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National Cancer Institute

16th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
10 July 2024

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

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The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 16th Virtual Meeting on 10 July 2024. The meeting was open to the public from 1:00 to 4:09 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. Carol J. Bult
Dr. John H. Bushweller
Dr. Timothy A. Chan
Dr. Lisa M. Coussens
Dr. Blossom A. Damania
Ms. Julie Papanek Grant
Dr. Angela M. Gronenborn
Dr. Mary J.C. Hendrix
Dr. Rodney J.Y. Ho
Dr. Allison Hubel
Dr. Dineo Khabele
Dr. Anant Madabhushi
Dr. Patrick Nana-Sinkam
Dr. Nilsa C. Ramirez Milan
Dr. Erle S. Robertson
Dr. Matthew G. Vander Heiden
Dr. Linda F. van Dyk

NCI Senior Leadership
Dr. James H. Doroshow
Dr. Kristin L. Komschlies
Ms. Anne Lubenow
Dr. W. Kimryn Rathmell
Dr. Dinah S. Singer

Executive Secretary
Dr. Christopher D. Kane

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I. OPENING REMARKS—DR. CANDACE S. JOHNSON

Dr. Candace S. Johnson, Chair, called to order the 16th 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 comments regarding items discussed during the meeting to Dr. Christopher D. Kane, Executive Secretary, in writing and within 10 days.

Motion. A motion to approve the minutes of the 11 March 2024 FNLAC meeting was approved unanimously.

Dr. Johnson called the Committee members' attention to the confirmed future meeting dates listed on the agenda, noting that the next FNLAC meeting will be held in person on 22–23 October 2024.

Motion. A motion to approve the 2026 FNLAC meeting dates was approved unanimously.

II. NCI DIRECTOR'S REPORT—DR. W. KIMRYN RATHMELL

Dr. W. Kimryn Rathmell, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. She expressed appreciation to the FNLAC members and remarked that she looks forward to convening in person. Dr. Rathmell began by recognizing a new FNLAC member, Dr. Matthew G. Vander Heiden, Director, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology. During her remarks, Dr. Rathmell reported on recent news and updates, the budget outlook, and research and program highlights.

NCI Recent News and Updates. Dr. Rathmell noted that the NCI Division of Extramural Activities will be hosting a holistic orientation for all its Boards later this year; further details will be forthcoming. She also commented that the NCI's Federally Funded Research and Development Center (FFRDC) contract recompetition is currently in the negotiation phase; details about proposals, competition, or negotiations cannot be discussed publicly. Proposals were due in February 2023, and the technical peer review occurred in May 2023. Negotiations were opened in early June 2024, and the award is scheduled for late December 2024.

Dr. Rathmell highlighted a visit to the National Institutes of Health (NIH) by Ms. Andrea Palm, Deputy Secretary, U.S. Department of Health and Human Services, on 18 June 2024. During her visit, Ms. Palm learned about the Frederick National Laboratory for Cancer Research (FNLCR) and its role in cancer drug development. Featured FNLCR programs included the RAS Initiative, Developmental Therapeutics Program, and NCI Experimental Therapeutics (NExT) Program. Dr. Rathmell underscored the importance of such engagements for NCI.

Dr. Rathmell presented highlights from the recent American Association for Cancer Research (AACR) and American Society of Clinical Oncology (ASCO) annual meetings. Dr. Steven Rosenberg, Chief, Surgery Branch, received the AACR Award for Lifetime Achievement in Cancer Research. Dr. Satish Gopal, Director, NCI Center for Global Health, received the ASCO Humanitarian Award for 2024. Dr. Rathmell's remarks at the AACR meeting highlighted new eras of biomedical research, with an emphasis on increased transparency, engagement, and input and a particular focus on NCI's various partners. Her remarks at the ASCO meeting addressed transforming clinical research, with consideration of distributed clinical trial design and forward thinking to advance patient care.

