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

14th Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
May 8, 2018

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

National Cancer Institute
14th Meeting of the Frederick National Laboratory Advisory Committee
May 8, 2018

Summary Minutes

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 14th meeting on May 8, 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, May 8, 2018, from 9:00 a.m. to 4:30 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. Gail A. Bishop (absent)
Dr. Lisa M. Coussens
Dr. Kevin J. Cullen
Dr. Levi A. Garraway (absent)
Dr. Angela M. Gronenborn
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. David I. Hirsh (absent)
Dr. Elizabeth M. Jaffee (absent)
Dr. Sanford D. Markowitz (absent)
Dr. Piermaria Oddone
Dr. Kenneth J. Pienta (absent)
Dr. Nilsa C. Ramirez-Milan (absent)
Dr. Cheryl L. Willman (absent)
Dr. Jedd D. Wolchok (absent)

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

Executive Secretary
Dr. Caron A. Lyman

TABLE OF CONTENTS

I. OPENING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Lawrence J. Marnett, Chair, called to order the 14th 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 October 30, 2017 FNLAC meeting was approved unanimously.

Dr. Marnett called Committee members' attention to future meeting dates listed on the agenda. He noted the following changes: the FNLAC July 20, 2018 meeting has been cancelled; the FNLAC 2019 meetings have been rescheduled for February, June, and October 2019, to better distribute the meeting dates.

Motion. A motion to approve the change in 2019 meeting dates was approved unanimously.

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

Dr. Norman E. Sharpless, Director, NCI, welcomed FNLAC members and attendees to the 14th meeting of the FNLAC and provided an update on NCI appropriations, intergovernmental affairs, and new and ongoing activities.

NCI Appropriations Outlook. Dr. Sharpless reported that the fiscal year (FY) 2018 budget was enacted mid-March 2018. House and Senate Appropriations Subcommittees on Labor, Health and Human Services, Education, and Related Agencies (LHHS) are considering the President's FY 2019 budget proposal and conducting hearings. Dr. Sharpless testified at the House LHHS appropriations budget hearing on April 11, 2018. The Senate LHHS briefing is scheduled for mid-May 2018. The National Institutes of Health (NIH)/NCI regular appropriations have increased for four consecutive years, i.e., from FYs 2014 - 2018. In addition to the regular appropriations, the NCI has received $300 million (M) in allocations for the Cancer Moonshot℠ for FYs 2017 and 2018 via the 21st Century Cures Act.

Congressional Outreach. Dr. Sharpless reported on ongoing congressional outreach and described a visit with the House Appropriations Subcommittee Chair, Representative Thomas J. Cole (R) of Oklahoma. On May 1, 2018, Rhode Island Senator Jack Reed (D) visited the NIH Clinical Center and participated in a roundtable discussion on childhood cancer research with members of the NCI's Pediatric Oncology Branch (POB), Center for Cancer Research (CCR), including Dr. Brigette Widemann, Chief, POB. The Senator then met with Dr. Widemann, one of her patients who is enrolled in the NCI Selumetinib/Neurofibromatosis Type 1 (NF1) clinical trial, and the patient's parents. Dr. Sharpless remarked that selumetinib could be the first U.S. Food and Drug Administration (FDA) approved drug for NF1. On May 2, 2018, Dr. Sharpless attended the University of Oklahoma Stephenson Cancer Center dedication ceremony, which recognized the Center as the Nation's 70th NCI-designated Cancer Center. He acknowledged members of Congress who attended this event and remarked that the continued congressional bipartisan support for the NIH and NCI remains strong.

Research Program Grant (RPG) Pool. Dr. Sharpless updated members on the RPG pool funding that supports investigator-initiated research (e.g., R01s, P01s, R21s). Despite a substantial increase (the largest increase since FY 2003) in the RPG pool funding in FY 2017, the funding success rates have remained relatively unchanged. Dr. Sharpless informed members that the increase in RPG pool funding has not translated into an increase in the funding success rate because the: 1) number of R01 applications has

steadily increased from FY 2003 to FY 2017 and is expected to increase by 11 percent in FY 2018 and, 2) NCI decided to fund the noncompeting continuation (Type 5) awards at 100 percent beginning in FY 2015. Dr. Sharpless remarked on the enthusiasm and interest in cancer research and the new scientific ideas being submitted to the NCI that this trend reflects. The NCI has the challenge of making compelling arguments to Congress for regular increased and sustained appropriations and, at the same time, explaining the unchanging funding success rates. The NCI estimates adding $100 M to the RPG pool to support FY 2018 awards, but other options are likely to be considered for the future.

NCI Intergovernmental Affairs. Dr. Sharpless reported that the NCI is actively engaged in discussions with the FDA and Centers for Medicare and Medicaid Services (CMS) on data sharing. Both CMS and FDA have large data sets that they expressed interest in sharing publicly and with the extramural community. The FDA Oncology Center of Excellence (which has been funded for FY 2018), joint training programs, and establishment of a cell culture manufacturing facility at the Frederick National Laboratory for Cancer Research (FNLCR) site were among the topics discussed. Dr. Sharpless will participate in upcoming FDA Grand Rounds.

Dr. Sharpless noted two ongoing interagency NCI collaborations, the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network, a tri-agency coalition with the Department of Defense (DoD) and the U.S. Department of Veterans Affairs (VA), and the NCI-Department of Energy (DOE) Joint Design of Advanced Computing Solutions for Cancer (JDACS4C). The APOLLO Network aims to perform genomic and proteomic analysis in the DoD and VA populations (e.g., veterans, active duty military personnel, beneficiaries) via APOLLO's state-of-the art sequencing, data integration, and adaptive learning health care systems, leveraging the existing VA and DoD electronic health record (EHR) system. The DOD and APOLLO leader, Col. Craig D. Shriver, Director, John P. Murtha Cancer Center, Walter Reed National Military Medical Center, hosted the first APOLLO retreat. Dr. Sharpless and APOLLO contributor, Dr. Henry Rodriguez, Director, Office of Cancer Clinical Proteomics Research, NCI, attended. The JDACS4C includes a pilot project that involves modeling the RAS protein in the plasma membrane and a pilot project focusing on using natural language processing to EHR mining in the Surveillance, Epidemiology, and End Results (SEER) data, primarily pathology reports.

Dr. Sharpless reminded FNLAC members that the President's Cancer Panel (PCP), which is independent of but managed by the NCI, has under the leadership of the current Chair, Dr. Barbara K. Rimer, issued reports on accelerating human papillomaviruses (HPV) vaccine uptake and improving cancer outcomes with connected health. The 2018 report, entitled *Promoting Value, Affordability, and Innovation in Cancer Drug Treatment*, was released parallel to the 2017 National Academies of Sciences, Engineering, and Medicine's *Making Medicines Affordable: A National Imperative* report and the 2018 Council of Economic Advisers' *Reforming Biopharmaceutical Pricing at Home and Abroad* report. The issue of value-based pricing is a common theme reflected in each of the reports and is being discussed in the NCI. Dr. Sharpless, Dr. Rimer, and Dr. Abby B. Sandler, Executive Secretary, PCP, attended a White House Domestic Policy Council (DPC) briefing hosted by DPC Director Mr. Andrew Bremberg to discuss the 2018 PCP report.

