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5th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
October 14, 2020

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
5th Virtual Meeting of the Frederick National Laboratory Advisory Committee
14 October 2020

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 5th Virtual Meeting on 14 October 2020. The meeting was open to the public on 14 October 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 (absent)
Dr. Kevin J. Cullen
Dr. Raymond N. DuBois
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. Scott W. Hiebert (absent)
Dr. David I. Hirsh
Dr. Candace S. Johnson
Dr. Nilsa C. Ramirez Milan
Dr. Denise J. Montell
Dr. Patrick Nana-Sinkam
Dr. Lincoln D. Stein
Dr. Cheryl L. Willman

***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
Ms. Donna Siegle
Dr. Dinah S. Singer

Executive Secretary
Dr. Caron A. Lyman

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I. OPENING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Lawrence J. Marnett, Chair, called to order the 5th 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 13 July 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 23 February 2021 and will be virtual.

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

Dr. Norman E. Sharpless, Director, NCI, also welcomed the FNLAC members and attendees to the meeting. He provided updates on the NCI appropriations and budget, the coronavirus disease 2019 (COVID-19) serology research, Frederick National Laboratory for Cancer Research (FNLCR) routine activities, and NCI activities, including rapid progress in cancer outcomes and plans to commemorate the 50th anniversary of the National Cancer Act of 1971.

Dr. Sharpless welcomed Dr. Denise J. Montell, Robert and Patricia Duggan Professor, Department of Molecular, Cellular, and Developmental Biology, University of California, Santa Barbara to the FNLAC. She is serving as a representative from the NCI Board of Scientific Counselors.

NCI Appropriations and Budget. Dr. Sharpless reported that the regular fiscal year (FY) 2020 budget process was preempted because of COVID-19 and noted that Congress rapidly enacted four emergency spending packages. The fourth bill included $306 million (M) for the NCI 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. Dr. Sharpless reflected that since FY 2015, the NCI regular appropriations have steadily increased and subsequently have included 21st Century Cures Act annual allotments for the Cancer Moonshot℠ beginning in FY 2017 and annual appropriation for the new Childhood Cancer Data Initiative (CCDI) commencing in FY 2020. The House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Labor–U.S. Department of Health and Human Services [HHS]) released its FY 2021 markup bill, which includes increases to the NCI regular appropriations and $414 M in emergency funding related to COVID-19 restart costs.

COVID-19 Serological Science. Dr. Sharpless provided a list of the NCI serological COVID-19 serological science efforts, many of which involve the FNLCR and some of which are supported by the COVID-19 supplemental funding. The NCI actively has been establishing the Serological Sciences Network for COVID-19 (SeroNet); validating commercially available COVID-19 antibody testing devices for the U.S. Food and Drug Administration (FDA); developing SARS-CoV-2 (the coronavirus causing COVID-19) serum-based standards and a serology study dashboard and database (Sero-tracker); and supporting real-world evidence gathering and seroprevalence studies. Dr. Sharpless highlighted two of NCI's serological science efforts, SeroNet and Sero-tracker, noting that detailed updates will be provided later in the meeting. For SeroNet, the NCI has issued 24 grants to support establishing Serological Sciences Centers of Excellence and conducting Serological Sciences Research Projects, as

well as 4 contracts to support establishing Serological Sciences Capacity Building Centers (CBCs), all in the extramural community. The FNLCR human papillomavirus (HPV)/SARS-CoV-2 Serology Laboratory will serve as the center of the activities and will manage a Serological Sciences Network Coordinating Center (SSNCC) that aims to foster collaborations (e.g., between academia and industry) across the Network. The NCI anticipates that SeroNet research will improve understanding of the fundamental questions that have urgent public health importance regarding COVID-19 immunity and reinfection, disease severity correlates, and outcomes and prevalence among different U.S. populations.

In July 2020, the HHS, Centers for Disease Control and Prevention (CDC), National Institute of Allergy and Infectious Diseases (NIAID), and FNLCR began collaborating to develop Sero-tracker for monitoring SARS-CoV-2 seroprevalence and U.S.-based studies. This compilation of results and methodologies—a proxy for the amount of SARS-CoV-2 infection and burden experienced in the U.S. population—leverages the expertise and infrastructure of the NCI Clinical Trials Reporting Program (CTRP). The FNLCR Biomedical Application Development Center, which has played a key role in the CTRP dashboard development, has been extracting data from the published literature and various data sources to populate the warehouse and has been testing a working prototype of the dashboard. In late August 2020, the NCI—through a Center for Biomedical Informatics and Information Technology (CBIIT)-sponsored contract—migrated this work to Essex Management, NCI's precision medicine contractor. A working version of the tracking dashboard soon will be available to the research community.

FNLCR Routine Activities. Dr. Sharpless remarked that the FNLCR Nanotechnology Characterization Laboratory (NCL), which is widely used by the nanotechnology community, has continued its work during the pandemic. In fact, the NCL and its uniform characterization of nanoparticles has assisted in novel formulations of drug design and delivery for HIV treatment.