Dr. Rathmell informed the FNLAC members about several NCI leadership transitions. Dr. Tom Misteli, Director, Center for Cancer Research (CCR), stepped down to focus on his research. Dr. James

Gulley, NCI Clinical Director, and Dr. Carol Thiele, CCR Deputy Director, are serving as Acting Co-directors of CCR. Dr. Glenn Merlino, Scientific Director for Basic Research, who previously served in this role recently retired. NCI intends to fill this role within the next year. Dr. Warren Kibbe, Chief Data Officer, Duke Cancer Institute, has been named as the new NCI Deputy Director for Data Science and Strategy, and Dr. Shaalan Beg has been named Senior Advisor for Clinical Research.

NCI is building leadership and leadership communication across the cancer research continuum, and NCI's Cancer Equity Leaders are working to reimagine and transform the future of cancer health equity. Additionally, the inaugural U.S.-based Black in Cancer (BIC) Conference was held in partnership with the FNLCR on 20–21 June 2024. Dr. Rathmell also announced an upcoming name change for the Center to Reduce Cancer Health Disparities to the Center for Cancer Health Equity.

NCI Budget. Dr. Rathmell reminded FNLAC members that NCI submits a Professional Judgment Budget Proposal (also called the Bypass Budget) directly to the White House and Congress. The Bypass Budget estimates the cost of the work that NCI is expected to perform. The Professional Judgment Budget Proposal for Fiscal Year (FY) 2023 was $7.8 billion (B), and the enacted budget was $7.3 B. For the FY 2024 Professional Judgment Budget, NCI proposed a budget increase to $10.0 B but received $7.2 B enacted. NCI was allotted an increase to enable its work, but the net decrease was $96 million. This is the first decrease in funding that NCI has had in several fiscal years. For the FY 2025 Professional Judgment Budget, NCI is proposing a budget increase to $11.5 B; the FY 2025 President's Budget Proposal is $9.3 B. Additionally, Dr. Rathmell shared a graph to show paylines for early-stage investigators and established investigators from 2015 to 2024. For FY 2024, 10th percentile for R01 grants to established and new investigators and 17th percentile for R01 grants to early-stage investigators.

Dr. Rathmell remarked that the National Cancer Plan (NCP), which was implemented in 2023, is a roadmap for defining the cancer agenda for the nation, focusing on goals to make significant advancements for cancer. The NCP has four health-centered goals—preventing cancer, detecting cancers early, developing effective treatments, and delivering optimal care—and four empowering goals—eliminating inequities, maximizing data utility, optimizing the workforce, and engaging every person. Dr. Rathmell also highlighted a set of values that can guide NCI's collective efforts: talent development, creativity and innovation, empowerment, and fiscal responsibility.

Cancer Research and Program Highlights. Dr. Rathmell spoke on key cancer research and program highlights. Recent scientific advances by the FNLCR include a new CRISPR screening platform, new information on the structure and function of the less-studied KRAS4a variant, the Self-collection for HPV testing to Improve Cervical Cancer Prevention (SHIP) Trial, a new dual inhibitor of KRAS G12C, and antibodies with potential for universal flu vaccine development.

Recent efforts to transform clinical research include decentralized clinical trial designs and broad innovation. NCI launched the Virtual Clinical Trials Office pilot program, which provides staffing remote support for clinical research activities in communities. NCI also launched the Clinical Trials Innovation Unit, which aims to conduct better, faster, and more accessible cancer clinical trials. The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial exemplifies how a decentralized trial can accrue rapidly and address multiple questions in a well-designed manner. Two NCI-MATCH successor trials, MyeloMATCH and ComboMATCH, are underway.

NCI established the Board of Scientific Advisors *ad hoc* Working Group to Enhance Community Cancer Research and Quality Care to provide guidance on the development of efforts to increase community capacity to conduct cancer research and enhance the ability to provide high-quality cancer care. Additionally, the Cancer Cabinet: Community Conversations series is convening 8–17 July 2024. The Cancer Cabinet agencies will provide updates on progress to advance the Cancer Moonshot^{SM} priority

actions. NCI's topic for this series relates to improving cancer outcomes by bringing research to rural communities.

