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

10th Virtual Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
June 27, 2022

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

National Cancer Institute
10th Virtual Meeting of the Frederick National Laboratory Advisory Committee

27 June 2022

Summary of Meeting

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 10th Virtual Meeting on 27 June 2022. The meeting was open to the public from 11:00 a.m. to 1:42 pm EDT. The FNLAC Chairperson, Dr. Candace. S. Johnson, President and CEO, M&T Bank Presidential Chair in Leadership, Roswell Park Comprehensive Cancer Center, presided.

FNLAC Members
Dr. Candace. S. Johnson (Chair)
Dr. Andrea H. Bild
Dr. Catherine M. Bollard
Dr. John H. Bushweller
Dr. Timothy A. Chan (absent)
Dr. Lisa M. Coussens
Dr. Scott W. Hiebert
Dr. Allison Hubel
Dr. Dineo Khabele
Dr. Nilsa C. Ramirez Milan
Dr. Denise J. Montell
Dr. Patrick Nana-Sinkam
Dr. Erle S. Robertson
Dr. Lincoln D. Stein
Dr. Linda F. van Dyk

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

Executive Secretary
Dr. Wlodek Lopaczynski

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I. OPENING REMARKS—DR. CANDACE S. JOHNSON

Dr. Candace. S. Johnson, Chair, called to order the 10th Virtual Meeting of the Frederick National Laboratory Advisory Committee (FNLAC) and welcomed the Committee members, National Cancer Institute (NCI) staff, and guests. Dr. Johnson reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Wlodek Lopaczynski, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Motion. A motion to approve the minutes of the 24 February 2022 FNLAC meeting was approved unanimously.

Dr. Johnson called Committee members' attention to the future meeting dates listed on the agenda, noting that the 2024 proposed meeting dates will need to be confirmed. Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), NCI, clarified that for the 2-day meetings, Committee members should reserve both dates on their calendars. Dr. Johnson also noted that the next FNLAC meeting will be held on 12–13 October 2022 and will be virtual.

Motion. A motion to confirm the 2024 FNLAC meeting dates was approved unanimously.

II. NCI ACTING DIRECTOR'S REPORT—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Acting Director, NCI, also welcomed the FNLAC members and attendees to the meeting. He provided updates on the fiscal year (FY) 2023 budget, FNLCR cancer research and training activities, and the Cancer Moonshot℠ initiative. Dr. Lowy reminded the Committee members of the FNLCR Awareness Campaign, which Mr. Richard Folkers, Senior Editor, Office of Communications and Public Liaison, discussed at the 24 February 2022 FNLAC meeting. Dr. Lowy noted that a request for proposals for the federally funded research and development center contract recompetition was posted on 23 June 2022, and the new award would be granted in about 2 years.

Dr. Lowy remarked that he was named as the NCI Deputy Director in 2010; since this time, he has served as the NCI Acting Director on three occasions. He noted that the NCI leadership team has remained committed to NCI's mission over the years. Dr. Lowy highlighted key NCI initiatives that occurred during his tenure as Acting Director, which include the Precision Medicine Initiative in Oncology, the National Cryo-Electron Microscopy Facility (NCEF), the Cancer Moonshot, a $40 million (M) increase to P30 support grants for NCI-Designated Cancer Centers (Cancer Centers), and Congress' recognition of NCI's low funding rates for investigator-initiated research. He also briefly highlighted current and near-future NCI activities, which include the Cancer Grand Challenges, the reignited Cancer Moonshot, Cancer Center support grants, and a new signature project for the FNLCR.

NCI Budget and Appropriations. Dr. Lowy mentioned that he participated in the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (Labor-HHS) hearing held on 11 May 2022. He remarked on the continued bipartisan support for the NIH and the NCI, and noted that he has maintained long-standing relationships with congressional leaders. Dr. Lowy reminded members that typically, the President's budget proposal has been lower than the expected appropriations, which he attributed to strong bipartisan support for cancer research across Congress and the appropriators' declining to cut funding in this area, even during challenging budget cycles. In terms of FY2023, Dr. Lowy indicated that Labor-HHS has proposed a $466 M increase for the NCI. He noted that members were sent a document with more information on the NCI budget and other legislative updates.