FNLAC members were reminded of the fastest accruing clinical trial in the history of the NCI, the successful NCI-Molecular Analysis for Therapy Choice (NCI-MATCH). The Adult NCI-MATCH trial, which tested at a large-scale, the Basket Trial, rapidly accrued 6,000 patients across 1,100 National Clinical Trials Network (NCTN) sites and randomized patients to targeted therapies. The NCI subsequently launched the Pediatric MATCH trial, and this trial is ongoing. In this next phase of the NCI-MATCH series, the NCI is sponsoring three successor trials: Combination (Combo) MATCH, ImmunoMATCH (iMATCH), and acute myeloid leukemia (AML)/Myelodysplastic Syndromes (MDS) MATCH (MyeloMATCH). Dr. Sharpless provided updates on two of the three trials.

The ComboMATCH trial will evaluate combinations of targeted drugs that are supported by pre-clinical *in vivo* evidence—in particular, patient-derived xenografts (PDX) and cell-line-derived xenograft (CDX) data—aiming to develop novel genomically directed target agent combinations. ComboMATCH will be activated across the NCTN and NCI Community Oncology Research Program (NCORP) sites, with each group managing four to six phase 2 single arm or randomized controlled clinical trials, accruing 35 to 50 patients in each study. Trial enrollment is anticipated to begin in the third quarter of FY 2021. The FNLCR will support ComboMATCH with pre-clinical validation of the novel therapy studies using the resources of the NCI Patient-Derived Models Repository (PDMR).

For the first time in NCTN history, MyeloMATCH, a national uniform clinical trial approach (i.e., master protocol), will match the entire spectrum of myeloid malignancies, from AML to MDS, to targeted therapies. The MATCH series of trials, including MyeloMATCH, required establishing a new laboratory network, Molecular and Immunologic Diagnostics Network (MDNet), to provide in-depth molecular determinations and disease assessment, all in a rapid timeline. The FNLCR is leading this effort, and the trial is estimated to launch mid-FY 2021. In the MyeloMATCH trial design, enrolled patients at NCTN sites, after screening and assessment by the NCI-supported Southwest Oncology Group

will transition from Tier 1–Initial Therapy, to Tier 2–Minimal Residual Disease-Directed, to Tier 3–Transplant/Consolidation, and end with Tier 4–Next-Generation Sequencing Validation. Patient samples will be analyzed in MDNet; data analysis will be performed by the MATCHBox informatics engine, Precision Medicine Analysis and Coordinating Center; and results will be returned to the enrolled site within 72 hours of collection. This process repeats for the next tier.

In addition to continuing the clinical trial support during COVID-19, the NCI Technology Transfer Center and FNLCR cohosted the 2020 Technology Showcase virtually on 9 September 2020. The showcase attracted the attention of 300 viewers worldwide and featured NCI and FNLCR inventors, educational panel sessions on technology commercialization, and a virtual poster session sponsored by the NCI Technology Transfer Ambassadors Program.

NCI Activities. Dr. Sharpless highlighted ongoing science at the NCI. In recent years, data sources, including the *Annual Report to the Nation on the Status of Cancer,* have revealed a significant decrease in lung cancer mortality but not a decrease in incidence. To address this perplexing pattern, the Division of Cancer Control and Population Sciences (DCCPS) Surveillance Research Program (SRP) investigators used novel analytical techniques to examine Surveillance, Epidemiology, and End Results (SEER) data collected from 2001 to 2016. A study led by Dr. Nadia Howlader, SRP, reported in the 13 August 2020 issue of the *New England Journal of Medicine* that the advances of lung cancer treatment, such as FDA-approved kinase inhibitors, contributed to a decrease in non-small cell lung cancer but not in small cell lung cancer. As lung cancer screening is more broadly implemented in the United States and new immunotherapies become common, Dr. Sharpless anticipates that lung cancer mortality will further decrease, illustrating what is possible as a result of cancer research.

The NCI continues to support cutting-edge, highly innovative basic science and on 27 August 2020 officially launched Cancer Grand Challenges (CGC), a partnership with Cancer Research United Kingdom (UK). The CGC initiative leverages the NCI Provocative Questions (PQ) Initiative, with an added emphasis on both international multidisciplinary teams and patient involvement. The CGC will use the PQ funds every other year (off years) and also is supported by Cancer Research UK funds. American scientists have successfully competed in the Cancer Research UK Grand Challenges program, a predecessor to this new program, a trend Dr. Sharpless anticipates continuing. On 14 October 2020, the NCI–Cancer Research UK Award Panel, in a process that solicited input from the research community, announced the 2021 Grand Challenges (framed as questions). The first stage of the competition involves expressions of interest from the teams, which will be accepted through April 2021. The CGC initiative complements the NCI investigator-initiated research and Research Project Grant research portfolio. It is expected to stimulate innovative ideas in overcoming barriers to research and make fundamental biological advances that will have a direct impact on cancer patients.

