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

7th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
June 28, 2021

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
7th Virtual Meeting of the Frederick National Laboratory Advisory Committee
28 June 2021

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 7th Virtual Meeting on 28 June 2021. The meeting was open to the public on 28 June 2021, from 1:00 p.m. to 4:35 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 (absent)
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 (absent)
Dr. Denise J. Montell
Dr. Patrick Nana-Sinkam
Dr. Lincoln D. Stein
Dr. Cheryl L. Willman

NCI Senior Leadership
Dr. Stephen J. Chanock (absent)
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage (absent)
Dr. Kristin Komschiles McConville
Dr. Douglas R. Lowy
Dr. Tom Misteli (absent)
Ms. Donna Siegle
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 7th 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 23 February 2021 FNLAC meeting was approved unanimously.

Dr. Marnett called Committee members' attention to the confirmed future meeting dates listed on the agenda, noting that the 2023 proposed meeting dates will need to be confirmed. Dr. Marnett also noted that the next FNLAC meeting will be held on 18–19 October 2021 and will be virtual.

Motion. A motion to confirm the 2023 FNLAC meeting dates 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 at Frederick, NCI budget, activities related to coronavirus disease 2019 (COVID-19), and NCI programs and initiatives.

NCI at Frederick. Dr. Sharpless reported that the Frederick National Laboratory for Cancer Research (FNLCR) website has been reorganized (https://frederick.cancer.gov) and redesigned to be more user friendly and easier to navigate. The new site went live 25 June 2021. He reminded the FNLAC members of NCI's plans (presented at the February 2021 FNLAC meeting) for enhancing awareness of the FNLCR, what it offers, and how it can be utilized by researchers. The goals are to increase usage of the FNLCR resources (e.g., National Cryo-Electron Microscopy Facility [NCEF]) and to educate a variety of audiences, including the extramural researchers, members of Congress, cancer research advocates, and current and potential partners. An internal working group composed of representatives from NCI-Frederick, Office of Communications and Public Liaison, and the FNLCR communications staff is planning the dissemination of key messages through photographs; digital, social, and traditional media; and videos. One such video accessible from the FNLCR website is a 2-minute film (featuring Dr. Sharpless and Dr. Anthony Fauci, Director, National Institute of Allergy and Infectious Diseases [NIAID]) describing the history and the vital role of FNLCR.

Dr. Sharpless reminded the FNLAC members that the FNLCR contract re-competition is in progress. A draft request for proposals (RFP) for this Federally Funded Research and Development Center (FFRDC) was issued on 24 June 2021 and is posted to the beta version of the SAM website (https://Beta.SAM.gov/). The response due date is 23 July 2021. The remainder of the timeline includes issuing a formal RFP in the first quarter of fiscal year (FY) 2022, receiving proposals in the third quarter, and awarding the contract in the fall of 2023. Dr. Sharpless announced that Dr. Sara S. Hook will be leaving the Office of Scientific Operations (OSO), NCI at Frederick, and joining the NCI Office of the Director as Associate Director for Strategic Scientific Partnerships, and that Dr. Kristin L. Komschlies McConville is the acting OSO Director. The OSO plays a major role in programming for the FFRDC contract, administratively and operationally, re-competition. As such, Dr. Komschlies now will now be overseeing these activities.

NCI Budget and Appropriations. Dr. Sharpless reported that the NCI funding, which has increased steadily since FY 2015, continues the appropriations for the Cancer Moonshot℠ of $190 million (M) and Childhood Cancer Data Initiative (CCDI) of $50 M. The NCI also received a $306 M supplemental appropriation to support COVID-19 serology, awarded in April 2020. The FY 2022 President's budget proposed $6.73 billion (B) for the NCI, a 2.73 percent increase over the FY 2021 enacted budget. Noting the costs of grants that will continue in the next year, inflation, other costs, and new investments (e.g., cybersecurity), Dr. Sharpless conveyed that an appropriation at this level limits the NCI's ability to increase paylines for new grants and to reach the goal of the 15th percentile by 2025 and likely would require cuts to noncompeting awards and internal programs. Dr. Sharpless remarked that progress in achieving the payline goals will be determined by the funds appropriated by Congress and the number of R01 applications NCI receives, which are important variables in determining success rates.

In addition to the base appropriation for the National Institutes of Health (NIH) and the NCI, the President's FY 2022 budget request also includes $6.5 B to establish a new entity: the Advanced Research Projects Agency for Health (ARPA-H) that emulates the Defense Advanced Research Projects Agency. ARPA-H would be housed within the NIH and focus on cancer, Alzheimer's disease, diabetes, and likely additional diseases and conditions. Discussions are ongoing on the specific ARPA-H capabilities and how it would function and be deployed for cancer research. Dr. Francis S. Collins, Director, NIH, and Dr. Eric Lander, Director, White House Office of Science and Technology Policy (OTSP), President's Science Advisor, shared their vision in the 22 June 2021 issue of *Science.*

NCI Cancer Research and Global Health. On 10 June 2021, President Joseph Biden and Prime Minister Boris Johnson, United Kingdom (U.K.), just prior to the Group Seven (or G7) Summit, revitalized the 80-year Atlantic Charter. Both leaders issued a joint statement committing to international bilateral cooperation in cancer research and to convene the first U.S.–U.K. Bilateral Cancer Summit. This summit aims to bring together researchers, patients, and other stakeholders to share ideas and identify opportunities for collaboration to accelerate advances in lifesaving approaches to cancer, which remains a leading cause of death worldwide. The summit builds on NCI's other international collaborations: the NCI–Cancer Research U.K. Cancer Grand Challenges and the renewed memorandum of understanding for the Ireland–Northern Ireland–NCI Cancer Consortium. These efforts have been led largely through the NCI Center for Global Health (CGH), which just celebrated its 10th Anniversary.

NCI COVID-19 Activities. Dr. Sharpless provided an update on several of the NCI COVID-19 research projects in which the FNLCR has played a key role. Specifically, the NCI COVID-19 in Cancer Patients Study (NCCAPS)—a prospective longitudinal study, is ongoing. As of 8 June 2021, 875 trial sites have been activated nationally. More than 1,100 patients have been screened and 894 enrolled in NCCAPS, and the trial is now open to pediatric cancer patients. COVID-19 infections in the United States have declined. With vaccination rates increasing, enrollment in NCCAPS has declined from 50 enrollments per week in May 2020 to less than 10 per week in May 2021. Interim data from NCCAPS were presented in two abstracts (#6565 and #6566) at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting. These findings revealed ongoing symptoms of COVID-19 patients after acute infection, cancer treatment disruptions in the initial months following SARS-CoV-2 infections, and hospital inpatient experiences.

