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

6th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
February 23, 2021

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
6th Virtual Meeting of the Frederick National Laboratory Advisory Committee
23 February 2021

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 6th Virtual Meeting on 23 February 2021. The meeting was open to the public on 23 February 2021, from 1:00 p.m. to 3:58 p.m. EST. The FNLAC Chairperson, Dr. Lawrence J. Marnett, Dean of Basic Sciences, University Professor, Mary Geddes Stahlman Professor of Cancer Research, and Professor of Biochemistry, Chemistry, and Pharmacology, Vanderbilt University School of Medicine, presided.

FNLAC Members
Dr. Lawrence J. Marnett (Chair)
Dr. Catherine M. Bollard
Dr. Timothy A. Chan
Dr. Lisa M. Coussens (absent)
Dr. Kevin J. Cullen
Dr. Raymond N. DuBois
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. Scott W. Hiebert
Dr. David I. Hirsh
Dr. Candace S. Johnson
Dr. Nilsa C. Ramirez Milan
Dr. Denise J. Montell
Dr. Patrick Nana-Sinkam
Dr. Lincoln D. Stein
Dr. Cheryl L. Willman (absent)

***Ex Officio* Members**
Dr. Stephen J. Chanock (absent)
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Sara S. Hook
Dr. Anthony Kerlavage
Dr. Douglas R. Lowy
Dr. Tom Misteli
Ms. Donna Siegle (absent)
Dr. Dinah S. Singer

Executive Secretary
Dr. Caron A. Lyman

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I. OPENING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Lawrence J. Marnett, Chair, called to order the 6th Virtual Meeting of the Frederick National Laboratory Advisory Committee (FNLAC) and welcomed the Committee members, National Cancer Institute (NCI) staff, and guests. Dr. Marnett reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Caron A. Lyman, 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 24 October 2020 FNLAC meeting was approved unanimously.

Dr. Marnett called Committee members' attention to the confirmed future meeting dates listed on the agenda. He noted that the next FNLAC meeting will be held on 28–29 June 2021 and will be virtual.

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

Dr. Norman E. Sharpless, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. He provided an update on the 50th anniversary of the National Cancer Act (NCA) of 1971, Cancer Moonshot℠ midpoint, NCI appropriations and paylines, coronavirus disease 2019 (COVID-19) impacts and activities, and non-COVID-19 activities. Dr. Sharpless welcomed Dr. Scott W. Hiebert, Hortense B. Ingram Chair in Cancer Research, Professor of Biochemistry, Department of Biochemistry, Vanderbilt University School of Medicine, and National Cancer Advisory Board (NCAB) Acting Chair. He is serving as a representative from the NCAB.

Noting the visits to the National Institutes of Health (NIH) and NCI from President Biden's Administration within 3 weeks following the inauguration, Dr. Sharpless elaborated on the 3 February 2021 virtual visit by the First Lady, Dr. Jill Biden. Featured presentations included highlights of the success and reach of the NCI Community Oncology Research Program (NCORP) in minority accruals for clinical trials, by Dr. Worta McCaskill-Stevens, Chief, Community Oncology and Prevention Trials Research Group, Division of Cancer Prevention; updates on cutting-edge treatments at the NIH Clinical Center, by Dr. Stephanie L. Goff, Associate Research Physician, Surgery Branch, Center for Cancer Research; and reports on the serology efforts in response to the COVID-19 pandemic, by Dr. Ligia Pinto, Director, Vaccine, Immunity and Cancer Program, Frederick National Laboratory for Cancer Research (FNLCR). In her remarks, Dr. Biden conveyed that cancer is one of her top three areas of focus as First Lady (the other two being education and support for military families).

50th Anniversary of the NCA of 1971. Dr. Sharpless announced that on 8 February 2021, the NCI launched the NCA-50 campaign in commemoration of the 50th Anniversary of the NCA of 1971, with the theme, "Nothing Will Stop Us." NCA-50 is an opportunity to ignite and inspire the next generation of cancer researchers and supporters of cancer research. The NCI is excited about the potential of the NCA-50 activities to spotlight the progress for cancer patients across the Nation and how these efforts remain dependent on basic science for translational research, including research services and survivorship research. Updates on the stories of progress can be accessed from the NCA-50 webpage.

Dr. Sharpless noted that the materials, tagline, and logo commemorating the NCA-50 are not NCI-branded and can be widely disseminated and used by any groups or individuals interested in cancer research. The NCI envisions that the NCI-Designated Cancer Centers (Cancer Centers) and FNLCR—as well as partner organizations, such as the American Society of Clinical Oncology (ASCO) and American Association for Cancer Research (AACR)—will develop campaigns specific to their own accomplishments in cancer care within the past 50 years.