In FY 2021, the NCI will commemorate the 50th anniversary of the National Cancer Act of 1971 and will develop an educational program conveying the message of its success and reach to the cancer research community. Since inception, this Act has accelerated a number of programs (e.g., NCI-Designated Cancer Centers and SEER) establishing the mainstay of the nation's investment in cancer research. The National Cancer Act assured high-level access of the NCI to Congress and the White House, appointed advisory committees (e.g., National Cancer Advisory Board and President's Cancer Panel), and enabled the NCI Bypass Budget (also called the Professional Judgement Budget) process. In addition, the Act established the FNLCR, providing the NCI with a government laboratory for targeted, high-priority cancer research projects. Importantly, the Act united patients, scientists, and doctors, as well as industry and government, in one vision.

In the discussion, the following points were made:

- Regarding ComboMATCH and the amount of time necessary to develop and test the *in vivo* models and select therapies and how that affects the trial design, no PDX or CDX will be individualized for each patient. Pre-clinical data reviews to assist in selecting the best possible therapies have been ongoing across the NCI cooperative groups, and no delays are anticipated. Because the possible drug combinations are larger than the capacity for any one clinical trial, the NCI plans to select combinations that have demonstrated effectiveness, with supporting evidence from multiple data sources.

- The iMATCH trial will establish a national standardized approach to conducting immunotherapy trials and will evaluate combination immunotherapies and cytotoxins. The outcomes of the Cancer Moonshot[SM]-supported Partnership for Accelerating Cancer Therapies and the NCI-sponsored Cancer Immune Monitoring and Analysis Centers (CIMACs) likely will inform iMATCH.

III. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) RESOURCES TO SUPPORT EXTRAMURAL RESEARCH—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, Division of Cancer Treatment and Diagnosis (DCTD), reviewed some of the progress in resource areas most active at the FNLCR in support of the extramural investigators, particularly the Biopharmaceutical Development Program (BDP) and the PDMR.

Biopharmaceutical Development Program. In 1993, the DCTD established the BDP to provide specialized and unique technical expertise and services to perform feasibility studies and develop new manufacturing processes for producing good manufacturing practice–grade biopharmaceuticals for early-stage trials. In addition, the BDP provides FDA and international regulatory documentation and support, transfers technology to commercial entities, and serves as a training site FDA inspector. Investigators seek assistance from the BDP to support projects intended for orphan indications, unmet medical needs, and limited markets. Projects may involve novel, high-risk, high-reward technologies and various types of biologicals. The BDP has a strong record with projects with regulatory uncertainty (e.g., first-in-class products). Dr. Doroshow emphasized that, although the BDP assists with process development, manufacturing from start to finish, and quality assurance and control, the project originators retain the intellectual property rights. More than 50 percent of the BDP projects are competitively selected extramural projects funded by the NCI Experimental Therapeutics (NExT) Program. The other sources include the NCI Center for Cancer Research (CCR) for intramural projects, other NIH Institutes and Centers (ICs), including NIAID and the National Center for Advancing Translational Sciences (NCATS), and other federal agencies.

The BDP occupies two floors of the FNLCR Advanced Technology Research Facility, housing instrumentation used in upstream (e.g., bioreactors and fermenters) and downstream (e.g., purification) processes and recently expanded capabilities to increase autologous cell therapy manufacturing. The BDP has developed several different types of products, including monoclonal antibodies, cancer vaccines, and virus vectors. Dr. Doroshow described two products that have been licensed and are commercially available for which the BDP had developed the manufacturing process and generated the national supply for U.S. and international human clinical trials. A monoclonal disialoganglioside (GD2) receptor antibody (ch.14.18) that targets surface receptors on neuroblastoma cells, in combination with cytokines and standard treatment, improved progression-free survival in pediatric patients with high-risk neuroblastoma in NCI-supported Children's Oncology Group (COG)–led clinical trials. This product, Unituxin (or

dinutuximab), is now FDA-approved. An immunotoxin (HA22), a cluster of differentiation-22 (CD22) receptor inhibitor, discovered and evaluated in NIH Clinical Center–supported trials by CCR investigator Dr. Ira Pastan, is FDA-approved (moxetumomab) for treating hairy cell leukemia. More than 14 products are currently nearing licensure, including a peptide vaccine to prevent cytomegalovirus recurrence in hematopoietic cell transplantation and a monoclonal antibody for imaging in primary amyloidosis. The BDP is supporting other NIH ICs and their projects addressing acute radiation syndrome (NIAID and NCATS), rare diseases (NCATS), viral-related cancers (NIAID), malaria (NIAID), and type 1 diabetes (National Institute of Diabetes and Digestive and Kidney Diseases), as well as multiple U.S. Department of Defense projects. Dr. Doroshow remarked that a major strength of the BDP has been its ability to develop and maintain standard operation procedures for the supported projects, serving as a resource for documentation and training. Further details can be accessed from the FNLCR website: BDP.

