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

# 15th Meeting
# Frederick National Laboratory Advisory Committee

**Summary of Meeting**
**October 29, 2018**

**Conference Room TE406, East Wing, Shady Grove Campus**
**National Cancer Institute**
**National Institutes of Health**
**Bethesda, Maryland**

**National Cancer Institute**
**15th Meeting of the Frederick National Laboratory Advisory Committee**
**October 29, 2018**

**Summary Minutes**

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 15th meeting on October 29, 2018, in Conference Room TE406, East Wing, Shady Grove Campus, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, October 29, 2018, from 9:00 a.m. to 3:50 p.m. The FNLAC Chairperson, Dr. Lawrence J. Marnett, Dean of Basic Sciences, 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. Andrea Califano* (absent)
Dr. Lisa M. Coussens (absent)
Dr. Kevin J. Cullen
Dr. Raymond N. DuBois (absent)
Dr. Angela M. Gronenborn
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. David I. Hirsh
Dr. Elizabeth M. Jaffee (absent)
Dr. Sanford D. Markowitz (absent)
Dr. Patrick Nana-Sinkam*
Dr. Piermaria Oddone
Dr. Kenneth J. Pienta (absent)
Dr. Nilsa C. Ramirez-Milan
Dr. Lincoln D. Stein* (absent)
Dr. Cheryl L. Willman (absent)
Dr. Jedd D. Wolchok (absent)

*pending appointment

***Ex Officio* Members**
Dr. Stephen J. Chanock
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Anthony Kerlavage
Dr. Douglas R. Lowy
Dr. Kristen Komschlies McConville
Dr. Tom Misteli (absent)
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 15th meeting of the Frederick National Laboratory Advisory Committee (FNLAC) and welcomed the Committee members, 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 May 8, 2018, FNLAC meeting was approved unanimously.

Dr. Marnett called Committee members' attention to the future meeting dates listed on the agenda, which need to be confirmed.

**Motion.** A motion to confirm the future meeting dates was approved unanimously.

Dr. Marnett also noted that the Department of Extramural Activities (DEA) has developed a FNLAC Orientation Book and will schedule an orientation session for new and ongoing members at the June 27, 2019 meeting.

## II. REPORT FROM THE NCI DIRECTOR—DR. NORMAN E. SHARPLESS

Dr. Norman E. Sharpless, Director, NCI, welcomed FNLAC members and attendees to the 15th meeting of the FNLAC and provided an update on NCI activities and highlighted several recent accomplishments. Dr. Sharpless acknowledged members new to the FNLAC and he introduced Dr. Patrick Nana-Sinkam, Professor of Medicine, Chair, Division of Pulmonary Disease and Critical Care Medicine, Virginiacommon Wealth University, who was present at today's meeting. Other new members not present today will be introduced at a future meeting.

**NCI Budget and Appropriations.** Dr. Sharpless reported that the fiscal year **(**FY) 2019 budget has been approved, marking a return to regular order, and that the NCI is afforded the opportunity to appropriate funds strategically for new and ongoing initiatives. The NCI budget and regular appropriations have increased for 4 consecutive years since FY 2015, and the FY 2019 budget—enacted on October 1, 2018—continues this trend. In addition to the regular appropriations, $300 million (M) was appropriated for the 21st Century Cures Cancer Moonshot℠ funding for FYs 2017 and 2018, and $400 M has been allotted for FY 2019. The NCI budget increases reflect the continued and strong bipartisan congressional support for the NIH and NCI. Dr. Sharpless reminded the FNLAC members that the Cancer Moonshot℠ appropriations for FYs 2017–2019 are the highest of the 7-year funding period. Beginning in FY 2020, the annual allotments will decrease by $200 M. The appropriation structure of the Cancer Moonshot℠ funding is not tied to a specific FY and provides flexibility in managing out-year costs. Dr. Sharpless emphasized that the Cancer Moonshot℠ funding is assisting the NCI in establishing new infrastructures, networks, programs, and collaborations that will extend beyond FY 2023. Dr. Dinah Singer, Acting Deputy Director, NCI and Director, Division of Cancer Biology, and NCI staff who are managing the Cancer Moonshot℠ implementation are actively developing plans to address the future changes. Dr. Sharpless pointed out that given the 21st Century Cures funding structure, FY 2019 will likely be the final year that a robust number of new requests will be funded. The balance of the appropriated funds for FY 2020 and beyond will be spent on out-year costs, supporting the 4- to 5-year cycle of funded research.

**Highlights of the Past Year.** Dr. Sharpless remarked that the 2018 *Annual Report to the Nation on the Status of Cancer*—a collaborative effort between the NCI, Centers for Disease Control and Prevention, and American Cancer Society—shows a decline in the incidence and mortality of cancer from 1999 to

2015. This overall decline in cancer mortality in the United States can be attributed to prevention, screening, tobacco control, and improved therapies. Although this progress is significant, it has not been distributed evenly across cancers, signifying the need for additional research and clinical trials. For example, non-Hodgkin's lymphoma and lung cancer mortality decreased annually during this period, but some cancers (e.g., pancreatic, uterine, and brain) continue to be refractory to progress regarding mortality. Furthermore, the incidence and mortality rates of liver cancer have been increasing. The NCI is tasked with making progress against all forms of cancer and is actively discussing ways to improve the overall burden of cancer, especially those that are refractory to treatment.