FNLCR Cancer Research and Training Activities. Dr. Lowy reminded the Committee members that Dr. Dwight Nissley, Director, Cancer Research and Technology Program, FNLCR, discussed plans at the 18 October 2021 FNLAC meeting to establish an NCEF training program. A 5-day training session is scheduled for September 2022, and the participants are 12 novice users from a wide range of institutions.

Ongoing activities at the FNLCR related to serology of SARS-CoV-2 include the development and standardization of serological testing. The U.S. national Human SARS-CoV-2 Serology Standard has, on request, been distributed to more than 150 laboratories. The standard was developed in coordination with the World Health Organization (WHO), and the WHO directs inquiring laboratories to contact the FNLCR for the standard.

Dr. Melinda G. Hollingshead, Chief, Biological Testing Branch, Developmental Therapeutics Program, NCI, recently spearheaded the development of Responses to Oncology Agents and Dosing in Models to Aid Preclinical Studies (ROADMAPS), an online database that contains all of NCI's xenograft testing results and data that can be used to identify dosing regimens.

Dr. Lowy reminded the Committee members that the first G12C inhibitor was approved by the U.S. Food and Drug Administration in May 2021. He explained that *KRAS* G12C mutant alleles are commonly observed in lung cancers, but *KRAS* G12D alleles are more common in pancreatic and colorectal cancers. *KRAS* is one of three human *RAS* (a family of genes mutated in more than 30% of cancers) genes and is involved in cell growth, cell maturation, and cell death. Preclinical data suggest that G12D inhibitors might be clinically useful; clinical trials using G12D inhibitors are planned for the near future. The FNLCR-led RAS Initiative has developed several unique reagents for the cancer research community.

Cancer Moonshot Update. The FNLAC members were provided an update on the Cancer Moonshot initiative. From 2017 to 2021, investigators produced 2,000 publications, launched 49 clinical trials, and filed more than 30 patent applications. FY 2023 marks the last year of funding for the initial Cancer Moonshot. Dr. Lowy remarked that the NCI strives to continue to support the most promising initiatives while developing additional activities to meet challenging new goals.

On 2 February 2022, President Joseph R. Biden announced three critical aspirational goals of the reignited Cancer Moonshot: (1) Decrease the national cancer death rate by half within the next 25 years, (2) transform the meaning of cancer, and (3) address cancer-associated inequities. The NCI is playing a critical role in helping to make these aspirational goals feasible. Four overarching approaches are to (1) invest in the pipeline of new drugs for cancer prevention, interception, and treatment; (2) expand clinical trials to speed evaluation of candidate interventions in diverse populations; (3) ensure equitable health care delivery of current and new standards of care; and (4) increase the diversity of cancer research and the cancer care workforce to make it more closely resemble the communities that we serve.

In FY 2023, the NCI is planning to support the next phase of the Cancer Moonshot through several activities. At the 14–15 June 2022 Board of Scientific Advisors (BSA) and National Cancer Advisory Board (NCAB) Joint Meeting, members unanimously approved two proposed funding opportunity announcements for a scholars diversity program for early-stage investigators and a feasibility trial for asymptomatic multi-cancer early detection and screening. In addition, the NCI plans to issue notices of special interest and requests for information (RFIs) for existing projects, including adapting visualization methods to enhance Cancer Moonshot data, harmonizing existing data to Human Tumor Atlas Network (HTAN) standards, and exploring fusion oncoproteins in childhood cancers.

In the discussion, the following points were made:

- In implementing the overarching approaches related to equity, Dr. Lowy remarked that the NCI is engaged with the NIH UNITE initiative, as well as the NIH Common Fund Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program. Drs. Gray and Lowy serve as the co-chairs of the NCI Equity Council, which is focused on providing funding to extramural investigators, supporting intramural programs, and examining performance metrics. Dr. Gray added that the Council also is focused on enhancing equity broadly across the scientific community (e.g., clinical trials, training). She noted that the Committee may be asked to provide input on these activities in the future.