Cancer Moonshot℠ Midpoint. FNLAC members were informed that the Cancer Moonshot℠ is at its midpoint and that progress remains impressive. Dr. Sharpless explained that Congress, in the 21st Century Cures Act, appropriated the NCI a 7-year funding allotment beginning in fiscal year (FY) 2017. The 240 research projects and initiatives funded during FY 2017–2020 span the cancer continuum, extending from fundamental understanding of the drivers of childhood cancer to genetic counseling and screening of individuals with inherited predispositions to cancers to direct engagement with patients. Although the NCI investments already are resulting in new national resources and clinical trials, it will take years to translate the projects into clinical benefit (i.e., diagnostics and treatments). Further details on progress can be accessed from the NCI *Cancer Currents: An NCI Cancer Research* blog. Dr. Sharpless and Dr. Dinah S. Singer, Deputy Director, Science Strategy and Development, NCI, soon will publish a Cancer Moonshot℠ midpoint progress update in *Cancer Cell*. The NCI is planning for future projects beyond the end of the 7-year funding period in FY 2023 and exploring ways to transition those efforts into existing programs.

To address the concerns in the cancer research community that only NCI-established and long-time investigators were receiving Cancer Moonshot℠ funding, the NCI Center for Research Strategy analyzed the extramural awards (excluding grant supplements). The data revealed that 75 percent of recipients were established extramural principal investigators, of whom 12 percent had no prior NCI funding, and 25 percent were new investigators. Of the 25 percent of new investigators, 5 percent were early-stage investigators (ESIs). Dr. Sharpless emphasized that these data demonstrate that the Cancer Moonshot℠ is achieving its key goal of increasing the pool and diversity of ideas about cancer research at the NCI.

NCI Appropriations and Paylines. Dr. Sharpless reported that the FY 2021 NIH budget includes an annual appropriation of $42.9 billion (B), which is an increase of $1.25 B above the FY 2020 enacted budget; and includes $6.56 B to the NCI, which is an increase of $119 million (M). The NCI regular appropriations include $195 M for the Cancer Moonshot℠ and $50 M for Year 2 of the Childhood Cancer Data Initiative (CCDI). The FY 2021 budget also designates $37.5 M to the NCI to (1) prioritize competing grants (e.g., Type 2) and (2) sustain the commitments in continuing grants (i.e., Noncompeting Continuation [Type 5] awards) within the Research Project Grant (RPG) pool. In FY 2020, the fourth COVID-19 emergency bill allotted the NCI $306 M for serology research, which the NCI is actively implementing.

Dr. Sharpless noted that the continued support and commitment from Congress has enabled the NCI to establish paylines for FY 2021 competing grants (Type 2, R01); 11th percentile for established and new investigators, 16th percentile for ESIs, and 9th percentile for exploratory grants (R21). Noncompeting Continuation Type 5 awards will be funded at 100 percent. In its *Annual Plan and Budget Proposal for Fiscal Year 2022* the NCI proposed a "15 by '25" plan to increase funding for the RPG pool, gradually reaching a 15th percentile payline for R01 grants for established investigators by FY 2025. The NCI is well on its way to achieving this aspirational and resource-intensive goal by FY 2025 without making cuts to major programs (e.g., Cancer Centers) outside of the RPG pool. Further details have been provided on the NCI blog, *NCI Bottom Line: A Blog About Grants and More*.

COVID-19 Impacts and Activities. Dr. Sharpless remarked on ways that the NCI and the FNLCR have contributed to the Nation's response to the COVID-19 pandemic, all while maintaining focus on the central mission—cancer research and ensuring progress for patients with cancer. The NCI COVID-19 in Cancer Patients Study (NCCAPS) has enrolled 994 patients from 873 trial sites across the NCI National Clinical Trials Network (NCTN) and NCORP in all 50 states; Washington, D.C.; Puerto Rico; and Canada. NCCAPS will allow for longitudinal data and biospecimen collections, all critical to understanding the natural history of SARS-CoV-2 (coronavirus causing COVID-19) infection in cancer

patients and those with weakened immune systems. Dr. Sharpless noted that further updates on NCI serology efforts will be reported later in the meeting.

The NCI has a history of supporting research addressing vaccine hesitancy, in particular, in its efforts to eradicate cervical/human papillomavirus (HPV)-associated cancer and hepatitis-related liver cancer. A recent NIH report, *COVID-19 Vaccination Communication: Applying Behavioral and Social Science to Address Vaccine Hesitancy and Foster Vaccine Confidence*—an effort led by the NCI Health Communications and Informatics Research Branch, Division of Cancer Control and Population Sciences (DCCPS) and the NIH Office of Behavioral and Social Sciences Research—focuses on the NCI's lessons learned on this topic. This report—which has been widely shared across the U.S. Department of Health and Human Services (HHS), National Science Foundation, and other public health agencies—makes a strong case for evidence-based communication adaptable to real-time changes in vaccine research.

NCI Non-COVID-19 Activities. In FY 2020, Congress appropriated $50 M to the NCI to initiate the CCDI 2020 (Year 1), supporting infrastructure and ongoing activities via supplements to existing grants. The NCI is planning and organizing projects for Year 2 and beyond for this initiative. CCDI leadership, Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, Division of Cancer Treatment and Diagnosis (DCTD), and Dr. Warren Kibbe, Chief, Translational Biomedical Informatics, Department of Biostatistics and Bioinformatics, Chief Data Officer, Duke Cancer Institute, Duke University School of Medicine, have outlined the CCDI governance structure. Four working groups—co-chaired by NCI and extramural experts and composed of members of the NCI staff, external experts, and advocates—will manage building and overseeing implementation of the CCDI three components: Childhood Cancer Data Platform, Childhood Molecular Characterization Protocol, and National Childhood Cancer Cohort; and address cutting-edge issues. A CCDI Steering Committee will oversee the activities of the four working groups and will be informed by a CCDI Engagement Committee to involve the wider childhood cancer community in the CCDI.