Dr. Sharpless reported that because of the support from Congress, the NCI was able to provide the Research Program Grant (RPG) Pool, which supports investigator-initiated research (e.g., R01s, P01s, R21s), its largest increase since 2003. Despite this new increase in the RPG Pool, the paylines remain flat, partly due to the increasing ratio of applications received to grants awarded, and funding the Noncompeting Continuation (Type 5) awards at 100 percent. The NCI was successful in increasing the number of Early Stage Investigators R01s by 25 percent in FY 2018, which aligns with the objectives of the 21st Century Cures Act. The FY 2019-enacted appropriation provides a $179 million (M) increase to the NCI above the FY 2018 enacted budget, which includes $100 M in Cancer Moonshot$^{SM}$ funding.

Dr. Sharpless elaborated on the advancements in cancer immunotherapy. There has been continued progress in cellular immunotherapies and checkpoint inhibitor-based therapies, and new studies demonstrating the efficacy of these approaches are ongoing. Dr. Steven A. Rosenberg and Center for Cancer Research (CCR) colleagues were the first to report successful examples of using immunotherapy to treat solid tumors. Dr. Rosenberg recently published data on a clinical trial that showed that immune recognition of somatic mutations led to complete durable regression in metastatic breast cancer in a patient unresponsive to other treatments. This innovative, personalized cancer therapy has been effective in a reasonable number of patients and the next steps will be to advance this highly research-based therapy to the broader cancer research community. Dr. Sharpless was happy to report that Dr. Rosenberg and two other NCI-supported researchers—Dr. James P. Allison, MD Anderson Cancer Center, and Dr. Carl H. June, Abramson Cancer Center—are co-recipients of the 2018 Albany Medical Center Prize in Medicine and Biomedical Research (Albany Prize). Dr. Allison also was awarded the 2018 Nobel Prize in Physiology for his milestone achievements in immunotherapy.

Dr. Sharpless informed FNLAC members that findings from the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), a large-scale de-escalation study that correlates good outcome with less therapy, had been reported. The study showed that more than 60 percent of women who had hormone receptor–positive breast cancer, who received hormonal therapy (e.g., Tamoxifen), and had an intermediate or low genetic risk score did not benefit from chemotherapy. Patients were therefore spared the cytotoxic effects (e.g., hair loss) of chemotherapy. TAILORx is a breakthrough for breast cancer that benefits patients, and health care savings are expected to be significant. The recent U.S. Food and Drug Administration (FDA) approval of moxetumomab for hairy-cell leukemia is one example of intramural research advancing into clinical practice. Dr. Ira Pastan, a CCR investigator, and colleagues originally discovered moxetumomab, which they began testing in clinical trials in 2001. A Division of Cancer Epidemiology and Genetics (DCEG)-led large retrospective trial that links low-dose radiation to leukemia suggests that medical imaging in children should be minimized to the extent possible.

**Notable NCI Research.** Dr. Sharpless reported that the Intramural Research Program has been productive in its basic science studies. Dr. Tim F. Greton, CCR, completed a study that showed that the gut microbiome can control antitumor immune function. Dr. Louis M. Staudt, CCR, completed a study that focuses on revising the molecular classification of the most common types of lymphoma, a culmination of his 20 years of non-Hodgkin's lymphoma research. Dr. Andre Nussenzweig and CCR colleagues identified a potential source of genomic instability. In addition to basic research, the NCI–National Institute on Aging study Aspirin in Reducing Events in the Elderly (commonly known as ASPREE), which is being conducted

in Australia and the United States, revealed an increased risk in mortality in healthy adults age 70 years and older who were receiving daily doses of aspirin for no prior indication. These findings align with recently published data and prior NCI studies. Regarding the precision oncology clinical trials, the NCI began disseminating initial findings from the NCI-Molecular Analysis for Therapy Choice (MATCH) trial, which tested several new therapies. The NCI-MATCH trial enrolled 6,000 patients at 1,100 sites across the United States and is one example of a successful, well-designed clinical trial that rapidly met its accrual goals. Another precision oncology trial, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (formerly known as ALCHEMIST) study, which tests agents in an adjuvant setting, also has been successful in accruing patients.

The NCI issued Cancer Moonshot[SM] funding opportunity announcements to support the recommendations of each of the 10 National Cancer Advisory Board Blue Ribbon Panel recommendations. In FY 2018, new initiatives have been supported, including fusion oncoproteins and pediatric cancer and the data ecosystem. Lastly, the NCI provided support in the decision-making process for two major announcements for cancer patients. The Centers for Medicare & Medicaid (CMS) Services national coverage determination (NCD) on next-generation sequencing (NGS) to manage the care of Medicare beneficiaries with advanced cancer was finalized. The FDA approved the Foundation One companion diagnostics assay (CDx™), which coincided with the CMS NCD for NGS.

**Challenges and Opportunities Ahead.** Dr. Sharpless informed the FNLAC members that the NCI released its *Annual Plan and Budget Proposal for Fiscal Year 2020*, which is patient focused, communicates the goals and priorities of the NCI, and details the NCI's four key focus areas—basic science, workforce development, big data, and clinical trials—where there are opportunities for progress and to accelerate cancer research. Dr. Sharpless noted NCI's ongoing recruitment for Directors for the Center for Global Health and Center for Biomedical Informatics and Information Technology and Associate Director for the FNLCR. The NCI will soon be recruiting a Cancer Therapy Evaluation Program Director to replace Dr. Jeffrey S. Abrams, who is retiring in December 2018.

**In discussion, the following points were made:**

- Dr. Sharpless actively communicated to the public, including the external research community and other stakeholders, about the ongoing initiatives and accomplishments in cancer research. Site visits to NCI-Designated Cancer Centers, blog posts, Twitter posts, and speeches at meetings are being used to update researchers on the NCI's efforts. Even then, the rationale for cancer research and therapeutic prioritizations are challenging to convey.