Dr. Rathmell also previewed upcoming FNLCR events; these include the NCI and FNLCR Annual Technology Showcase, which will be held 4 September 2024, and the Fifth RAS Initiative Symposium, which will be held 8–10 October 2024. More information can be found on the FNLCR website.

In closing, Dr. Rathmell solicited the FNLAC members to provide input on how best to utilize FNLCR's assets to achieve the goals of the NCP. She asked them to consider whether NCI has allocated the appropriate balance of laboratory resources to build necessary capacity for the nation's cancer efforts. Additionally, Dr. Rathmell requested suggestions for approaches to help NCI move forward more quickly in cancer research. She underscored the value of members' input.

In the discussion, the following points were made:

- An estimated 500 individuals attended the Black in Cancer meeting, including representation from all career levels and both clinical and basic research. The presentation topics included career development, as well as various scientific topics (e.g., ancestry and cancer risk).

- A framework for NIH reform was published recently by Rep. Cathy McMorris Rodgers (R-WA). The framework did not involve restructuring NCI, but NCI is closely monitoring developments on this matter.

- NCI prioritizes innovation and is working to make this priority clear across the research community. This topic is challenging to address for grant reviews, particularly for projects submitted by junior investigators. Review committees often are risk averse, but guidance on this topic could be beneficial for reviewers.

- More work is needed to leverage large amounts of data across NCI's cooperative groups. Artificial intelligence algorithms could be used for developing novel predictive prognostic assays, identifying patients who would benefit from therapies, and revisiting negative trials. NCI is committed to promoting data sharing across groups; Dr. Kibbe will play a significant role in these efforts.

- The FNLCR can leverage existing resources (e.g., methodologies) available through the NCI-Designated Cancer Centers. This strategy might save funds and help NCI achieve its goals more quickly. These efforts also would help build and strengthen networks. Additionally, the FNLCR can serve as a point of nucleation to foster collaborations among both internal and external groups.

III. FREDERICK NATIONAL LABORATORY/NCI SUPPORT OF FRIENDS OF CANCER RESEARCH'S TUMOR MUTATIONAL BURDEN (TMB) AND HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD) HARMONIZATION PROJECTS— DR. CHRIS KARLOVICH

Dr. Chris Karlovich, Director, Molecular Characterization Laboratory (MoCha), FNLCR, presented updates on two recent harmonization projects conducted in partnership with Friends of Cancer Research. The first effort, the TMB Harmonization Project, aimed to establish standards and best practices for estimating and reporting TMB, a measure of the number of somatic mutations per portion of the tumor's genome (mutations per megabase). TMB is a predictive biomarker and has been shown to correlate with neoantigen load, as well as clinical benefit from cancer immunotherapies. Methods of TMB

estimation and reporting vary widely across clinical studies. The project, which was initiated in 2017, involved convening a working group of interested parties to generate evidence to drive alignment and consensus solutions.

The project involved establishing a universal reference standard for TMB—a whole-exome sequencing (WES) score (i.e., WES TMB score) with agreed-upon metrics—and comparing laboratory-generated data from 11 participating laboratories to the reference standard to identify sources of variability. Each participating laboratory calculated TMB from the subset of the exome restricted to the genes covered by their targeted panel using their own bioinformatics pipeline (panel TMB score). The laboratory-specific panels evaluated non-synonymous and synonymous mutations between 324 and 607 cancer-related genes covering areas from 800 kilobases to 1.72 megabases Phase 1 of the project involved *in silico* analysis of publicly available data for 32 tumor types from The Cancer Genome Atlas (TCGA) to identify sources of variability introduced via different calculation methods. TMB estimates varied substantially between participating laboratories. Of the participating laboratories, eight of the laboratory's panel TMB scores overestimated TMB compared with the reference standard. Cancer-dependent relationships also were observed. For example, all panel scores overestimated TMB in bladder cancer samples compared with the WES score.