Patient-Derived Models Repository. Dr. Doroshow reminded the FNLAC members that the PDMR, which launched in May 2017, is a national repository of PDX, CDX, patient-derived organoids (PDorgs), patient-derived tumor cell cultures (PDCs), and cancer-associated fibroblast (CAF) models. The PDMR serves as a resource for academic discovery efforts and public–private partnerships for drug discovery. The goal is to collect and develop clinically annotated and molecularly characterized models for the research community in collaboration with the NCORP Community and Minority/Underserved Community sites, all at a low cost compared with other distributors.

The PDMR currently has 429 models publicly available that span several solid-tumor histologies (common and rare cancers), and 223 additional models are awaiting a final quality control, which has been delayed by laboratory closures due to the pandemic. The PDMR distributes median subculture passage (e.g., passage 2) clinically annotated and molecularly characterized models. Dr. Doroshow noted the significantly high number of understudied cancer histologies (e.g., Merkel Cell carcinoma) that are represented in the available PDX models. Currently, 119 two-dimensional PDCs, 200 CAFs, and 88 PDOrg models are publicly available. Another goal, whenever possible, is to develop all four models from matched specimens for comparative pre-clinical studies. A total of 87 matched PDX, PDOrg, PDC, and CAF models are contained in the PDMR and can support mid- to high-throughput translational screening. Regarding distribution to the public, the PDMR has distributed 1,416 total models among the academic, commercial, and intramural communities as of March 2020. Nearly 50 percent of NCI-Designated Cancer Centers have requested one or more PDMR models. Major biotechnology and pharmaceutical companies have requested a large number of models to supplement their existing activities.

Dr. Doroshow emphasized that the DCTD will continue to increase awareness in the extramural community about the PDMR resources and molecular information that can be downloaded at no cost. The cost remains reasonably low, at $250 per model. Ongoing efforts include completing the proteomic and phospho-proteomic analysis of the first 200 models in collaboration with the NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC), planning PDX tissue microarray panels, performing human leukocyte antigen-typing of all PDX models, collaborating with Tempus, Inc., on a cross-laboratory study to evaluate the *in vivo* response in PDOrg models, and conducting pre-clinical studies using matched PDXs and PDorgs to assess consistency of response in models from the same patient.

In the discussion, the following points were made:

- The PDMR resources, including materials and models, all are available to the public and can be accessed from the NCI website, with links to other sites (e.g., Human Cancer Models Initiative Catalog) potentially available in the future.

IV. STATUS REPORT: SERONET—DR. DINAH S. SINGER

Dr. Dinah S. Singer, Deputy Director, Science Strategy and Development, NCI, provided an update on SeroNet. She explained that the NCI received supplemental funding—via the Paycheck Protection Program and Health Care Enhancement Act—for serological sciences research and testing. At the 21 May 2020 FNLAC meeting, the NCI proposed the concept of a SeroNet as one approach to implementing this congressional mandate. The goal is to increase the national capacity for serological testing and advance understanding of all aspects of immune response to SARS-CoV-2. In a rapid timeline, the NCI issued requests for applications for the centers of excellence and research projects and a request for proposals for the CBCs in June 2020 and reviewed applications in mid-August 2020. The funding plan was presented to the NCI Scientific Program Leadership Committee on 8 September 2020, and grants and contracts were awarded in late September 2020, all completed in FY 2020. The SeroNet kickoff meeting is planned for 15 October 2020. FNLAC members interested in attending were invited to contact Dr. Singer for further details.

Within the overarching goals, the NCI has defined several SeroNet objectives: develop and deploy novel serological assays; characterize the biological mechanisms driving the innate, cell-mediated, and humoral immune responses to SARS-CoV-2; determine the factors (genetic or environmental) that modulate the immune response; determine the serological correlates of disease pathogenesis and protection against future infection; and identify and address barriers to serological testing.

In launching SeroNet, the NCI has funded 4 CBCs, 8 U54 Serological Sciences Centers of Excellence, and 13 U01 Serological Sciences Research Projects across the United States and is supporting the FNLCR Serology Laboratory and the SSNCC. The areas of investigation of the SeroNet grantees and the funded institutions address the NCI objectives for the Network. The four CBCs will develop, validate, and deploy serology tests in the local community and conduct surveillance clinical trials. The FNLCR Serology Laboratory will procure and characterize serum samples from SARS-CoV-2 patients and controls and establish serum panels; develop qualified assay standards and generate novel reagents; and share assays, reagents, and standards within SeroNet. The SSNCC will be housed at the FNLCR and will manage all aspects of SeroNet coordination, including organizing steering committee meetings, managing communications and outreach, and coordinating resources sharing.

