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National Cancer Institute (NCI)

10th Meeting of the Frederick National Laboratory Advisory Committee (FNLAC)
May 11, 2016

Summary Minutes

Conference Room TE406, Terrace Floor
Shady Grove Campus, East Wing
Rockville, Maryland

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The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 10th meeting on 11 May 2016, at the Shady Grove Campus, East Wing, Conference Room TE406, Terrace Floor, Rockville, Maryland. The meeting was open to the public on Wednesday, 11 May 2016, from 8:30 a.m. to 4:25 p.m. The FNLAC Chairperson, Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, OHSU Center for Spatial Systems Biomedicine, Oregon Health & Science University, presided.

FNLAC Members
Dr. Joe W. Gray (Chair)
Dr. Gail A. Bishop (absent)
Dr. Vicki L. Colvin (absent)
Dr. Levi A. Garraway
Dr. Robert L. Grossman
Dr. David I. Hirsh
Dr. Elizabeth M. Jaffee (absent)
Dr. Alexandra L. Joyner
Dr. Lawrence J. Marnett
Dr. Jill P. Mesirov
Dr. Piermaria Oddone
Dr. Julie M. Overbaugh
Dr. Kenneth J. Pienta
Dr. Cheryl L. Willman
Dr. Jedd D. Wolchok (absent)

***Ex Officio* Members**
Dr. Lynn Austin
Dr. Stephen J. Chanock
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Warren A. Kibbe
Dr. Tom Misteli (absent)
Dr. Craig W. Reynolds
Dr. Dinah S. Singer

Executive Secretary
Dr. Peter J. Wirth

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I. OPENING REMARKS—DRS. JOE W. GRAY AND DOUGLAS R. LOWY

Dr. Joe W. Gray, Chair, called to order the 10th meeting of the FNLAC and welcomed the Committee members. Dr. Gray reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Peter J. Wirth, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

II. REPORT FROM THE ACTING DIRECTOR—DR. DOUGLAS R. LOWY

Dr. Douglas R. Lowy, Acting Director, National Cancer Institute (NCI), welcomed Committee members and other attendees. Dr. Lowy reviewed the agenda for today's meeting and stated that Dr. Dinah Singer, Acting Deputy Director, NCI, would provide an overview of the Vice President's Cancer Initiative (VPCI), Cancer Moonshot, and Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, NCI, would update the Committee on the President's Precision Medicine for Oncology Initiative (PMI-O).

A Positive Outlook for Cancer Research. Dr. Lowy highlighted NCI's activities of interest to the FNLAC members. The outlook for cancer research is quite positive, with many opportunities available to accelerate progress, and the public remains enthused about cancer treatment as toxic effects continue to be minimized. The NCI will capitalize on this momentum, with research continued in basic research, etiology, pathogenesis, prevention, screening, treatment, and survivorship. Implementation research and disseminating information about current knowledge and discoveries also are important and together will help to improve cancer health by increasing the standard of care uptake and promoting healthy lifestyles.

Dr. Lowy stated that NCI's progress would be measured in several different outcomes: (1) advancing the understanding of cancer, preventing it, screening for it, treating it, and improving the quality of life after a cancer diagnosis; (2) decreasing cancer mortality rates overall and for specific cancers; and (3) attracting and retaining high-quality young investigators. Overall, the U.S. mortality rates for all cancers declined by 10 percent from 1994 to 2003 and by 13 percent from 2004 to 2013. For women, the mortality rates declined by 12 percent from 2004 to 2013, compared to 7 percent from 1994 to 2003. In addition, the mortality rates decreased for most cancer sites from 2003 to 2013; however, liver and pancreatic cancers have seen the smallest declines. The decreases in mortality can be attributed to a combination of screening processes, treatment, and prevention.

FNLCR and FNLAC. Members were reminded of the Frederick National Laboratory for Cancer Research (FNLCR) role to conduct and coordinate research that would be difficult or less efficient if carried out by other mechanisms, such as the flagship project, the RAS Initiative, and the cryo-electron microscopy (Cryo-EM) user facility recommended by the FNLCR during its September 2015 meeting. The Titan Krios microscope has been delivered and is now being installed. The facility plans to open in the fall of 2016. Dr. Sriram Subramaniam, Senior Investigator, Center for Cancer Research, NCI, will lead the initiative and currently is organizing the oversight steering committee.

The NCI Budget Outlook. Dr. Lowy noted the positive outlook for the fiscal year (FY) 2016 and proposed FY 2017 budgets. Congress is showing strong bipartisan support for the NCI and the National Institutes of Health (NIH), largely due to the role of advocacy and the faster progress for patients. In 2015, the NIH received an increase in appropriations for the first time in more than 10 years, which resulted in a 5 percent increase in NCI's budget. The potential exists for continuing increases in federal cancer research funding and coordination with private funding efforts. A review of NCI's budget history from 1998 to the present shows that, even with the appropriated increases, funding will still remain at the levels it was in 2000–2001 when accounting for inflation. The proposal for FY 2017 requests a 13 percent increase for the NCI. The FY 2016 $256 million (M) increase was allocated to support the PMI-O, investigator-initiated research, and Cancer Center support grants, as well as overhead and inflation costs.