Dr. Sharpless informed members that the COVID-19 pandemic has affected cancer screening significantly in the United States. The NCI's Population-based Research to Optimize the Screening Process (PROSPR) network, a consortium designed to evaluate improved cancer screening processes and outcomes, provided a perspective on this topic in the March 2021 issue of *Gastroenterology*. In this retrospective analysis, PROSPR researchers compared breast, cervical, colorectal, and lung cancer screening rates before and during the pandemic. Data were collected in eight large health care systems in seven states, evaluating 11 million individuals. The results revealed a near-zero screening rate across

target populations for all cancer types studied during the early phase of the pandemic. Estimates suggest 10 million fewer screening events in the United States occurred during the pandemic: a reduction that will significantly affect the stage of cancer diagnosis and outcomes in some patients. Interestingly, fecal immunochemical test home-based screening decreased less, suggesting that this examination is robust during certain kinds of public health problems not observed with hospital-based or client-based screening.

NCI Equity and Inclusion Program. Dr. Sharpless informed members that the NCI has been working closely with the new NIH initiative, UNITE, to address structural racism in biomedical research and has established an NCI Equity and Inclusion Program. The program (consisting of an NCI Equity Council and five working groups) is addressing three broad aspects of inclusion: cancer health disparities, research workforce, and equitable community, some of which Dr. Sharpless highlighted. An internal survey assessing the culture and work environment at NCI revealed that 60 percent of the NCI administrative workforce is Black/African American or Hispanic, compared to 29 percent of the U.S. civilian labor force. The NCI is evaluating the current state and developing tangible and sustainable ways to address these critically important issues. Two immediate actions include establishing an Early Investigator Advancement program and a Connecting Underrepresented Populations to Clinical Trials (CUSP2CT) program. Dr. Sharpless is the Council chair, and Dr. Paulette S. Gray serves as co-chair. The working groups have convened meetings and presented detailed reports at the June 2021 Joint Board of Scientific Advisors (BSA) and National Cancer Advisory Board (NCAB) meeting. Recordings of those presentations are accessible from the NIH VideoCast website.

NCI Surveillance, Epidemiology, And End Results (SEER) Program. Dr. Sharpless noted that SEER is one of the programs that originated with the National Cancer Act (NCA) of 1971 and represents capabilities the NCI has been focused on building. In 1975, SEER provided coverage that represented 9 percent of the U.S. population. As of June 2021, the coverage of the U.S. population in SEER has expanded to 48 percent, and the program collects data on hundreds of thousands of patients annually. The NCI also is expanding SEER data capture through linkages with external partners that are holding key clinical data and using automated methods for data capture through deep learning and natural language processing.

Cancer Moonshot℠. Dr. Sharpless pointed out that the Cancer Moonshot℠ is at its midpoint, and the progress of various initiatives is being shared with the public in several ways. Dr. Sharpless and Dr. Dinah S. Singer, Deputy Director, Scientific Strategy and Development, NCI, published a Cancer Moonshot℠ midpoint progress update in *Cancer Cell*, in which they summarized the progress of the 70 programs and initiatives across 240 projects. The NCI is planning for projects beyond the end of the 7-year funding period in FY 2023 and is exploring ways to transition those efforts into existing programs. Webinars describing the individual initiatives can be accessed from the NCI website, two of which Dr. Sharpless highlighted: Human Tumor Atlas Network (HTAN) and Cancer Center Cessation Initiative (C3I).

HTAN is a large network focusing on constructing three-dimensional atlases of the cellular, biological, and molecular features of human cancers through time and represents a diverse population of people with cancer. More than 10 reports describing the initial analysis and HTAN findings across eight organ sites are anticipated for publication later this fall. Pre-prints are available in the bioRxiv HTAN Channel. The data and metadata have been provided through an online portal accessible to the broader research community. Initial data from the first nine atlases have been added to the portal, with additional data being released throughout the summer.

The C3I was developed in response to the lack of tobacco cessation services within NCI-Designated Cancer Centers (Cancer Centers). The long-term goal is to help Cancer Centers build and implement sustainable tobacco cessation treatment programs to address tobacco cessation routinely with

cancer patients. Since 2018, C3I has reached more than 50,000 patients with tobacco treatment programs, which this implementation more than doubles. The NCI is exploring whether the combination of a broader adoption of lung cancer screening and cessation counseling can affect lung cancer rates.

Community Outreach: National Meetings. Dr. Sharpless remarked that several NCI-supported science advances were reported at the 2021 ASCO Annual Meeting. He noted that Olaparib as Adjuvant Treatment in Patients with Germline BRCA Mutated High-Risk HER2 Negative Primary Breast Cancer (commonly called OlympiA) trial, sponsored by the NCI and AstraZeneca, demonstrated that adjuvant treatment with Olaparib after completion of neoadjuvant chemotherapy significantly improved 3-year invasive disease–free survival and distant disease–free survival for BRCA1 mutated HER2-negative early breast cancer. Other research reported included core data from the PROSPR consortium showing low adherence to lung cancer screening recommendations, an evaluation of compliance with trial eligibility criteria among Cancer Therapy Evaluation Program (CTEP) trials, and updated data from the NCI Pediatric Molecular Analysis for Therapy Choice (MATCH) trial on participant enrollment and factors affecting treatment protocol enrollment. The NCI continues to present exciting advances at national meetings—such as ASCO, the American Association for Cancer Research (AACR), and American Society for Radiation Oncology (ASTRO)—highlighting what Dr. Sharpless referred to as a golden age of cancer research.

NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC). Dr. Sharpless highlighted recent publications of the CPTAC. In the April 2021 issue of *Cancer Cell*, the Consortium reported on the proteogenomic and metabolomic characterization of human glioblastoma. This study was a large initiative to connect genomic and proteomic data collected in 99 patients, which makes it the largest and most detailed proteomic characterization of adult glioblastoma. New signaling hubs and immune glioblastoma subtypes have been discovered, suggesting an approach to identify patients more likely to benefit from immunotherapies. Exceeding its goals, the Consortium has characterized 14 tumor types in 4.5 years: 10 by CPTAC teams and 4 through international collaborations.

The FNLCR has been critical to managing the CPTAC tumor collection program and to the success of the program in exceeding its goals of 5 tumor types in 5 years. In addition, the NCI Antibody Characterization Laboratory housed at the FNLCR and the NCI RAS (a family of genes mutated in more than 30 percent of cancers) Initiative collaborated with the CPTAC program to develop proteomic assays to quantify RAS signaling networks to enable new cancer therapies. This cancer community resource of 256 validated multiplexed mass spectrometer–based assays for quantifying protein expression and phosphorylation through the RAS signaling networks was published recently in the 14 June 2021 issue of *Cell Reports Methods* and replaces more than 60 Western blots with higher specificity and precision. All standard operating procedures (SOPs), validation data, and reagents are publicly available via the CPTAC online portal.