Dr. Sharpless informed the FNLAC members that the NCI Equity and Inclusion program consists of an NCI Equity Council; Dr. Sharpless is the Council chair, and Dr. Paulette S. Gray serves as vice-chair. The Council comprises five working groups, three of which will address the program content represented in three broad aspects of inclusion: Working Group 1, enhancing research to address cancer health disparities; Working Group 2, ensuring diversity of thought and background in the cancer research workforce; and Working Group 3, promoting an inclusive and equitable community at the NCI. Working Groups 4 and 5 will address crosscutting themes on equity activities, including systemic tracking and evaluation and community outreach, respectively.

The NCI partnered with Cancer Research United Kingdom (UK) to sponsor the Cancer Grand Challenges (CGC) to award grants to international multidisciplinary research teams seeking to address cancer research problems. Nine CGC were published in October 2020 and can be accessed from the NCI website. The first stage of the competition, expressions of interest from the teams, will be accepted through April 2021. The CGC leverages the NCI Provocative Questions (PQ) Initiative, will use the PQ Initiative funds every other year, and is supported by Cancer Research UK funds. Dr. Sharpless informed FNLAC that the NCI is taking this opportunity to conduct an internal program evaluation of the PQ Initiative, commencing in FY 2021.

Dr. Sharpless highlighted two publications that feature recent cancer research progress related to prostate and melanoma cancers with links to the NCI Intramural Research Program (IRP). Results from a large-scale international trans-ancestry genome-wide association meta-analysis of prostate cancer, funded in part by the DCCPS, was published in the 4 January 2021 issue of *Nature Genetics*. The 230 authors, including Division of Cancer Epidemiology and Genetics (DCEG) investigators, examined diverse ancestries in men of European, African, East Asian, and Hispanic/Latino descent and identified 86 new

genetic risk variants that independently associate with prostate cancer risk. This study demonstrates an improved ability to conduct personalized risk prediction using a polygenic risk model. IRP investigators collaborated with University of Pittsburgh Medical Center Hillman Cancer Center to treat immunotherapy-refractory melanoma patients using fecal microbiota transplant (FMT). This first-of-a-kind FMT study, reported in the 3 February 2021 issue of *Science*, revealed that FMT promotes an improved response in these patients treated with a challenged dose of an immune checkpoint inhibitor, suggesting that the composition of the colonic microbiome can augment the efficacy of these immunotherapy agents.

The NCI chimeric antigen receptor (CAR) T-cell manufacturing program to support immunotherapy clinical trials is operational at the FNLCR and has the capacity for enabling multicenter trials. A new video describing this program has been developed and can be accessed here on the NCI website. Further details on the CAR T-cell trials will be provided later in the meeting.

In the discussion, the following points were made:

- Although the initial focus has been on conducting CAR T-cell trials, the NCI plans to extend its cell-based immunotherapy approaches to other areas (e.g., tumor-infiltrating lymphocytes) and soon will expand capacity at the FNLCR.

- Investigators interested in cell-based immunotherapies for cancer research can apply through the NCI Experimental Therapeutics (NExT) program.

- The FNLCR's vector manufacturing services should be advertised to the extramural community, and possibly commercialized.

- A small consortium could be established to showcase the NIH-wide cell therapy resources linked to the FNLCR's capabilities. Other research groups could be leveraged with the capacity for cell therapy initiatives, such as Case Western Reserve University's National Center for Regenerative Medicine.

- The interest in cellular therapy across federal agencies and for various applications remains high; the NCI recognizes the need for coordinating and building the necessary resources for cancer. The outcomes of the 2020 NCI cell-based immunotherapy workshops will help to inform decisions on new funding opportunities.

- Benefits of supporting CAR T-cell manufacturing at the FNLCR and conducting the associated trials at the NIH Clinical Center include disseminating lessons learned and training to other groups performing this work.

III. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) CONTRACT RE-COMPETITION AND COMMUNICATING FREDERICK NATIONAL LABORATORY (FNL) CAPABILITIES—DR. SARA S. HOOK AND MS. NANCY SIEBERT MURPHY

Dr. Sara S. Hook, Associate Director, NCI-Frederick, provided a review of the FNLCR (a Federally Funded Research and Development Center, FFRDC) as a critical component of the research enterprise and plans on a vision for the future. She also updated the FNLAC members about the FNLCR contract re-competition, including the timeline. Dr. Hook was joined by Ms. Nancy Siebert Murphy, Communications Lead Manager, Office of Communications and Public Liaison (OCPL), NCI, who described plans for conveying the FNLCR vision through NCI communications and outreach activities.