- As the number of available cancer drugs increases, additional efforts to match drugs to patients will be needed. Additionally, the evolving nature of cancer (e.g., in metastatic patients) must be considered. Best practices must continue to be emphasized in cancer research; this effort will require education, as well as implementation research.

- The NCI does not envision continuing to support all of the first Cancer Moonshot programs, but several highly promising projects will be continued. Analyses of these programs are ongoing. Additionally, several of these programs have transitioned to appropriated funding.

- The reignited Cancer Moonshot will not encompass all of cancer research; interventions under consideration relate to prevention, interception, and treatment. Many areas are being considered in this effort and likely will be continued going forward.

III. CHEMICAL BIOLOGY CONSORTIUM (CBC) UPDATE—DRS. JAMES H. DOROSHOW, STEPHEN W. FESIK, AND WILLIAM P. TANSEY

Review of the CBC. Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, Division of Cancer Treatment and Diagnosis, NCI, presented an update on the CBC. He explained that the CBC is part of the NCI Experimental Therapeutics (NExT) program, a government–academic–industry partnership for cancer drug discovery. The NExT program was established following the completion of the NIH Molecular Libraries Program, building on NCI's experience in cancer drug development and its interactions with academic institutions.

The CBC provided a new way for investigators to pursue drug discovery efforts within the NExT program. Members are part of a consortium for sharing drug development services and relevant data. The members take on projects primarily from investigators across the United States, with a focus on underrepresented malignancies and challenging targets. Dr. Doroshow emphasized that the NCI has the capacity for both discovery and development, and the CBC spans inception, proof-of-concept target development, and clinical trials. The CBC comprises both dedicated and specialized centers affiliated with academic institutions and nonprofits.

Projects can enter the NExT pipeline on a competitive basis at any stage. Since the program's inception, investigators have submitted more than 900 applications, and the success rate has been 10 percent to 14 percent. Funded areas include small molecules, biologics, imaging, nanoparticles, natural products, radiotherapy, and devices. Projects are submitted by academic institutions, biotechnology companies, nonprofits, pharmaceutical companies, and government agencies. Most top-tier projects have been submitted by academic institutions and nonprofits. A total of 24 percent of top-tier proposals are for discovery projects, of which 91 percent are in the area of small molecules.

Applications are evaluated in three cycles per year by a Special Emphasis Panel. Proposals encompass a broad range of topics (e.g., small molecules, biologics, imaging agents) and range from target validation to early-phase trials. The projects are ranked and divided into two categories. The smaller category is evaluated by an Investigational Drug Steering Committee, and early-phase trials are taken to fruition through the Early Therapeutics Clinical Trials Network (ETCTN). The larger category is evaluated by a steering committee composed of CBC members. Projects then are assessed primarily for their feasibility. Dr. Doroshow explained that all projects must go through a "trust but verify" phase to ensure their reproducibility. Applicants send their reagents, cell lines, antibodies, and compounds for qualification. Dr. Doroshow noted that about one-third of applications fail at this stage.

Dr. Doroshow briefly highlighted projects within the current NExT pipeline. Projects in the discovery stage include several inhibitors (e.g., CUL4, PI5P4K, FAK, SHP2, beta-catenin) and a Bcl-xL proteolysis-targeting chimera. Projects in the preclinical development stage also include several inhibitors (e.g., Mcl1, LDHA, p97, WDR5-MLL1). Projects in the development stage include inhibitors (e.g., ER kinase, p97, DNMT1), anti-amyloid light chain antibody, endoxifen, and several imaging agents (e.g., near-infrared fluorophore, cathepsin-activatable fluorescent probe, EGFR-panitumumab infrared dye). Dr. Doroshow noted that some promising novel targets have failed within the NExT pipeline because they were unable to yield a therapeutic index that was reproducible *in vivo.*

Several promising compounds are in the development phase. Dr. Doroshow highlighted the example of 5-aza-4'-thio-2'-deoxycytidine, an inhibitor of DNA methyltransferase that is highly orally bioavailable. The NCI filed an Investigational New Drug Application for this model in 2019, and a clinical trial is ongoing. Dr. Doroshow also discussed the development of a monoclonal antibody, 11-1F4, for patients with amyloid light chain amyloidosis. This antibody, which had been used previously as an imaging agent, was found to cause dissolution of amyloid fibrils in organs. This finding initiated a phase 1/2 trials program. Other noteworthy scientific accomplishments of the CBC include a portfolio of the first high-resolution structures of targets, numerous publications and patents, and outlicensing efforts.