NCA 50th Anniversary. Dr. Sharpless reminded the FNLAC members that the NCI is continuing to commemorate the 50th anniversary of the NCA of 1971. He noted that this provides an opportunity to convey progress that has been made over the last five decades and the obstacles that remain. The NCI has been energized and inspired by the President and First Lady's commitment to "end cancer as we know it." This is a striking moment in cancer research, with several positive factors converging to ignite public enthusiasm for cancer research. Communities across the nation are reopening thanks to science, allowing people to resume being with their friends and families in-person. A societal movement has focused on racial justice, which is bringing additional light to cancer health disparities, an area in which the NCI hopes to make progress to end cancer for all patients. The NCI tagline "Nothing Will Stop Us" conveys NCI's commitment to promote its mission, regardless of the circumstance.

In the discussion, the following points were made:

- The description of ARPA-H in the President's FY 2022 budget request provides limited details on the allocations for cancer research or how it would be administered. Discussions are ongoing in Congress and the strong emphasis remains on crosscutting scientific initiatives and engineering challenges. Dr. Sharpless conveyed that during a discussion at the House and Senate FY 2022 budget hearings, Dr. Collins discussed the idea of using ARPA-H capabilities to evaluate multi-cancer early-detection blood-based tests (e.g., Thrive or Grail) to screen healthy populations for cancer.

- NCI programs focused on opportunities in artificial intelligence (AI) for addressing diagnostic management reside primarily within two categories: AI in imaging analysis (resulting in 70 U.S. Food and Drug Administration [FDA]-approved devices) and AI in data analysis. A trans-NCI AI Working Group is exploring opportunities on this topic. Dr. Sharpless and Dr. Anthony Kerlavage, Director, Center for Biomedical Informatics and Information Technology (CBIIT), co-authored a report titled "The Potential of AI in Cancer Care and Research," in which they outlined key priority areas.

III. UPDATE: NCI–DEPARTMENT OF ENERGY (DOE) COLLABORATION—IMPLEMENTATION OF NCI–DOE COLLABORATION TASK FORCE RECOMMENDATIONS—DRS. DOUGLAS R. LOWY AND EMILY J. GREENSPAN

Dr. Douglas R. Lowy, Principal Deputy Director, NCI, provided an update on the NCI–DOE Collaboration Task Force charge and recommendations. Dr. Lowy stated that this Collaboration is a component of the NCI Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) program. Partners include the FNLCR and four DOE National Laboratories: Argonne, Lawrence Livermore, Los Alamos, and Oak Ridge. The Task Force, established in October 2019, first convened in May 2020 and was charged to review and assess the merits of the individual projects, evaluate whether the NCI–DOE Collaboration should continue and become a sustainable and stable partnership, and recommend future directions for the NCI–DOE Collaboration.

The Task Force final report and recommendations, which were presented to the FNLAC in October 2020, were summarized by Dr. Lowy:

Overall Recommendations. Continue the NCI–DOE Collaboration, which is uniquely suited to address certain critical challenges in cancer research. Evaluate the existing Pilots as large-scale projects. Develop and review future projects using a more structured and rigorous approach. Increase engagement with the NCI extramural community. Establish project-specific advisory groups.

Project-Specific Recommendations. Conclude Pilot 1, Predictive Modeling for Preclinical Screening—because of insufficient available and pertinent data and insufficient integration with NCI investigators doing predictive modeling. Continue Pilot 2, RAS Biology on Membranes, with greater focus on refining the coarse-grain models based on data from the atomic-level simulations and experimental validation. Continue Pilot 3, Precision Cancer Surveillance, with greater focus on implementation and multi-institutional deployment of the developed application programming interfaces (APIs) and expansion beyond the SEER program.

Dr. Emily J. Greenspan, Program Director, CBIIT, and Executive Secretary, FNLAC NCI–DOE Collaborations Working Group, updated FNLAC members on the NCI implementation plans of the Task Force recommendations.

Governance and Oversight Implementation Plans. The governance and oversight of the NCI–DOE Collaboration will be restructured into three components: (1) DOE Office of Science Advanced Scientific Computing Advisory Committee (ASCAC) Subcommittee, (2) Scientific and Technical Advisory Committees, and (3) Executive Committee. The Federal Advisory Committee Act (FACA) level oversight of the Collaboration is shifting from the FNLAC to the ASCAC, which will advise the DOE and will share recommendations, as appropriate, with the NCI. Cancer biologist, machine learning (ML), and functional genomics expert, Dr. Jill P. Mesirov, Professor of Medicine, Division of Medical Genetics, Associate Vice Chancellor for Computational Health Sciences, University of California (UC) San Diego School of Medicine, Moores Cancer Center UC San Diego, has been added officially to the ASCAC.

The ASCAC Subcommittee will consist of 8 to 12 extramural scientists with expertise across collaboration areas (e.g., cancer biology, advanced computing, data science) and will have oversight of the Collaboration. The FNLAC NCI–DOE Collaborations Working Group has concluded, and some of those members will be asked to join this Subcommittee for continuity. The ASCAC Subcommittee is charged to assess the current projects, opportunities, and challenges; and identify strategies to address those challenges and deliver on opportunities recommended by the Task Force.

Each NCI–DOE Collaboration Scientific and Technical Advisory Committee will consist of four to six scientists with targeted, deep expertise relevant to the assigned project. This committee will be managed by the DOE National Laboratories and FNLCR. Because of FACA rules, the government may not be in charge of project-specific advisory committees, but representatives can attend meetings as observers. The goals are to provide project-specific, in-depth scientific and technical guidance and advice.

The NCI–DOE Collaboration Executive Committee will be composed of NCI leadership: Drs. Sharpless, Lowy, and Singer; and DOE leadership: Drs. J. Steven Binkley and Barbara Helland of the Office of Science, and Dr. Mark Anderson and Ms. Thuc Hoang of the National Nuclear Security Administration. The Executive Committee is anticipated to meet quarterly, with the first meeting scheduled for the end of July 2021. This committee is charged with interagency strategic partnership status and relationship health, overall funding, program priorities, and implementation of ASCAC recommendations.

Scientific and Technical Implementation Plans. Pilot 1 is sunsetting and will conclude July 2021. The NCI and DOE teams are finalizing the open release of data models and software. The data release will consist of AI- and ML-ready (i.e., gathered, integrated, labeled, normalized, and curated) data sets from multiple cell line studies and the NCI A Large Matrix of AntiNeoplastic Agent Combinations (ALMANAC), Genomic Data Commons (GDC), Patient-Derived Models Repository (PDMR), and Patient-Derived Xenograft (PDX) Development and Trial Centers Research Network (PDXNet). These data sets can be accessed from the NCI Predictive Oncology Model and Data Clearinghouse (MoDac). Dr. Greenspan highlighted that the FNLCR played a key role in developing MoDac and has performed independent validation and verification of the models following release by the DOE. The computational models and software associated with publications will be released along with documentation. The Pilot 1 models include multiple deep learning models for predicting drug response to single drugs or combination drugs. These can be accessed via the CBIIT website: NCI–DOE Collaboration Capabilities. In addition, all manuscripts in progress will be completed and submitted to peer-reviewed journals.