Dr. Hook explained that one contract operates the activities of the FNLCR, under which the laboratory performs work on behalf of the NCI Divisions, Offices, and Centers (DOCs); 17 other NIH Institutes and Centers (ICs); and 6 other federal agencies. Typically, 70 percent of the FNLCR contracted work is devoted to the NCI and cancer research, and 30 percent is devoted to infectious diseases and other biomedical research. During the COVID-19 pandemic, the workload has been equally distributed at 50 percent between cancer research and infectious diseases. The largest NIH partner at the FNLCR is the National Institute of Allergy and Infectious Diseases (NIAID).

Regarding major accomplishments, the FNLCR supports more than 400 NIH-sponsored clinical trials worldwide annually; has produced more than 130 biopharmaceutical products, of which 60 are in clinical trials; has characterized more than 440 candidate nanoformations, 2 of which recently received market approvals; and was the first to develop a test to screen the Nation's blood supply for HIV. In the past 5 years, the FNLCR has produced 70 lots of clinical products through two good manufacturing practices (GMP) programs. The FNLCR has supported several projects, including the Cancer Moonshot^{SM}, NCI-Molecular Analysis for Therapy Choice (NCI-MATCH), and The Cancer Genome Atlas. The most recent projects supported by the FNLCR include the Serological Sciences Network for COVID-19 (SeroNet), NCI–U.S. Food and Drug Administration (FDA) SARS-CoV-2 serology validation project, and 22 NIAID-led COVID-19 clinical trials being conducted in the United States and internationally. Long-term, ongoing FNLCR efforts include support of the NIAID-sponsored Partnership for Research on Ebola Vaccines in Liberia (commonly called PREVAIL) trial and the National Center for Advancing Translational Sciences (NCATS) Therapeutics for Rare and Neglected Diseases (TRND) program.

Moving forward (envisioning the future), the NCI proposes the following operational principles critical for the success of the FNLCR: Pursue high-risk/high-reward projects; maintain a full intellectual scientific partnership with the NIH; build relational bridges for shared success; nurture a spirit of organizational excellence; operate in a transparent, accountable, and effective manner; and demonstrate boldness and creativity in ideas and execution. To advance biomedical research, the NCI envisions three fundamental tasks for the FNLCR: (1) Provide NCI-supported investigators access to services, tools, and resources not readily available to individual laboratories; (2) serve as a hub for technology development, and (3) function as a nucleus for large-scale projects.

Dr. Hook reminded the FNLAC members that the FNLCR contract re-competition 3-year process began with the Board of Scientific Advisors (BSA) concept approval in December 2020 and involves the solicitation of proposals, evaluations, and negotiations. On 8 April 2021, the NCI will host a virtual Federally Funded Research and Development Center (FFRDC) Re-competition Industry Day to showcase the FNLCR's innovative work, present on its mission, and address applicants' questions. The NCI anticipates awarding the contract in August 2023. Further details can be accessed from the NCI/FNLCR acquisition portal.

Ms. Murphy described the benefits of increasing the visibility of the FNLCR in the broader community, all in support of the NCI's long-term plan for this national laboratory. The main objective is to encourage use of FNLCR services and resources among extramural researchers, with secondary objectives being to foster academic and industry partnerships, attract new talent, motivate existing staff, showcase NCI and NIAID intramural research, and build good will among local and regional communities. The OCPL will develop a concrete communications plan to raise awareness of the FNLCR, increase understanding of its role as technology hub, and increase appreciation of its life-saving mission to the American public. The first primary audience focus of the communications plan will be the extramural biomedical research community, encompassing academia and Cancer Centers. OCPL will work with the NCI DOCs to determine programs that would benefit from additional emphasis and

identify the associated audiences. In parallel, the OCPL will communicate internally with the NCI, HHS, and other government agencies utilizing the FNLCR, as well as policymakers and advocates.

The communications developed will convey the FNLCR's story: It pursues high-risk/high-reward projects and is the only FFRDC dedicated to biomedical research. Some key messages being developed highlight the FNLCR as bridging basic research and clinical practice, consisting of a team of highly passionate scientists, representing all scientific disciplines, and solving the toughest challenges in cancer and infectious diseases. The OCPL is developing a 3-minute FNLCR welcome video (featuring Dr. Sharpless, Dr. Hook, and Dr. Anthony Fauci, Director, NIAID) for the April 2021 Industry Day and the FNLCR website is being updated.

Ms. Murphy informed the FNLAC members that the next step in the 2021–2022 FNLCR communications approach will be to assemble a working group consisting of representatives from NCI-Frederick, OCPL, and the FNLCR communications staff. The group will be tasked with planning the dissemination of key messages through videos; photographs; and digital, social, and traditional media.

In the discussion, the following points were made:

- For the recompetition, we welcome proposals from any entity that can perform the work. The objective is to be less descriptive and more inclusive of different operating models.

- Dr. Sharpless explained that discussions have been ongoing in the NCI about which structure would work best for the FNLCR, with the conclusion to develop the statement of work (SOW) utilizing capabilities needed at the FNLCR to address the biomedical research goals of the NIH and NCI. The offerors are best suited to make their arguments describing how they would optimally meet these goals.

- The Federal Acquisitions Regulations regarding FFRDCs outlines who can apply. Any offeror meeting the technical capabilities of the SOW is encouraged to submit a proposal.