NCI Scientific Activities. Members were informed that the rosters for the National Cancer Advisory Board (NCAB) *ad hoc* Working Groups on Global Health, Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR), and Informatics have been completed. The Global Health Working Group met for its first in-person meeting on April 30, 2018. The SBIR/STTR Working Group is scheduled to meet on May 29, 2018, and a meeting of the Informatics Working Group is being planned. Dr. Sharpless remarked on the Cancer Moonshot^{SM} process extending from the NCAB Blue Ribbon Panel (BRP) 10 recommendations in FY 2016 to issuing the first funding opportunity announcements (FOAs) in FY 2017. He acknowledged Dr. Dinah Singer, Acting Deputy Director, NCI, for her leadership in this effort. New FOAs covering each of the 10 recommendations are being issued for FY 2018 and beyond. The annual allotments of Cancer Moonshot^{SM} funding are not evenly distributed across

the 7-year funding period and pose a challenge to implementation, which the NCI is actively addressing. He highlighted two Cancer Moonshot[SM] recommendations—a National Cancer Data Ecosystem for Sharing and Analysis and a Retrospective Analysis of Biospecimens from Patients Treated with Standard of Care—that would be of particular interest to the FNLAC.

Other initiatives funded through the Cancer Moonshot[SM] include the Partnership for Accelerating Cancer Therapies (PACT), a 5-year public-private research partnership between the NCI and 12 pharmaceutical companies interested in promoting immuno-oncology. PACT partner investments ($60 M total) and NCI matching funds have established and will maintain a laboratory network of four Cancer Immune Monitoring and Analysis Centers (CIMACs) and one Cancer Immunologic Data Commons (CIDC). The goal of PACT is to develop a precompetitive biomarker standardization and validation for immuno-oncology discovery and NCI-sponsored clinical trials initially. The NCI anticipates that over time, the PACT also will focus on industry-sponsored trials. The CIMAC-CIDC (or Network) Laboratory Coordinating Committee had its first meeting parallel to the 2018 American Association for Cancer Research (AACR) to discuss its plans and other logistics; the PACT Executive Committee also has met to address the Network's concerns. Dr. Sharpless called attention to two related Moonshot[SM] initiatives, the Immuno-Oncology Translational Network (IOTN) and the Pediatric Immunotherapy Discovery and Development Network (PIDDN), which are expected to be awarded soon.

To address the growing need for clinical grade T lymphocyte (T cell) manufacturing at the NIH, Dr. Sharpless informed the FNLAC that the NCI is developing a new cell therapy facility at the FNLCR that leverages existing Current Good Manufacturing Practice (cGMP) capabilities of the FNLCR. In the long term, the NCI hopes that the new facility will provide services to the extramural community, standardize procedures across academic institutions and GMP facilities, assist in conducting multi-institutional immunotherapy trials, and support vector production.

Dr. Sharpless announced NCI's future direction and four key interrelated focus areas—workforce development, basic science, big data, and clinical trials—in which the NCI could recommit its efforts. Workforce development supports clinical trials; basic science underpins all that the NCI does; and the use of big data speeds work across the research enterprise. He noted that the key focus areas evolved from a 6-month listening-and-learning tour of the NCI that involved conversations with stakeholders, including patients and patient advocacy groups, physicians, scientists, clinical trialists, federal officials, and NCI staff. He elaborated on the NCI's current initiatives focused on workforce development and big data. To address workforce development and training as it aligns with the 21st Century Cures Act, the NCI has set aside funding to increase the paylines for Early Stage Investigators (ESIs) R01s to 15 to 16 percent, which will result in a 25 percent increase in new ESI R01s. In addition, the NCI officially implemented the MERIT R37 award mechanism for new competing awards for FY 2018. The same conditions regarding budget, reporting requirements, and length of time as the R01 apply. The exception is that an ESI MERIT R37 awardee may, toward the end of the initial award period, apply for a 2-year extension. In 10 years, the NCI will assess whether the additional 2 years of funding benefited the MERIT grantees over the traditional R01 grantees. NCI's big data efforts support linkage of existing data sets, maintain a data ecosystem, establish common data standards, and incentivize sharing and aggregation.

In discussion, the following points were made:

- Dr. Sharpless explained that the MERIT R37 is treated no different than a traditional R01. The good news is that ESIs have the advantage of applying for an additional 2 years of funding by submitting less paperwork similar to a noncompeting renewal of an R01, rather than the more rigorous process for a new R01. By using this structure, which is similar to the awards system of some foundations (e.g., Damon Runyan Cancer Research Foundation), the NCI hopes to have an effect on the biomedical workforce pipeline to broadly increase the representation of underrepresented minorities (groups).

- To update the FNLAC members on the re-competition of the operations and technical support for the FNLCR (a Federally Funded Research and Development Center [FFRDC]), Dr. Lowy pointed out that a short-term, sole source contract (i.e., Bridge Award) with Leidos Biomedical Research, Inc. (Leidos) is still in process at the NIH Office of General Council. He reminded members that the FFRDC contract re-competition was postponed based on FNLAC's recommendations for adequate time to assess the goals for the new FNLCR and the impact of the BRP Cancer Moonshot℠ recommendations. The NCI anticipates that the FNLAC will be able to address these concerns after the re-competition process resumes.

- The proposed new FNLCR cell manufacturing facility will be regulated by the FDA, aims to be GMP certified, and will leverage existing Clinical Cancer Center initiatives. The NCI is partnering with such federal agencies as the FDA for advice (e.g., preconsultation) on building a state-of the-art facility to address the needs of the NCI and NIH, as well as the extramural community, in the long term. The NCI is interested in incorporating innovative technology and low-cost, high-throughput, closed-loop systems, such as the CliniMACS Prodigy® platform.

- The FDA and CMS have data-sharing proposals that are of interest to the NCI. The CMS Medicare and Medicaid claims data would be best suited for the SEER Program. The FDA and pharmaceutical sponsors are responsibly sharing clinical trial toxicology data with the European Medicines Agency and have expressed interest in sharing these data with the cancer research community. The NCI is holding discussions with the FDA and pharmaceutical industry representatives on how best to share these data. Self-organizing initiatives, such as Project Data Sphere, are providing platforms for researchers to share clinical trial data that authorized users can access.