For Pilot 2, efforts will focus to expand the multiscale simulation framework by adding modeling capabilities to facilitate discovery of new biology and applying advance uncertainty quantification methods. The team will perform a large-scale RAS-RAF complex multiscale simulation and continue experimental validations of simulations. The outreach activities will include hosting a workshop to engage the broader RAS biology research community; continuing to work closely with the FNLAC RAS

Working Group, and working with FNLCR to identify sub-explorations that can be performed on computational resources that are more widely available.

The Pilot 3 team will expand AI solutions for precision cancer surveillance. This will entail integrating the electronic pathology (e-path) API into the production workflow of six SEER registries and expanding the deep learning model for depicting recurrent metastatic disease and biomarker data from e-path and radiology reports. Efforts also will focus on incorporating enhancements and deploying privacy-preserving APIs for secure model sharing with the broader stakeholder community. In terms of outreach, the team will continue to host hands-on hackathons, present and participate in national cancer and medical informatics conferences, and continue existing and pursue new collaborations.

New NCI–DOE Collaboration Projects. Dr. Greenspan highlighted new Collaboration projects that will be starting in FY 2022 and beyond. The NCI and DOE leadership approved the Innovative Methodologies and New Data for Predictive Oncology Model Evaluation (IMPROVE) project poised to leverage the foundational ML models, related research, and infrastructure for predicting tumor drug response to single and combination agents from Pilot 1 and the lessons learned. The goals are to create well-documented and well-characterized approaches to constructing, training, and validating predictive cancer drug response computational models, with the aims of developing a model comparison framework and generating data to improve drug response models. The NCI will fund three to five extramural model design groups to collaborate actively with ANL in developing deep-learning drug response models. The DOE ANL will fund one or more data generation groups from the public and/or private sectors.

Since 2019, the NCI and DOE have been using the Envisioning Computational Innovations for Cancer Challenges (ECICC) community as an incubator for new ideas and for engaging the extramural researchers. Dr. Greenspan described the ECICC activities. In March 2019, the DOE hosted a Scoping Meeting to identify cancer research challenges needing AI and advanced computing; that meeting led to the July 2020 Cancer Patient Digital Twin (CPDT) Ideas Lab 5-day virtual event. Five 6-month CPDT projects were co-funded by the NCI and the DOE and will be concluding in summer 2021. In March 2021, the NCI partnered with the DOE and ASTRO to sponsor the Accelerating Precision Radiation Oncology through Advanced Computing and AI workshops. A comprehensive report will be generated, and the NCI and the DOE are discussing how best to sponsor a joint project. Further details can be accessed on the ECICC community platform and website: https://ncihub.org/groups/cicc.

In the discussion, the following points were made:

- No further discussion was held on this topic.

IV. UPDATE: NCI EXPERIMENTAL THERAPEUTICS (NExT) PROGRAM—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, Director, Division of Cancer Treatment and Diagnosis (DCTD), provided an update on the NExT program. Dr. Doroshow informed members that the NExT program, which was established in 2009, is a government, academic, and industry partnership for cancer drug discovery that builds on more than 50 years of NCI experience in cancer drug development. NExT focuses on developing therapies for underrepresented malignancies and challenging cancer targets, but is not a grant program. The Chemical Biology Consortium (CBC), the drug discovery component of NExT, is composed of 21 organizations based in academic centers, contract research organizations, and nonprofits. NExT advances projects through a development pipeline from early stage discovery to Phase I and II trials. Since its inception, the NExT program has received 900 applications, of which the majority were from academia (40 percent) and

biotechnology companies (38 percent). Sixty-four percent of projects evaluate small molecules and 31 percent evaluate biologics.

In the NExT process, projects are submitted to the program in three cycles per year, averaging 20 to 30 applications each cycle and can enter the pipeline at any stage. A Special Emphasis Panel (SEP) composed of experts from academia and industry reviews and evaluates the applications and selects the top 10 to 15 projects. Highly ranked projects are prioritized by the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and are reviewed and endorsed by the CBC Steering Committee, which is composed of members representing the 21 centers in the Network. Selected projects enter a planning process, an RFP is issued, a CBC specialty and comprehensive center is selected, the project team is assembled, and a kickoff meeting is scheduled. Dr. Doroshow emphasized that the first milestone for projects is the "trust but verify" evaluation that involves reproducing key data using the applicants' reagents and protocols in the NCI laboratories. Roughly one-third of the projects fail this evaluation. The NExT pipeline consists of a diverse set of projects in the discovery, preclinical development, and development phases. Some have been discontinued because of insufficient hit-to-lead compounds, lack of proof of mechanism or proof of tractable molecules, or inability to verify the target.

Dr. Doroshow detailed the status of projects that have advanced in the NExT pipeline—some either licensed out or in the clinic. Specifically, he highlighted active out-licensing efforts, therapeutic agents originating from the CBC pipeline that have entered the clinic, and therapeutic projects with anticipated IND submission in 2021.

Myeloid Cell Leukemia 1 (MCL-1) Inhibitor. The MCL-1 inhibitor project by Dr. Stephen W. Fesik at Vanderbilt University (VU) and his colleague, Dr. William Tansley at VU, identified a novel chromatin binding partner of Myc, WD repeat domain 5 (WDR5), that controls genes involved in protein synthesis and is an important target for leukemias and other malignancies. During drug development, the Fesik laboratory used fragment-based methods and structure design to develop a subnanomolar concentration of structurally similar compounds, which showed significant proof of mechanism of action *in vivo*. The VU0914813 compound has advanced as a candidate for IND-enabling studies, particularly a first-in-class study. Dr. Doroshow remarked that this will be the first molecule that has advanced in the NExT pipeline from target validation to a clinical trial.