- The messaging to the audience should be tailored within the FNLCR communications plan. For example, details about the FNLCR resources relevant to the research needs of the extramural community (e.g., National Cryo-Electron Microscopy Facility [NCEF]) should be included, and patient stories and examples of success that more readily resonate with the general public should be provided.

- The FNLAC, kept up to date on the communications plan, can be advocates in the FNLCR messaging campaign. Groups such as ASCO and AACR could assist with disseminating information about CAR T-cell trials and details on translational research.

IV. STATUS REPORT ON DEVELOPMENT OF NEW FNL PROJECT—DR. DINAH S. SINGER

Dr. Singer provided an update on identifying new large-scale programs for the FNLCR. She noted that this report follows up on the dialogue from the 13 July 2020 FNLAC meeting. Dr. Singer reiterated the NCI vision statement for the FNLCR, addressing the three fundamental tasks described earlier by Dr. Hook. To extend beyond the current FNLCR research programs and technology development efforts, the NCI released a request for information (RFI) in November 2020 to solicit ideas on new national programs appropriate for the FNLCR. Communications and outreach advertising this RFI consisted of posts on the NCI website and NCI RAS Initiative listserv, emails to NCI stakeholder

contacts, and an announcement in the NCI Director's Report during the February 2021 NCAB meeting. This RFI closed on 19 February 2021 and, despite the promotional activities, fewer responses were received than anticipated.

Dr. Singer and her team compiled and categorized the FNLAC input and the RFI responses into an initial list of national programs. For research projects, the ideas include establishing programs in spatial proteomics and genomics, functional precision medicine, a central repository of premalignant lesions, clinical informatics, precision medicine immunogenic biomarkers, and molecular and social determinants of cancer in underrepresented populations. In terms of technology and infrastructure development, the program ideas include new technologies focusing on cancer prevention, volume electron microscopy for cellular/tissue three-dimensional imaging, and the data ecosystem. One overarching theme is establishing a national training program in clinical research for team members and project managers that establishes standards and best practices and ensures fundamental knowledge and capabilities across the U.S. cancer research enterprise.

Dr. Singer requested input from the FNLAC on the next steps, such as the solicitation of ideas at BSA, Board of Scientific Counselors, and NCAB meetings, as well as broader outreach to the research community through workshops or discussion of ideas and prioritization within the NCI and FNLAC. She emphasized the need to develop criteria and a process to discontinue mature programs sufficiently established elsewhere in the research community.

In the discussion, the following points were made:

- The NCI could consider deferring the decision on a new national program for the FNLCR until the communications plan is implemented and then issue a new RFI to restart the brainstorming of ideas.

- Members suggested that sponsoring small workshops (i.e., parallel to the PQ Initiative process) would be optimal for conveying that the process to select a new national program is open and transparent.

- One approach would be to sponsor a prize competition to solicit novel ideas for a new large-scale program for the FNLCR.

- A program analysis that encompasses a review of the status of the initiatives would be necessary before reaching any decisions on which mature programs to discontinue.

V. UPDATE: SEROLOGICAL SCIENCE AND MORE AT FNL—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Principal Deputy Director, NCI, reported on NCI's SARS-CoV-2 serology projects; outlined the effects of SARS-CoV-2 in cancer patients, particularly regarding the immune response to the COVID-19 vaccinations; and presented data describing SARS-CoV-2 antibodies associated with a decreased risk of new infection. He reminded the FNLAC members that in March 2020, the FNLCR HPV Serology Laboratory diverted some of its resources to perform SARS-CoV-2 serology. In April 2020, the FDA requested assistance from the NCI to evaluate the quality of commercial serology devices submitted for Emergency Use Authorization (EUA) approval by the FDA. Informal HHS collaborations essential to the success of this effort include NIAID, Centers for Disease Control and Prevention (CDC), Biomedical Advanced Research and Development Authority (BARDA), and Cancer Centers. These efforts led to congressional funding for serology research. On 24 April 2020, the NCI received $306 M through the Paycheck Protection Program and Health Care Enhancement Act to

develop, validate, improve, and implement serological testing and associated technologies. This NCI COVID-19 appropriation, which is separate from the NCI regular appropriations, has allowed the NCI to support a wide range of SARS-CoV-2-related serology research. Dr. Lowy acknowledged the FNLCR/NCI serology leadership: Dr. James M. Cherry, Scientific Program Director, Office of Scientific Operations, NCI-Frederick; Dr. Troy Kemp, Scientific Manager I, HPV Serology Laboratory, FNLCR; and Dr. Pinto.

SeroNet launched in October 2020 with 13 U01 Serological Sciences Research Projects, 4 Serological Sciences Capacity Building Centers, and 8 U54 Serological Sciences Centers of Excellence across the United States and is supporting the Serological Sciences Network Coordinating Center housed at the FNLCR. The NCI convened a SeroNet members meeting on 22 February 2021 to discuss SARS-CoV-2 antibody studies, and more than 70 people attended. The main objectives of this network are to develop novel serological assays and deploy them broadly; characterize the biological mechanisms driving the innate, humoral, and cellular responses to SARS-CoV-2; and determine factors that modulate the immune response. Designed to be a highly interactive network, SeroNet involves sharing data and resources and embodies a commitment to open-access publication. With the recent FDA approvals of EUA of COVID-19 vaccines, SeroNet is evaluating the serologic response to these vaccinations in cancer patients. The SeroNet COVID-19 studies will address questions on (1) whether specific groups whose immune response is similar to that of the general population differ from those whose initial or long-term response is inferior and (2) whether those with inferior responses benefit from additional booster vaccine dose and/or earlier booster dose. These studies will be conducted across SeroNet and other networks and will include Black/African American and Hispanic/Latino cancer patients.