## III. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR): CURRENT WORK AND FUTURE DIRECTIONS—DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos) discussed FNLCR's current and future work. The FNLCR is a national resource that conducts research to prevent, diagnose, and treat AIDS, infectious diseases, and emerging public health challenges and acts jointly with the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID) and other NIH Institutes and Centers (ICs). As a bidirectional hub and spoke model of serving public health, the FNLCR also serves in areas not readily addressed elsewhere. To continue to do its work, in FY 2018, the FNLCR was awarded a total of 81 task orders from NIH ICs and NCI Divisions, Offices, and Centers. Dr. Dmitrovsky announced two new staff changes in the Leidos/FNLCR Leadership: Ms. Beth Baseler is now Director of the Clinical Monitoring Research Program, and Dr. Eric Stahlberg is now Director of Biomedical Informatics and Data Science.

FNLAC members were informed that the FNLCR leadership established an initiative to define core values to shape FNLCR's identity as a national laboratory. Dr. David Lindsay, Director, Vaccine Clinical

Materials Research Program, and Christopher March, Director, Human Resources, are leading this effort and have worked to engage employees across the FNLCR. To support employees and their families and caregivers who are dealing with cancer, Leidos Biomedical Research/FNLCR will implement the Johns Hopkins University Work Stride: Managing Cancer at Work benefits program. Work Stride provides Web-based tools, is supported by a nurse navigator, and maintains employee confidentiality. Service is provided at no cost to the enrolled employees.

Dr. Dmitrovsky's outreach activities have included a listening-and-learning tour of the FNLCR; an executive leadership retreat; establishing collaboration with local, national, and international centers; and speaking engagements at cancer centers, academic institutions, and professional societies. The NCI-Hood College cancer meeting was reestablished and the FNLCR Director's Distinguished Lecture Series was launched. The inaugural FNLCR-Hood College Cancer Science Symposium titled "Imaging in Cancer Biology" is scheduled to be held June 21–23, 2019. To increase reach and service to the community, the FNLCR has finalized memoranda of understanding (MOU) with Georgetown University, Hood College, Howard University, and Mount Saint Mary's University. Partnerships have been established with the NCI Intramural Continuing Umbrella of Research Experiences (iCURE) program, the University of Maryland Center for Research and Education in Science and Technology (known as CREST), and the National Cancer Institute, Mexico.

Dr. Dmitrovsky elaborated on FNLCR's main types of research—discovery science, advanced core facility support, collaborative science, team science, and advanced technologies—and highlighted some of the current projects and research findings. The Carrington laboratory at FNLCR reported that the immune response genotypes determine survival of HIV-infected cells. Efforts are now being focused on investigating similar relationships in immune-based therapies. The Lifson laboratory at FNLCR discovered that antiretroviral therapy begun early after infection can clear the initial HIV infection in nonhuman primates. One example of an advanced core facility, the Laboratory Animal Sciences Program (LASP) is an essential core capability of the FNLCR that operates the NCI animal facilities to support investigators on the Bethesda and Frederick campuses. The LASP also houses many state-of-the-art core facilities that support the NCI mouse repository, Gnotobiotics Facility (GF), and Genome Modification Core (GMC). Shipment requests and available strains have increased by 15 to 20 percent since FY 2016. To date, the GMC has served 44 CCR investigators and assisted in the completion of 77 projects. In addition, the GF doubled in size and usage over the past year of operation.

The FNLCR assists the NIH/NIAID Vaccine Research Center in vaccine production for Zika and Ebola viruses; supports the Accelerating Therapeutics for Opportunities in Medicine (ATOM) Consortium, a public-private partnership; and supports the new effort, NCI chimeric antigen receptor (CAR)-T cell clinical trials. The RAS Initiative, an example of a team science effort that is centralized at the FNLCR, continues to make progress in directly targeting KRAS and understanding the biology of KRAS in the context of the plasma membrane. Therapeutic drug screening assays to identify lead compounds are ongoing as are collaborations with the Department of Energy (DOE) to bridge experimental gaps using high-performance computing in the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) initiative. The FNLCR will have a payload launching to the International Space Station in December 2018 to form enhanced RAS crystals for X-ray diffraction studies. The National Cryo Electron Microscopy (Cryo-EM) Facility (NCEF), is an example of providing advanced technology support to the extramural community. The NCEF currently houses two Titan™ Krios microscopes and a third could be added if the demand increases. Since the 2017 launch, more than 144 projects from 26 institutions across the United States have been completed and the data are being published. Dr. Dmitrovsky announced that Dr. Sriram Subramaniam, former NCEF Program Director, has left the NCI to pursue a position at the University of British Columbia and will continue as an NCEF consultant.

**In the discussion, the following points were made:**

- Although it is challenging for the FNLAC to evaluate the direction and commitment of resources just based on highlights of the FNLCR five research areas, the pending bridge contract precludes providing granular details on fund allocations. Additional details on funding allocations and research priorities will be considered at a future meeting.

- The goal of the FNLCR is to share information in the public domain. The type of agreement with biotechnology partners, such as the Contractor Cooperative Research and Development Agreements (cCRADA) or Technical Services Agreement, defines the level of confidentiality and sets the limitations on data sharing.

