agricultural Improvement Act, commonly known as the Farm Bill; and the National Defense Authorization Act for FY 2024. Ms. Holohan noted that the House is focused on the oversight of federal programs to prevent waste and fraud (with an emphasis on the COVID-19 response). Possible activities for the future include legislation on drug pricing and oversight hearings convened by the Health, Education, Labor and Pensions Committee and Energy and Commerce Committee.

IV. MOLECULAR PHARMACODYNAMICS OF AN ANTIBODY DRUG CONJUGATE (ADC): DS-8201A—DR. RALPH E. PARCHMENT

Dr. Ralph E. Parchment, Managing Director, Pharmacodynamic Biomarkers Program, Leidos Biomedical Research, Inc., discussed recent work involving mechanism-of-action studies of DS-8201a, an ADC that is constructed by chemically linking a small-molecule drug and payload. Trastuzumab deruxtecan (DS-8201A) is the active pharmaceutical ingredient in ENHERTU®, an approved drug product for both HER2-positive breast cancer and HER2-low breast cancer. Dr. Parchment remarked that profound biological differences are present between the two tumor types.

Published work by other groups have demonstrated that the payload is permeable to the cell membrane; thus, when the linker is cleaved and the payload is released as the drug monomer that targets the DNA topoisomerase (TOP1) within the nucleus, it is capable of diffusing across plasma membranes to kill neighboring cells even if they do not express the ADC target – the so-called "by-stander effect". These dynamics have been demonstrated experimentally in mixtures of two tumor types, one of which expresses the HER2 drug target and one that does not. An analog of Trastuzumab deruxtecan's payload was developed with an ionizable molecule that cannot permeate lipid membranes after cleavage of the linker and release inside of HER2-positive cells; this compound could not kill adjacent, target-negative cells via a by-stander effect and therefore was insufficient in shrinking a mixed tumor model composed of HER2-positive and -negative tumor cells. Taken together, these results help explain the drug's clinical activity in tumors that show heterogenous tumor cell expression of the HER2 drug target. Variability in the response of HER2-positive tumors to the treatment has been documented clinically, indicating that other mechanistic factors are present.

Dr. Parchment's team is investigating whether the payload acts as a classical inhibitor at the level of TOP1 complex formation and resulting DNA damage once it is released from the ADC by cleavage of the linker. Three biomarkers have been developed to measure the target engagement by trastuzumab deruxtecan's payload and its downstream biochemical consequences using fluorescence microscopy. These markers have been used in clinical trials, as well as preclinical cancer models. Multiplex assays have been developed to measure the markers simultaneously. Dr. Parchment explained that this approach provides increased probability of measuring the DNA damage response in a clinical biopsy when the timing of that biopsy is limited to a single timepoint following the start of drug treatment. Additionally, he noted that translational standard operating procedures have been developed to preserve labile phosphorylation sites in tumor specimens through snap freezing at the clinical point of collection followed by controlled thawing in the research laboratory, which enables assessments of this post-translational modification as a component of drug response. Researchers also used additional biomarkers to segment the tumor cells within designated regions of interest in tumor biopsy specimens, which restricts the biomarker analyses to the tumor cells only and enables precise measurements of drug effect in tumor cells without measurement interference from non-tumor cells in the biopsy.

Engagement of the drug target and the mechanism of action of the released payload have been demonstrated using HER2-positive human tumor xenograft models. Using the models, Dr. Parchment's team investigated the molecular pharmacological pathways. Declines in TOP1 were observed in a delayed effect, consistent with upstream events. They measured the cleavable complex, but limited signal was detected. Next, they examined induced DNA damage responses in the xenografts; a persistent response was observed that was consistent with the proposed mechanism of action of the payload. These data

suggest that the conjugated antibody is acting as a depot form of the drug, in which a large dose delivered to the tumor is released over time, leading to sustained inhibition of the TOP1 target.