III. FREDERICK NATIONAL LABORATORY: CURRENT OPERATIONS AND FUTURE PLANS—DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, discussed FNLCR's current operations and future plans. The FNLCR (formerly called the Frederick Cancer Research and Development Center) began in 1972 with 300 employees; met the criteria to be a FFRDC in 1975; was officially designated a FFRDC and national laboratory in 2012 and renamed the FNLCR; and has since grown in size to 2,200 employees today. As a national resource that conducts research to prevent, diagnose, and treat AIDS, cancer, infectious diseases, and emerging public health challenges, the FNLCR—acting jointly with other NIH Institutes and Centers (ICs), including the NCI and the National Institute of Allergy and Infectious Diseases (NIAID)— serves the public interest. Dr. Dmitrovsky highlighted recent achievements and support in the extramural community. The RAS Initiative has been successful in elucidating new insights on the RAS biology to enable drug discovery for RAS-driven cancers. In 2017, the Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium—in partnership with the founding institutions: Lawrence Livermore National Laboratory (LLNL), GlaxoSmithKline plc (GSK), and the University of California, San Francisco (UCSF)—was established to accelerate preclinical target and drug validation, and the National Cryo-Electron Microscopy (EM) Facility (NCEF) was also launched. In addition, the FNLCR supported NIAID's vaccine development efforts for the Zika and Ebola viruses and HPV. Major achievements in the extramural community that FNLCR helped to support include discovery and commercialization, via Contractor Cooperative Research and Development Agreements (cCRADA), of immunotoxins targeting CD22 for remissions in hairy cell leukemia; development of monoclonal antibodies targeting GD2 that increased survival in high-risk neuroblastoma pediatric patients; facilitated the development of the HIV-1 kit to secure safety of the Nation's blood supply; and development of vaccines for emerging infectious diseases. Also, the FNLCR supports NCI-sponsored clinical trials—including the NCI-Molecular Analysis for Therapy Choice (NCI MATCH), NCI Experimental Therapeutics (NExT), and

Oncolytic Recombinant Poliovirus (PVS-RIPO) for glioblastoma trials—as well as such large-scale initiatives as the Cancer Moonshot[SM].

Dr. Dmitrovsky elaborated on FNLCR's main areas of research and support—discovery and translational science, advanced core facilities, team science, collaborative science, and advanced technologies—that reflect the depth, breadth, and scope of work. He also detailed some of the current projects and research findings. Regarding discovery and translational science, investigators have shown and recently published in Science that immune response genotypes determine whether innate immune cells kill or let HIV-infected cells survive. This trailblazing discovery of Dr. Mary Carrington's laboratory has broad implications for HIV biology and cancer. A project devoted to eradicating aneuploid cancers by invoking anaphase catastrophe that the Dmitrovsky laboratory first developed at the University of Texas MD Anderson Cancer Center will be further investigated at the FNLCR for application to RAS-driven cancers. Advanced core facilities are sophisticated platforms supporting interdisciplinary intra- and extramural collaborations, two of which are the Laboratory Animal Sciences Program (LASP) and the Nanotechnology Characterization Laboratory (NCL). The LASP, an essential core capability of the FNLCR led by Dr. Steve Jones, 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 gnotobiotics, small-animal imaging, and genome modification. The NCL has and continues to foster partnerships in the scientific community and with pharmaceutical and biotechnology (biotech) companies on several aspects of nanomaterial development, methods, and basic research. Work of the NCL informs regulatory agencies, has resulted in new publications in peer-reviewed journals, and has led to trans-national collaborations.

Implementing the RAS Initiative is one prime example of a team science effort, which is centralized at the FNLCR and engages a RAS research community that consists of intramural laboratories, NCI-supported extramural laboratories, the pharmaceutical industry, and contract research organizations. The RAS Initiative led by Dr. Frank McCormick (UCSF) along with Dr. Dwight Nissley (FNLCR) focuses on directly targeting KRAS and understanding the biology of KRAS in the context of the plasma membrane. Progress to date includes development of a novel class of compounds that specifically target KRAS and multiple screening assays to identify lead compounds. Also, Dr. Dwight Nissley, Director, Cancer Research Technology Program, FNLCR, and LLNL scientists are co-leading the work with the DOE to bridge experimental gaps using high-performance computing in the JDACS4C team science effort described earlier. Last, partnering with academia, pharmaceutical and biotech companies, and NIH ICs to develop promising drug candidates for clinical use also is in progress. The FNLCR hosted RAS Initiative Symposiums in 2017 and 2018, and the attendance is robust and growing. One other team science effort that is gaining momentum in the extramural community is the ATOM consortium. Dr. Eric Stahlberg, Director, High-Performance Computing, FNLCR, provided an update on ATOM later in the meeting.

Dr. Dmitrovsky described FNLCR's collaborative science efforts acting jointly with the NCI, NIAID, other NIH ICs, and national laboratories. Global support of vaccine trials is provided that spans from Phase I to Phase III and requires a firm understanding of cultures and infrastructures in different countries. In this capacity, the FNLCR is a hub for activities not being supported elsewhere. He highlighted the NCI–Bill & Melinda Gates Foundation (Gates Foundation)-sponsored HPV Vaccine Trial being conducted in Costa Rica to determine whether a single dose, relative to a second or third dose, of FDA-approved prophylactic HPV vaccines would provide durable protection against cervical cancer. Dr. Dmitrovsky noted that this trial culminates much of the work of NCI investigators, Dr. Douglas R. Lowy and Dr. John T. Schiller. An NCI–Gates Foundation-sponsored HPV Serology Laboratory has been established at the FNLCR; this collaborative science effort is one way that the FNLCR is serving the public interest. Other efforts include assisting the NIH/NIAID Vaccine Research Center (VRC) in cGMP pilot-scale production of vaccines and the management of diverse projects related to vaccine development and manufacturing. Support of the VRC has led to many advances, such as the Zika virus DNA vaccine discovery, which now is being tested in clinical trials worldwide. In addition, the FNLCR provides operational and dedicated technical support for all phases of the Division of Cancer Treatment and Diagnosis' NExT Program and is the scientific project

manager for the NExT's Chemical Biology Consortium (CBC). The first CBC was established in 2008; it was successfully recompeted in 2015 and now consists of seven Dedicated Centers and 15 Specialty Centers. Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research and Director, Division of Cancer Treatment and Diagnosis (DCTD), NCI, provided an update on the NExT Program later in the meeting. In support of the Cancer Moonshot[SM], the FNLCR is assisting in the establishment of a national cancer biobank of longitudinally acquired biospecimens of newly diagnosed cancer patients. The NCEF is an example of providing advanced technology support to the extramural community. The NCEF uses focused ion beam scanning microscopy technology, which enables imaging of whole cells in three dimensions. Dr. Sriram Subramaniam, Senior Investigator, Laboratory of Cell Biology (LCB), CCR, NCI , provided an update on the NCEF later in the meeting.

Dr. Dmitrovsky described FNLCR's other activities. A listening-and-learning tour of the FNLCR, which involves conversations with staff in small group or one-on-one meetings, has been launched. A leadership retreat was held in 2018 to define core values. To convey its commitment to training the next generation, the FNLCR has finalized memoranda of understanding (MOU) with Georgetown University, Hood College, and the National Cancer Institute, Mexico. Plans are to establish collaborations with Mount Saint Mary University, the University of Maryland School of Engineering, and Howard University. The Hood College Oncogene Science Conference was reestablished. The first meeting, entitled "Imaging Science Meets Cancer Biology," is planned for 2019.

