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

4th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
July 13, 2020

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

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4th Virtual Meeting of the Frederick National Laboratory Advisory Committee
13 July 2020

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 4th Virtual Meeting on 13 July 2020. The meeting was open to the public on 13 July 2020, from 1:00 p.m. to 4:03 p.m. 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
Dr. Kevin J. Cullen
Dr. Raymond N. DuBois
Dr. Angela M. Gronenborn
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. David I. Hirsh (absent)
Dr. Elizabeth M. Jaffee (absent)
Dr. Candice S. Johnson
Dr. Patrick Nana-Sinkam
Dr. Nilsa C. Ramirez Milan
Dr. Lincoln D. Stein (absent)
Dr. Cheryl L. Willman

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

Executive Secretary
Dr. Caron A. Lyman

TABLE OF CONTENTS

I. OPENING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Lawrence J. Marnett, Chair, called to order the 4th 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 21 May 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 14 October 2020 and will be virtual. Dr. Marnett explained that the Committee will need to confirm the 2022 meeting dates.

Motion. A motion to approve the FNLAC future meeting dates—24 February 2022, 27–28 June 2022, and 12–13 October 2022—was approved unanimously.

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 updates on the NCI appropriations and budget, the NCI coronavirus disease 2019 (COVID-19) response, and the Frederick National Laboratory for Cancer Research (FNLCR) infrastructure and resources, including large-scale initiatives.

Dr. Sharpless remarked on the recent social unrest unfolding in our nation stemming from unresponsiveness to longstanding racial issues. Cancer researchers, scientists, and doctors have called upon the NCI to be aware of, and active in, helping to relieve the tensions and turmoil. Although systemic racism neither exists nor is tolerated in the NCI, he conveyed the support of the NCI leadership in promoting a racially just and healthy society. Within its purview, the NCI can lend efforts to reduce cancer health disparities, promote a racially and ethnically diverse workforce (e.g., R01-funded researchers), and create a culturally diverse research community.

NCI Appropriations and Budget. Dr. Sharpless reported that the House Appropriations Subcommittee on Health and Human Services, Education, and Related Agencies (Labor-HHS) released its fiscal year (FY) 2021 proposed budget, which includes $400 million (M) in emergency funding for the NCI to support resuming operations delayed in FY 2020 because of the COVID-19 pandemic. The proposed budget also includes increases to the NCI regular appropriations, and the special appropriations for the Cancer Moonshot℠ and Childhood Cancer Data Initiative (CCDI) are continuing. Congress primarily has focused on the supplemental COVID-19 funding and enacted four emergency spending packages in FY 2020. In the fourth Phase 3b bill—Paycheck Protection Program and Health Care Enhancement Act—the NCI received $306 M to develop, validate, improve, and implement serological testing and associated technologies. Appropriators currently are deliberating on a fifth emergency supplemental spending package, which may include funds for the National Institutes of Health (NIH) and the NCI to support restart costs at academic institutions.

NCI COVID-19 Response. Dr. Sharpless remarked that the NCI's research and operational response to the COVID-19 has been underway for the past 4 months, noting that detailed reports can be accessed from the NCI website. He briefly touched on two key initiatives, which will be discussed in detail later in the meeting. The NCI issued three funding opportunity announcements to support

establishing the extramural Serological Sciences Network for COVID-19 Research (SeroNet). The NCI anticipates issuing awards in September 2020. On 21 May 2020, the NCI launched the NCI COVID 19 in Cancer Patients Study (NCCAPS). As of 7 July 2020, 612 trial sites had been activated across the Experimental Therapeutics Clinical Trials Network (ETCTN), NCI National Clinical Trials Network (NCTN), and NCI Community Oncology Research Program (NCORP) in 45 states. Dr. Sharpless expressed appreciation to Dr. Dinah Singer, Deputy Director, Science Strategy and Development, NCI, for her role in leading the SeroNet initiative and Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, Director, Division of Cancer Treatment and Diagnosis (DCTD), as well as to other NCI staff for their support in initiating the NCCAPS.

Regarding flexibility to support NCI grantees during the pandemic, FNLAC was informed that the NIH is extending deadlines for applications, with no justification required, and is allowing institutions the use of NCI grant funds to maintain salaries and stipends. The NCI is extending project timelines and reporting requirements, as well as eligibility periods for early-stage investigators and trainees and permitting carryover of institutional training grants (e.g., T35, T32, and K12), with prior approval. On 6 July 2020, the NCI issued a notice of special interest to provide administrative supplements to existing NIH grants as emergency support to postdoctoral fellows to compensate for lost stipends previously provided by nonprofit funders.