## IV. A FUTURE PERSPECTIVE ON THE FNLCR—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Deputy Director, NCI, updated the FNLAC on the contracting processes and current and future activities at FNLCR. Dr. Lowy acknowledged NCI staff members who have played a key role in framing a future perspective of the FNLCR, which he endorses. This perspective being presented also sets the stage for FNLAC members to provide their individual perspective. The process entails going from the current Leidos contract to a bridge award, to resumption of the re-competition for a new contract, and award of a new contract. The U.S. Department of Health and Human Services Office of General Council determined that a peer review, rather than a technical evaluation of the Leidos proposal, would be needed prior to making a bridge award. Compliance with the peer review required an extension of the current contract to ensure no lapse in service. In the bridge contract award process, the NCI DEA completed a peer review of the proposed bridge contract. The target date for issuing the Leidos bridge award is planned for the second quarter of FY 2019. Once awarded, the bridge contract will have a 1-year base ordering period and four 1-year optional ordering periods; it must end by FY 2024 or earlier. A resumption of the initial full and open re-competition activities would include conducting market research, releasing a draft proposal request, and conducting a pre-proposal conference. This initial phase could begin after input from the FNLAC. Since the time for the resumption of activities for making a new award is estimated to be 3 years, the NCI actively addressed what could be implemented in the short-term.

Dr. Lowy reported that the NCI has been engaged in a number of activities to strengthen the NCI-FNLCR interactions. An internal review committee recommended establishing an FNLCR Associate Director, and a search being chaired by Dr. Toby Hecht, Deputy Director, Division of Cancer Treatment and Diagnosis (DCTD) is in progress. Dr. Lowy has been appointed Acting Associate Director and meets regularly with the FNLCR leadership and the Office of Scientific Operations (OSO) and Management and Operations Support Branch (MOSB). The new Associate Director also will meet with laboratories and branches. The NCI Divisions and Offices are working more closely with the OSO and MOSB, and the NCI and NIAID also have strengthened their interactions. In addition, the OSO has established groups to further enhance communications and efficiency between the NCI and FNLCR.

Regarding components supported by FNLCR, approximately 15 percent of NCI funds to the FNLCR support intramural research, including core facilities. Roughly 85 percent of NCI funds to the FNLCR support extramural research. The Board of Scientific Advisors and, in some cases, the FNLAC provide oversight. Each activity is coordinated by an extramural Division or by the NCI Office of the Director. Examples include the Biopharmaceutical Development Program (BDP) and the Patient-Derived Models Repository (PDMR), which will be discussed later in the meeting. Special projects consisting of a FNLCR component and an extramural component are large-scale efforts that address important biological or technological problems. Projects are approved through a vetting and/or competitive process, which could involve FNLAC and also have finite life spans to accommodate new initiatives. Examples include the RAS Initiative and the NCEF.

Discussions are ongoing in the NCI about the feasibility of FNLCR's serving as a hub for technology development at Frederick and in the extramural community. At FNLCR, efforts would focus on technology innovation, emerging technologies, specialized technologies, and convening conferences. In the extramural community, efforts would focus on establishing cutting-edge technology development core facilities at academic institutions and leveraging existing FNLCR cores and capabilities. Cores would remain in place until the technology is made available, not to exceed 5 years. Oversight is envisioned as a combined responsibility of the FNLAC and other specific advisory committees.

Dr. Lowy conveyed that the NCI is seeking input on FNLCR's new contract and contractor status. The possibilities include continuing a single contract covering both administrative and scientific activities; separate administrative and scientific contracts; a corporate entity with one or more academic partners; an academic entity; or a corporate entity in which academic partners are recruited for specific projects.

**In the discussion, the following points were made:**

- In the FNLCR/Leidos research development contract peer review process, external reviewers met via teleconferences and provided comments. Scores were not assigned, and the contract received a rating of either acceptable or unacceptable. The DEA shared this information with the contracting officer and the NCI Executive Officer, which they later communicated to Leidos.

- Although models of a single academic institution's functioning as a research and administrative contractor without a corporate sponsor are limited, market research shows significant interest in FFRDC contracts among large companies and multiple organizations.

- The bridge award, which is a year-to-year contracting mechanism, does not provide assurance of continuity in activities and can be distracting to the normal mode of operation for the FNLCR. A single contract supporting both administrative and scientific activities is the current model. The question is whether to continue with current model or separate contracts for administrative and scientific activities.

- The unique features of the FNLCR—flexibility, capability for rapid response, and increased efficiency—combined with prior successes has set the pace for conducting signature and high-risk projects in the future. Identifying and prioritizing resources would be critical. Also, support for technology development as a national resource should be a priority. It is essential that allocation of resources be centralized and aligned with scientific priorities, especially if the NCI sets those priorities. The role of academic partners should be clearly defined.

- Engaging more than one or two academic institutions could be challenging in assigning roles and responsibilities. The FNLCR should be operated inclusive of the whole community. Unlike other FFRDCs, FNLCR does not focus on any one specific topic/theme, which might present a challenge in defining the role of an academic institution as partner or administrator. Identifying the gaps in research being addressed by FNLCR would be critical.

## V. NCI MOUSE REPOSITORY: UTILIZATION AND FUTURE DIRECTIONS—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, DCTD, presented an update on the NCI mouse repository (formerly known as the PDMR), an NCI Precision Oncology Initiative℠ resource that is being housed at FNLCR. The PDMR (Repository) was established in response to recommendations from the 2012 NCI-hosted Target Validation Meeting to develop a national repository of clinically annotated cancer models to enhance drug discovery. The goal is

to develop patient-derived xenograft (PDX), patient-derived tumor cell cultures (PDCs), cancer associated fibroblasts (CAFs), and patient-derived organoid (PDOrg) models to support *in vitro* drug screening and *in vivo* molecular characterization of patient tumors. The NCI-designated Cancer Centers and NCI Community Oncology Research Program (NCORP) Community and Minority/Underserved Community sites are supporting this effort.