Phase 2 involved empirical analysis of cells derived from human tumors to identify methodological sources of variability. Each laboratory was sent nucleic acids extracted from 10 cell line samples (extracted by a collaborating laboratory) and 29 clinical samples (extracted by MoCha). Panel TMB scores were compared with a standard WES TMB score calculated by MoCha researchers. Once again, variability between laboratories was observed, and most of the 16 participating laboratories overestimated TMB. Calibration approaches based on the Phase 1 TCGA data were applied across the participating panels to align the scores. For example, filtering known pathogenic cancer mutations improved panel TMB scores relative to WES TMB. Germline variant filtering also robustly affected panel TMB scores; filtering out 100 percent of germline variants was the panel approach that most closely approximated the WES TMB. A calibration function for individual laboratories to calculate estimated WES TMB from observed panel TMB was determined using data from all TCGA samples or from the cell line samples. For each panel, linear regression analyses that modeled panel TMB as a function of WES TMB were calculated and found to capture approximately 95 percent of the intended panel TMB values. Calibration approaches using TCGA data performed better than cell line data—likely because the TCGA data set comprised approximately 4,000 samples—and might be a viable approach for aligning panel TMB scores.

Dr. Karlovich also described the HRD Harmonization Project, another effort in collaboration with the Friends of Cancer Research. HRD is a complex biomarker that helps identify patients who might benefit most from poly ADP-ribose polymerase (PARP) inhibitors, a class of drugs that targets mechanisms involved in DNA repair by homologous recombination. Different causal and consequential indicators are assessed to create HRD scores and apply different score thresholds. Variability in HRD measurements and assays can lead to different treatment decisions and patient outcomes. The HRD Harmonization Project aims to compare different HRD assays and investigate reasons for variability between them. Phase 1 involved a landscape assessment, Phase 2 involved *in silico* and clinical analyses of various HRD assays using shared data sets, and Phase 3 involved a clinical contextualization that interpreted and shared the project's findings.

For the *in silico* analysis, 348 ovarian cancer sample files from TCGA were shared with 11 HRD assay developers who ran the samples through their pipelines and reported each sample's HRD status. The statistics team in NCI's Biometric Research Program (BRP) determined the agreement level between the various status calls, and the HRD Harmonization Working Group reviewed and reported the findings.

The assay developers deemed approximately half of the samples HRD-positive (median 49 percent, mean 44 percent), and the percent HRD positivity ranged widely (from 9 percent to 67 percent).

During the clinical analysis, MoCha extracted and distributed nucleic acids from 90 archival ovarian cancer samples. The samples were sequenced by 17 participating laboratories (which measured and reported their HRD status), and the BRP team assessed the level of agreement between the results. Because an agreed-upon reference standard was lacking, observed variability across assays became the focus of the analysis. The assay developers deemed approximately half of the samples HRD-positive (median 52 percent, mean 52 percent), and the percent HRD positivity ranged widely (from 23 percent to 74 percent). Overall, pairwise concordance values for HRD calls were highest for samples with mutated *BRCA1* and *BRCA2* genes (compared with samples with wild-type *BRCA1* and *BRCA2*). Other factors that were associated with agreement between assays were race and amplification of the *CCNE1* gene. Sample characteristics were not associated with concordance, but higher-quality samples were used. Survival analysis was performed to assess patients' clinical outcomes after platinum-based therapy for samples in three different categories: an HRD-negative cluster, an HRD-positive and *BRCA* mutation–positive cluster (i.e., *BRCA* clusters), and an HRD-positive and *BRCA* mutation–negative cluster (i.e., consequences cluster). Recurrence-free survival was highest in the *BRCA* cluster (29.2 months), followed by the consequences cluster (24.0 months) and the HRD-negative cluster (18.7 months). Overall survival was higher in the HRD-negative cluster (91.6 months) than in the *BRCA* cluster (72.6 months). The consequences cluster trended to better overall survival than the HRD-negative cluster, but the difference was not statistically significant. Only 15 out of 90 patients received PARP inhibitors as maintenance therapy, so the clinical performance of assays (i.e., for selecting patients likely to benefit from these drugs) could not be assessed.