Dr. Sharpless called attention to a topic that is of great concern to the NCI and has attracted increased media coverage news: the impact of the changes in operations (e.g., postponing elective procedures) in hospitals and clinics because of the COVID-19 pandemic. In the 19 June 2020 issue of *Science*, Dr. Sharpless reported the estimated effects on cancer mortality based on the NCI-supported Cancer Intervention and Surveillance Modeling Network (CISNET) assessments. Using reasonable assumptions (e.g., moderate disruption in care that completely resolves after 6 months) for two common cancers—breast and colon—CISNET modelers estimate 10,000 (i.e., 1%) additional cancer deaths over the next 10 years compared with a scenario without delayed screening and diagnosis. This conservative analysis of a 1 percent increase in mortality does not account for other cancer types, additional nonlethal morbidity from upstaging, or regional variations in the response to the pandemic. Not wanting to see a reversal in the decades of progress in cancer mortality and morbidity, the NCI will make every effort to ensure that cancer care in the United States resumes in a manner that is safe for both patients and health care providers. The NCI is actively evaluating novel telehealth approaches and implementation science measures to lessen the impact of the pandemic on cancer care. In addition, the NCI has solicited advice from the 71 NCI-Designated Cancer Centers (Cancer Centers) and is building on lessons learned from epicenters of the pandemic, including New York University Langone Health.

FNLCR Infrastructure and Resources. Dr. Sharpless reminded the FNLAC that 70 percent of the FNLCR's effort supports cancer research at the NCI. The remaining 30 percent of effort focuses on biomedical research in general; in this area, the National Institute of Allergy and Infectious Diseases (NIAID) is the major consumer of FNLCR expertise and resources. Support for research in other diseases—such as HIV, human papillomavirus (HPV), and recently COVID-19—crosscut cancer and biomedical research activities, as well as shared resources and capabilities. The NCI is seeking advice on how best to convey to the research community FNLCR's unique capabilities, which have attracted interest, especially amid the response to the pandemic. In addition, the open competition to select the FNLCR prime contractor (i.e., contract recompete) is approaching, and the NCI wants to communicate the laboratory's activities in a clear and concise manner. Dr. Sharpless highlighted some national capabilities of the FNLCR that would be of interest to researchers in the biomedical community, including the Genomic Data Commons (GDC), National Cryo-Electron Microscopy Facility (NCEF), animal models, and repositories. The FNLCR major large-scale national initiatives are the Cancer Genomics Research Laboratory, NCI Experimental Therapeutics (NExT) program, The Cancer Genome

Atlas (TCGA), individualized immuno-oncology research, AIDS-related malignancies studies, RAS (i.e., RAS gene family, mutated in human cancers) Initiative, and (recently) SeroNet.

Dr. Sharpless remarked on the vigorous science being conducted at the FNLCR and emphasized that even with launching new major efforts in FY 2020, the NCI is confident that the laboratory can accommodate at least one additional large-scale national initiative. He noted that Dr. Singer would further elaborate on this topic later in the meeting.

In the discussion, the following points were made:

- In the messaging to the extramural research community, it would be good to consider including statements that the FNLCR is an NCI investment in establishing national research resources (e.g., TCGA).

- How the FNLCR research resources can be accessed and best used by the extramural research community should be clearly conveyed and might entail supporting pilot projects in the Cancer Centers.

- Developing a public relations/communication approach (or approaches) that emphasizes NCI's transparency would serve to improve understanding of the current NCI–FNLCR funding structure.

III. FREDERICK NATIONAL LABORATORY (FNL) OPERATIONS DURING THE PANDEMIC—DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos Biomed), reviewed the FNL's operational response to the COVID-19 pandemic, its responsibility as a Federally Funded Research and Development Center (FFRDC), and the Emergency Operations Center (EOC). In an emergency, the FNLCR has a contractual responsibility to maintain an emergency management program that encompasses laboratory activities and the infrastructure (e.g., planning, preparedness, response, readiness, and assurance procedures) that informs the Continuity of Operations Program (COOP). The two operational missions are to (1) maintain essential services and (2) continue essential clinical, scientific, and administrative services without disruption. The EOC, which provides structure and focus to ensure that the minimal essential functions are activated, is based on Federal Emergency Management Agency (FEMA) Incident Management System guidelines.