An external evaluation of the CBC was conducted recently. Dr. Doroshow reminded the FNLAC members that they were provided a booklet describing current projects and outcomes of the evaluation. He briefly highlighted messages from the evaluation, noting that the strongest recommendations were to continue science-based, tumor biology–based drug discovery. Dr. Doroshow explained that teams have been developed with expertise in high-level tumor biology, as well as chemical biology. He noted also that reviewers expressed support for CBC's capacity to bring together academic investigators with appropriate support from contract research organizations. Dr. Doroshow also underscored the importance of funding as many projects as possible, noting that more outreach to the academic community is needed. Additionally, he remarked on the value of learning lessons from projects that were discontinued within the pipeline.

WDR5 Inhibitors for the Treatment of Cancer. Dr. Stephen W. Fesik, Professor of Biochemistry & Pharmacology & Chemistry, Department of Biochemistry, Vanderbilt University School of Medicine (VUSM), and Dr. William P. Tansey, Professor of Cell and Developmental Biology, Department of Cell and Developmental Biology, VUSM, presented on the identification of WDR5 inhibitors for the treatment of cancer. This project has been supported by the NExT program since 2015. WDR5 is a high-value target for cancer research, is overexpressed in numerous malignancies, and its overexpression often correlates with poor clinical outcomes. WDR5 may play a critical role in cancers caused by various specific oncogenic drivers.

The VUSM group's project is focused on chemical blockage of the WIN site of WDR5, an arginine-binding cavity. The original premise of the project was that binding of MLL1 to the WIN site is essential for WDR5's enzymatic activity, and WIN site inhibitors would block histone methyltransferase

activity of the complex and drive changes in epigenetic modifications, resulting in the selective inhibition of cancer cells with MLL1 rearrangements. Dr. Tansey explained that this premise has been proven incorrect, and the project has provided new insights into the biology of this system. Several challenges are present in targeting WDR5 for cancer. WDR5 is pan-essential and a versatile cellular multitasker (e.g., epigenetics, bookmarking, mitotic spindle, recruitment to chromatin).

WDR5 is a conserved regulator of protein synthesis gene expression. The group generated an atlas of WDR5 localization and function in a disparate collection of cell types. From this effort, they learned that WDR5 binds to and regulates a highly predictable set of genes linked to protein synthesis. Additionally, they learned that the WIN site tethers WDR5 to chromatin. They developed a working model in which WDR5 is recruited by a chromatin-resident WIN motif protein; several candidate proteins have been proposed. Additionally, the function of WDR5 at ribosomal protein genes is to recruit Myc. Genetic disruption of this interaction promotes rapid and sustainable tumor regression, and WIN site inhibitors evict WIN from chromatin at WDR5 targets. Dr. Tansey explained that WIN site inhibitors disrupt only a subset of WDR5 function; although WDR5 is pan-essential, the WIN site is not. WIN site inhibitors lead to a rapid decrease in protein synthesis gene expression. He also presented the model for the mechanism of action of WIN site inhibitors: chromatin displacement at ribosomal protein genes, ribosome inventory, and nucleolar stress response. The model requires oncogenic vulnerability and a response mechanism (e.g., p53 activation apoptosis, p53-independent response).

The VUSM group also examined clinical indications in a horizon cell-line screening effort. They found that blood-borne cancers, mixed-lineage leukemia rearranged (MLLr) cancers, and diffuse large B-cell lymphoma cancers were strongly represented, and wild-type p53 was not required for a response. Additionally, CRISPR screens were performed in MLLr and solid cancer cell lines to inform synergy choices. This effort has yielded several actionable synergies. Dr. Tansey summarized the following points: WIN site inhibitors evict WDR5 and Myc from chromatin at ribosomal protein genes, WIN site inhibitors are selective for loss-of-function agents, WIN site inhibitors induce a translational choke, WIN site inhibitors act via p53-dependent and independent ways, single-agent activity is expected in blood-borne cancers, and drug synergy could lead to expanded and improved activity.