In closing, Dr. Dmitrovsky emphasized that the FNLCR is a national resource focused primarily on biomedical research; works with the NCI and other NIH ICs to resolve problems that are distinct from those addressed by academia, industry, and other national laboratories; and is proud to be in service to the public's health.

In the discussion, the following points were made:

- The FNLCR has a separate, complementary mission from the NCI, and many of its activities serve the extramural community, but its full value may be underappreciated. Increased awareness of its resources and ways to engage in the laboratory's activities (e.g., core facility) should be publicized to the extramural community.

- The FNLCR is a remarkable capability that was granted to the NCI by rights of the Cancer Act of 1973 to establish other cancer centers to support the national cancer effort. The FNLCR has an understated scale and scope; engages in work not done elsewhere; and takes on new projects of preset timelines that are usually short. Overall, the FNLCR takes on disparate research topics/projects and, therefore, does not have one overarching theme.

- The capabilities of the NCI Mouse Repository, operated by the FNLCR, can be leveraged to identify a set of animal models that could be made available to the research community specifically for testing potential cancer therapies.

- Although, the FNLCR, as an FFRDC, does not compete with the commercial sector or perform work that other governmental agencies are capable of doing, the decision-making process that the NCI's Office of Scientific Operations uses for selecting large-scale projects, such as the RAS Initiative or the NCEF, could be conveyed to the FNLAC. The percentage of research projects conceptualized internally at the FNLCR compared to projects supported, including NCI's large-scale projects, also could be conveyed.

- The educational and training MOUs are a good segue into the existing visiting scholars and postdoctoral programs at the FNLCR.

IV. NATIONAL CRYO-EM FACILITY (NCEF) UPDATE—DR. SRIRAM SUBRAMANIAM

Dr. Subramaniam provided an update on the NCI-NCEF and also discussed the cryo-EM technology, its growth, and NCI's cryo-EM research. He reflected on the initial presentations to the FNLAC during a 3-year period from 2013 to 2015 and the rapid growth of the cryo-EM technology, which drove the NIH and NCI's decision to pursue an NCEF at FNLCR. The proposal was approved by the FNLAC in 2015, and the facility launched on May 15, 2017 (www.cancer.gov/research/resources/cryoem). He reported on the Subramaniam laboratory's, the LCB's, and other NCI Intramural Research Program investigators' cryo-EM work, which have been able to be transitioned to supporting the NCEF.

The use of single particle cryo-EM to elucidate biological structures has increased significantly during the past 10 years. Dr. Subramaniam noted key factors that have led to this growth and popularity. First, data accessed from EMDataBank, a unified repository for all cryo-EM structural data published worldwide, revealed that single-particle cryo-EM for the first time was able to elucidate structures at atomic resolutions, a feature that previously was possible only with X-ray crystallography (XRC) or nuclear magnetic resonance (NMR) spectroscopy. Second, the 2017 Nobel Prize in Chemistry was awarded to three cryo-EM pioneers whose methods date to the 1970s and 1980s and have stood the test of time. Third, the focus has shifted from the traditional cryo-EM targets that were large and symmetrical and allowed easy-to-align images (e.g., viruses, ribosomes, proteasomes) to a growing list of diverse targets, including smaller protein complexes (e.g., glutamate dehydrogenase). Relevant to the NCI's mission is the ability to use the information from cryo-EM to guide mechanistic studies and drug design.

He highlighted four examples of challenging problems, which are direct applications to cancer research that the Subramaniam laboratory, in collaborations with others, resolved using cryo-EM. In collaboration with the National Center for Advancing Translational Science (NCATS) to investigate isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2), which are mutated in many cancers, the group was able to visualize drug localization in mutant IDH1 using two small-molecule inhibitors, NCATS ML-309 and GSK 321A. In collaboration with the NExT CBC, the group was able to advance structural studies of the cancer target p97 and, for the first time, visualize the detailed structure of the inhibitor binding site of p97. In collaboration with the Patel laboratory at Memorial Sloan Kettering Cancer Center, the laboratory solved asymmetrical structures of a clustered regularly interspaced short palindromic repeats (CRISPR)-Cas surveillance complex. In collaboration with the Kelly and Bai laboratories, CCR, the laboratory was able to elucidate the structural mechanisms of centromeric nucleosome recognition by the kinetochore protein centromere protein N (CENP-N).

Dr. Subramaniam remarked on the NCEF's progress and future plans. He noted the key personnel who are responsible for daily operations of the NCEF, which include FNLCR leadership Drs. Dmitrovsky and Nissley; Dr. Ulrich Baxa, Senior Microscopist and Technical Lead; Dr. Thomas Edwards, Junior Microscopist; Mr. Matt Hutchison, Information Technology and Microscopy Support Specialist; and Ms. Helen Wang, Scientific Project Manager. To date, the NCEF has supported more than 90 extramural user projects from 20 different academic institutions. Because of the competency and professionalism of the NCEF staff, feedback from the cryo-EM community has been positive. Dr. Subramaniam emphasized that the NCEF is fulfilling its mission to bridge the gap between the need for cryo-EM and access to expensive instrumentation. The time from data collection to results to publication is approximately 8 months. Results of data collected from the first NCEF users are beginning to be published. The newly designed microscope facility at the Advanced Technology Research Facility (ATRF) on the FNLCR campus is on schedule to be completed in June 2018 and will have space to house four microscopes.

Regarding technology development in general, Dr. Subramaniam commented on his laboratory's efforts to develop a 12-year structural program to bridge the gap beginning with studies in tissues in the 2000s to those in 2015–2016 that involve small proteins. What seemed impossible then is now possible, which he described as the essential message of the NCEF. Dr. Subramaniam called attention to the three

user communities likely to benefit from the NCEF that were identified early on with input from the FNLAC and the cancer research community. Group 1, researchers already experienced in cryo-EM technology; Group 2, structural biologists in adjacent disciplines, such as XRC or NMR spectroscopy; and Group 3, researchers who have interesting cancer-related targets but are new to cryo-EM technology. In its first year of operation, the NCEF has focused on Group 1 users, who are primarily early stage investigators and comprise the largest group contributing to the rapid growth of the field. The next phase, which already has begun, will expand the customer base to include Group 2 users. The NCI welcomes input from the FNLAC on the potential for increasing the NCEF's expansion of scope and activities and their effects.

In the discussion, the following point was made:

- FNLAC members encouraged the FNLCR to explore potential opportunities to partner with the DOE to assertively address developing cryo-EM data capabilities and, in the long term, consider approaches to processing data for the cryo-EM community.