Dr. Dmitrovsky explained that this pandemic was the first time the FNLCR EOC has been fully activated for an extended time. Activating the EOC highlighted a need for optimized collaboration and improved communication to enable the necessary rapid response, which the FNLCR actively addressed. Demonstrating that the FNLCR can effectively support emergency operations amid this pandemic, he reported that, of the 50 individuals working at the FNLCR symptomatic for possible COVID-19 identified at the onset of the process, 12 tested positive and were immediately quarantined at home, and none required hospitalization. In addition, no single case of a spread of SARS-CoV-2 infection across the FNLCR multiple sites occurred.

The organizational structure of the EOC is composed of the NCI and FNLCR leaderships, and the lead command is Ms. Terri Bray, Director, Environment, Health, and Safety, FNLCR. In support of operations, the FNLCR finance and contracts and project management staff teleworked and delivered task order (TO) proposals. Program staff held weekly teleconferences, and the executive leadership team met at least twice per week. To assure continuity of services in essential areas they were staffed at no more than 50 percent levels so that teams could be rotated into the workplace without placing entire teams at

risk for quarantine should a COVID-19 case occur in a team member. Also, their activities were prioritized to those addressing mission-critical and safety. The logistics, warehouse, and travel staff used discretionary leave, when appropriate. The scientific response to the pandemic involved activating the EOC and supporting personnel's telework by deploying laptops equipped with virtual private network accounts, establishing more than 60 Microsoft teams, and configuring remote jump boxes. Custodial (i.e., protective) teams were established to identify and prioritize the areas at highest risk for the spread of COVID-19. The Institutional Biosafety Committee prioritized its work to COVID-19 activities. Staff distributed surplus N-95 respirators to the NIH Clinical Center and other clinical colleagues in need, and the Vaccine Clinical Materials Program repurposed its Pilot Plant to produce hand sanitizer for the local community. These efforts were consistent with an FFRDC's public health service mission.

Despite the COVID-19 pandemic, the continuity of veterinary and clinical services within the FNLCR Directorates was maintained. Dr. Michael Baseler, Director, Applied and Developmental Research Directorate, and his staff provided oversight for biorepositories and conducted laboratory studies redirected for COVID-19 research. Ms. Beth Baseler, Director, Clinical Monitoring Research Program, and her team enabled and conducted international COVID-19 trials. Dr. David Lindsey, Director, Vaccine Clinical Materials Program, redirected the Pilot Plant to produce hand sanitizer. Dr. Gautam (George) Mitra, Director, Biopharmaceutical Development Program, and his team manufactured chimeric antigen receptor (CAR) T-cells for childhood acute myeloid leukemia (AML) patients. Dr. Barry L. Gause, Chief Medical Officer, FNLCR, Director, Clinical Research Directorate, assisted deployment of his group to conduct COVID-19 case studies. To maintain the NCI vivarium facilities (Bethesda and Frederick), 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. With this staffing model, the possibility of an entire team's being quarantined because of COVID-19 had little to no chance of occurring.

In concert with the NCI, to combat COVID-19, the FNLCR provided support in three major areas that span across projects and initiatives: identifying genetic determinants of SARS-CoV-2 (the virus that causes COVID-19) susceptibility and outcome; testing and validating SARS-CoV-2 serologic assays; and performing high-throughput screening for small-molecule inhibitors of SARS-CoV-2 proteins. These areas leveraged the expertise of the FNLCR Cancer Genomics Research Laboratory and the HPV Serology Laboratory, as well as technology developed in the RAS Initiative. Amid the pandemic, peer-reviewed publications have resulted from both the COVID-19 research and core mission efforts.

Dr. Dmitrovsky provided an overview of the NIAID–FNLCR collaborations on international clinical trials. The FNLCR supported the Adaptive COVID-19 Treatment Trial (ACTT), a multicenter international trial evaluating remdesivir in hospitalized COVID-19 patients. The ACTT, which opened on 21 February 2020 and ended on 19 April 2020, enrolled 1,063 patients across 60 clinical sites worldwide. Initial reports revealed that hospitalized COVID-19 patients treated with remdesivir were discharged from the hospital 31 percent sooner than patients not receiving the drug. The subsequent follow-on trial, ACTT-2, which opened on 8 April 2020 and closed on 30 June 2020, rapidly enrolled 1,034 patients with no lag time. ACCT-2 evaluated dual therapy of remdesivir and baricitinib. In addition, support is continuing in the NIAID-sponsored Ebola randomized controlled trial in the Democratic Republic of Congo and the international Zika virus trial, including Zika vaccine development. The FNLCR support of international trials illustrates the rapid response capability of this FFRDC. To broadly disseminate these data, the FNLCR—in partnership with the U.S. Department of Health and Human Services (HHS), NIH, NIAID, and a subcontractor—developed and now manages a COVID-19 treatment guideline website: https://www.covid19treatmentguidelines.nih.gov/. Over a 3-month period beginning in April 2020, more than 2.5 million viewers accessed this national resource.