The Committee was updated that in response to a request from the CDC, HHS, and NIAID to develop a serology data warehouse and dashboard for tracking SARS-CoV-2 seroprevalence and other U.S.-based serology studies, the NCI developed the COVID-19 Seroprevalence Studies Hub (COVID-19 SeroHub). The aims are to systematically identify published and ongoing SARS-CoV-2 seroprevalence studies and to offer an interactive dashboard to visualize SARS-CoV-2 seroprevalence estimates over time and by geography, population, and other factors. SeroHub is updated daily with new functionalities. The NCI is coordinating with international efforts through SeroTracker, which is supported by the Public Health Agency of Canada and is hosted through University of Calgary's Center for Health Informatics.

The FNLCR led efforts to develop a U.S. human SARS-CoV-2 serology standard (i.e., assay calibrator) to harmonize assays that measure anti-SARS-CoV-2 antibodies to increase comparability of results across studies. The aliquoted, calibrated, and validated U.S. serology standard—pooled plasma from blood donors with SARS-CoV-2 antibodies—is readily available and obtainable through the FNLCR. The request form can be accessed from the NCI/FNLCR website. The U.S. SARS-CoV-2 serology standard will be calibrated to the World Health Organization (WHO) International Standard when it becomes available.

Dr. Lowy summarized the process in the SARS-CoV-2 serology validation project—a collaborative effort engaging the NCI, NIAID, CDC, BARDA, and academic groups. The FNLCR investigators first developed an evaluation panel (production to quantification) to measure immunoglobulin G (IgG) and IgM antibody levels. This panel consists of enzyme-linked immunosorbent assay (ELISA)-based tests and assays for lateral flow devices, directed against the SARS-CoV-2 spike and nucleocapsid proteins. The evaluation panel was then used to assess positive and negative samples. Characterizations were performed in both the FNLCR and CDC serology laboratories. The commercial assay performance evaluations were determined and are used by the FDA in its EUA decision-making process. To date, the FNLCR HPV Serology Laboratory has evaluated more than 100 commercial serology devices (IgG and IgM-based), and 50 have been approved by the FDA. These data are publicly available on the FDA website. Acknowledging the value of such an evaluation approach and

collaboration with the NCI, the FDA, in the 18 February 2021 issue of the *New England Journal of Medicine (NEJM)*, reported the agency's experience with COVID-19 antibody tests. For future epidemics, the authors recommended establishing capacity within (or on behalf of) the federal government to evaluate test performance before an outbreak occurs, enabling independent and rapid evaluations during such an outbreak.

Dr. Lowy detailed research enabled by commercially available high-quality COVID-19 antibody tests in the United States. The NCI Surveillance Research Program (SRP) Surveillance, Epidemiology, and End Results (SEER) program—spearheaded by Dr. Lynn T. Penberthy, Associate Director, SRP, Division of Cancer Control and Population Sciences (DCCPS), and her staff—partnered with HealthVerity, Inc. to use its proprietary real-world data aggregation technology to link these data for COVID-19 research. In a pilot study, investigators addressed whether serum antibodies developed after SARS-CoV-2 infection associate with a decreased risk of a new infection and whether such a question could be addressed with anonymized real-world data. The HealthVerity data ecosystem provides an infrastructure to connect data from more than 75 unique data sources, uses a secure encrypted linkage process, and permits access to the broad categories of data on millions of individuals, with linkage to electronic medical records. HealthVerity collected serum antibody tests on approximately 4 million patients from commercial laboratories and diagnostic tests on approximately 20 million patients. During the study period, spanning from January 2020 to September 2020, the team evaluated viral RNA shedding using the nucleic acid amplification test. All data were de-identified. The index event for the 4 million antibody tests was 88 percent negative and 11 percent positive, with 30 day follow-ups. The results showed similar positive rates in antibody-negative patients over multiple 30 day periods, whereas the antibody-positive patients had progressively declining positive rates. The observed decrease in risk during the more than 90 day period was roughly tenfold. The main conclusion was that antibodies to SARS-CoV-2 were associated with a reduced risk of developing a subsequent symptomatic SARS-CoV-2 infection, suggesting that commercial SARS-CoV-2 antibody tests are reliable. An article describing this research, "Association of SARS-CoV-2 Seropositive Antibody Test with Risk of Future Infection," is in press at the *Journal of American Medical Association Internal Medicine*.

Dr. Lowy noted several implications of the HealthVerity study. First, the risk of new infection differs for antibody-positive and antibody-negative people. Second, when considering herd immunity, the population antibody-positive after natural infection could be added to the population antibody-positive after vaccination. Third, if an activity requires proof of vaccination (private or public sector), a positive antibody test might be an acceptable alternative.