Dr. Karlovich listed several recommendations for HRD assay development. He suggested identifying the best approaches for reporting HRD to enhance consistency, aligning on expectations for analytical validation, considering approaches for developing a reference standard (including use of reference materials), and using supplemental *in silico* comparisons. He thanked all the TMB and HRD project partners for their efforts.

In the discussion, the following points were made:

- The working group has not considered a functional HRD assay (measuring RAD51 foci) developed by researchers at the Washington University School of Medicine in St. Louis. However, researchers at FNLCR have the ability to interrogate RAD51 foci and compare that method to other HRD approaches.

- The TMB Harmonization Project can coordinate with the U.S. Food and Drug Administration (FDA) and industry partners to harmonize TMB-related activities. Querying the FDA about their standards when evaluating new TMB assays for approval might be informative.

IV. RAS INITIATIVE UPDATE: TESTING OUR DRUGS IN THE CLINIC—DR. FRANK MCCORMICK

Dr. Frank McCormick, RAS National Program Advisor, FNLCR, and Professor, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, shared an update on clinical studies involving compounds developed by the RAS Initiative. He reminded the meeting participants that RAS proteins (i.e., HRAS, KRAS, NRAS) are small GTPases that transduce signals from growth factors to activate downstream transcription pathways that regulate cell proliferation, migration, and survival. The GTP-bound form of RAS is the active form. Because mutant forms of RAS (e.g., G12C, G12V, G12D) are resistant to GTPase-activating protein (or GAP) activity, which converts RAS to its inactive form, these mutations drive pro-tumorigenic growth pathways and are found in many forms of cancer.

Sotorasib, agarasib, and other similar compounds have been developed to target RAS by binding to its inactive state and blocking its activation. These drugs have been approved by the FDA for therapy, but clinical responses to them have not been robust because tumor cells can overcome the block by activating more upstream growth signals and producing more RAS protein.

The RAS Initiative's approach has been to target the active form of RAS. Using a combination of structural biology, drug screening, medicinal chemistry, and computational approaches, a compound that covalently binds and inhibits both the active (GTP-bound) and inactive (GDP-bound) forms of KRAS G12C (i.e., a dual inhibitor) was developed. The first-in-class compound, BBO-8520, rapidly and selectively binds only KRAS; inhibits phosphorylation of extracellular signal-regulated kinase (or ERK), which is downstream of KRAS activation, at subnanomolar levels; and is highly potent in live cells and xenograft models. Active RAS proteins exist in equilibrium between an open State 1 conformation, which cannot bind effector proteins, and a closed State 2 conformation, which can. Structural analysis determined that BBO-8520 shifts KRAS toward a State 1 conformation, disrupting effector binding. This mechanism of action has been carried over into compounds targeting other alleles (e.g., G12V and G12D), hopefully leading to additional mutation-specific inhibitors of active RAS. BBO-8520 currently is being evaluated in Phase 1 clinical trials. The drug is being tested in U.S. patients (who have progressed after treatment with an inhibitor of inactive G12C) and Australian patients (many of whom are treatment-naive).

Dr. McCormick reviewed efforts to inhibit the interaction between KRAS and phosphoinositide 3-kinase alpha (PI3Kα), which also have led to clinical trials. The interaction between RAS and PI3Kα plays a driving role in oncogenesis. For example, mice with an engineered mutation in the catalytic subunit of PI3Kα that blocks its ability to interact with RAS are highly resistant to KRAS-induced tumorigenesis. However, direct inhibition of PI3Kα in human cancers has been limited by side effects related to glucose metabolism, which also is regulated by PI3Kα activation. Drugs that specifically block the RAS–PI3Kα interaction hopefully will inhibit tumor cell signaling without dangerous side effects.