V. OVERVIEW OF THE NCI EXPERIMENTAL THERAPEUTICS (NExT) PROGRAM—DR. JAMES H. DOROSHOW

Dr. Doroshow presented an overview of the NExT Program, the CBC, and drug discovery. Most of NCI's therapeutic drug discovery activities are supported in the NExT, which advances compounds through a development pipeline from early stage discovery to Phase I and II trials. He reminded members that project applications are submitted to NExT in three cycles each year. The scope of the projects can vary from a request for medicinal chemistry resources, to support for a Phase I trial and provision of other services necessary to further advance a drug development program. A Special Emphasis Panel (SEP) composed of experts from academia and industry reviews and evaluates approximately 100 applications each year and selects the top 10 to 15 projects. Evaluation involves a "trust but verify" set of experiments. Roughly one-third of the projects fail the evaluation. Highly ranked projects are reviewed and endorsed by the CBC Steering Committee, which is composed of members representing the 22 centers in the Network. Selected projects enter a planning process, which includes scientific verification and validation and selection of a CBC specialty and comprehensive center. Prioritizations reflect the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and NExT portfolios. The NExT pipeline consists of a diverse set of projects in the discovery, preclinical development, and development phases. The annual NExT portfolio review is scheduled for August 2018, and projects in the current CBC discovery portfolio will be prioritized and ranked based on feasibility and chemistry.

Dr. Doroshow reported on projects that have advanced in the NExT pipeline from discovery to preclinical development to development. The Myeloid Cell Leukemia 1 **(**MCL-1) inhibitor project by Dr. Stephen W. Fesik at Vanderbilt University used fragment-based methods and structure design to develop a subnanomolar concentration compound, which showed significant proof of mechanism (PoM) of action *in vivo*. In January 2018, Vanderbilt University licensed the MCL-1 inhibitor candidate to Boehringer Ingelheim for preclinical studies. The mutant IDH1 project that originated at the University of North Carolina at Chapel Hill entered the pipeline in 2011 as a collaborative effort with NCATS and the NCATS Chemical Genomics Center (NCGC). During a 5-year span, molecules were improved and optimized, which resulted in an agent with high selectivity and demonstrated exemplary pharmacokinetic/pharmacodynamic (PK/PD) profiles compared to the NCGC model. In April 2018, the clinical compound was outlicensed to Fortress Biotech, Inc. Targeting p97 presented a novel opportunity to modulate protein homeostasis in cancer. Dr. Donna Huryn and colleagues at the University of Pittsburgh developed allosteric p97 inhibitors. During a 2-year period, the group successfully optimized a compound with low potency and low therapeutic activity to a compound with biochemical and target-level activity equivalent to the compound developed by the only other competitor in the field, Cleave Biosciences, Inc. (Cleave).

Dr. Doroshow remarked on the unique ability of the NExT CBC to rapidly move agents forward in the pipeline. In December 2017, Cleave joined the CBC p97 team to assist in evaluating its backup allosteric p97 inhibitors after the Cleave first-generation drug failed first-in-human trials as a result of off-target inhibition of prostaglandin E6 (PDE6). A second-generation Cleave p97 allosteric inhibitor (CB 5339) with comparable *in vitro* and *in vivo* potency profiles and a 40-times-reduced effect on PDE6 was selected from a group of four lead compounds. A 2018–2019 timeline for developing the GMP-grade CB 5339 compound in the NExT was generated, and safety and toxicity studies in the canine animal model are currently in progress. After successful toxicity studies are completed, the next steps will be a series of evaluations in a canine spontaneous non-Hodgkin's lymphoma model. A significant factor in a decision to close the program would be a failure to see a reduced effect on PDE6 in the disease model.

Dr. Doroshow highlighted a NExT pipeline project submitted by the Southern Research Institute that is currently in Phase I /II studies investigating an oral formulation of DNA methyltransferase-1 (DNMT1) inhibitor, thiodeoxycytidine (TdCyd). The first-in-human trial was activated in May 2016 in the CCR clinic; 20 solid tumor patients have been enrolled; and toxic effects have been limited. Additional responses to treatment will be reported on at a future meeting. He also noted a potential project the NCI could consider investigating, endoxifen for estrogen receptor-alpha positive malignancies, which would leverage the work of a prior NCI Breast Cancer Specialized Programs of Research Excellence (SPORE) program project.

In the discussion, the following point was made:

- The canine models used in the NExT preclinical studies were initially developed by Dr. Lee J. Helman, Acting Director, CCR, while he was investigator in the POB, CCR. Today the Comparative Oncology Trials Consortium (COTC), a network of 20 academic comparative oncology centers, is centrally managed by the Comparative Oncology Program, CCR. The COTC designs and executes clinical trials in dogs with cancer to assess novel therapies.

VI. ROLE OF MOLECULAR PHARMACODYNAMICS IN BOTH DRUG DISCOVERY AND DEVELOPMENT—DR. RALPH E. PARCHMENT

Dr. Ralph E. Parchment, Managing Director, DCTD Program in Pharmacodynamic Biomarkers (PD Biomarker Program), Leidos, FNLCR, provided an update on the FNLCR's PD efforts in support of the extramural community through the NExT Program. He noted two underlying principles of PD— proof of mechanism (PoM) and proof of concept (PoC)—that provide the framework for assessing new drugs. The mechanistic information often drives the clinical development plan (e.g., drug dosing), and it is important to confirm that the mechanism of action in humans is the same one that was intended by the drug discovery phase. Relating a drug's mechanism of action on its intended target to its efficacy is what constitutes a PoC. The FNLCR PD Biomarker Program focuses on PoM and PoC studies, which are illustrated in the prior studies on MET oncogene tyrosine kinase inhibitors (MET-TKIs). For example, three MET-TKI compounds tested in single PoM studies in mouse xenograft MET-driven tumors revealed that the dose and dosing schedule necessary to achieve and maintain an equal level of molecular target control were different for the three agents. In this study, the target control was a measure of the kinase activity (phosphorylation) of MET (phospho-MET) on tyrosine residue 1235 (Y1235). PoC studies conducted using PD-guided dose scheduling were able to achieve the same degree of tumor control, independent of the structure of the compound. The next step was to develop an antibody specific for phospho-MET Y1235, which is now available to the research community via the NIH-sponsored Developmental Studies Hybridoma Bank located at the University of Iowa.

Dr. Parchment noted that phospho-MET, similar to other phosphorylated proteins involved in rapid molecular responses, was found to be very labile (unstable) during tumor sampling (biopsy collections), handling, and processing during MET PD studies. Efforts were focused on establishing standard operating

procedures (SOPs) to address these issues. This work resulted in validated phospho-MET assays, specimen-handling SOPs, and reagent sources for clinical assessment of MET, which are now available and can be accessed from the NCI website (dctd.cancer.gov/researchresources/researchresources-biomarkers.htm). He reported that the SOPs for preserving phosphoproteins in biospecimens also were used to resolve long-time instability issues with a well-known PD biomarker, phospho-AKT. In fact, reproducible measurements of phospho-AKT in preclinical models are now possible with the newly developed assay used in conjunction with the specimen handling SOP. Furthermore, the capability of measuring key phosphorylation sites of AKT as indicators of kinase activity to assess biological function and variability now exists. Dr. Parchment emphasized thawing the snap-frozen biospecimens in extraction buffer containing protease and phosphatase inhibitors or thawing in neutral buffered formalin as the best options to stabilize phosphoproteins, regardless of the use or analysis being performed.