Dr. Singer emphasized that SeroNet is designed to be a highly interactive network, in which data and resources are widely shared internally and also with the broader research community. All publications will be open access and data and resources made publicly available. The first-year cost is estimated at $48.8 M, with a total cost of $213.2 M for 5 years. The NCI has allowed for a 10 percent budget set-aside for post-award collaborative projects. Because of the rapidly changing landscape of COVID-19, the NCI will conduct an assessment and evaluation after 2 years of funding. Dr. Singer expressed appreciation to NCI, FNLCR, and NIAID staff who worked tirelessly to establish and launch SeroNet.

In the discussion, the following points were made:

- The efforts to conceive, establish, fund, and launch SeroNet rapidly likely have not been successfully carried out previously in the history of a government agency.

- In addition to NCI's leadership and its role in establishing SeroNet, the NCI also can be credited for the novel, nimble contracting mechanisms and the unique features of FNLCR, including the Office of Acquisitions.

V. RAS INITIATIVE PROGRESS REPORT—DR. FRANK MCCORMICK

Dr. Frank McCormick, RAS National Initiative Advisor, FNLCR, and Professor, University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, provided an update on the NCI RAS (a family of genes mutated in more than 30 percent of cancers) Initiative. Dr. McCormick reminded the FNLAC members of the project goals. The first is to identify compounds that bind directly to KRAS (one of three human RAS genes involved in cell growth, cell maturation, and cell death) or prevent KRAS from activating with its immediate effectors, such as RAF 1 kinase and phosphoinositide 3-kinase (PI3K). The second is to understand at the molecular level the interaction between KRAS, RAF1, and the plasma membrane.

The NCI, specifically the FNLCR, and the U.S. Department of Energy (DOE) National Laboratories (Argonne [ANL], Lawrence Livermore [LLNL], Los Alamos [LANL], and Oak Ridge [ORNL]), are collaborating on the Initiative's second goal. Dr. McCormick noted that further details on this collaboration will be discussed later in the meeting. A recent RAS Initiative publication "Uncovering a Membrane-Distal Conformation of KRAS Available to Recruit RAF to the Plasma Membrane" in the *Proceedings of the National Academy of Sciences* summarizes some of the FNLCR biochemical and biophysical approaches being used to inform the DOE computational methods. The DOE collaborators recently reported their methods, "Machine Learning-Driven Multiscale Modeling Reveals Lipid-Dependent Dynamics of RAS Signaling Proteins," in *Biophysics Computational Biology*. In an iterative process, the biochemical and biophysical properties of RAS protein interactions with the plasma membrane defined by the FNLCR inform the DOE molecular modeling to make predictions. These predictions are corroborated by the FNLCR cell-based analyses to help inform better predictive models.

Dr. McCormick reviewed the RAS Initiative resources and interactions, including the reagents, community outreach and engagement, collaborations, and contractor Cooperative Research and Development Agreements (cCRADAs). The cCRADAs remain a major part of the Initiative's small-molecule drug discovery efforts and comprise a long list of collaborators and partners. He highlighted the RAS Initiative's publications released over the past year, demonstrating productive collaborations and outreach to the broader RAS community. For example, Dr. Channing Der at The University of North Carolina at Chapel Hill collaborated with the RAS Structural Biology Group lead, Dr. Dhirendra Simanshu, and his team to solve the crystal structure of KRAS mutant G12R to understand its biochemical properties more fully.

Dr. McCormick remarked on the RAS Initiative cCRADAs, acknowledging a long list of collaborators and partners. He further elaborated on two of these as illustrations of different ways the RAS Initiative is interacting with the extramural community. New insights into RAS biology are resulting from a collaboration between the FNLCR and TheRas, Inc. TheRas is a small biotechnology company based in San Francisco, California, the majority of whose work supporting the cCRADA is performed at the FNLCR. Dr. McCormick acknowledged members of the RAS Initiative team: Drs. Anna Maciag: David Turner; and Simanshu; and the Ras Medicinal Chemistry & Chemical Development head, Dr. Eli Wallace, who are leading this effort. He noted external partners as well, including LLNL and the Francis Crick Institute. Dr. McCormick described the three projects being investigated for directly targeting KRAS. Project 1—Preventing KRAS4b Processing by Blocking Cysteine (C)185, in which compounds (covalent binders) have been developed and appear to be on target and active in human cancer cells. Project 2—Targeting Histidine (H) 95 on KRAS, revealed to be unique to this RAS isoform, with effector regions in close proximity to the nucleotide binding pocket. Project 3—Genetically Blocking Activation of PI3K by KRAS, in which compounds disrupting PI3K alpha binding have been developed and will be advancing to pre-clinical studies.