Lactate Dehydrogenase A (LDHA) Inhibitors. The LDHA inhibitors project by Dr. Chi V. Dang, then-principal investigator at the University of Pennsylvania, entered the pipeline in 2010, based on his earlier observations that targeting LDHA might be of therapeutic interest in cancer research. The first small molecule interrogated was unsuccessful, and in collaboration with NCATS, the CBC team generated more than 700 compounds and identified promising candidates with optimal *in vivo* properties. Tumor growth inhibition in highly glycolytic tumor models *in vivo* was modest, even at high LDH inhibition. Medicinal chemistry modifications could not overcome the toxicity approaching the maximum tolerated dose. A member of the LDH team, who also was investigating other diseases, discovered a new application for the LDHA inhibitor compounds, the lethal metabolic disease primary hyperoxaluria (PH1). Characterized by increased endogenous oxalate synthesis in the liver resulting in deposits of calcium oxalate, damaging tissues throughout the body, PH1 results in end-stage renal disease. Preclinical studies using the NExT LDHA inhibitors showed maximal suppression of oxalate production in livers of mice treated orally, with restoration to baseline levels. These compounds recently have been licensed out, and the supporting company expects to have a candidate ready for clinical trials in late 2021 to early 2022.

Adrenocortical Carcinoma (ACC) Therapy. Orphagen Pharmaceuticals (San Diego, California) partnered with the NExT program on a target validation project to develop and test *in vivo* models of ACC using its compound, OR-449. This compound targets the transcription factor, SFI, gene

product. SF1 is amplified in more than 90 percent of pediatric ACCs and would be a novel target for this disease, for which effective, safe treatment is limited. In pediatric ACC xenograft models obtained by the NExT program, OR-449 was shown to be active and well tolerated at doses more than threefold the efficacious amount. Toxicity studies are planned, with the anticipation that the agent advances to a natural history ACC clinical trial.

CB-5339 p97 Inhibitor. The NCI collaborated with Cleave Therapeutics (San Francisco, California) to perform IND-enabling studies in a backup compound as a clinical candidate. The company's NExT project of the first-in-human trial evaluating the first-generation molecule, CB-5083, was deemed unsuccessful because of off-target ocular toxicity. After a series of preclinical toxicity studies and evaluations in cancer models, the second-generation compound, CB-5339, demonstrated high selectivity for p97, with reduced toxicity. In January 2021, a Phase I AML/myelodysplastic syndromes trial of CB-5339 opened, and the first seven patients were enrolled. To date, the safety profile has been favorable with a multiple-dose escalation regimen. Dr. Doroshow remarked on how this project illustrates the unique ability of the NExT CBC to move agents forward in the pipeline rapidly.

DNA Methyltransferase-1 (DNMT1) Inhibitor. The Southern Research NExT project investigated an oral formulation of DNMT1 inhibitor, 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC), a candidate with no intellectual property (i.e., unidentified tangible benefit) at the time of the study. Aza-TdC demonstrates sufficient oral bioavailability and has a higher DNA incorporation rate at lower levels of toxicity than decitabine *in vivo*. Aza-TdC also showed improved preclinical anti-tumor activity, compared to other hypomethylating agents in solid-tumor xenograft models. The FDA IND was filed in late 2018, and the Phase I Trial of Aza-TdC in patients with advanced solid tumors is in progress. The first 18 patients enrolled in the trial at the CCR clinic experienced mild myelosuppression at the maximum tolerated dose and showed proof of mechanism (i.e., p16 expression in circulating tumor cells) after two cycles of treatment. The study recently was expanded to collect tumor biopsies in patients to identify gene signatures associated with Aza-TdC.

Dr. Doroshow described two imaging agents that were developed in the NExT pipeline, both being used in the clinic.

Lumicell (LUM) 015. Dr. David G. Kirsch at Duke University and colleagues at Massachusetts Institute of Technology and Lumicell were supported in a NExT imaging project. The team developed a new tumor-specific imaging agent (VM249) activated by cathepsins to aid in detection of surgical positive margins, particularly in sarcomas and breast cancers. The NCI provided pre-IND toxicity studies evaluating the fluorescent optical contrast agent, LUM015, with a handheld imaging device. In breast cancer patients, LUM015 delineated large invasive tumors and ductal carcinoma *in situ*, with demonstrated concordance to pathology. This technique and device were evaluated in clinical trials during breast-conserving surgery; the trials have been completed and results have been published.

IRDye800CW-Panitumumab. Dr. Eben Rosenthal at Stanford University and his colleagues developed an optical imaging technique to detect head and neck squamous cell carcinoma (HNSCC) tumors intraoperatively. The NExT program generated the GMP-grade imaging molecule for the studies, consisting of a combination epidermal growth factor receptor monoclonal antibody drug, panitumumab, and an investigational dye, IRDye800CW. Systemic administration of IRDye800CW-panitumumab in preclinical models was sensitive and specific for detection of subclinical disease. A Phase II trial for nodal detection in HNSCC is complete and data has been published.

In closing, Dr. Doroshow reviewed the NExT program's noteworthy scientific accomplishments and publications (more than 50) and patents (10 filed) and expressed appreciation to the NCI's many internal and external collaborators.

In the discussion, the following points were made:

- In the NExT program, the NCI takes on high-risk projects showing efficacy and low toxicity for agents and has succeeded in advancing compounds beyond the phase between research and effective innovation. NExT has enabled the success of companies to license and advance drugs to the clinic that began with limited intellectual property or those for orphan diseases.

- The NExT program is not intended to replicate pharmaceutical companies. It does, however, advance high-risk novel compounds to the clinic regardless of cost. Drugs completing the FDA investigational new drug (IND) process that are effective against a disease affecting a specific population and are challenging to produce can be a means of providing this therapy to patients at no cost.

- The NExT program interacts with the pharmaceutical companies to better understand the Phase I drugs that are promising for clinical use. The CBC partners and/or principal investigators retain the intellectual property rights to their agents and arrange the licensing.

- With additional funding, the NExT program could advance many compounds and untapped ideas from its network of investigators.

V. UPDATE: FREDERICK NATIONAL LABORATORY (FNL) OPERATIONS— DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos Biomed), provided an update of the FNLCR's operational response to the COVID-19 pandemic and the continuity of operations as an FFRDC. Dr. Dmitrovsky also reviewed the NCI and NIAID federally funded research and development projects. Operating under an FFRDC contract, the FNLCR portfolio consists of operational task orders (TOs), which have annual appropriations, and nonoperational TOs, in which benefits are received upon completion of the work. Five operational TOs are active, supporting the NCI and NIAID, and 104 nonoperational TOs are supporting clinical and scientific groups and facilities or infrastructure refurbishments. Subcontracts support extensive outreach efforts to the broader research community.

FNLCR's operational response to the COVID-19 pandemic fulfills a vital aspect of its mission as an FFRDC to serve its staff and the community. One such example is the Asymptomatic COVID Testing program established to serve all NIH employees and contractors. Four clinics are in operation, three in Frederick, Maryland, and one at the NCI Shady Grove campus. Staff operating the testing clinics have consistently monitored employees' exposures and COVID-19-related illness and to date have conducted 10,300 tests, with a seropositivity rate of 0.2 percent.