Dr. Doroshow detailed the PDMR inventory. The Repository currently has 193 PDX models available for distribution that span across several solid tumor histologies. This initial set consists of models that have been limited for research studies, including head and neck squamous-cell carcinomas, melanomas, and adult soft-tissue sarcomas. As the collections increase, PDX models for pediatric and rare cancers also will be developed and tumors from underrepresented minority groups will be characterized. Details and associated data on the models, including genomic sequencing, histology, and therapeutic responses are publicly available and can be downloaded from the NCI/PDMR website at no cost.

Since inception, the Repository has received 2,372 tissue specimens, and the average specimen take-rate (i.e., growth in culture) is 33 percent, which varies across disease states. Colorectal cancer, the predominant tumor submitted from supporting sites, has a 60 to 70 percent take-rate, whereas hormone-responsive breast cancers, prostate cancers, and renal cancers take-rates range from 7 to 18 percent. Of the 193 PDX models, 77 represent rare tumor PDX models of diseases that are not well studied, and for which no effective treatments exist. The Repository is leveraging the resources of the Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors (formerly known as DART) clinical trial being led by the Southwest Oncology Group. Fifty-two conditionally reprogrammed PDCs and 108 CAFs are available for distribution as of October 22, 2018, and approximately 50 PDOrgs are expected to be made available in January 2019. The goal, whenever possible, is to develop all four models from one individual tissue specimen. To date, more than 500 total models have been distributed to more than 50 different U.S. laboratories and six biotechnology companies.

Dr. Doroshow described the efforts being led by the DCTD's Biological Testing Branch and Clinical Laboratory Improvement Amendments-certified Molecular Characterization Laboratory (MoCha) to address the stability of the Repository PDX models. After three to five subcultures (i.e., cell passages), the genetic stability between the initial patient specimen and the PDX material was assessed for copy number alteration (CNA), variant allele frequency, microsatellite instability, and tumor mutation burden using whole exome sequencing. No significant alterations were observed in the majority of the models. Efforts next focused on establishing best practices for assessing the effect of passages on CNA. The optimal approach is to compare whole-exome sequencing of PDX to patient material when the germline is available; use germline sequencing to correct for human stromal cellularity in patient material; and remove the mouse reads from PDX sequencing. The objective is to distribute only low-passage models that reflect the original specimen and have accurate clinical annotations. In the PDMR models, a large number of models have stable CNA and variant allele frequency across passages from passage zero (P0) to P3. The levels of microsatellite instability and high tumor mutational burden are consistent across PDX models. Also, histomorphology was maintained across passages for 85 percent of the models tested.

Dr. Doroshow explained that higher incidences of spontaneous metastases have been observed in PDX models. To assess metastasis in the PDMR models and in the PDX-bearing NOD scid gamma (NSG) host mice, 49 models were evaluated prospectively using various imaging techniques, including magnetic resonance imaging, and were supported by the FNLCR Small Animal Imaging Program and the NCI Cancer Imaging Program. Of the 49 models assessed, three had spontaneous metastases with the primary tumor in place (i.e., pre-excision) and 12 had spontaneous metastases post-excision. In further evaluation of the bladder cancer PDX model, pre and post-excision spontaneous metastases were observed, and also were responsive to temozolomide treatment. Dr. Doroshow noted that these imaging data are being included in a landing page in The Cancer Imaging Archive (TCIA) hosted by the University of Arkansas for Medical Sciences and will be linked to the NCI/PDMR website.

The PDMR team supported by the NCI-FNLCR Pharmacodynamic Assay Development and Implementation Section next investigated the presence of circulating tumor cells (CTCs) in known metastatic human bladder cancer models they previously characterized. Blood samples from 32 PDX-bearing NSG mice with palpable tumors were collected, enriched, and assessed using multiparameter analytical cytometry. Results showed that CTCs increase with increasing tumor size, were significant in number, and are present at low tumor burden. Within the CTCs, a complex cellular phenotype exists consisting of either epithelial or mesenchymal cells or epithelial-mesenchymal transition phase cells. Similar results were observed in metastatic colorectal, lung, head and neck, and ovarian cancer PDX models. The next steps will be to expand assessment to other metastatic PDX models, assess tumorgenicity and heterogenicity of CTCs from PDX-bearing mice, and evaluate biomarkers in live animals.

Dr. Doroshow reported that the PDMR team recently completed a PDX preclinical study with standard-of-care anticancer agents. Drug response across seven study treatment arms was assessed in a preliminary screen of three animals of the squamous-cell carcinoma PDX model that were dosed with standard agents. Leveraging the efforts of the Pediatric Preclinical Testing Program, the relative median to event-free survival (RM-EFS), a measure of tumor quadrupling time, was determined for all agents. RM-EFS were correlated to survival and compared to the known clinical response rate. These data are still being evaluated. Future plans for the PDMR will be to continue the goal of housing 1,000 patient-derived models for each of the four types, support the NCI-funded PDX Development and Trial Centers Research Network (PDXNet) prescreening efforts, establish a screening program for rare tumor PDX models, and continue to build the matched models from the same patient inventory.

In closing, Dr. Doroshow acknowledged the many contributors to the PDMR initiative who have supported the project at various stages of development. He conveyed to the FNLAC the NCI's interest in establishing a Working Group on Cancer Models and Therapeutics Development to oversee the process and provide guidance on the future direction of the PDMR.