The compound BBO-10203, emerged from structural studies of the KRAS–PI3Kα protein complex. KRAS and PI3Kα bind with low affinity when not in the presence of the plasma membrane. "Glue" compounds are molecules that can be added to increase the stability of particular interactions. One such glue compound acted as a complex inducer that increased the affinity of the KRAS–PI3Kα interaction approximately a thousandfold, enabling the structure of the complex to be solved. This glue compound was exploited and modified into a breaker compound that binds specifically and covalently to the RAS-binding domain of PI3Kα, preventing the RAS–PI3Kα interaction and downstream oncogenic signaling without affecting PI3K kinase activity.

When tested on cancer cells with different genotypes, the breaker compound consistently bound its KRAS–PI3Kα target but had varying effects on downstream signaling. The breaker has an intermediate effect on KRAS or PI3Kα mutant cells and a strong effect on cells with amplified human epidermal growth factor receptor 2 (or HER2/neu). The impact on HER2/neu cells was unexpected because HER2/neu-dependent activation of PI3Kα was thought to be independent of RAS. In KRAS G12C cell lines, most PI3Kα activity is inhibited by the breaker compound or by an inhibitor of H-, K-, M-, and N-RAS. Residual activity is thought to be driven directly by the upstream receptor. In HER2/neu-amplified cell lines, the breaker compound—but not the H-, K-, M-, and N-RAS inhibitor—inhibits PI3Kα activity, indicating that breaker-sensitive PI3Kα activity in these cells is being driven by an unknown RAS protein. Notably, studies in mice have demonstrated that the breaker compound, BBO-10203, inhibits RAS-specific PI3Kα activity without inducing hyperglycemia.

The G12C dual inhibitor and breaker compound are being evaluated as a combination therapy. Treatment with BBO-8520 and BBO-10203 is effective in sensitive cancer cell lines (which respond to

treatment with one drug) and, notably, resistant cell lines (which do not respond effectively to either drug). When taken in combination, the breaker compound also improves the efficacy of three drugs routinely used to treat breast cancer (i.e., trastuzumab, fulvestrant, palbociclib). Dr. McCormick thanked his colleagues at FNLCR, BridgeBio Gene Therapy, and the Lawrence Livermore National Laboratory for their contributions to these efforts.

In the discussion, the following points were made:

- Mutations in other RAS family members are conserved in the same region as the G12C mutation, and efforts are being made to target these mutations. A compound that inhibits the active form of both G12D and G12V (which are important in pancreatic cancer) will soon be evaluated in clinical trials.

- Several publications related to these results are expected shortly. NCI and FNLCR should promote the clinical trial efforts to the lay public.

- Results from the HER2 experiments indicate that the breaker compound might be effective in cells that are resistant to traditional RAS inhibitors. Identification of the breaker's mechanism of action in the HER2 setting might reveal new therapeutic possibilities for the drug.

- Clinical studies are evaluating the breaker compound as a single agent for safety and efficacy purposes before it is tested in combination therapy.

V. THE SEROLGOCIAL SCIENCES NETWORK (SERONET): NCI'S RESPONSE TO COVID-19—DRS. DINAH S. SINGER AND LIGIA PINTO

Dr. Dinah S. Singer, Deputy Director for Scientific Strategy and Development, NCI, and Dr. Ligia Pinto, Director, Vaccine, Immunity, and Cancer Directorate (VICD), FNLCR, presented an update on the Serological Sciences Network (SeroNet), which was established in 2020 to provide serological testing and research support on the immune response to SARS-CoV-2. Dr. Singer stated that the goals of SeroNet were to develop and deploy broadly serological assays, characterize immune responses to SARS-CoV-2, examine the role of confounding host factors in the response, determine serological correlative protection, and identify and address societal barriers to vaccination.