Even with the COVID-19 pandemic, 227 Leidos Biomed staff-maintained continuity of services, particularly veterinary and clinical services within the FNLCR Directorates. Dr. Stephen Jones, Director, Laboratory Animal Sciences Program (LASP), and his staff worked in teams of non-overlapping duties during split shifts across elongated work weeks. Teams did not rotate between the NCI Bethesda and Frederick vivarium facilities, lessening the potential of the entire team's being quarantined because of COVID-19. The FNLCR leadership established the Vaccine, Immunity, and Cancer Directorate. Under the leadership of Dr. Ligia Pinto, this Directorate is providing critical support to the Serological Sciences Network for COVID-19 (SeroNet) program. Ms. Beth Baseler, Director, Clinical Monitoring Research Program (CMRP), and her team continued the clinical trials, including international COVID-19 trials. In

addition, data generated using LASP services continued to be published in peer-reviewed journals, many high impact.

The FNLCR Biopharmaceutical Development Program manufactured chimeric antigen receptor (CAR) T-cells supporting the NCI CAR T-cell clinical trials, including the Pediatric Blood and Marrow Transplant Consortium–led 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). Seven AML patients—five at the NIH Clinical Center and two at the Children's Hospital of Philadelphia—have been enrolled. The FNLCR will be supporting a pediatric neuroblastoma/osteosarcoma trial of ganglioside antigen, GD2, which is anticipated to open in July 2021.

The FNLCR is supporting SeroNet, of which the primary goal is to develop and standardize novel serological assays and deploy them to the extramural community. The FNLCR operates the SARS-CoV-2 Serology Laboratory (expanded human papillomavirus [HPV] Serology Laboratory) and manages the SeroNet Coordinating Center. Within this center, the FNLCR manages the contracts of the extramural-based Serological Sciences Capacity Building Centers. Other activities include providing project management for meetings and operations; distributing serology reagents to the Network and wider scientific community; and coordinating storage, sharing, and curation of serology data, enabling the SeroNet database. Prior to SeroNet, the FNLCR Serology Laboratory independently evaluated approximately 100 commercial serological tests for the FDA.

Dr. Dmitrovsky reported that the FNLCR-supported NIAID COVID-19 clinical trials evaluating the safety and efficacy of investigational therapeutics to treat COVID-19 in adult hospitalized patients have been proceeding rapidly. He reminded the FNLAC members that the Adaptive COVID-19 Treatment Trial (ACTT)-1 (remdesivir versus placebo) was 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 Emergency Use Authorization (EUA) for remdesivir, and subsequent full FDA approval. In addition, ACTT-2 (remdesivir with or without baricitinib or placebo), 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. A third trial, Accelerating COVID-19 Therapeutic Interventions and Vaccines-3 (remdesivir with or without LY-CoV555 monoclonal antibody), was activated across 31 sites and evaluated in 314 patients, resulting in preliminary data reported in the *NEJM*. This trial was discontinued because of futility following the study's interim review. Dr. Dmitrovsky emphasized these studies illustrate where the therapeutics are effective in the span of the COVID-19 caseload.

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, western DRC, and 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, two of which, Inmazeb and Ebanga, were FDA approved in October 2020 and December 2020, respectively. On 3 May 2021, the World Health Organization (WHO) declared the DRC outbreaks controlled. The recent Nyiragongo volcano eruptions near the city of Goma in eastern DRC required the PALM team to suspend its activities until deemed safe to return. In North Kivu Province, the Ebola viruses from patients have been sequenced and show a high level of sequence homology to the same virus present during the 2020 outbreak. These data suggest sustained Ebola infections in the survivors and possible sexual transmission of the virus. A recent Ebola outbreak in the Republic of Guinea was short-lived, credited to new therapeutics and trial management by the PALM Consortium. On 19 June 2021, the WHO declared an end to this outbreak.

The FNLCR manages diverse projects related to vaccine development and manufacturing in partnership with the NIAID Vaccine Research Center (VRC). Four infectious agents are being targeted and novel therapeutics are being developed accordingly. Human immunodeficiency virus (HIV) therapeutics include a neutralizing monoclonal antibody and the Trimer vaccine. For filoviruses (e.g., Ebola), targeting agents include biospecific and monoclonal antibodies. A new therapy in development to target influenza is a nanoparticle vaccine. Last, a targeted antibody for malaria is being evaluated. The FNLCR Vaccine Clinical Materials Program is providing clinical manufacturing support to the VRC and has been developing novel therapeutics actively, including those just described.

The NCEF, housed at the FNLCR and launched in 2017, has supported extramural investigators in 34 academic and research institutions with more than 400 cancer-related projects. Despite a mandated pause in April 2020 due to COVID-19, new imaging projects have exceeded the original goals and have incorporated COVID-19 research. In the past year, data on solving high-resolution structures were published in 24 peer-reviewed journals, many high impact.

Continuity of operations was maintained in FNLCR extramural investigator collaborations. The AIDS and Cancer Virus Program (ACVP), under the leadership of Dr. Jeffrey D. Lifson, is collaborating with Dr. Louis Picker at Oregon Health & Science University on a novel engineered cytomegalovirus vector-based HIV vaccine, with demonstrated viral protection, as reported recently in *Science*. Dr. Dmitrovsky called attention to a companion study reported in the March 2021 issue of *Science Immunology*, which explains the mechanism of the CMV-vectored HIV vaccine. He added that a contractor Cooperative Research and Development Agreement (cCRADA) through the NIAID is funding this ACVP collaboration and that the cCRADA also partners with Dr. Dan H. Barouch at Beth Israel Deaconess Medical Center and Harvard Medical School.

The FNLCR, as an FFRDC, serves the extramural community and public health through its science and its education and training efforts, some of which leverage the distinct NCI and NIAID research programs. Dr. Dmitrovsky highlighted some of those efforts. The third RAS Initiative Symposium was held in May 2021, with nearly 1,800 attending and 126 abstracts submitted. Topics included RAS Biology, its structure and therapeutics; and RASopathies. A milestone is the recent FDA approval of a LUMAKRAS™, a KRAS G12C-targeting agent. The Leidos Biomed–Hood College Cancer Science Symposium held its inaugural Life Science Conference in June 2019, and its next meeting is scheduled for 2022. The CMRP plans to launch educational modules (at no cost to the government) for extramural investigators focusing on conducting international clinical trials in resource-constrained and politically unstable countries. Trainees will receive continuing education credits and a certificate of completion.

In the discussion, the following points were made:

- Although the FNLCR is operating the SARS-CoV-2 Serology Laboratory, whether those efforts extend to investigating other pathogens would be up to the NCI leadership to decide.