The FNLCR collaborates extensively with the extramural community; has 159 unique partners at

universities, research institutions, and industry; and has 53 executed Contractor Cooperative Research and Development Agreements (cCRADAs). New partnerships include the HPV Serology Laboratory–London School of Hygiene & Tropical Medicine–Bill and Melinda Gates Foundation (Gates Foundation) to investigate immune responses to the HPV vaccine in Tanzania and the AIDS and Cancer Virus Program–Beth Israel Deaconess Medical Center–Gates Foundation to identify potential viral reservoir biomarkers in rhesus macaques experimentally challenged with the simian immunodeficiency virus.

Dr. Dmitrovsky conveyed FNLCR's commitment to uphold its responsibility to conduct work that serves the educational interests of the extramural community. The Leidos Biomed–Hood College Cancer Science Symposium held its first annual meeting in June 2019, and its next meeting is scheduled for April 2021. Dr. Sara Hook, Director, Office of Scientific Operations, NCI-Frederick, and Dr. Dmitrovsky established the FNLCR-NCI Cancer Survivorship Seminar series and hosted the first session in February 2020. The FNLCR Biomedical Informatics and Data Science (BIDS) facilitates outreach efforts to engage the extramural community in the Accelerating Therapeutics for Opportunities in Medicine (ATOM)—a public–private partnership to accelerate cancer drug discovery. Since the last update, Dr. Leonard P. Freedman, Chief Science Officer, FNLCR, has joined the ATOM governing board, and Dr. Eric Stahlberg, Director, BIDS, became the ATOM co-lead. Three National Laboratories (Argonne, Oakridge, and Brookhaven) have joined ATOM, and the Consortium is consulting legal counsel on establishing 501(c)3 status. As part of the educational component, the ATOM Consortium is virtually hosting pharmacy interns and has published four manuscripts.

The FNLAC members were reminded that, as an FFRDC, the FNLCR contract portfolio consists of operational 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, 84 nonoperational TOs supporting clinical and scientific groups and facility refurbishment, and 5 supplemental funding TOs supporting the Cancer Moonshot℠ or COVID-19 research.

In the discussion, the following points were made:

- The NCI has worked with the Frederick, Maryland, community hospital to conduct COVID-19 testing for FNLCR personnel. Some of these analyses were performed at the NIH Clinical Center and others through the individuals' private insurers.

IV. OVERVIEW: COVID-19 RESEARCH INITIATIVES AT THE FNL—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Principal Deputy Director, NCI, provided an update on the serology research efforts at the FNL, including the extramural SeroNet, tracking SARS-CoV-2 seroprevalence, NCCAPS, and improved cancer prevention and screening. He reminded the FNLAC that the NCI COVID-19 appropriation, which is separate from the NCI regular appropriations, is supporting the FNLCR new and ongoing serology research. In collaboration with the NIAID, Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), and Mount Sinai Hospital, the FNLCR HPV Serology Laboratory was successfully converted to perform SARS-CoV-2 serology. The short-term goals are to characterize different serological assays, correlate the data with existing validated assays, and interact closely with the FDA on approvals. In the long term, the NCI anticipates improving understanding of the implications of being seropositive in terms of resistance and duration of infection and participating in cohort-oriented COVID-19 projects (e.g., NCCAPS).

To date, the HPV Serology Laboratory used qualitative immunoglobulin G (IgG)–based antibody tests to evaluate more than 70 commercial serology devices. Among the 70 devices tested, the sensitivity

varied from 30 to 100 percent. The specificity also varied across devices and was within 87 to 100 percent. The results have been sent to the FDA to help determine devices suitable for emergency use authorization, and some of these data are publicly available on the FDA website. In addition, the FNLCR Protein Expression Laboratory is producing large amounts of SARS-CoV-2 antigens to support serologic assays both in house and at the National Institute of Biomedical Imaging and Bioengineering. The HPV Serology Laboratory is developing quantitative SARS-CoV-2 assays and—in collaboration with NIAID, CDC, and the Biomedical Advanced Research and Development Authority—is establishing a serology standard for the U.S. government. The aim is to link the U.S. national standard with the World Health Organization global standard when it becomes available. Dr. Lowy called attention to some key questions concerning whether being antibody-positive is associated with active or prior SARS-CoV-2 infection, which the NCI is co-funding extramural research with the NIAID and CDC to address.