SeroNet is a coordinated research network that includes grants (U54, U01), FNLCR contracts (i.e., Capacity Building Centers [CBCs]), FNLCR's Serology Lab, and a Coordinating Center. SeroNet's efforts are focused on special populations (e.g., cancer patients, patients with immune-mediated inflammatory diseases). It is guided by three key principles: First, research funded through SeroNet must be published in an open-access format. Second, all data underlying the research must be shared immediately upon publication. Third, SeroNet maintains a network-wide agreement to share information before publication and to collaborate extensively.

Because SeroNet was established during the COVID-19 pandemic, the team anticipated that changes would be needed over time. A 2-year reassessment was put in place for the CBCs and grants. The review was conducted by an internal panel of experts from NCI and the National Institute of Allergy and Infectious Diseases, comprising expert scientists who were not directly involved with the program. The panel recommended that SeroNet maintain one of the CBCs to respond to possible resurgence in the pandemic and continue some of the research efforts and the longitudinal cohorts. All but one of the grants were approved for continuation, with flexibility to adjust scientific aims to pivot alongside the pandemic. Dr. Singer emphasized that SeroNet was highly successful from a scientific perspective. Key publication topics included immune responses, vaccine responses in cancer patients, and vaccine responses in other

special populations. Dr. Singer also noted that SeroNet ranks above comparative groups in the frequency of appearing in the top 1 percent of articles.

Next, Dr. Pinto outlined how FNLCR's Serology Lab worked with SeroNet to support NCI's response to the COVID-19 pandemic. Her group operates within the Science and Technology Group at FNLCR, and its directorate includes the Human Papillomavirus (HPV) Serology Laboratory; Cancer Immunoprevention Laboratory; and SeroNet, which includes the COVID-19 Serology Lab, SeroNet Coordinating Center, and Center of Excellence for Serology Development and Emergency Preparedness (CESDEP). The group's mission is to study immune responses to HPV and SARS-CoV-2 infection and vaccines, as well as other cancer preventive strategies in the context of clinical and preclinical studies, with the goal of translating laboratory science into public health benefits.

Dr. Pinto has been working for the past 2 decades on HPV immunology and serology, and the team's work includes support for NCI vaccine trials and large epidemiological studies. It played a critical role in understanding how HPV vaccines work and was one of the first to demonstrate long-term antibody responses after a single dose of HPV vaccine, suggesting that the single dose may be as effective as the originally recommended and approved two- or three-dose schedules. With the increasing number of trials for novel HPV vaccine regimen recommendations and novel vaccines' relying on serology as primary endpoints to inform regulatory decisions, the team recognized the urgent need to standardize HPV serology because no standardized assays or procedures were available. To address this gap, in 2017, they established the HPV Serology Standardization Initiative, which has been led by the HPV Serology Lab and is sponsored by NCI and the Bill & Melinda Gates Foundation.

The mission of this initiative is to work in partnership with the international HPV serology community to promote standardization, harmonization, and proficiency of HPV serology assays to evaluate vaccine immunogenicity in clinical trials. They also created high-throughput testing capability for clinical trials. Partners include FNLCR, NCI, the Bill & Melinda Gates Foundation, the Centers for Disease Control and Prevention, Public Health England, the Karolinska Institute, and the National Institutes for Biological Standards and Control, as well as academic laboratories, vaccine industry laboratories, and other regulatory bodies.

To date, the group has conducted more than 100,000 immunogenicity tests on a large number of HPV vaccine trials, covering a global range, diverse age groups, and male and female individuals. Using standardized assays and validated technologies, they have generated reliable and comparable data in clinical trials that have been used in part for the recent endorsement of a one-dose HPV vaccine by the World Health Organization (WHO). Dr. Pinto emphasized that standardization is the key to fighting most effectively against cancer, as well as potentially eliminating cancer.