Dr. Parchment remarked that the SOPs for the preservation of phosphoprotein biomarkers at the point of collection and point of processing have broad applications to nuclear markers, including the ETCTN portfolio of DNA damage-repair modifiers. A newly developed immunofluorescent assay that measures three nuclear biomarkers of DNA damage—γ-H2AX, phospho-Nijmegen breakage syndrome (NBS1), and RAD51—was able to detect the heterogeneity in biomarker baseline levels and provided three independent assessments of DNA damage in colorectal cancer biopsies. This multiplex evaluation of the DNA damage response is being confirmed in a larger set of patient biopsies. In addition, an imaging analysis pipeline is being developed to assess and interpret DNA damage biomarker response relative to a cancer treatment. The γ-H2AX biomarker is responsive to DNA double-strand breaks, both direct (e.g., chemotherapeutic agent-induced) and indirect (e.g., apoptosis-induced). An immunofluorescent assay to distinguish drug-induced DNA double-strand breaks from apoptosis by measuring γ-H2AX in the presence or absence of activated cleaved caspase-3 was developed and later tested in a canine clinical trial studying investigational topoisomerase-1 inhibitors in spontaneous non-Hodgkin's lymphoma. Results showed an apoptotic-specific profile (cells that are double positive for γ-H2AX and cleaved caspase-3) in patients responding to treatment and two clinically quantifiable endpoints: the percentage of apoptotic cells and the maximum number of apoptotic cells. A validated intrinsic apoptosis ELISA assay consisting of 15 apoptosis biomarkers also was developed in collaboration with Dr. Dominic Esposito, Protein Expression Laboratory, FNLCR. The assay has informed drug discovery and the work of the NExT CBC MCL-1 inhibitors Project Team, and has been modified, and is now commercially available.

In closing, Dr. Parchment elaborated on the contributions of the FNLCR PD Biomarker Program to the extramural community, which he organized into two broad categories (1) assay support of the NExT CBC Discovery and ETCTN Development Teams and (2) the initiative to improve core biopsy quality and suitability for PD and other biomarker analyses. He noted the new biomarker targets that the Program will be addressing for the CBC and the ETCTN.

In the discussion, the following point was made:

- The acceptance and utilization of PD biomarker resources (e.g., SOPs), dissemination of information on the NCI website, and the incorporation of biomarker practices, reviews and updates into ETCTN trials, all are tangible measures of FNLCR's PD Biomarker Program impact in the community.

VII. NCI'S EARLY THERAPEUTIC TRIALS NETWORK: HOW WE MOVE NEW AGENTS INTO THE CLINIC—DR. JEFFREY A. MOSCOW

Dr. Jeffery A. Moscow, Acting Branch Chief, Investigational Drug Branch (IDB), Cancer Therapy Evaluation Program (CTEP), DCTD, presented on the interactions of the Experimental Therapeutics Clinical Trials Network (ETCTN) and FNLCR's PD Biomarker Program. The primary endpoints of the Network's early-phase clinical trials (i.e., Phase I and II trials) are clinical endpoints of drug response and

toxicity and also translational endpoints of target engagement and pharmacodynamic effects. Dr. Moscow described how the NExT Program relates to the ETCTN. Pharmaceutical companies apply to NExT for NCI-sponsored development of agents. Pharmaceutical companies ask NCI for help in developing novel agents because NCI has access to agents from other companies; because NCI will invest public funds in potential therapeutic indications that may not be competitive for limited corporate resources but that are in the public interest; because ETCTN creates access to a network of experienced early-phase clinical trialists; and because the ETCTN focusses on correlative science studies—guided by the FNLCR's PD Biomarker Program—that expand knowledge of the agent. The NExT Special Emphasis Panel (SEP) selects agents for NCI-sponsored preclinical and clinical development. Clinical agents for Phase I and II trials are assigned to the IDB, CTEP for development in the ETCTN.

Dr. Moscow detailed that the ETCTN mission is to design and perform early-phase clinical studies of NExT approved agents. When clinical agents come into the program through NExT, NCI negotiates CRADAs with the pharmaceutical applicant for clinical trial development and assumes the regulatory responsibility as the investigational new drug (IND) holder. At the same time IDB physicians work with ETCTN investigators and other extramural experts in project teams to formulate NCI's initial drug development plan. The Investigational Drug Steering Committee is the external advisory group to the IDB regarding ETCTN trials and reviews the initial drug development plan. The ETCTN conducts clinical trials of these agents through the cooperative agreement funding mechanism (i.e., UM1) to ETCTN clinical trial sites. To date, the ETCTN has 41 sites across the United States and Canada, 70 agents currently under CRADA, and 70 active Phase I and Phase II studies and is expected to enroll (accrue) 1,000 patients to clinical trials in 2018. Clinical trial proposals to the ETCTN are reviewed on two levels: the validity of the study concept and design is reviewed by the Protocol Review Committee, and the Biomarker Review Committee (BRC) reviews the evidence for reproducibility of assays that are incorporated in trials. The ETCTN has extensive centralized clinical trial support for the Network, including a central institutional review board (CIRB) dedicated to early therapeutics; identity and access management systems; regulatory support services to support interactions with pharmaceutical company partners and the FDA; clinical data collection and management services; and adverse event reporting systems. Once clinical trials are underway, IDB physician staff monitor the safety of the ETCTN trials.

Dr. Moscow remarked on the high-impact NCI-IND agent clinical trials involving agents that have been approved by the FDA partly because of their development in the CTEP's collaborative early-phase programs. He called attention to an agent developed in the NCI, dinutuximab, which is FDA-approved for pediatric neuroblastoma. The initial trials were conducted in the ETCTN, and a subsequent pivotal trial was performed in the NCI Children's Oncology Group. Validating biomarkers for the ETCTN is an objective of the NCI and early phase trials. The majority of ETCTN trials incorporate biopsies and correlative studies to determine the relationship of tumor biology and target engagement to the clinical response. Numerous factors affect the reliability and reproducibility of the studies, such as biopsy quality and pre-analytic variables. The FNLCR PD Biomarker Program staff have played a major role in clinical trial development in the ETCTN by demonstrating the need for rigor in biomarker assay development and providing the laboratory science expertise to inform biospecimen collection and analyses. The FNLCR PD Biomarker Program has significantly affected the ETCTN. The Program engages research pathologists and interventional radiologists at the ETCTN sites, provides expertise for scientific review of biomarker assays to the BRC and grantees, and performs PD assays on biopsy material collected in ETCTN studies.