Dr. McCormick reported that the RAS Structural Biology Group, the first in the field, has solved the crystal structure of the KRAS RAS binding domain (RBD) in a complex with the RAF1- cysteine-rich domain (CRD), suggesting a larger footprint in this region of RAS than previously described. Further evaluations by Dr. Andy Stephen, RAS Biochemical and Biophysical Group lead, and his team revealed that CRD contributes less to the binding energy than does the RBD. Dr. McCormick emphasized that disrupting CRD binding with small molecules could potentially advance drug discovery efforts. Two approaches being considered for developing such inhibitors include developing compounds that bind the RBD–CRD region or KRAS:RBD–CRD complex. Internal efforts to disrupt this interaction using cysteine tethering and other methods are in progress at the FNLCR. In addition, Dr. McCormick informed the FNLAC that in April 2020, a cCRADA with Sanofi-Aventis (Sanofi) was finalized to develop RAF1 inhibitors. Most of the work will be conducted at the Sanofi facility, with oversight by the FNLCR, particularly the RAS Initiative groups supporting the project. Several screening strategies to identify hit compounds that could perturb RAF1 RBD–CRD interaction have been proposed. In this model of research collaboration, Dr. McCormick anticipates that this effort will identify compounds binding a new pocket in the RAS protein, resulting in new therapeutic benefits for cancer patients.

FNLAC members were updated on the FNLCR internal efforts supporting the RAS Initiative. Dr. Dominic Esposito and the RAS Reagents Group have completed developing a KRAS cysteine surface mutagenesis library, in which 95 KRAS cysteine mutants were prepared at sites of interest on the protein surface. In parallel, Drs. Turner, Maciag, and Vandana Kumari have been developing an updated disulfide tethering library of 2,000 high-quality and chemically diverse fragments, which leverages the prior work of UCSF investigators. To date, 1,163 suitable compounds have been developed and validated. Testing the cysteine surface mutagenesis library against potential tethering lead compounds (i.e., hit) identified a single high-labeled hit, the active (GTP-bound) form of KRAS G12C/C118). Preliminary structural biology and nuclear magnetic resonance analysis suggest that this compound has high affinity to a new KRAS binding pocket not previously described in the literature. Dr. McCormick remarked on the level of biochemical, molecular simulation, and computational work that is supporting this topic. The goals of the internal cysteine project are to optimize promising hits using the available binding pocket/structural information and discover new pockets not detectable in crystal structures (i.e., cryptic pockets). Efforts will focus on several approaches involving the use of computer-aided drug design for molecular docking (MD) for pose prediction, molecular dynamics simulations for pose refinement, and enhanced MD for cryptic pocket identifications.

In the discussion, the following points were made:

- The H95 targeting studies revealed selectivity for KRAS and also enhanced protein turnover using a tool compound attached to a strong electrophile, but the mechanisms are not well understood. The RAS Initiative team—under the guidance of The Ras Medicinal Chemistry & Chemical Development head, Dr. Wallace—has made progress addressing the complex chemistry of H95 and improving the binding properties of promising drug candidates.

- The FNLCR updated tethering library is approaching 2,000 fragments. It was optimized against a broad range of physical and chemical properties, using medicinal and computational methods, all aiming for low-affinity tethered hits.

VI. REPORT FROM THE NCI TASK FORCE TO EVALUATE THE NCI–DOE COLLABORATION—DR. JOE W. GRAY

Dr. Joe W. Gray, Professor and Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, Center for Spatial Systems Biomedicine, Associate Director for Biophysical

Oncology, Knight Cancer Institute, Oregon Health & Science University, presented the FNLAC NCI Task Force to Evaluate the NCI–DOE Collaboration (Task Force) report. The Task Force charge was threefold: (1) conduct an in-depth technical review of the established projects; (2) provide insights and observations on the Pilots, programs, and projects; and (3) make recommendations to indicate whether the NCI–DOE collaborations should continue into Years 4 and 5 and beyond. Dr. Gray acknowledged the Task Force members who also were asked to provide input on the importance of the DOE unique high-performance computing (HPC) capabilities to the projects.

To provide background, in June 2016, the NCI and DOE signed a 5-year memorandum of understanding to establish the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C), aiming to harness the DOE HPC resources and computer science expertise to address cancer research problems of importance to the NCI. Other partners in the JDACS4C 5-year program include the FNLCR and four National Laboratories operating under the DOE: ANL, ORNL, LLNL, and LANL. The NCI–DOE collaboration was expected to deepen the national understanding of cancer biology through the collaborative development of computer simulations and predictive models; produce approaches to identify treatment options; and transform cancer care by applying natural language processing to organize and interpret data from cancer patients in real time (i.e., actual patients).

The JDACS4C consists of three Pilot projects encompassing three levels of research. Pilot 1, a cellular-level project, aims to develop predictive computational models of pre-clinical therapeutic response using PDX data. Pilot 2, a molecular-level project, is using computer simulations to better characterize RAS membrane biology. Pilot 3, a population-level project, aims to integrate, analyze, and model cancer surveillance data acquired through the SEER program. Dr. Gray noted that uncertainty quantification (UQ), CANcer Distributed Learning Environment (CANDLE), and Accelerating Therapeutics for Opportunities in Medicine (ATOM) are JDACS4C crosscutting projects but were not included in the Task Force evaluation.