The team was well positioned to respond to the COVID-19 pandemic in March 2020. Dr. Pinto highlighted the team's key contributions and milestones during this time. The team developed serology assays, as well as standards for serology and it was approached by the FDA at the beginning of the pandemic to assist in the evaluation of COVID-19 serology assays for emergency use authorization. As part of this endeavor, the team developed validation panels with well-characterized samples that were tested in more than 115 commercial tests. Dr. Pinto emphasized that this effort marked the instance that the federal government evaluated tests itself to inform FDA authorizations. The team also played a key role in the production and distribution of U.S. serology standards and received more than 185 requests from researchers in the United States and globally. Furthermore, they implemented immunological assays and validated enzyme-linked immunosorbent assays and multiplex assays. Using validated technologies, the team investigated the immune response to the approved vaccines and has tested more than 80,000 samples. They also played a key role in establishing SeroNet and helped manage all activities within the Coordinating Center, including managing subcontracts with CBCs to build a repository of serum and

peripheral blood mononuclear cells, collected from healthy individuals, cancer patients, and other immunocompromised patients after infection and vaccination. The samples were prepared using established standard operating procedures. The samples have been used by the Serology Lab for various ongoing studies, as well as by SeroNet members. Dr. Pinto emphasized the value of agility and collaboration in these efforts.

A Clinical and Translational Serology Task Force (CTTF) was established in February 2021to bring together and engage various government organizations and various SeroNet members. Dr. Pinto highlighted major outcomes resulting from the CTTF including a real-world data infrastructure that was developed to evaluate the impact of infection and vaccine effectiveness in healthy individuals and in immunocompromised individuals, with an emphasis on cancer patients. Additionally, the Center of Excellence for Serology Development was developed to enable agile sample acquisition with biospecimens that will be well characterized and annotated, as well as high-quality serology and other immunological testing (e.g., T-cell assays). The CESDEP's vision is to leverage capabilities and expertise in serology and standardization across multiple organizations to control current and future outbreaks. They are focused on addressing critical gaps, as well as rapid development and validation of assays that can be used to provide accurate information about immune responses to infection and vaccination to serve the public health needs.

The team's success was enabled by its strong network of partners with expertise and capabilities, standardized data management infrastructure, and the sharing of tools across the scientific community. Long-term plans include sustaining established capabilities and leveraging existing infrastructure and expertise for public–private partnerships. Dr. Pinto noted that FNLCR's infrastructure is key to these efforts. She also emphasized that more work is needed to understand the risks associated with COVID-19 infection among cancer patients. Furthermore, this work and infrastructure are relevant to address public health challenges beyond COVID-19.

In the discussion, the following points were made:

- FNLCR's efforts in serological testing can serve as a model for other national laboratories. The team has disseminated its experiences through method-focused journals, as well as in online standard operating procedures and validation guidelines. Biospecimen-focused journals also could be considered for dissemination.
- Certain cancers might have an increased incidence in patients with Long COVID and cancer patients may have a higher incidence of Long COVID. Several investigators in SeroNet are exploring these questions and are characterizing the correlation between Long COVID and cancer. More work and data are needed to better understand these dynamics, and real-world data infrastructure is crucial.
- SeroNet does not have a formal partnership with the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative, but NCI staff are in communication with RECOVER staff and are sharing information. Additionally, SeroNet requires that all data be made publicly available immediately upon publication; the Coordinating Center is responsible for these efforts.
- The biospecimen repository will be made publicly available to the research community and can be used by investigators who are interested in various research questions. Multiple opportunities are available to leverage this unique set of specimens and data. The team will consider an organized approach to manage and facilitate such engagements.

VI. CLOSING REMARKS—DR. CANDACE S. JOHNSON

Dr. Johnson expressed appreciation to the Committee members and other participants for attending.

VII. ADJOURNMENT—DR. CANDACE S. JOHNSON

There being no further business, Dr. Johnson adjourned the 16th Virtual Meeting of the FNLAC at 4:09 p.m. EDT on Wednesday, 10 July 2024.

October 24, 2024 /s/
Date Candace S. Johnson, Ph.D., Chair

October 24, 2024 /s/
Date Christopher D. Kane, Ph.D., Executive Secretary