**In the discussion, the following points were made:**

- The PDMR team is partnering with the Pediatric Oncology Branch, CCR, to collect pediatric tumor specimens, but hematopoietic malignancies are limited. Obtaining samples for patients 12 years old and younger also will be challenging.

- The quality of publications resulting from this effort, in addition to the quality of the science conducted and facilitated, will be measures of long-term impact. The main goal is to facilitate effective clinical trials.

- Although ideal knowledge-sharing might not occur in the case of every publication that results from these models, investigators in the PDXNet are committed to keeping the Repository team informed of studies using PDMR models that advance to the clinical stage.

- The NCI anticipates that animal models eventually would be humanized. Until that occurs, the PDMR will produce a variety of models, use them in a variety of studies, and will leverage other NCI initiatives, including the Comparative Oncology Program. Advice from the extramural community on how to humanize animal models could be one component of the proposed Working Group's charge.

- In the JDACS4C Pilot 1, a prioritized list of models and drugs have been received and the PDX models currently are being evaluated for tumor take-rate, which will take months to complete.

- The FNLCR Working Group on Cancer Models should include both FNLAC and extramural experts and should meet at least twice per year. The Working Group also could incorporate many of the important individual components of the PDMR and remain flexible to adapt to any advances that occur.

**Motion.** A motion to concur with establishing an FNLCR *ad hoc* Working Group on Cancer Models and Therapeutics Development was approved unanimously.

## VI. BIOPHARMACEUTICAL DEVELOPMENT PROGRAM (BDP) AND CELL THERAPY FACILITY DEVELOPMENT—DR. ANTHONY R. WELCH

Dr. Anthony R. Welch, Project Director, Biological Resources Branch, Developmental Therapeutics Program, DCTD, provided an overview of cell therapy production at the BDP, FNLCR. The BDP is a biopharmaceutical manufacturing capability at the FNLCR with current Good Manufacturing Practices (cGMP) that includes process development, quality control, manufacturing, and regulatory affairs. It is primarily a bench-to- beside resource for the community to try to remove the risk from projects that look promising but are not being conducted in the pharmaceutical industry. Over the last 25 years, roughly 50 different products that have been processed through the BDP have advanced to clinical trials, including Lumoxiti (i.e., moxetumomab) and unituxen. The BDP standard operating procedures (SOPs) for cGMP manufacturing from quality systems are available online at no cost to the user. Resources also are made available to the research community, and the BDP serves as a cGMP training site for the NIH community and the FDA. Autologous cell therapy was recently approved by the FDA as the first gene-modified cell therapy approved in the United States. The preclinical work that led to this approval resulted from the efforts of NCI-funded investigators.

Dr. Welch explained that in CAR-T cell therapy, the functionality of a T cell with the antigen recognition properties is retained and CAR is a customized receptor. The CAR-T cell autologous transplant basically involves removing and engineering the patient's T cells externally and then returning those cells to the patient. The traditional open manufacturing production process is not trivial and involves leukaphereses, enriching, depleting or isolating T cells; expansion; quality control steps; and reinfusion into the patient. Although this type of work is being performed at cancer centers, blood banks, and transfusion centers, the applications are limited because of issues with quality and reproducibility across platforms and/or centers. The NCI had discussions on whether this capability could be built in the BDP to serve the cell therapy community. Dr. Welch remarked that in theory, the BDP could serve as a centralized manufacturing facility to produce CAR-T cells and provide products to the various institutions. The BDP also could manufacture retroviruses. Not having autologous cell therapy expertise in the BDP, the first steps were to develop a reproducible manufacturing and testing platform using state-of-the-art technology. The DCTD decided on the use of a closed system—CliniMACS Prodigy®—to build CAR-T cell capacity in the BDP and is planning to collaborate with the FDA, the National Institute of Standards and Technology (NIST), and other stakeholders to standardize product testing.

Dr. Welch discussed the timeline and decisions for cell therapy resources at the BDP, progress to date, and future planning. The Prodigy system, which is cGMP compliant, was installed at the BDP in August 2018, technology transfer of the CD19/CD22 CAR-T cell from the NIH Clinical Center, Department of Transfusion Medicine to the BDP was opened in October 2018; and assay development for product release is ongoing. The decision was made to manufacture CD33 CAR-T cells for the multisite acute myeloid leukemia clinical trial being sponsored by the National Marrow Donor Program. Validations, quality control, optimizations, and reproducibility testing are ongoing. The CD33 CAR-T cell process development efforts are scheduled to begin in November 2018. Future planning includes hosting a DCTD-sponsored Workshop on Cell Therapy for Solid Tumors to be held December 10–11, 2018, converting current research laboratories into a cGMP cell therapy production suite, gaining experience in centralized manufacturing logistics, and releasing test SOPs to improve reproducibility.

**In the discussion, the following points were made:**

- In the current setup, the BDP has the capacity to treat four patients per month. The FDA has guidelines on supporting clinical trials, which begins with one patient per month and a slow increase in dose escalation.

- The potential for *quid pro quo* services and capturing genomics data could be considered, but the logistics would need to be further investigated.

- NIST is heavily invested in standardizing cell therapies across platforms and is leading this effort. The opportunity exists for the BDP at FNLCR to develop assays to support cell therapy standardizations.