In the discussion, the following points were made:

- The antibody assays in the HealthVerity pilot study were primarily of convenience and were performed based on the patient's desire to be tested, rather than for cause.

VI. FNL OPERATIONS AND ADDITIONAL UPDATES—DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos Biomed), reviewed the FNLCR's operational response to the COVID-19 pandemic and the continuity of operations as an FFRDC. He also provided an update on recent progress in assisting the NCI and NIAID-related programs. FNLAC members were reminded that the FNLCR contract portfolio consists of operational task orders (TOs), which have annual appropriations, and nonoperational TOs, in which benefits are received upon completion of the work. Currently active are 5 operational TOs supporting the NCI and NIAID and 98 nonoperational TOs supporting clinical and scientific groups and facility refurbishment. Subcontracts support the extensive outreach efforts to the broader research community.

In response to COVID-19, the FNLCR—in concert with the NCI—provided support in three major areas: identifying genetic determinants of SARS-CoV-2 susceptibility and outcome; testing and validating SARS-CoV-2 serologic assays; and assisting in COVID-19 clinical trials through high-throughput screening for small-molecule inhibitors of SARS-CoV-2 domain proteins. Dr. Dmitrovsky highlighted some of those activities. The FNLCR collaborated with Massachusetts General Hospital, Brigham and Women's Hospital, University of California, San Francisco, and Emory University to analyze 2,200 COVID-19 patient biospecimens with mild to severe disease. The aim was to determine whether recognition of SARS-CoV-2-specific peptides can result in viral protection. Dr. Mary N. Carrington, Head, Human Leukocyte Antigen (HLA) Immunogenetics Section, and her laboratory are evaluating the protective immune response of peptides resulting from highly polymorphic HLA loci. Dr. Stephen J. Chanock, Director, DCEG, and the FNLCR Cancer Genomics Research Laboratory presently are genotyping a subset (approximately 1,607) of these samples.

The FNLCR's Protein Expression Laboratory produced and optimized large quantities of SARS-CoV-2 spike, receptor binding domain, and nucleocapsid proteins; the procedure and protocols for this effort have been published. These proteins are being used for serology applications by multiple collaborators (e.g., the trans-NIH nationwide serosurvey for antibody protection, SeroNet, rapid response for external serology needs).

The FNLCR collaborated with NIAID in supporting SeroNet to implement and qualify SARS-CoV-2 assays; develop qualified assay standards and generate novel reagents; procure and characterize serum samples from SARS-CoV-2 patients and controls and establish serum panels; and share assays, reagents, and standards. Recognizing this growing prominence of serological science, the FNLCR leadership established the Vaccine, Immunity, and Cancer Directorate. Under the leadership of Dr. Pinto, this Directorate rapidly identified new laboratory and office space, relocated the required staff, and addressed cybersecurity needs. This nimble, flexible, and non-administrative process (characteristics of an FFRDC) involved using social media outlets to engage the extramural community, partnering with other government agencies to shorten the time needed for background checks, and pivoting 11 employees to work on SeroNet temporarily.

Regarding COVID-19 clinical trials, the FNCLR and NIAID implemented a practice-changing platform—Adaptive COVID-19 Treatment Trial (ACTT)—an international multicenter, adaptive, randomized, blinded, controlled trial evaluating the safety and efficacy of investigational therapeutics to treat COVID-19 in adult hospitalized patients. In FY 2020, three such trials were completed: ACTT-1 (remdesivir versus placebo), ACTT-2 (remdesivir with or without baricitinib or placebo), and ACTT-3 (remdesivir with or without interferon beta-1a or placebo). A fourth trial, ACTT-4 (remdesivir with dexamethasone or placebo versus baricitinib or placebo) is enrolling patients at U.S. and international clinical sites. Collectively, the ACTTs have been conducted rapidly in more than 70 institutions and enrolled 3,500 patients since February 2020. Specifically, ACTT-1 activated across 60 sites evaluating 1,063 COVID-19 cases and completed accrual in 2 months, resulting in data reported in the *NEJM*, FDA-approved EUA for remdesivir, and subsequent full FDA approval. ACTT-2 activated across 71 sites evaluating 1,034 COVID-19 cases, completed accrual in 1.5 months, resulting in data reported in the *NEJM* and EUA for use of remdesivir/baricitinib dual therapy.

In addition, support is continuing in the NIAID-sponsored Ebola randomized controlled trial in the Democratic Republic of Congo (DRC) in response to outbreaks in eastern DRC, now declared controlled by the WHO, and western DRC, Equateur Province. An infrastructure consisting of content experts was first built to conduct these trials. The Pamoja Tulinde Maisha (PALM) trial is organized by a public-private partnership, or PALM consortium, composed of Institut National de Recherche Biomédicale, NIAID-DCR, Leidos Biomed, The Mitchell Group, and other multilateral partners. PALM

has evaluated four investigational new drugs: remdesivir, Zmapp, mAb114, and REGN EB3. The FNLCR-developed mAb114 (named Ebanga or ansuvimab by Ridgeback Biotherapeutics) was granted FDA Orphan Drug and Breakthrough Therapy designation. REGN EB3 (named Inmazeb by Regeneron Pharmaceuticals, Inc.) was granted FDA Orphan Drug and Breakthrough Therapy designation and European Medicines Agency approval. Inmazeb and Ebanga were FDA approved in October 2020 and December 2020, respectively. Dr. Dmitrovsky emphasized that as an FFRDC, the FNLCR fulfills an unmet need and is not in competition with the pharmaceutical industry or academia. After completion of the FNLCR cycle of discovery for MAb114 with positive results, the trial data and agent were transferred to Ridgeback Biotherapeutics to complete the manufacturing. The FNLCR's support of international trials illustrates the rapid response capability of this FFRDC.