In collaboration with the NIAID, the NCI is establishing an extramural SeroNet to rapidly increase understanding of all aspects of the SARS-CoV-2–related immune response. Establishing this network will increase the national capacity for high-quality serology testing. The HPV Serology Laboratory will develop serological assays, which can be deployed for testing SARS-CoV-2–induced immune responses. The goals are to understand the mechanisms involved in the serological, humoral, and cellular immune responses and determine the serological correlates of disease pathogenesis and protection against future infection. The SeroNet will consist of extramural Serological Sciences Capacity Building Centers (CBCs), Serological Sciences Centers of Excellence, Serological Sciences Research Projects, and a Network Coordinating Center housed at the FNLCR. The NCI issued two requests for applications (RFAs) (one for the centers of excellence and another for the science projects) and a request for proposals (RFP) for the CBCs. The RFP applications are due 19 July 2020, and the RFAs are due 22 July 2020. The NCI anticipates supporting 4 to 8 contracts for the CBCs with the academic and/or private sector through the FNLCR, 4 to 8 U54 awards for the Serological Sciences Centers of Excellence, and 5 to 10 U01 awards for the Serological Sciences Research Projects.

The Committee was informed that the NCI, in collaboration with the CDC and NIAID, is developing a serology data warehouse and dashboard for tracking SARS-CoV-2 (Sero-tracker) seroprevalence and other U.S.-based serology studies. This effort will leverage the dashboard expertise of the FNLCR developed within the NCI Clinical Trials Reporting Program and other databases. Dr. Lowy noted the key features, a publicly accessible data warehouse and near-real-time COVID-19 status, and vision for Sero-tracker, which is being built to store information and allow the user to access the dashboard and reports. The prototype version of the dashboard soon will receive and test data from the CDC and NIAID.

In support of the NCCAPS—a longitudinal natural history trial that aims to enroll more than 2,000 cancer patients with COVID-19 across the NCI clinical trials networks to evaluate outcomes—the FNLCR will assess anti-SARS-CoV-2 antibody development, cytokine abnormalities, and genetic polymorphisms associated with severe COVID-19. The NCCAPS will establish a biobank of clinical data, research blood specimens, and radiological images for future research, all housed at the FNLCR. Dr. Lowy explained that modifications to the NCI clinical trial processes to enable opening NCCAPS at the participating NCTN, ETCTN, and NCORP sites and rapidly accruing patients include allowing remote informed consent, eliminating the need for extra site visits, and temporarily relaxing the requirement for onsite processing of research blood samples. The NCI anticipates utilizing these types of measures to address clinical site feasibility issues beyond the response to a pandemic. These improvements are not expected to decrease the quality of the research or patient care.

Last, Dr. Lowy noted one example of how the COVID-19 pandemic could potentially stimulate modified approaches to cancer screening. According to the Surveillance, Epidemiology, and End Results (SEER) data, from 1975 to 2015, the incidence of cervical cancer steadily decreased for both

White/Caucasian and Black/African American women. Today the mortality rates remain 50 percent higher in Black/African American women than in White/Caucasian women, partly due to underscreening. Because of the COVID-19 pandemic, the FDA is willing to consider self-collected vaginal specimens for cervical cancer screening. If eventually approved as a standard method, this approach could enable screening of women with limited access to care, which could potentially decrease cervical cancer incidence and mortality. Dr. Lowy noted that the President's Cancer Panel will be taking the initiative to review different population-wide screening approaches and evaluate innovations for improvements.

In the discussion, the following points were made:

- Establishing a Board of Scientific Advisors (BSA) or National Cancer Advisory Board (NCAB) Working Group would be one way to address expanding self-sampling efforts in existing colorectal cancer-screening campaigns. Increasing the scope of activities of an existing Working Group also might be appropriate.

- The NCI could consider ways to adapt the SARS-CoV-2 seroprevalence tracking software beyond COVID-19 trials to other NCI clinical trials.