## VII. UPDATE: ACCELERATING THERAPEUTICS FOR OPPORTUNITIES IN MEDICINE (ATOM)—DR. ERIC STAHLBERG

Dr. Stahlberg, Director, Biomedical Informatics and Data Science, FNLCR, reminded FNLAC members that ATOM is an open public-private Consortium that launched under a Cooperative Research and Development Agreement (CRADA) and establishes a national precompetitive resource to accelerate cancer drug development. The aim is to address the preclinical issues of drug discovery, including the long and costly discovery phase and the high failure rate. The mission of ATOM is to accelerate the development of effective therapies for patients. The vision is to transform drug discovery from a slow, sequential, and high failure rate process into a model that merges diverse biological data, high-performance computing, and emerging biotech capabilities into an integrated precompetitive platform. The goal is to reduce the preclinical time to develop a drug from 5.5 years to one year.

The ATOM integrated platform is an emerging resource and has challenges to overcome to transform from the traditional model to a rapid, integrated, and patient-centric model. Computational predictions at the protein, cell, tumor, tissue, and organ level will require multiple streams of data. Rapid empirical testing will be necessary to validate and optimize computational predictions. In silico and complex models will need to be developed, and regulatory requirements will need to be addressed. In the ATOM workflow, patient-specific data and samples are incorporated into the ATOM platform consisting of an integrated traditional empirical drug discovery approach (e.g., assay, synthesis, safety and efficacy studies) and an in silico framework of design, simulation, and active learning. The outputs are predictive models of drug behavior in humans that benefit the patient and also inform the science. Dr. Stahlberg reiterated that the platform software is considered open, with generated data and reference models also publicly available. ATOM provides the opportunity to target a precise medication for a known target for an individual patient, which engages the precision medicine approach.

The ATOM organizational structure consists of a governing board, scientific advisory board, head (leadership), joint research committee, operations, and workforce. The ATOM Governing Board comprises organizational leads from each Consortium member organization—GlaxoSmithKline (GSK), Lawrence Livermore National Laboratory (LLNL), the FNLCR, and University of California at San Francisco (UCSF)— who meet on a regular basis and recently reviewed and approved phase 2 of the research plan. The ATOM Joint Research Committee (JRC) is composed of scientific leads from each Consortium member organization and is charged with overseeing the CRADA activities. The ATOM Scientific Advisory Board is being assembled, and two members have been recruited. The ATOM integrated workforce is centrally located near UCSF's Mission Bay Campus.

Regarding the ATOM Consortium development, Dr. Stahlberg explained that efforts have been focused on growing the ATOM ecosystem, which embodies six sectors: technology, experimental areas,

academic partners, governmental laboratories, and pharmaceutical companies. ATOM provides organizations the opportunity to partner as members or collaborators. The ATOM outreach team has engaged more than 149 organizations across multiple sectors, including technology hardware and software. The Consortium has convened more than 300 external meetings with potential partners; conducted more than 150 internal ATOM discussions; and executed 31 Confidentiality Disclosure Agreements (CDAs). The interest in ATOM is growing and FNLCR staff is assisting in such logistics as reviewing intellectual property agreements and CDAs. Four potential partner members are in discussion and one pharmaceutical company pilot project is at the statement of work phase. One additional collaborator has joined, and three others are in contract negotiations.

The ATOM community engagement has been robust. The outreach team collectively attended and made presentations at 34 conferences/meetings and has been effective in growing the ATOM partnership pipeline and broader community. The ATOM Internet website analytics showed 8,000 visits and 1,300 page views that resulted in 51 new contacts, including two pharmaceutical companies. The ATOM website also can be accessed from the FNLCR website. Dr. Stahlberg remarked that ATOM engagement is an integrated effort involving an ATOM communications team whose members span the Consortium. He summarized the technical progress to date. Data and modeling efforts are underway, including receipt of public and private data sets and establishing the automated framework for developing and tracking models. Multiple baseline models for pharmacokinetic data and safety data have been developed and ATOM DeepChem models have been benchmarked. Novel model development also is in progress as well as and proof-of-concept active learning processes.

Regarding future directions, in 2019, efforts will be focused on incorporating quantitative systems, building the toxicology pipeline, and performing pilot projects. In 2020, the goals are to validate the active learning platform and initiate the proof-of-concept project. Ultimately, in 2021, the proof-of-concept project would have been delivered with the expectation that a target to a candidate can be identified in the subsequent 12 months.

**In the discussion, the following points were made:**

- The ATOM Consortium currently is working to identify candidate molecules and potential targets to evaluate and build confidence in the ATOM integrated platform models. Models developed using public, not proprietary, data sets will be made available to the public after approval from the ATOM Governing Board. Data to validate and, where possible, regenerate released models will also be publicly available.

- The unique features of ATOM should be clearly defined and conveyed to the research community.

## VIII. RAS INITIATIVE PROGRESS AND WORKING GROUP UPDATE—DRS. DWIGHT V. NISSLEY AND DAVID A. TUVESON

Dr. Dwight V. Nissley, Director, Cancer Research Technology Program, FNLCR, provided an update on the RAS Initiative (Initiative) on behalf of Dr. Frank McCormick, Scientific Advisor, RAS Initiative, who sends his regrets in not being able to attend the meeting. He was joined by Dr. David A. Tuveson, Roy J. Zuckerberg Professor, Director of the Cancer Center, Cold Spring Harbor Laboratory, and RAS Working Group Chair, who provided input on the Working Group's perspective. FNLAC members were reminded that the major goals of the Initiative are to discover small molecules that directly bind RAS or disrupt RAS/effector interactions using RAS-based assays and biophysical and *in silico* screens and to investigate the molecular description of the RAS/RAF signaling complexes in the plasma membrane using biochemical, biophysical, and structural biology techniques. Efforts also are focused on partnering through cCRADAs with RAS Initiative collaborators who have potential RAS inhibitors that can be validated. The

RAS Initiative serves as a hub for several strategic, industrial, and academic collaborations and provides resources generated in-house to the RAS research community. Such materials as plasmids, cell lines, and reagents have been widely distributed across the United States and internationally. Dr. Nissley called attention to the NCI-funded RAS Synthetic Lethality Network, which supports six teams who also are investigating synthetic lesions targetable for KRAS-driven cancers.