In the evaluation process, the Task Force held six virtual meetings from July to October 2020. The first item addressed was to develop evaluation questions for assessing the Pilots. The NCI co-leads (in consultation with the DOE co-leads) of each Pilot project provided programmatic presentations and addressed questions. The Task Force then assessed each Pilot and the efficacy of management and oversight provided by the NCI using five evaluation questions: (1) What impact has the collaboration overall, and the Pilots specifically, had on the cancer research community? (2) How have the unique HPC and computer science expertise provided by the DOE contributed to cancer research? (3) Has the effort effectively engaged and benefitted the greater cancer research community? (4) Are there additional research opportunities to collaborate with the DOE and HPC in cancer? (5) Has the NCI oversight been adequate, and should NCI continue to support this collaboration?

Dr. Gray summarized the Task Force assessments and recommendations.

Pilot 1—Predictive Modeling for Pre-Clinical Screening. Developing predictive models for tumor drug response is a laudable goal, but Pilot 1 was launched prematurely. The necessary data were not available initially, and valuable time was spent gathering additional data sets. The compiled data sets had already been examined thoroughly using other methodologies. The Pilot 1 activities were primarily computational and did not lend appropriate consideration to underlying biologic constraints. Productivity has not been commensurate with investment. The NCI did not provide appropriate and ongoing management, oversight, or engagement. The recommendations are to release the aggregated data sets compiled in support of Pilot 1 and conclude the project.

Pilot 2—RAS Biology in Membranes. Engagement with the community at the FNLCR was satisfactory, but engagement with the broader biophysics community could be improved. The Pilot 2

studies leveraged DOE HPC capabilities appropriately, and productivity was acceptable. Experimental validation of computer models was lacking, and collaborative efforts between the biologists and the computational scientists should be increased. The recommendations are to continue Pilot 2 with greater emphasis on fine-grain modeling, experimental validation, and increased community engagement.

Pilot 3—Population Information Integration, Analysis, and Modeling for Comprehensive Cancer Surveillance. Pilot 3 effectively used computational science expertise from the DOE, dramatically reducing the time from data entry to reporting for five SEER data elements, but did not leverage HPC. The activities were insular to the SEER registry community, and the capabilities have limited usefulness to the greater cancer registry community because of the SEER data curation. The recommendations are to continue Pilot 3, with a stronger focus on implementation and community applicability beyond SEER. Future directions should be informed by an external advisory group.

NCI Management of the NCI–DOE Collaboration. Improved management and oversight by the NCI were indicated for all Pilot projects. The Pilots were insular and not adequately engaged with the extramural community, resulting in missed opportunities to leverage existing knowledge and amplify project impact. The Pilots were driven largely by computational considerations and were not conducted in the context of realistic biologic constraints. The recommendations are to establish a mechanism to support collaboration between the extramural community and the NCI and DOE.

Regarding lessons learned, the Task Force pointed out the critical need to assess project feasibility in advance of a launch. The projects should have milestones and external oversight. The projects should have close and ongoing engagement from the NCI and connection with the extramural cancer research community.

Dr. Gray provided overall conclusions from the Task Force evaluation. Continue the NCI–DOE collaboration because it is uniquely suited for research that would be challenging to achieve elsewhere. Reassess the current Pilots and their level of funding. Increase engagement with the NCI extramural community. Increase cancer expertise and oversight for each project by including NCI extramural divisions in project management, establishing external scientific advisory groups, and assessing the project's appropriateness and feasibility. Increase project planning efforts to ensure the quality and availability of data, biologic relevance of planned models, and impact on cancer research.

In the discussion, the following points were made:

- In 2016, the JDACS4C program started as an exascale project, the landscape was different. The expectation was that the project would influence cancer research, which would become a driving force for machine learning and artificial intelligence (AI). Currently, AI is most important to cancer research and has broad scientific applications. Exascale is less strategic and is not the dominant architecture used in AI.

- The DOE selected which national laboratories would be involved in each Pilot with minimal input from the NCI. A better approach would be to establish a scientific idea, then have groups at the NCI and DOE compete for inclusion in a project in a process like the Cancer Grand Challenges.

- The Pilot projects have proven that an NCI–DOE collaboration is possible, which was not obvious at the inception of the JDACS4C program.

- Time, training, and interest are needed to foster cross-education between computer scientists and biologists. The NCI has systems biologists who might play an interface role. Long-term opportunities may act as incentives for DOE physicists and computational scientists to develop sustained engagement with biologists.

Motion. A motion to accept the final report of the NCI Task Force to Evaluate the NCI–DOE Collaboration was approved unanimously.