These studies have informed clinical trial design. Rapid reduction in TOP1 precludes analysis in patient biopsies, but the team has identified biomarkers that are fit for purpose for clinical use; a biopsy sampling window has been identified. The multiple biomarkers provide an opportunity to corroborate the mechanism of action. More work is needed to understand the release and diffusion of the drug payload, as well as the potential mechanism for cell death. The biomarker's robust response indicates the need to trace subsequent biochemical events, cell cycle context, and the potential connection between DNA damage and activation of cell death pathways. Dr. Parchment emphasized the need to distinguish catastrophic and reparable DNA damage to explain the differences in shrinkage among the tumors models.

This work could inform the development of patient selection markers and has been translated into a pilot study that is being conducted at NCI's Developmental Therapeutics Clinic. Researchers are investigating TOP1 response and DNA damage in patients with advanced solid tumors, representing a range of HER2 levels, during treatment with DS-8201a. Currently, the group is evaluating models that differ in HER2 levels and TOP1 inhibitor sensitivity. Dr. Parchment emphasized that more work is needed to understand the downstream mechanism causing catastrophic versus repairable DNA damage. The team envisions developing a panel of cell lines that reflect the molecular features of the different tumor types that respond to the drug in patients. A biomarker profile could help distinguish differences in tumor responsiveness among patients.

In the discussion, the following points were made:

- The team also is examining accessory cells in tumors and possible immune responses because some of the antibodies possess additional drug activities besides delivering the TOP1 inhibitor payload. This system is highly complex, and more work will be needed to build out from the key findings.

- The response sustainability might be related to the antibody's high stability and delivered dose. The signal could be a tradeoff between the number of payload molecules per antibody molecule and the cell surface density of the HER2 target. This work would provide insight into the response of tumors that exhibit variable HER2 expression levels within heterogenous cell populations and/or that exhibit low levels of HER2 but are highly susceptible to catastrophic DNA damage from low levels of payload.

V. THE CANCER GENOMICS RESEARCH LABORATORY AND DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS (DCEG): A GREAT PARTNERSHIP— DR. STEPHEN J. CHANOCK

Dr. Stephen J. Chanock, Director, DCEG, NCI, spoke on the value of DCEG's partnership with the Cancer Genomics Research Laboratory (CGR). He explained that the DCEG is focused on using epidemiologic and genetic tools to understand the causes of cancer and provide the fundamental insights that inform both preventive and early intervention steps. He emphasized the broad diversity of DCEG's research activities and underscored the importance of interdisciplinary teams, collaborative resources, rapid responses, and long-term investments. The DCEG is composed of eight branches under a trans-divisional research program.

The CGR specializes in the areas of variant detection (e.g., targeted genotyping, exome sequencing, whole-genome sequencing), functional assessment (e.g., methylation arrays, telomere length, functional sequencing), and nonhuman studies (e.g., human papillomavirus [HPV] sequencing,

metagenomic sequencing). The CGR has coauthored more than 400 publications in high-impact journals. Dr. Chanock emphasized that this national resource has been essential to many of DCEG's studies.

The CGR is integrally involved in DCEG's activities from planning to publication; these activities include genotyping, sequencing, sample aliquoting, extraction, quality control, staging, histopathology, functional support, and bioinformatics. This partnership involves technology development, laboratory information management systems, project management, quality management, information technology, and administration. Additionally, the work engages the resources available through the NCI-Frederick biorepository. CGR's dedication to quality management involves the "four Ms": man, method, materials, and machine. This approach involves continual improvement via an active standard operating procedures system, extensive documentation, and benchmarking and controls for all new wet laboratory and analytical pipelines.

The CGR and DCEG have been leading genome-wide association studies (GWAS) since 2006; this work involves developing robust pipelines, with automation to achieve high throughput and quality. Additionally, the work supports several large consortia and involves rare and common cancers, various ancestries, and risk factors shared between cancer and other chronic diseases. These efforts have enabled the development of new maps that can lead to polygenic risk scores with potential clinical implications.