Dr. Nissley reported that the RAS Structural Biology Group solved crystal structures for active forms (i.e., bound to GTP/5'-guanylyl imidodiphosphate [GMPPNP] and magnesium [Mg]) of wild-type KRAS and six mutant forms of KRAS (G12C, G12D, G12V, G13D, Q61L, and Q61R) and also discovered hydrophobic pockets that can be targeted for drug discovery. The RAS Initiative is collaborating with the London laboratory at the Weizmann Institute for Science to perform *in silico* screening of potential KRAS G12C binding compounds. Six compounds that showed weak binding to the KRAS G12C mutant using surface plasmon resonance (SPR) are being confirmed using nuclear magnetic resonance (NMR). *In silico* screens of other KRAS mutants are planned.

Dr. Nissley provided an update on the status of the RAS Initiative cCRADAs and highlighted three that are currently active. The FNLCR is collaborating with Sanofi-Aventis (Sanofi) to identify small molecules targeting KRAS activity in cells with significant selectivity for HRAS over NRAS. The project team has consisted of up to eight FNLCR staff and 24 Sanofi staff at various times over the last two years. High-throughput screening against a 920,000 compound library has been completed, and promising lead compounds are being further evaluated. All efforts are in-kind. The Beatson Institute for Cancer Research (Beatson) cCRADA is validating and further characterizing Beatson's high-affinity KRAS binding compound. Beatson funds supported five full-time staff in the initial phase of the project. The FNLCR in-house discovery efforts led by Dr. Ana Maciag, FNLCR, transitioned to a cCRADA with TheRas, Inc. to test potential compounds targeting C185 and develop FNLCR/UCSF-owned RAS inhibitors. Six full-time staff members funded by the RAS Initiative are supporting this project, which aims to block RAS processing using a modified tethering approach. The UCSF tethering screen library was used to identify lead compounds, which the Maciag group confirmed using mass spectroscopy and modified using medicinal chemistry techniques. Using a tool compound (i.e., chemical probe), the group has determined that covalent binders to C185 (1) are KRAS4b specific, (2) prevent prenylation at C185, (3) prevent membrane localization, and (4) inhibit proliferation in KRAS4b mouse embryo fibroblasts. In addition, the LLNL molecular dynamics (MD) simulations suggest that the hypervariable region (HVR) is interacting with the G domain in the helix 3/helix 4 region. The potency and selectivity of the tool compound were increased using computer-aided drug discovery/Med Chem. Analogues to the tool compound are being designed and synthesized. In another series of experiments targeting H95, the group showed that H95C binders also are KRAS specific and bind to KRAS and not RhoA, based on SPR analyses. MD simulations suggest a pocket between helix 3/switch 2, which was confirmed by NMR. Design and synthesis of analogues also are in progress.

Dr. Nissley described efforts in the JDACS4C Pilot 2 to address experimental gaps in biological approaches to increase understanding of the molecular mechanisms of RAS/RAF activation, which occurs at the plasma membrane. The RAS Initiative is using different experimental approaches, which will inform the DOE MD simulations and computational models. The RAS Imaging Group investigated RAS dynamics of the plasma membrane using Halo-tagged RAS in live cells and showed that KRAS4b exists in three states in the plasma membrane—fast, slow, and intermediate—which they are further confirming using biophysical characterizations of synthetic lipid membranes and advanced microscopy methods to evaluate diffusion. The RAS Biochemistry and Biophysics Group is using paramagnetic relaxation enhancement–NMR and neutron reflectivity analysis to study KRAS on nanodiscs. The DOE has designed a framework to couple atomistic (micro scale) and coarse-grain (macro scale) MD simulations, which DOE further scaled to simulations of longer time and length. The first-of-a-kind simulations that model RAS dynamics on the DOE Sierra super computer are in progress.

Dr. Tuveson remarked that the RAS Initiative, a national program, is evolving to become a thought leader in RAS biology in terms of molecular structure. Scientists have solved an unprecedented number of high-quality RAS crystal structures in the RAS Initiative, which has enabled in silico models to be generated with ease. New approaches to developing small molecules in real-time, such as the modified tethering method or docking, are possible. In the RAS Initiative, several reagents and resources are available to the research community and innovative approaches to targeting RAS have been identified, all of which are strengths.

**In discussion, the following points were made:**

- The strategy for partnering with pharmaceutical and biotechnology companies is to facilitate advancing promising drug candidates to the clinic through financial investments and/or leveraging their internal resources. The NCI Experimental Therapeutics Program may also be leveraged at later stages in the drug-development pipeline.

## IX. ONGOING AND NEW BUSINESS—DR. LAWRENCE J. MARNETT

Dr. Marnett requested input from the Committee regarding any remaining issues. Members lauded the efforts of the NCI DEA in producing the FNLAC Orientation Book. Dr. Marnett reminded members that the next FNLAC meeting will be virtual and is scheduled for February 20, 2019, and that the next in-person meeting is scheduled for June 27, 2019. Members expressed interest in meeting at NCI-Frederick for the October 24, 2019, in-person meeting. Further details will be forthcoming.

## XI. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other invitees for attending. There being no further business, the 15th meeting of the FNLAC was adjourned at 3:50 p.m. on Monday, October 29, 2018.