VII. COVID-19 SERO-TRACKER—DR. NEAL D. FREEDMAN AND MR. BRENT D. COFFEY

Dr. Neal D. Freedman, Senior Investigator, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, presented background information about the COVID-19 Seroprevalence Tracking dashboard (named COVALENT) and acknowledged the CDC–NIH serology database team. The COVALENT project leverages existing NCI programs and initiatives (e.g., CTRP) and expertise across the HHS. The aims 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, calendar time, and population.

Dr. Freedman noted the needs for seroprevalence tracking. Officially reported cases of SARS-CoV-2 do not reflect true incidence, because asymptomatic cases are not included. As highlighted at the 7 May 2020 virtual workshop titled "COVID-19 Serology Studies," seroprevalence studies may include asymptomatic cases and thereby inform mitigation efforts and vaccine efficacy trials. Analysis of seroprevalence studies also can improve predictive models of the pandemic and distinguish natural immunity from vaccine immunity. Combining the results of multiple studies is challenging but essential to increase data strength and clearly characterize the impact of COVID-19 in the United States. It is difficult to draw conclusions based on the combined results of seroprevalence studies, because the studies vary in design, methods, and scope.

Many seroprevalence studies have been initiated worldwide, ranging from those that are large and inclusive to those that focus on specific geographic areas or special populations (e.g., health care workers, pregnant women, dialysis patients). Studies also may have a cross-sectional or longitudinal design or collect data over different periods of time or frequency. Dr. Freedman reviewed some examples of seroprevalence data recently published, including the CDC Ten-Site Commercial Laboratory Seroprevalence Survey and noted the challenges to understanding these data. 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 way exists to share plans, methods, or results. The traditional method of sharing information at the time of publication results in delays that may cause duplicate efforts and critical gaps in understanding the COVID-19 epidemiology.

The COVALENT dashboard should help users answer questions regarding studies in progress, seroprevalence in a specific place over time, population-specific studies, and the types of tests being used by various researchers. A working group consisting of members from the CDC, NCI, and NIAID identified several existing data fields to be included, such as 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.

Dr. Freedman summarized the progress made in developing the COVALENT dashboard. Common data elements to extract from each study have been defined, and a prototype for recording data

has been developed. Infrastructure has been developed to store and deconvolute seroprevalence results for ease of comparison. A team of extractors has imported 41 studies, and a prototype for displaying information about those studies has been developed. The development team is engaged with key stakeholders to define the scope and capabilities of the dashboard and to encourage use of the resource. Discussion also is underway with the NIH Office of Communications and Public Liaison to assist with the landing page, a dedicated email address, Section 508 compliance, branding, and logos. Next steps include the development of an initial landing webpage and the ongoing incorporation of feedback from key stakeholders. The team will continue to develop robust standard operating procedures and acquire new data. A study catalog and results dashboard are planned for release, and a methodology for study quality assessment is being developed. An online user data entry interface and an application programming interface (API) will be finalized to make data inclusion more efficient.

Mr. Brent D. Coffey, Vice President, Technical Strategy, Essex Management, LLC, a contractor with CBIIT, demonstrated the COVALENT dashboard prototype. The prototype has been used to quickly gather requirements from stakeholders, and the landing page is scheduled for release in the next few weeks. Geospatial data are presented on the landing page as an interactive map of the United States showing where the data from each report were obtained. States are color coded to indicate the number of reports abstracted. Filters that will indicate more precise location of abstracted studies, such as county or ZIP Code, can be applied. Additional filters also can be applied, including project title, lead organization, population type, population sampling framework, primary design, study status, test type, and the collection period beginning and end. A data table on the landing page lists all reports included in the interactive map. A user can select a report of interest and be directed to a report-specific page where report data are presented with CDC seroprevalence data. Mr. Coffey explained that the CDC data, which are color coded to differentiate them from report data, serve as a baseline for comparison. Scatterplots can be accessed from a tab on the landing page that displays data indicating changes in seroprevalence over time. The colors of each plotted point represent population types. The data can be filtered by state or time of collection.

In the discussion, the following points were made:

- Release of the COVALENT landing page is scheduled a few weeks from this meeting. Additional phases will be released after the team incorporates stakeholder and user feedback on the initial launch. Maps and graphics will be updated as additional data are collected.

- The number of studies on COVID-19 seroprevalence is expected to increase. The development team will leverage increasing public awareness of the COVALENT dashboard to maximize data inclusion. Researchers are encouraged to contact the team about their projects.

- Clinical trials do not use a standardized testing methodology. The development team is working with the NCI SeroNet projects funded by the NIAID and state and local health departments funded by the CDC to maximize data inclusion.

VIII. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lyman. There being no further business, the 5th Virtual Meeting of the FNLAC was adjourned at 4:03 p.m. on Wednesday, 14 October 2020.

Date	Lawrence J. Marnett, Ph.D., Chair
Date	Caron A. Lyman, Ph.D., Executive Secretary