Dr. Moscow noted that several agents are currently in the ETCTN pipeline, including Poly ADP-ribose polymerase (PARP) inhibitors, MET inhibitors, and radiopharmaceuticals (e.g., Ra-223), a new class of agents being developed in the Network. He reviewed the impact of the FNLCR's validated PD assays on the CTEP portfolio. The MET inhibitor, ARQ197, already included in the ETCTN portfolio and with PoM studies that have likely been completed, was discontinued after it failed the validated phospho-MET assay and therefore failed PD biomarker PoM studies. The PARP inhibitor, BSI-201, also was discontinued for similar reasons. In both cases, a clinical trial using these agents was preempted. In another PARP inhibitor,

veliparib, PD assays revealed that the PD effect differed from what had previously been indicated. In fact, veliparib administered daily did not have target engagement that lasted 24 hours. The ETCTN conducted a Phase 0 trial to determine the scheduling of veliparib for constant control of PARP, which led to the twice-daily dosing Phase I trial of veliparib used in combination with temozolomide in acute myeloid leukemia patients. This trial demonstrated target engagement and showed significant downregulation of PARP-1 and -2 activities in patients responding to treatment (responders). Dr. Moscow emphasized that although there had been target engagement and now a reliable PARP assay, there was no clear difference in responders and nonresponders, suggesting that other factors could be involved in the drug response. This valuable information assisted the ETCTN in planning the next veliparib trial.

Dr. Moscow pointed out that the ETCTN is in the process of incorporating the FNLCR PD Biomarker Program's DNA damage-response assays into early-phase trials. PoM studies of the Wee-1 inhibitor AZD1775 looked promising, and a Phase I study of a DNA-PK inhibitor, M3814, is being planned. Regarding the future of the FNLCR PD Biomarker Program and the interactions of the ETCTN, he emphasized efforts to provide supplemental funding to ETCTN investigators for biomarker development to begin to bridge the gulf that divides the laboratory science discipline and the approach of basic scientists in analysis of clinical samples. The ETCTN will continue to rely on the FNLCR PD Biomarker Program for the development of PD assays for clinical trials.

In the discussion, the following points were made:

- Two factors affect a CIRB's success: whether the institution accepts the CIRB and whether the CIRB has a clear understanding of its roles.

- Although training could bridge the gulf between the laboratory science discipline and the approach of basic scientists in addressing clinical sample analysis, investigators must prove that they can accurately measure analytes by incorporating calibrators and internal controls in their assays.

- The CBC Discovery, PD Biomarker Program, and Early Clinical Projects groups meet weekly to discuss the status of agents in the NExT pipeline, address logistics, and plan supporting activities for future clinical trials.

VIII. ACCELERATING THERAPEUTICS FOR OPPORTUNITIES IN MEDICINE (ATOM) UPDATE—DR. ERIC STAHLBERG

Dr. Stahlberg provided an update on the ATOM Consortium (atomscience.org), including progress and future directions. An open public-private consortium, ATOM launched under a CRADA and established a national precompetitive resource to accelerate cancer drug development. The aim is to seek a better way to get medicines to patients. The motivating challenge to industry is that the average time to develop a drug through the preclinical stages is 5.5 years, and 33 percent of the total cost of medicine development is spent in this phase. Also, millions of compounds are tested, thousands are produced, and many fail, resulting in a clinical success rate of 12 percent. 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 rapid integrated and patient-centric model that merges diverse biological data, high-performance computing, and emerging biotech capabilities into an integrated precompetitive platform. The goal is to reduce the time to develop a drug from 5.5 years to 1 year.

Dr. Stahlberg described the ATOM Consortium and its organizational structure. The foundations for an open ATOM Consortium began in 2016, when the partnership between GSK, the DOE, and the NCI was announced as one of the Cancer Moonshot^{SM} task forces. In January 2017, GSK, the DOE, and the NCI signed a memorandum of agreement to establish a public-private partnership, and UCSF joined discussions soon after. In October 2017, ATOM was officially established with four founding members: GSK, LLNL,

the FNLCR, and UCSF. The Consortium serves as the organizational framework for academia, industry, and government to collaborate, is open to new members, and aligns with the NCI-DOE collaboration. The creation of the ATOM platform was launched with a multiyear CRADA, which supports active learning integration across experiments and data simulations. 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 and has begun to hold regular meetings. The ATOM Scientific Advisory Board is still being developed. The ATOM Head is composed of a three-member interim co-leadership team comprised of predominantly onsite senior personnel. The ATOM Joint Research Committee (JRC) is composed of scientific leads from each Consortium member organization and is charged to guide the technical research plan. The ATOM Operations team supports outreach, legal, procurement, and personnel activities across the collaborating organizations. Key to the organizational structure is the ATOM integrated workforce, which is centrally located near UCSF's Mission Bay Campus. The FNLCR support and leadership in ATOM include Drs. Dmitrovsky and Stahlberg, ATOM Governing Board; Dr. Nissley, ATOM JRC; and Dr. Debra Hope, ATOM Operations lead. NCI support and leadership include Dr. Emily Greenspan, Program Lead, and Dr. Izumi Hinkson, Outreach, ATOM Operations. The FNLCR ATOM workforce will include two postdoctoral fellows and one onsite data scientist.

Dr. Stahlberg explained that the ATOM workflow supports target-specific drug discovery and transforms the traditional empirical drug discovery approach (e.g., assay, synthesis, safety and efficacy studies) into an integrated *in silico* framework of design, simulation, and active learning. The outputs are computational models of drug behavior in humans. These models will then inform the science. The ATOM integrated platform is an emerging resource and has challenges to overcome before transitioning 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. Data generated in ATOM are aggregated, stored on the LLNL secure data server (i.e., trusted third party), and data owners decide which individuals access their data. The ATOM precompetitive platform delivers models, software, and derived data. Since October 2017, data policy and infrastructure have been established; public and private data sets have been deposited and analyzed; and gaps have been identified. Some PK, safety, and mechanistic models are being built and tested.

Dr. Stahlberg remarked on the theme of ATOM's approach to drug discovery, which is the integration of empirical data; computational and experimental capabilities; machine learning and mechanistic models; and the ecosystem of partners. The research and development plan consist of six crosscutting capabilities, including computing infrastructure; data and model lake; mechanistic modeling tools; data-driven modeling tools; chemical and biological delivery; and chemistry, biology, and engineering innovations. These crosscutting capabilities are divided across four integrated project teams—PK, safety, efficacy, and chemistry design—which are coordinated by the Pharmacology and Active Learning Workflow Project Team.

Dr. Stahlberg called attention to the ATOM roadmap, a multiyear strategy to reduce drug discovery timelines and cost, consists of three stages to transition drug discovery from its current state to the future ATOM state. Stages 1 and 2 will focus on reducing the lead discovery and optimization times. Stage 3 will involve PoC studies using the models and tools developed in the prior years to identify compounds that modulate the selected cancer-relevant target. Dr. Stahlberg noted that ATOM is progressing forward. The first stage of research using available data as well as simulations and modeling are in progress; staff are onsite; integrated cross-discipline and cross-organization teams have been established; the initial research plan is in place; and outreach to potential new Consortium members is ongoing. To realize the accelerated drug discovery goals of ATOM, the research community, including the pharmaceutical industry, needs to be willing to share data, expertise, insight, and knowledge about cancer.