V. IMMUNE CELL ENGINEERING FOR THE EXTRAMURAL COMMUNITY: RECENT PROGRESS AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) —DR. ROSEMARIE AURIGEMMA

Dr. Rosemarie Aurigemma, Associate Deputy Director, Developmental Therapeutics Branch, DCTD, presented project and capability updates for the cellular therapy program and noted facility upgrades and potential new projects. The Biopharmaceutical Development Program (BDP), located in the Advanced Technology Research Facility (ATRF) at the FNLCR, is a facility that manufactures biotechnology products under current Good Manufacturing Practices (cGMP) to support Phase I/II clinical trials. The BDP has a long history of providing biological resources and material for these trials, including monoclonal antibodies, recombinant proteins, and virus vectors. The expertise of the BDP includes process development, quality control, manufacturing, and regulatory affairs. Dr. Aurigemma noted that after the October 2018 update to the FNLAC, the ATRF Virus Production Facility was converted into a cell therapy production suite. In addition, the BDF staff gained experience in centralized manufacturing logistics and release-testing under standard operating procedures to improve reproducibility, enabling faster technology transfer to point-of-care options. On 10–11 December 2018, the DCTD hosted a workshop on cell-based immunotherapy for solid tumors to gain input from the extramural community on what support NCI might provide to advance cell therapies. Workshop participants identified the research needs and outlined clinical development, technology, and regulatory challenges. A second cell-based workshop to discuss the progress is planned for December 2020.

Dr. Aurigemma reviewed the cell-based immunotherapy approaches, including those developed in the NCI Cancer Center for Research (CCR). The CCR investigator, Dr. Steven A. Rosenberg, pioneered the tumor-infiltrating lymphocytes (TIL) process, which involves isolating lymphocytes from an excised patient tumor, culturing them *in vivo*, and administering the cancer-specific reactive TILs back to the patient. CCR investigators also have been working with T-cells that have been transduced with a T-cell receptor (i.e., TCR T-cells) specific for a particular cancer antigen and chimeric antigen receptor (CAR) T-cells, which are the topic of today's update. In CAR T-cell therapy, the T-cells are transduced externally with viruses that express the CAR (i.e., customized receptor and antigen signaling domain) specific for a cancer antigen and then administered to the patient.

Once a patient is enrolled in a CAR T-cell treatment trial, the production of CAR T is a complex process consisting of several steps—apheresis and T-cell selection; stimulation and transduction;

expansion; quality control and safety testing. During this time the patient undergoes lymphodepletion prior to infusion of the final CAR T product. Dr. Aurigemma emphasized that because the clinical site is distant from the BDP, which manufactures the CAR T product using apheresis material sent from the clinical site, conducting a multicenter CAR T-cell trial is not without logistical challenges. The BDP developed an efficient, well-timed process for transfer of the cryopreserved apheresis product from the clinical site to the BDP, with the manufacturing team on standby to receive the starting material and processing it according to a scheduled calendar and product testing plan. The cryopreserved CAR T-cell product is then shipped back to the clinical site for administering to the patient.

Harnessing the expertise of the BDP to support cell therapy for cancer is proving to be an excellent resource for the extramural community. The cGMP manufacturing provides quality assurance rigor and reproducibility has the product chain logistics to support multicenter trials. The BDP will also begin to provide cGMP-grade transduction vectors (e.g., lentivirus, gamma-retrovirus, and adeno-associated virus) used for generating CAR T. Via the DCTD, the BDP collaborates with the FDA, the National Institute of Standards and Technology, and other stakeholders to standardize product characterization assays for the cell therapy community. ATRF autologous cell manufacturing utilizes an automated closed system, CliniMACS Prodigy®, which are fitted with disposable pouches and tubes for individual patient apheresis material and provides access points to draw samples during manufacturing for quality control testing.

Dr. Aurigemma reported that, under funding from DCTD, the BDP currently is providing the CAR T manufacturing support for the Pediatric Blood & Marrow Transplant Consortium-sponsored Phase I/II study of anti-cluster of differentiation (CD) 33 CAR-expressing T-cells in children and young adults with relapsed/refractory AML. NCI CCR investigator Dr. Nirali Shah and Children's Hospital of Philadelphia (CHOP) investigator Dr. Richard Aplenc are co-leading the study. The Investigational New Drug (IND) Application was filed with the FDA in July 2019, and the first clinical site was activated on 8 January 2020. The first patient was enrolled on 12 February 2020, and two patients have been treated as of today's meeting, with referrals being delayed because of the COVID-19 pandemic. In addition, enrollment is necessarily slow since the FDA requires a longer observation period between patient infusions for a first cohort in a trial of this type. DCTD is also supporting a second CAR T project with the BDP providing the patient-specific manufactured product to clinical sites. The Pediatric Cancer Immunotherapy Trials Network (PED-CITN) is supporting the ganglioside antigen, GD2, CAR Production and Engineering of GD2-Targeted, Receptor Modified T-Cells for Sarcoma and Neuroblastoma to Increase Systemic Tumor Exposure (PERSIST) trial. NCI CCR investigator Dr. Rosandra N. Kaplan and Stanford University investigator Dr. Crystal L. Mackall are co-leading the study. The BDP has developed the GD2 PERSIST manufacturing process, and the IND submission for that protocol is planned for August 2020.