Dr. Fesik described the process for discovery of WDR5-MLL inhibitors. The first step involves a fragment screen and generation of correlation maps, which provide information on the compound's binding location. The screen identified molecules that bind WDR5 at the WIN site, indicated through chemical shift changes. The molecules bind the arginine-binding site in the S2 unit. Next, the group obtained molecular structures via X-ray crystallography, which they modeled within the binding pockets. Using this approach, they identified a molecule with an inhibitory constant of 1.3 nanomolar. The compound then was modified to develop a control compound. Next, using a different molecule for the initial structure, the group optimized the compound to achieve an inhibitory constant of 100 picomolar. Dr. Fesik emphasized that the NExT program provided the capabilities for rapid findings.

The VUSM group then obtained the molecular structure of the identified compound. They modified the compound to improve its activity and pharmaceutical properties. Next, they explored additional modifications to the core and S2, S4, and S7 units to enhance target potency, pharmacokinetic properties, and safety profiles. Dr. Fesik emphasized that this modification step often is the most time consuming. The group increased oral bioavailability through S2 modification. Additionally, structure-based design of the bicyclic heteroaryl P7 units enhanced potency and accessibility. With the modified compound, *in vivo* tumor growth inhibition was achieved in a dose-dependent manner. The group has identified two candidate compounds, VU0914813 and VU0935191. VU0914813 has been tested in mice, rats, and dogs. VU0935191 has been tested in mice, and a study using dogs is scheduled for early July 2022.

Dr. Fesik concluded by providing a summary of WDR4-MLL program progress, which includes filing of eight patents, synthesis of more than 2,800 new compounds, solution of 85 molecular structures, assay development, determination of mechanism of action, pharmacokinetic testing, and testing in animal efficacy models. He emphasized that this work has provided new knowledge in an area of biology that could not have been explored in a pharmaceutical setting.

In the discussion, the following points were made:

- The NExT program is developing a dashboard to synthesize various types of data resulting from this effort. These data will be made available to extramural investigators.

- Many investigators remain unaware of the NExT program. Current efforts to increase awareness include symposia and blast emails, and planned future efforts include publication of a review article. An additional strategy could involve engaging Cancer Center Directors. Dr. Doroshow invited the Committee members to contact him with additional suggestions for outreach.

- Members of the Special Emphasis Panel are directed to identify projects that are unlikely to be supported by the pharmaceutical industry. Many of the Panel members themselves are from the pharmaceutical or biotechnology industries.

- The VUSM group had planned to pursue oral bioavailability in efficacy testing initially, but they explored intraperitoneal dosing for initial identification of compounds.

IV. DIVERSITY AND DETERMINANTS OF THE IMMUNE RESPONSE TO SARS-COV-2 IN IMMUNOCOMPROMISED POPULATIONS—DR. JANE C. FIGUEIREDO

Dr. Jane C. Figueiredo, Professor, Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, presented on behalf of the NCI Serological Sciences Network (SeroNet) Coronavirus Risk Associations and Longitudinal Evaluation (CORALE) study group. She first reminded the FNLAC members of SeroNet, which is composed of 8 Centers of Excellence, 4 Capacity Building Centers, and 13 Research Projects. SeroNet supports a broad range of serological sciences research to advance the understanding of all aspects of the immune response to SARS-CoV-2. Topics include assay development and deployment, immune response to infection and vaccination, serosurveillance studies, at-risk populations, and barriers to communication. Several working groups have been established in the areas of serology assays, samples, and materials; cell and molecular assays, samples, and materials; data submission, access, and integration; and epidemiology and population studies.