VI. UPDATE: SEROHUB— DR. NEAL D. FREEDMAN

Dr. Neal D. Freedman, Senior Investigator, Division of Cancer Epidemiology and Genetics, updated the FNLAC on the COVID-19 Seroprevalence Studies Hub (COVID-19 SeroHub) and acknowledged key contributors from the Centers for Disease Control and Prevention (CDC), NIAID, and the NCI. Dr. Freedman stated that the CDC estimates that only one in four people with COVID-19 have their cases reported. This difference between the number of people truly infected and case reporting

reflects both individuals with symptomatic infections not seeking health care or not being tested and/or individuals with asymptomatic infections. Seroprevalence studies provide insight into the true cumulative incidence of exposure. To date, U.S.-based seroprevalence studies have been conducted with different designs, antibody tests, and populations. The CDC and NIH discussed the need for an interactive database to identify and integrate studies to capture infection trends over time and within different geographic areas of the United States. The NCI, which was asked to lead this effort, leverages the expertise of the FNLCR gained from the NCI Clinical Trials Reporting Program regarding storing, extracting, and disseminating information to the scientific community in a standard manner.

The aims of SeroHub are to develop: (1) a transparent and publicly accessible repository to document and track SARS-CoV-2 seroprevalence studies in the United States; (2) a harmonized method to catalog and display seroprevalence test results across studies; and (3) an interactive dashboard to visualize and compare SARS-CoV-2 seroprevalence studies and results by geography, date, and population. Dr. Freedman emphasized the continued significance of seroprevalence studies even with the availability of COVID-19 vaccines. According to CDC data, the proportion of people in the United States who are vaccinated fully varies by state, and rates can differ by 30 percent. States with the highest vaccination rates have the lowest COVID-19 diagnosis rates per 100,000 people. These trends suggest that among the U.S. population, the regions most protected from COVID-19 will be those containing the largest natural and vaccine-mediated immune populaces.

Dr. Freedman noted that an emerging concept is that seroprevalence studies could provide insight into the contributions of natural immunity versus vaccine-induced immunity, and he explained the rationale. The NCI and other NIH Institutes and Centers have put forth significant effort to develop reliable SARS-CoV-2 serology tests. Most of the antibody tests have been developed against either the spike glycoprotein or the nucleocapsid, but natural immunity will reflect positivity to both spike and nucleocapsid. To date, the FDA EUA COVID-19 vaccines target only the spike protein, thus vaccinated individuals will test positive for this protein and will differ from those indicating natural immunity.

Many seroprevalence studies have been initiated internationally and domestically, including the CDC Commercial Laboratory Seroprevalence Survey, county-based studies, and studies in special populations (e.g., health care workers, pregnant women, athletic organizations, first responders). Findings may be published as peer-reviewed articles, website content, or press releases, and many are difficult to locate without substantial effort. Study objectives and methodologies vary, and no standardized approach exists to share plans, methods, or results. Dr. Freedman reviewed some of the U.S.-based seroprevalence studies illustrating the overlapping and complementary data. He noted that traditional meta-analyses have been used to track seroprevalence studies and called attention to a large-scale effort: the Public Health Agency of Canada SeroTracker, a platform that monitors seroprevalence worldwide. SeroTracker presents data across countries and studies, but how the prevalence changes over time is unknown. SeroHub, which aims to track how seroprevalence has changed in the United States over time and by geographic region and population, is complementary to SeroTracker.

Regarding methods, the SeroHub study abstraction team identifies seroprevalence studies contained in MedRxiv, PubMed, LITCOVID, SeroTracker, and journal tables of contents and determines the relevancy of those studies. Studies and papers are extracted for common data elements, and the team contacts study authors if additional information is needed. Stringent quality control processes are in place, and SOPs exist for study identification, data extraction, and data entry quality control. SeroHub's data fields include study title and affiliation, study design, population represented, study location, data collection period and frequency, test and performance characteristics, data generation and data location, seroprevalence results per demographic determinants, and study quality.

In terms of processing, infrastructure has been developed to store data, test information, and seroprevalence results, and each result is tagged with the appropriate identifiers. The team developed easy-to-use visualization tools to help users view results and conduct simple and more sophisticated analyses. Dr. Freedman demonstrated the interactive seroprevalence tool, highlighting the data fields, search functions, maps, and study pages. Next steps include continuing study abstractions into the SeroHub database and integrating longitudinal data from the Nationwide Blood Donor Seroprevalence Survey.

In the discussion, the following points were made:

- The approach in the COVID-19 SeroHub is to incorporate all U.S. seroprevalence studies and then provide information on the various serological assays used. Investigators can interrogate the database to learn more about the quality of these assays.

- From an epidemiological perspective, representative sampling frames are limited in the current studies. Most samples are collected out of convenience voluntarily or during routine doctor visits via blood tests.

- Determining the current seroprevalence of the US population remains challenging because most of the data from large-scale studies with anti-spike data have not yet been released. In addition, it is important to focus on seroprevalence at a local level as well.

VII. COMMUNICATING FNL SERVICES TO THE SCIENTIFIC COMMUNITY—DR. ROSEMARIE AURIGEMMA

Dr. Rosemarie Aurigemma, Acting Associate Director, Developmental Therapeutics Branch, DCTD, provided an update on the FNLCR's vector and cell therapy services and efforts to disseminate those services in the extramural community. Dr. Aurigemma also reported on the facility upgrades, capabilities, outreach efforts, and additional areas of support. She reminded FNLAC members of the December 2018 DCTD-hosted workshop on cell-based immunotherapy for solid tumors, during which participants identified research needs and outlined clinical development, technology, and regulatory challenges. The NCI has been working to address these research needs and challenges.

From 2018 to 2021, efforts have been ongoing in support of cell therapy at the NCI. These include starting operation of a current good manufacturing practices (cGMP) cell therapy and quality control suite in September 2020 and returning viral vector manufacturing capabilities to the Virus Production Facility. CTEP assisted in filing the IND for the anti-GD2 CAR T-cell trial, on which the Cancer Center for Research (CCR), NCI, and Stanford University are collaborators. The FNLCR Biopharmaceutical Development Program (BDP) has the capabilities to support two multicenter autologous cell therapy clinical trials. Renovations are underway for three supplementary GMP suites and to expand cell therapy-related activities. In addition, the BDP has posted cell therapy–related SOPs online, bringing the number of GMP biopharmaceutical manufacturing SOPs to 300; developed processes for manufacturing lentivirus and retrovirus products for cell transduction; and started CRISPR/Cas9-based editing development in September 2020.

Regarding the Division's efforts, Dr. Aurigemma explained that the DCTD supported six P30 and P50 grantees with their supplements for technology development to overcome barriers to broad-based adoption of cell therapy for cancer. In September 2020, Dr. Marc Ernstoff joined the DCTD as Medical Officer and Chief, ImmunoOncology Branch. The NCAB *ad hoc* Subcommittee on Experimental Therapeutics, whose charge is to advise DCTD on opportunities to assist the extramural community to discover and develop new cancer treatments, reconvened on 1 September 2020 after a 10-year hiatus.