Establishing CAR-T manufacturing at the BDP required several collaborations, including extensive partnering with the CCR investigators who provided expertise and guidance. The NIH Clinical Center, Department of Transfusion Medicine assisted in transferring the technology for the cell manufacturing process to the FNLCR. For the CD33 CAR-T trial, the lentivirus was provided by CHOP and leveraged the preclinical studies completed by CHOP and Children's Hospital Colorado investigators. The NIH Clinical Center and CHOP are the two active sites enrolling patients, with other children's hospitals scheduled to join. The CD33 CAR T-cells are manufactured in a 7-day process extending from acquisition of the apheresis starting material to cryopreservation of the final product, but the process flow and timeline may vary according to each clinical project. Efficacy studies in tumor-bearing mice demonstrated that the Prodigy-manufactured CD33 CAR T-cells were active and that all tumor cells were eradicated by 17 days after CAR-T administration. Since the amount of CD3 positive cells (T cells) may vary in the apheresis material that is collected from AML patients, the Prodigy-manufacturing process enriched for this cell population, with nearly 100 percent CD3 T cells showing more than 90 percent

viability at harvest. For the GD2 CAR T trial, the BDP is using gamma-retrovirus acquired from Bellicum, Inc., and leveraged the preclinical research and development performed at Stanford University. A next step in DCTD's goal for expanding cell therapy support is for the BDP to set up the capability for producing cGMP-grade virus vectors. The manufacturing team has developed a scalable 4-plasmid lentivirus production platform to support a CCR pilot project and is currently in the process of obtaining the cGMP-grade plasmids. The fully cGMP manufacturing process is expected to be established in early 2021.

Dr. Aurigemma summarized the FNLCR current cell therapy and virus manufacturing capacity. Thus far, the autologous cell therapy program is Prodigy-based only and has been expanded into a new GMP suite which is in the final stages of validation. Using two parallel Prodigy systems, four clinical products can be generated per month. In its current configuration, the Virus Production Facility can support four virus production campaigns annually for lentivirus and gamma-retrovirus. New construction on the ATRF third floor will begin in October 2020, is expected to be completed in 2022, and will expand capacity for cell therapy or virus vectors. Lessons learned suggest that cell therapy development and IND filing will take 12 to 15 months to complete for each clinical project and vector development and manufacturing will take 9 to 13 months for each virus product. Regarding the future of cell therapy and vector production at the FNLCR, plans are to launch gene-editing (e.g., CRISPR) technology development for cell-based immunotherapy in September 2020. The DCTD is planning to establish a cGMP queue as the most cost-effective means to use the manufacturing capabilities while minimizing time to set up new platforms and cell therapies. Investigators will be encouraged to apply via the NExT program.

In the discussion, the following points were made:

- The BDP has not, as of yet, worked with Foundation for the Accreditation of Cellular Therapy (FACT)–accredited transfusion medicine groups but the DCTD-supported clinical sites do adhere to the International Society of Blood Transfusion guidelines. In addition, the NCI and FNLCR leaderships could explore achieving FACT accreditation for the BDP cell therapy manufacturing facility.

- Current BDP vector manufacturing efforts are focused on transient transfection systems to support early clinical trials but the FNCLR could consider generating GMP-grade producer cell lines in the future.

- Although many academic centers have established cell manufacturing facilities, those facilities primarily support research specific to those centers, and the platforms and processes vary. The NCI anticipates that establishing cell manufacturing at the FNLCR BDP will provide standardized manufacturing processes to the research community, improve multicenter clinical trial enrollment, and accelerate FDA approvals.