Key aspects of this partnership include leveraging sequencing technologies, managing high-throughput samples, leveraging aliquoting capabilities for new efforts, and expanding molecular and digital pathology to enable somatic studies. Dr. Chanock emphasized that the partnership drives discovery in various areas, including supporting functional validation or characterization of findings, understanding how genetic variations affect cancer susceptibility and outcome, evaluating the functional consequence of genomic and epigenomic alterations, determining the pathogenesis of cancer, and supporting the training of students and fellows.

Dr. Chanock briefly highlighted large-scale initiatives that leverage the partnership. The Sherlock-Lung Study is performing ongoing mutational signature analyses in non-smoking lung adenocarcinoma. The CGR manages the work, generates RNA and methylation data, and supports digital pathology efforts. The Confluence Project is developing a large, cloud-based research resource to better understand breast cancer genetics through GWAS using a diverse population. Additionally, the team is performing follow-up studies on individuals affected by the Chernobyl disaster; the efforts include comprehensive genomic characterization, hosting of an international tissue bank, and a family study to examine potential transgenerational effects, both laying the foundation for important public health considerations. Microbiome studies also have been critical and are focused on methodological work, with a focus on cost-effectiveness and standardization. Other efforts have focused on human genetics and COVID-19 - both with respect to susceptibility to severe COVID and the basic biology of host response.

The DCEG has leveraged CGR's expertise for HPV assay development at high throughput and low cost. This work involves the use of methylation biomarkers, as well as screenfire optimization (e.g., temperature-stable reagents, low-cost instrumentation, screening for high-risk types only) for high-risk screening in low- and middle-income countries. These efforts leverage existing resources and expertise, and laboratory staff are embedded within the existing structure and production lines. This technology now is supporting NCI vaccine trials in Costa Rica.

Dr. Chanock also emphasized that the partnership drives and supports FAIR (Findability, Accessibility, Interoperability, and Reusability) Data Principles. Their work involves pipeline optimization and migration; support for investigator-driven analysis for functional and biological insights; development of support for new applications for single-cell, spatial biology, and artificial intelligence–based applications; a dedicated bioinformatics staff; and active coordination with DCEG's Bioinformatics Virtual Core.

VI. UPDATE: RAS INITIATIVE—DR. FRANK MCCORMICK

Dr. Frank McCormick, RAS National Program Advisor, FNLCR, David A. Wood Distinguished Professorship of Tumor Biology and Cancer Research, Professor, Helen Diller Family Comprehensive Cancer Center and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, reviewed progress made by the RAS Initiative and future program goals. Many cancers are driven by mutations in the *RAS* gene family (e.g., *HRAS*, *KRAS*, *NRAS*), but mutant RAS proteins were deemed undruggable because they lack binding pockets for drug interactions. The goals of the RAS Initiative during the next 5 years include clinically testing direct inhibitors of the active forms of KRAS and RAS–PI3Kα interaction inhibitors; developing molecular descriptions of the activation of rapidly accelerated fibrosarcoma (RAF) kinase by RAS; performing structural analyses of RAS protein complexes to facilitate new approaches to drug discovery; elucidating mechanisms of resistance to RAS and RAS-related inhibitors; developing NRAS inhibitors and inhibitors of other GTPases; identifying RAS proteoforms (i.e., distinct molecular forms of a protein product arising from a single gene); and elucidating the mechanisms that regulate the neurofibromin (NF1) protein, a GTPase-activating protein that functions as a tumor suppressor by turning off RAS signaling.

Dr. McCormick explained that the RAS Initiative has served as a hub in a hub-and-spoke research model. Strategic collaborations with commercial, government, and academic "spoke" organizations are ongoing and essential to the program. The RAS Initiative is committed to community engagement through networking and scientific presentations at RAS Initiative symposia and the RAS Initiative website, which attracts more than 11,000 visitors each month.

The RAS Initiative has distributed high-quality reagents to 623 universities and nonprofit organizations in 43 U.S. states and 45 countries on six continents. Addgene, a nonprofit plasmid repository, has helped distribute 13,127 RAS Initiative plasmids and vectors to the scientific community. The FNLCR has shared 1,503 cell lines generated by the RAS Initiative. RAS-dependent mouse embryonic fibroblast cell lines have been licensed to 23 companies and distributed by 97 academic groups. Farnesylated and fully processed KRAS materials have been licensed to seven companies. The RAS Initiative team is developing a catalog of the RAS isoform variations across tumors. Additionally, biochemical and structural analysis of various *KRAS* mutants can offer insights into resistance to NF1 for the research community.