Dr. Figueiredo and her colleagues at Cedars-Sinai Medical Center are interested in studying immunocompromised populations (e.g., patients with cancer, recipients of solid organ or stem cell transplants, individuals with severe primary immunodeficiency, people with advanced or untreated HIV, individuals receiving treatment with immunosuppressive or immunomodulatory agents). These groups are at increased risk for prolonged SARS-CoV-2 infection and shedding, severe COVID-19 outcomes, viral evolution during infection and treatment, transmission to household contacts, and impaired vaccine response. Dr. Figueiredo emphasized that these populations remain vulnerable as the pandemic evolves, and an opportunity exists to expand knowledge on underlying biology. Systematic analyses have shown that cancer patients are at greater risk of mortality following SARS-CoV-2 infection, and sex, age, ethnic/racial disparities are present.

This project began in September 2020, prior to the availability of COVID-19 vaccines. The group is interested in understanding infection and reinfection in immunocompromised individuals, as well as individuals with occupational exposures (e.g., health care workers). This work initially was focused on

the effects of chemotherapy, immunotherapies, transplant, and immunosuppression. The group now has pivoted to examine vaccine response, breakthrough infections, severity of COVID-19, post-acute sequelae of SARS-CoV-2 infection (PASC), and emergence of viral variants. They also are interested in cancer-related outcomes and side effects. Dr. Figueiredo emphasized that this work reflects a highly collaborative effort among multiple institutions.

Dr. Figueiredo briefly outlined the cancer cohort; e-surveys and questionnaires are collected at various points during the vaccination dosage process. The cancer cohort comprises 800 adults who have recently been diagnosed with cancer, with an emphasis on the recruitment of patients with B-cell malignancies, patients who have received bone marrow transplants, and patients with solid tumors who are receiving immunotherapies. Recruitment was initiated in November 2020 and has remained ongoing for the duration of the award. The Cedars-Sinai Health System serves a diverse community, and the cohort includes individuals from across the lifespan and across racial/ethnic groups. The study includes patients with hematologic and solid tumors and various types of cancers. Patient-Reported Outcomes Measurement Information System (PROMIS) metrics were used to collect information on the mental health of participants.

Dr. Figueiredo explained that because cancer patients were excluded from phase 3 vaccine trials, cancer patients might experience greater vaccine hesitancy. Data on vaccine perspectives indicated that the cohort's concerns were related to adverse reactions, rushed vaccine development, and insufficient knowledge. Women were more hesitant than men and tended to experience more numerous adverse reactions. Reactions also differed by types of cancer and treatment received. Peak and sustained antibody responses differed by cancer, vaccine, and treatment. Additionally, vaccine effectiveness was lower in patients with cancer. Dr. Figueiredo stated that the majority of cancer patients elected to become vaccinated and boosted. Breakthrough infections increased after the emergence of the SARS-CoV-2 Omicron variant, even among individuals who had received additional vaccine doses.

Ongoing and new projects include studies of PASC, as well as use of a high-definition single-cell assay for rare event detection in the liquid biopsy. This assay is being applied to identify patients at greater risk of PASC. Last, the Cedars-Sinai group is focusing on sequencing and detecting antigen-specific T cells. They found that the T-cell response is similar to the antibody response. Differences were noted by vaccine type, prior COVID-19 infection, and treatment. Various assays are in development to better understand diversity and determinants of the immune-inflammatory response to SARS-CoV-2. Dr. Figueiredo also noted that this work can serve as a valuable resource for future research, and the group is interested in sharing data with other investigators. Presently, data are being harmonized to facilitate analysis. Metrics on immunocompromised individuals are being collected to foster collaboration across SeroNet.

In the discussion, the following points were made:

- About half of the CORALE cohort are from minority populations; these numbers do not yet fully match the diversity of the Los Angeles community. Additionally, the group plans to address ethnic-specific diversity of the immune response in future analyses.

V. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) NEW INITIATIVE IDEAS—DR. SEAN E. HANLON

Dr. Sean E. Hanlon, Acting Deputy Director, Center for Strategic Scientific Initiatives, NCI, presented on plans for future FNLCR-coordinated projects, with a focus on community workshops that are being organized to explore potential projects. He stated that the FNLCR is envisioned as functioning in support of the mission of NCI with three fundamental tasks, to (1) serve as a nucleus for large-scale

projects, (2) serve as a hub for technology development, and (3) sustain the extramural and intramural components of the NCI. Dr. Hanlon explained that his presentation would focus on the first two elements of that vision.