VI. ROUND ROBIN DISCUSSION: NEW NATIONAL PROGRAMS AT THE NCI'S FNLCR—DR. DINAH S. SINGER

Dr. Singer noted that this round robin discussion will be a continuance of the dialogue from the 24 October 2019 FNLAC meeting. The purpose of today's discussion is to seek the Committee's input on the most important needs and promising opportunities in cancer research that are challenging to address on an individual research laboratory level. When the FNLCR was established as a national laboratory in 2012, one of its goals was to be a locus to take on large, high-risk projects not easily pursued through investigator-initiated research or existing networks. Examples include the RAS Initiative, which began in 2013 to investigate this undruggable target; the NCEF, which became operational in 2017; the cellular

immunotherapy program, which started in 2018; and the recent SeroNet. In a hub-and-spoke model of research and collaboration, the FNLCR is at the center of these national initiatives. The NCI envisions potential new projects that, if additional resources were available, could advance cancer research progress.

Dr. Singer opened the discussion by asking FNLAC members to identify and provide a brief background about a problem in cancer research and to provide a rationale for a program to address this problem that would be supported by the FNLCR.

In the discussion, the following points were made:

- The strength of the FNLCR is the suite of novel technology, instrumentation, and methodology used. Efforts have been successful in managing the hub-and-spoke model within the large-scale national research initiatives and connecting with, and incorporating information from, the Cancer Centers.

- The recent efforts to strategically redirect the HPV Virology Laboratory to SARS-CoV-2 serology demonstrate that a national diagnostics program could be supported at the FNLCR. Such a program would involve developing new technologies focusing on cancer prevention or partnering with diagnostics-based biotechnology companies already doing this work.

- Although meritorious, many areas of large-scale research remain unfunded. Establishing a broad-scale program focusing on discovery research could potentially lead to novel cancer diagnostics and therapeutics.

- A significant amount of research on spatial proteomics and genomics is ongoing but often overlaps across research laboratories. The NCI could consider a national program focusing on spatial biology at scale by coordinating the existing initiatives, including harmonizing those data.

- Many groups at smaller academic instructions are challenged to provide in-depth computational sciences and big data approaches to evaluate their data. This puts these investigators, who are experts in this field, at a disadvantage in competing with counterparts at larger, well-resourced institutions. A national program analogous to the TCGA that focuses on big data analysis in a common consortium would benefit both junior and senior investigators who lack access to state-of-the-art bioinformatics or computational resources.

- The current immunotherapy tools are expensive and insufficient to fully eradicate advanced-stage tumors. Establishing a program at the FNLCR that leverages clinical informatics could advance this field.

- Advances have improved early detection, prevention, and screening, but gaps in knowledge remain. The opportunity exists to support research on early-stage characterization of signals and pathways and other changes that occur in premalignant lesions. Leveraging the Cancer Moonshot℠ Pre-Cancer Genome Atlas would be one place to start to establish a central repository and unify efforts.

- The SEER data are not representative of all the U.S. states or harmonized across cancer registries, but they provide exceedingly valuable information. The FNLCR could focus on a mechanism to enable SEER data from all states and make these data available in formats easily utilized in the research community to support new discoveries.

- Studies evaluating the genetic basis of the differences in patients' immune responses to viruses, including SARS-CoV-2, are limited. The field would benefit from having a precision medicine immunogenic biomarker study to determine these effects at various stages (e.g., mild to severe) of viral infection.

- Cancer health disparities are well known, have been linked to social determinants of health, and are highly visible in recent outbreaks, especially in COVID-19. The FNLCR could take the lead in serving as a catalyst to better understand the molecular determinants of cancer in underrepresented populations in the United States and additionally could serve as a focal point to assist investigators in ways to integrate both social and molecular determinants of health. The FNLCR could partner with the Cancer Centers already providing service to underrepresented populations to gain access to existing data.

- The quality of biospecimens, particularly solid tumors, remains a concern for investigators and is subject to different interpretations by pathologists when used in studies resulting in therapies for patients. Developing artificial intelligence approaches and algorithms that further delineate the clinical data would assist in examining biospecimens and improving accuracy in decision-making about treatments.

- Although the NCI–Department of Energy Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) Pilot 3 project—Population Information Integration, Analysis, and Modeling for Comprehensive Cancer Surveillance—focusing on SEER data has been successful and is incorporating real-time data, the FNLCR could consider expanding the efforts beyond a small-scale, short-term project. A large, integrated, and searchable database not siloed within different programs would be innovative for the SEER data and extend beyond the Cancer Centers' catchment areas.

Dr. Sharpless expressed appreciation to the FNLAC members for their participation and ideas, which the NCI will consider when focusing efforts for a next national program for the FNLCR. In addition, the NCI will review crosscutting themes and address any issues that overlap with existing NIH programs.

VII. 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 4th Virtual Meeting of the FNLAC was adjourned at 4:03 p.m. on Monday, 13 July 2020.

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

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