A major goal of the RAS Initiative has been to elucidate the molecular mechanisms of RAF membrane recruitment and activation by RAS. An area of interest for the RAS Initiative is RAF activation via the low-affinity interaction of RAS with the RAF RAS-binding domain (RBD) and cysteine-rich domain (CRD). The RAS–RAF interface can be targeted by RBDCRD binders that sterically inhibit RAS binding or by compounds that bind to the KRAS–RAF complex and target the entire structure for degradation. The SHOC2–MRAS–PP1C (SMP) complex, a potential druggable target, dephosphorylates serine 259 on RAF, a critical component of RAS signaling that is activated in cancers caused by mutant *RAS*. The RAS Initiative and other groups recently have solved high-resolution crystal structures of the SMP complex.

The AI-Driven Multiscale Investigation of the RAS/RAF Activation Lifecycle (or ADMIRRAL) project is part of a series of efforts in the U.S. Department of Energy–FNLCR collaboration to elucidate the RAS–RAF activation life cycle through molecular dynamics simulation at multiple scales. Multiscale Machine-learned Modeling Infrastructure (or MuMMI) is being used to study RAS–membrane dynamics. This effort led to the identification of lipid fingerprints associated with RAS clusters that influence RAS orientations and behavior. These findings will be applied to develop models for RAF activation.

The mutant cysteine in KRAS G12C is a reactive side group that can be exploited to covalently target the mutated form of the protein. The first generation of KRAS G12C inhibitors decreased RAS affinity for GTP relative to GDP, impairing nucleotide exchange from GDP to GTP and blocking

RAS–RAF effector interactions. These drugs showed low efficacy in clinical trials, however, because they preferentially bound the inactive form of KRAS G12C. The team is developing compounds to target the active form of KRAS G12C and plans to begin clinical testing later this year; drugs targeting active KRAS G12D and G12V also are being developed.

The interaction between RAS and PI3Kα plays a driving role in oncogenesis. Inhibition of PI3Kα in human cancer, however, has been limited by various adverse effects (e.g., hyperglycemia). The role of the RAS–PIK3α interaction has been demonstrated using mouse models. The RAS Initiative has developed a potent, orally available compound that binds to PI3Kα and prevents RAS activation without affecting glucose uptake. The compound has been tested in a panel of cell lines and mouse models, and clinical trials will be performed within the next year.

Tumors often develop resistance to drugs used in the clinic. Dr. McCormick summarized anticipated mechanisms of drug resistance for the KRAS G12 ON inhibitors (e.g., point mutations that prevent drug binding, activation of other *RAS* genes and proteins in the RAS pathway, differentiation state changes to escape RAS dependency, activation of alternate signaling pathways) and the RAS–PI3Kα breaker compounds (e.g., point mutations that prevent drug binding, activation of alternate signaling pathways or phosphoinositide kinases, loss of the phosphatase and tensin homolog protein). He concluded by expressing appreciation to colleagues at the RAS Initiative and partner institutes for their contributions.

In the discussion, the following points were made:

- The RAS Initiative is interested in expanding to other forms of *RAS* and is exploring whether the principles could be extended to other GTPases. Pan-RAS compounds also could provide new capabilities for treatment.

VII. CLOSING REMARKS—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.

VIII. ADJOURNMENT—DR. CANDACE S. JOHNSON

There being no further business, Dr. Johnson adjourned the 13th Virtual Meeting of the FNLAC at 3:50 p.m. EDT on Monday, 10 July 2023.

October 23, 2023 — /s/
Date — Candace S. Johnson, Ph.D., Chair

October 25, 2023 — /s/
Date — Wlodek Lopaczynski, M.D., Ph.D., Executive Secretary