The Vice President's Cancer Initiative (VPCI, Cancer Moonshot). Dr. Lowy provided context for the Cancer Moonshot, which has the goal of accelerating progress in cancer, including prevention and screening, from cutting-edge basic research to wider uptake of standard of care. This aim is to encourage greater cooperation and help break down the silos within and between academia, government, and industry. Data sharing is a central motif in this effort. NCI's Genomic Data Commons, which is an annotated patient-level clinical data and -omics center, will become accessible in June 2016. The VPCI will take advantage of current advances in the understanding of cancer and recent technological innovation and apply the knowledge and innovation to focus on specific projects that can have a substantial impact on understanding the disease and improving patient outcomes. Dr. Lowy affirmed NCI's commitment to support other meritorious research, including new research initiatives.

Dr. Singer provided an overview of the VPCI, which was announced at President Obama's January 2016 State of the Union Address as a Moonshot to advance cancer research. Vice President Biden is leading the initiative, along with a Cancer Moonshot Federal Task Force composed of the heads of the executive departments and offices from 13 federal agencies. The Task Force has five goals: accelerate our understanding of cancer, its prevention, early detection, treatment, and cure; support greater access to new research, data, and computational capabilities; improve patient access and care; identify and address any unnecessary regulatory barriers and consider ways to expedite administrative reforms; and identify opportunities to develop public-private partnerships and increase coordination of the federal government's effort with the private sector, as appropriate. To achieve its goals, the Task Force was directed to consult with external experts, including the presidentially appointed National Cancer Advisory Board (NCAB).

The NCI has been charged to form a Blue Ribbon Panel (BRP) that is established as a working group of the NCAB to assess the scientific opportunities that could be accelerated through the VPCI. Twenty-eight members comprise the BRP who represent a spectrum of scientific, clinical, and private sector expertise, as well as members of the advocacy community. Members were told that the BRP has met twice and is charged with: identifying major scientific opportunities that are poised to be accelerated with additional emphasis on funding; identifying major scientific and regulatory hurdles that can be overcome with additional emphasis on funding; and facilitating progress by suggesting mechanisms to address research gaps in knowledge, develop key technologies, and overcome impediments. Working Groups are focusing on the specific areas of cancer immunology and prevention, tumor evolution and progression, precision prevention and early detection, expanding clinical trials, pediatric cancer, enhanced data sharing, and implementation science. Each working group will generate two or three recommendations, and the BRP will synthesize and prioritize the cross-cutting recommendations. The findings will be compiled into final recommendations that will be presented to the NCAB which will, in turn, deliver its recommendations to the NCI. Concurrently, ideas and recommendations will be obtained from the patient and broader communities through an online idea repository accessible from NCI's website as well as email and professional meetings.

Precision Medicine for Oncology Initiative. Dr. Doroshow provided an update on the PMI-O that was allocated $70 M from the FY 2016 budget. PMI-O will expand genomics-based targeted agents and immunotherapy, and work to understand and overcome resistance to targeted drugs, drug combinations, and immunotherapy. In addition, the initiative will focus on improving preclinical models for evaluating targeted therapeutics and immunotherapy, and on developing a national cancer database to integrate genomic information with clinical response and outcome. One facet of the PMI-O will be the expansion of the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial—a foundational treatment and discovery clinical trial platform that assigns therapy based on molecular abnormalities that are beyond the scope of the standard of care. NCI-MATCH enrolled 800 patients in 3 months, and is the fast accruing trial in NCI's history. The NCI-MATCH trial will reopen in the fall of 2016 to include an expanded accrual from 3,000 to 5,000 patients, enabling a 20 to 25 percent estimated match rate and a more detailed molecular analyses profile for treated patients. In addition, a pediatric MATCH trial is in the final stages of

protocol development and is expected to begin enrollment in December 2016. The NCI also has used administrative supplements to expand support for molecular characterization of immunotherapy trials and is proposing to develop an NCI Virtual Formulary. Improvements to preclinical cancer models are underway, and the NCI is considering canine models to evaluate spontaneously occurring tumors and to develop immunotherapies.

Dr. Doroshow mentioned NCI's plan to develop a preclinical model's collaborative for testing new drugs at multiple sites and the establishment of the Genomic Data Commons (GDC) as a national database that integrates genomic data with clinical response and outcome. The GDC will be accessible to the broad research community and is coordinated by the NCI Center for Biomedical Informatics and Information Technology (CBIIT).