The NCI is soliciting community input on potential FNLCR-coordinated research projects and technology resources. In late 2020, the research community was invited to respond to an RFI with potential ideas, and the responses to this RFI were shared by Dr. Dinah Singer, Deputy Director for Scientific Strategy and Development, NCI, during the 23 February 2021 FNLAC meeting. A series of small workshops were organized for 2022 to gather input from the cancer research community on the most important needs and promising opportunities in cancer research that may benefit from an FNLCR-coordinated initiative. Dr. Hanlon explained that the workshops targeted broad thinkers who can consider areas beyond their own research interests. He reminded the attendees that all FNLAC members were invited to participate in the workshops.

Workshop participants were informed of the important characteristics of FNLCR projects: challenges that are emerging or currently intractable; research distinct from what is supported by other NCI programs; opportunities that are poised to make progress in 5 years; challenges that cannot be addressed by a single laboratory or small group; research that requires centralized coordination; research that requires a centralized resource or capability; and technologies that, if made more robust or widely available, would have a significant impact on cancer research. Ten workshops were held in March and May 2022. Of these workshops, eight were general sessions and two were focused on the areas of artificial intelligence/computation and imaging. More than 110 individuals were invited to participate, and 58 participants attended the workshops. The ideas generated in the workshops are being organized and categorized with the ideas received previously through the RFIs.

Ideas for research project proposals were related to drug development, the non-coding genome, low-frequency drivers, variants of unknown significance, combination therapies, complex biological effects of radiation, environmental determinants of cancer, characterizing and targeting the tumor microenvironment, ancestry-driven differences in tumor immunology, cellular neighborhoods, protein–protein interactions, protein complexes, and the role of glycobiology. Ideas for drug development included initiatives related to Myc, PI3K, p53, challenging targets (e.g., fusion proteins, transcription factors, telomerase), immune targeting of KRAS, bacterial cancer therapies, the blood–brain barrier, and E3 ligase targets.

Ideas related to technology and resources included spatial-omics, experimental models (e.g., preclinical animal models, cancer organoids, humanized mouse models), microbiome resources (e.g., resident microbiome, standardized mouse models of the microbiome), placebo production, screening platforms, a fully synthetic open reading frame library, and a CAR T-cell resource facility. Specific ideas related to spatial-omics included access to technologies, reagent validation, platform comparisons, technology refinement, bioprinting and tissue engineering, data analysis pipelines, data storage and management, and spatial-omics satellite cores.

Dr. Hanlon concluded by outlining next steps, which include planning additional targeted workshops (e.g., mRNA vaccines, population science), identifying crosscutting themes that emerged from the workshops and RFI, organizing focused workshops for in-depth discussion of crosscutting themes, and discussing highest priority ideas with the FNLAC and NCI Scientific Program leadership.

In the discussion, the following points were made:

- Dissemination and outreach should be included in future projects. The FNLAC members can play a role in this effort by sharing information about FNLCR resources with their respective institutions.

- The workshops are being coordinated by NCI staff and decisions about prioritization will be made with input from across the NCI. Dr. Hanlon also clarified that the ideas outlined in his presentation have not yet been organized or prioritized; these efforts are underway.

- The NCI Patient-Derived Models Repository (PDMR) contains nearly 300 organoids, and more will be available in the near future. These resources are available for the research community at a lower cost than standard cell lines. Additionally, the repository is being leveraged for the development of a high-throughput organoid screening system.

- Searchable databases for NExT projects have been developed, but dissemination of this resource has been challenging.

VI. ADJOURNMENT—DR. CANDACE S. JOHNSON

Dr. Johnson expressed appreciation to the Committee members and other participants for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lopaczynski. There being no further business, the 10th Virtual Meeting of the FNLAC was adjourned at 1:42 p.m. EDT on Monday, 27 June 2022.

_____	/s/
Date	Candace S. Johnson, Ph.D., Chair
_____	/s/
Date	Wlodek Lopaczynski, M.D., Ph.D., Executive Secretary