Even with the COVID-19 pandemic, 227 Leidos Biomed staff maintained continuity of services, particularly veterinary and clinical services within the FNLCR Directorates. Dr. Dmitrovsky highlighted some of the new approaches implemented during the pandemic. Dr. Stephen Jones, Director, Laboratory Animal Sciences Program, and his staff worked in three teams of non-overlapping duties during split shifts across elongated work weeks. Teams did not rotate between the NCI Bethesda and Frederick vivarium facilities. With this staffing model, the possibility of an entire team's being quarantined because of COVID-19 had little to no chance of occurring.

For CAR T-cell clinical trials, the FNLCR Biopharmaceutical Development Program is manufacturing CAR T-cells using the state-of-the art Prodigy system. The FNLCR is partnering with the Pediatric Blood & Marrow Transplant Consortium on a Phase I/II study of anti-cluster of differentiation (CD) 33 CAR expressing T-cells in children and young adults with relapsed/refractory acute myeloid leukemia (AML). Four AML patients—three at the NIH Clinical Center and one at the Children's Hospital of Philadelphia—have been enrolled. In addition, the FNLCR will be supporting a pediatric neuroblastoma/osteosarcoma trial of ganglioside antigen, GD2, which is anticipated to open in spring 2021.

Launched in 2017 and housed at the FNLCR, the NCEF has supported extramural investigators in 34 academic/research institutions with more than 400 cancer-related projects. After a mandated pause in April 2020 due to COVID-19, services have since resumed, with a new imaging project goal that exceeds the original target and incorporates COVID-19 research. In the past year, data on solving high-resolution structures were published in 18 peer-reviewed journals, some high-impact.

Dr. Dmitrovsky announced recent FNLCR honors and achievements: Dr. Ruth Nussinov, Senior Investigator, Laboratory of Cancer Immunometabolism and Head, Computational Structural Biology Section, was named 2020 Fellow of the American Physical Society; Dr. Jeffrey Lifson, Director, AIDS and Cancer Virus Program, was named 2020 Fellow of the American Association for the Advancement of Science; and Dr. Carrington was named 2021 Fellow of the American Academy of Microbiology.

Fulfilling another aspect of its mission as an FFRDC to serve its staff and the community, the FNLCR, within weeks, established an Asymptomatic COVID Testing program to serve all NIH employees and contractors. Five clinics are in operation—three in Frederick, Maryland, and one at the NCI Shady Grove campus. To date, the Asymptomatic COVID Testing program has conducted more than 5,600 tests, with a seropositivity rate of 0.2 percent. The FNLCR Human Resources department has established programs to assist FNLCR staff in teleworking mode, including the concierge services for child and elderly care and fortified programs with Johns Hopkins Medicine programs to assist staff diagnosed with cancer and other diseases or serving as caretaker. The Johns Hopkins Medicine programs include Work Stride, HealthyWorks, and Decision-Making Education for Choices In Diabetes Everyday (commonly called DECIDE). The FNLCR began a new community service initiative addressing food insecurity, Nourish our Neighbors, through which staff are donating to support three local charity groups.

The FNLCR's academic partnerships and outreach efforts span the national, regional, and local communities. Some of the FNLCR projects and collaborations assist with appointment and exchange of scientific staff, provide sabbatical opportunities for senior faculty, and support postdoctoral fellowships and student internships. During the COVID-19 pandemic, virtual training sessions with students at Butler, Columbia, and Georgetown Universities have been established and have been effective. Dr. Dmitrovsky recently was invited to join the American Cancer Society Research Council. He expressed appreciation to the NCI, NIAID, and NIH colleagues along with the key staff and FNLCR Directorate Heads and their teams for their support during the COVID-19 pandemic.

In the discussion, the following points were made:

- FNLAC complimented the FNLCR on its efforts in the NCI COVID-19 response, attributed to its FFRDC role to provide rapid, nimble, and flexible services with non-administrative processes.

VII. CLOSING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Marnett remarked on the accomplishments of the FNLCR in continuing to provide excellent research and support for the extramural community, a trend not disrupted by the COVID-19 pandemic.

VIII. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lyman. There being no further business, the 6th Virtual Meeting of the FNLAC was adjourned at 3:58 p.m. on Tuesday, 23 February 2021.

June 30, 2021 /s/

Date Lawrence J. Marnett, Ph.D., Chair

June 30, 2021 /s/

Date Caron A. Lyman, Ph.D., Executive Secretary