This Subcommittee identified two priority topics for the DCTD: cellular immunotherapies and other complex biologics for cancer and intelligent drug discovery based on biochemistry, structure, and mechanisms, including AI-driven drug discovery.

On 10–11 December 2020, the DCTD hosted its second workshop on cell-based immunotherapy for solid tumors; between 650 and 900 participants logged in to the meeting each day. A workshop report has been drafted and is in press at the *Journal for ImmunoTherapy of Cancer*. Workshop participants highlighted ongoing scientific questions regarding solid tumors, cell product quality, the cell engineering process, representative animal models, and imaging. Persistent logistical challenges also were identified, related to reagent and equipment availability; access to manufacturing GMP vectors, reagents, and cells; and the ability to perform small, proof-of-concept trials. To address these scientific questions and challenges, the DCTD established the Cell Therapy Think Tank, with the charge to merge expertise to support cancer cell therapy enterprise and create opportunities to support innovation and progress.

Dr. Aurigemma reported on the status of the clinical trials supported by FNLCR GMP cell therapy manufacturing. The Pediatric Blood and Marrow Transplant Consortium–sponsored Phase I/II study of anti-CD 33 CAR expressing T-cells in children and young adults with relapsed/refractory AML has treated eight patients at the CCR in the third cohort and is preparing product for the ninth patient at the Children's Hospital of Philadelphia. No serious adverse events have been reported and the investigators are considering expanding to a fourth cohort. In October 2020, the FDA approved the IND for the CTEP and Pediatric Cancer Immunotherapy Trials Network (PED-CITN)-sponsored GD2 CAR Production and Engineering of GD2-Targeted, Receptor Modified T-Cells for Sarcoma and Neuroblastoma to Increase Systemic Tumor Exposure (PERSIST) trial. Enrollment soon will begin at the NIH Clinical Center.

In terms of cell therapy and virus manufacturing capacity of the Virus Production Facility, as of June 2021, the CliniMACS Prodigy® system generates four autologous cell therapy products per month. The BDP cGMP process enables four lentivirus vector and four gamma retrovirus vector campaigns annually. The three new suites becoming operational in 2022 will increase significantly autologous cell therapy product capacity. Dr. Aurigemma highlighted some of the current projects. The manufacturing team has developed a scalable four-plasmid lentivirus production platform to support a pilot project of CCR investigator Dr. Rosandra N. Kaplan, who is evaluating lentivirus genetically engineered myeloid cells to limit metastatic progression of solid tumors. An IND submission is planned and the BDP will be generating the cGMP-grade vectors. The manufacturing team also has developed a scalable one-plasmid gamma-retrovirus production platform generated in cells adapted to grow serum free in suspension. This platform is now available to support projects. In June 2021, the BDP initiated three virus development projects: CD123xCD3 retrovirus for recurrent/refractory CD123-positive myeloid malignancy; somatostatin receptor type 2 (SSTR2) retrovirus for imaging tumor-infiltrating lymphocytes; and anti-mesothelin humanized antibody, hYP218, lentivirus for treating mesothelioma. Regarding gene-editing technology, the BDP completed the CRISPR/Cas9-based T-cell receptor alpha gene knock-out and is attempting the GFP and CD33 CAR gene knock-in experiments. Last, efforts are focusing on expanding the production platform to use the Gas Permeable Rapid Expansion (G-Rex®) technology for cell amplification to increase scalability at a reduced cost.

Outreach efforts (e.g., news stories, Twitter posts, emails, announcements at advisory board meetings) have been ongoing to build the cGMP queue and notify the extramural community of the new cell therapy and vector resources at the FNLCR. In May 2021, the DCTD Deputy Director, Dr. Toby Hecht, emailed more than 1,000 NCI grantees—including cell therapy workshop registrants—inviting submission of a Letter of Intent (LOI) to receive cGMP DNA as a raw material to modify cells directly or for the production of viral vectors for cell-based immunotherapy trials. Five LOIs were received, and three invited proposals are being reviewed. In 2021, four cell therapy proposals have been received in the

NExT program, exceeding the number of applications submitted in the past 2 years. Outreach also extends to the DCTD Preclinical Development Consultation Service available to NExT applicants.

In the discussion, the following points were made:

- No further discussion was held on this topic.

VIII. RECOGNITION OF RETIRING FNLAC MEMBERS—DR. NORMAN E. SHARPLESS

On behalf of the NCI, Dr. Sharpless recognized the contributions made by members of the FNLAC whose terms have expired. He expressed appreciation for their service and dedication over the course of their terms. The following retiring FNLAC members are:

- 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
- Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenebaum Cancer Center, Professor of Medicine, University of Maryland School of Medicine
- Dr. Robert L. Grossman, Jim and Karen Frank Director for Data Intensive Science, Frederick H. Rawson Professor of Medicine, Department of Medicine, The University of Chicago
- Dr. Klaus M. Hahn, Ronald Thurman Distinguished Professor of Pharmacology, Director, UNC-Olympus Imaging Center, Department of Pharmacology, The University of North Carolina at Chapel Hill
- Dr. David I. Hirsh, Professor, Department of Biochemistry and Molecular Biophysics, College of Physicians and Surgeons, Columbia University
- Dr. Cheryl L. Willman, The Maurice and Margaret Liberman Distinguished Endowed Chair in Cancer Research, The University of New Mexico (UNM) Distinguished Professor of Pathology, UNM School of Medicine, Director and CEO, UNM Comprehensive Cancer Center, UNM.

IX. 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. He reflected on his time on the FNLAC, the former NCI-Frederick Advisory Committee (NFAC), and the initial discussions on refocusing efforts to establish the FNLCR as a national laboratory dedicated to biology and the decision to begin the RAS Initiative project. Dr. Marnett commented on how the national laboratory status and leading a large-scale project had created a name, structure, and identity for the FNLCR. Serving in the capacity of an FFRDC, demonstrating unique qualities of rapid response, flexibility, and adapting to such national challenges as the COVID-19 pandemic, Dr. Marnett remarked, positions the FNLCR to be responsive to new initiatives, such as ARPA-H. Dr. Marnett expressed appreciation to NCI leadership, the Division of Extramural Activities, and FNLAC members, chairs, and executive secretaries for their support over the past 10 years.

X. 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. Paulette S. Gray. There being no further business, the 7th Virtual Meeting of the FNLAC was adjourned at 4:35 p.m. EDT on Tuesday, 28 June 2021.

Date	Lawrence J. Marnett, Ph.D., Chair
Date	Paulette S. Gray, Ph.D., Executive Secretary