In the discussion, the following point was made:

- Specific details on the ATOM initiative should be presented at a future meeting. Also, providing examples that can be evaluated would be helpful.

IX. NCI-DOE COLLABORATIONS WORKING GROUP REPORT—DRS. PIERMARIA J. ODDONE AND MELISSA C. SMITH

Dr. Piermaria J. Oddone, Director Emeritus, Fermi National Accelerator Laboratory, and Dr. Melissa C. Smith, Associate Professor, Electrical and Computer Engineering, Clemson University, presented the report of the FNLAC NCI-DOE Collaborations Working Group. Dr. Oddone indicated that the goal of the collaboration is to develop new and leverage existing exascale computational technologies of the DOE to apply to large complex cancer-related data sets. The DOE is not only interested in using its technology to advance cancer research and improve patient treatment options, but is also concerned with deriving benefit from use of its advanced high-performance computing. He reviewed the three pilot projects of the JDACS4C. Cellular Level Pilot 1 examines the predictive models for preclinical screening, Molecular Level Pilot 2 focuses on the behavior of RAS on cellular membranes, and Population Level Pilot 3 looks at population information integration, analysis, and modeling. The approach of Pilot 3 is to use deep-learning techniques to extract pathological data from the NCI SEER database. The crosscutting project—Uncertainty Quantification (UQ)—evaluates the level of uncertainty for all three pilots. The CANcer Distributed Learning Environment (CANDLE) crosscutting project focuses on developing a machine-learning framework for studying cancer and making the data available to a broader community. Another collaborative crosscutting initiative is ATOM. Dr. Oddone described the aims for each pilot.

For Pilot 1, large data sets (e.g., RNA sequencing) are collected and analyzed from the high-throughput preclinical screening of therapeutic cancer drugs using cell lines, patient-derived xenografts (PDXs), and organoids. The approach—a Drug Pair Synergy and Uncertainly Landscape plot—computationally predicts responses across multiple tumor types using different drug combinations. Dr. Oddone commented that Pilot 1 is an ambitious project with well-defined milestones and positive results. The results show that the per-drug fraction of synergistic interactions appears to be predictable from drug features, and the predicted performance in breast cancer is significantly better than for other tissue types. The proposed next steps include assessing the bottleneck of dataflow to accelerate the experimental feedback loop and developing mechanisms to engage the extramural community for collaborations and gather data on human-derived samples. An *ad hoc* working group with deep-learning expertise is proposed for Pilot 1.

Pilot 2 uses computational predictive simulations to understand how RAS behaves alone or in a protein complex on the cell membrane. The simulations of RAS activation are validated experimentally in the laboratory with testable hypotheses. Adaptive sampling, molecular dynamics simulation codes, and machine-learning guided approaches are additional methods to assess RAS activity. Dr. Oddone pointed out that Pilot 2 has a strong team working on the project, which is part of the larger RAS initiative. Results from this project show a change in the dynamics of KRAS and RAF on the lipid membrane with observable mutated hypervariable regions. When RAF kinase was incorporated in experiments, membrane association of isolated RAF-cysteine-rich domains was observed in the simulations. The planned next steps include engaging the private sector for data acquisition, collaboration, and project acceleration and identifying mechanisms to access additional data sets. An *ad hoc* working group with expertise in molecular dynamics simulations is proposed for Pilot 2.

Dr. Smith presented the results of Pilot 3, which focuses on population information integration, analysis, and modeling. The goals of Pilot 3 are to (1) use natural language processing (NLP) and advanced machine learning for scalable information capture from unstructured clinical reports to semiautomate data

from the SEER program; (2) create new data analytical techniques for patient information integration, employing scalable graph and visual analytics to understand the association between patient trajectories and outcomes; and (3) develop data-driven integrated modeling and simulation for precision oncology, such as *in silico* clinical trials. She summarized the findings from Pilot 3 by saying that the project has made good progress with interactions with the community, despite the relatively slow start on accessing registries. The Pilot 3 team developed, deployed, and refined an annotation pipeline and developed NLP tools for automated identification of primary site, laterality, histology, grade, and behavior. They also developed breast cancer schema for biomarkers and recurrence data elements and benchmarked four supervised deep-learning architectures. Moving forward, the team plans to incorporate different types of patient reports, including whole slide images and radiology reports, and determine how SEER data could be more relevant to precision medicine. An *ad hoc* working group with expertise in deep-learning application is proposed for Pilot 3.

Dr. Smith reviewed the crosscutting projects under the NCI-DOE collaboration. The goals of CANDLE involve using deep learning to help others increase productivity, supporting established deep-learning frameworks (e.g., Google) to run on DOE supercomputers, and managing CANDLE training data. Dr. Smith described the various contributions of CANDLE for each pilot and indicated that this crosscutting project has clearly defined future milestones. CANDLE has created a prototype deep neural network (DNN) for information extraction from clinical reports for Pilot 3 and provided the first version of Combo in CANDLE, delivered to Pilot 1. Another contribution is that CANDLE has created a prototype DNN that performs unsupervised feature learning for Pilot 2. Regarding UQ, Dr. Smith reiterated that this project is central to all scientific results and pilots. Because of the high technical nature of UQ, this project requires outside expertise. She mentioned that certain UQ-related tasks also are implemented in CANDLE. Dr. Smith highlighted the strong public-private partnership in ATOM.

Dr. Smith outlined the next steps for CANDLE, UQ, and ATOM. The CANDLE team plans to improve the application of the project by partnering with NCI's Informatics Technology for Cancer Research program. For UQ, the plans are to specify the sources of uncertainty and address validation in relation to UQ. The next step for ATOM is to establish a nonprofit entity and expand partnerships to gain more relevant data sets. Dr. Smith noted that all three pilots are progressing well. The overall proposed next steps include strengthening the FNLCR hub to increase connectivity between the DOE and NCI-supported programs. An *ad hoc* working group for all three crosscutting projects and proposal-driven scientific research using the created tools would be beneficial.

In discussion, the following points were made:

- The team of Pilot 1 is using a private company to test the hypothesis (using cell lines) generated from simulated models. The learnability of the deep-learning model can be tested experimentally. Pilot 3 used laterality to extract information from NLP characteristics, which also is testable and can be scored.

- The Working Group should consider conveying to the project leaders the value of including genetics in the NCI-DOE JDACS4C Pilot Project 3.

Motion. A motion to accept the report of the a*d hoc* NCI-DOE Collaborations Working Group was approved unanimously.

X. ONGOING AND NEW BUSINESS—DR. LAWRENCE J. MARNETT

Dr. Marnett requested input from the Committee regarding any remaining issues. FNLAC members commented on the FNLCR support of projects that are integrative, collaborative, of high quality, and promote innovative science. Dr. Marnett reminded members that the next FNLAC meeting is scheduled for

October 29–30, 2018, at the NCI Shady Grove Campus. Members will be contacted with further details on the 2019 meeting times and locations.

XI. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other invitees for attending. There being no further business, the 14th meeting of the FNLAC was adjourned at 3:50 p.m. on Tuesday, May 8, 2018.