In the discussion, the following points were made:

- The FNLCR involvement in the VPCI likely will occur through implementation of BRP's innovative recommendations to accelerate large-scale efforts similar to the RAS project.

- The NCI Virtual Formulary represents a major step to improve the access to drugs.

- The "accruals to MATCH" in the NCI-MATCH trials refers to the number of patients screened per number actually enrolled. The accrual was expanded to 5,000 based on the statistical interim analysis.

III. COMPUTATIONAL OPPORTUNITIES AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR)— DRS. WARREN A. KIBBE, DIMITRI KUSNEZOV, FRANK McCORMICK AND FRED STREITZ

NCI Computing and the NCI-DOE Collaboration. Dr. Warren A. Kibbe, Acting Deputy Director, NCI, updated the committee on the U.S. Department of Energy (DOE) and NCI collaborations across the National Laboratories. He cited NCI's mission to support the science behind understanding cancer risk, susceptibility, early detection, and improving treatments and outcomes for patients. The NCI-DOE collaboration contained projects that addressed different parts of NCI's mission. The three pilot projects include three data types: genomic, clinical diagnostic, and pathology data (i.e., PMI-O preclinical models); molecular and atomistic scale data (i.e., RAS Initiative data); and population-level cancer incidence and outcomes data (i.e., Surveillance, Epidemiology and End Results [SEER] registry data). The FNLCR is heavily engaged in the PMI-O preclinical models and the RAS Initiative data projects. Presidential Executive Orders have laid the groundwork for the NCI-DOE collaboration with the January 2015 PMI, the July 2015 National Strategic Computing Initiative (NSCI), and now the Vice President's Cancer Initiative (VPCI). Working with DOE computational scientists to conduct molecular computation and predictions using the RAS data and developing predictive oncology models that would be useful in the clinic will help the NCI to understand how to do computational analyses in a way fundamentally different from previous efforts.

DOE and Computing. Dr. Dimitri Kusnezov, Chief Scientist and a senior advisor to the Secretary, DOE, noted DOE's long-standing mission to investigate low-dose radiation and cancer. The DOE has statutory responsibilities that are driven today largely through simulation, and they have responsibilities to inform decisions for which experiments cannot be directly performed and understanding the complex situations can only be understood virtually. Over the decades, the DOE has developed methodologies that are still being pushed forward and are built into the workings of the department. The DOE attracts experiments and expertise into its 17 national laboratories and always is looking for important problems to drive the Agency's mission forward. The NCI-DOE collaboration is one such example.

Dr. Kusnezov commented that the DOE and its predecessors have been the world leaders in computation since the inception of computing. They have had a transformative and international leadership role in high-performance computing, beginning in about 1952 and extending to their exascale mission to develop the next-generation architecture by the early 2020s. The DOE has made major investments in next-generation tools, and the NCI pilot projects fit into this scheme. He commented that the DOE has aggressively developed code and solved problems with industry and academia partners that are analogous to the partnership being developed with the NCI. The joint effort will drive the intersection of simulation, machine learning and data analytics to rethink simulation with new classes of possibilities that do not yet exist. The NCI pilot projects are challenges that will push the DOE forward. The DOE is a lead agency for the NSCI, and will provide the technology component for the VPCI. In the framework of an ecosystem, the DOE would create exascale systems in partnership with industry, with scale-backs to fit the user preferences. For the field of oncology that could mean having a 100 teraflop (trillion floating-point operations per second) desktop system or 1 teraflop wearables. The Collaboration with Oak Ridge, Argonne, and Livermore National Laboratories (CORAL) stands to develop machine learning architecture that can be incorporated and applied to NCI's projects.

RAS Molecular Scale Pilot. Dr. Frank McCormick, Director, University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, and RAS Program Consultant, FNLCR, discussed the problems that the FNLCR is expecting to address in the RAS molecular scale pilot (Pilot 2) and the technology available at the laboratory. The goal of the RAS Initiative is to find ways to prevent RAS signaling. The RAS protein acts as a binary molecular switch that is inactive when bound to guanosine diphosphate and active when complexed with guanosine triphosphate. Activated RAS then turns on a signal transduction cascade leading to biological function, all of which occurs in the plasma membrane. The mechanism associated with RAS interactions and the plasma membrane are yet to be resolved, and identifying it is one problem Pilot 2 will be addressing. Published reports have shown that in simulations, RAS has two distinct orientations when bound to the plasma membrane. This suggests that drugs capable of blocking RAS from the plasma membrane would disrupt the signal transduction pathway.

The FNLCR has created fully processed KRAS and has performed biophysical analysis of the RAS protein tethered to synthetic membranes to better understand the membrane interactions and how it influences signaling. The laboratory is studying the structural and functional analysis of KRAS on a membrane using the nanodisc platform and nuclear magnetic resonance (NMR) evaluations. In addition, single-cell tracking methodology is being used to visualize RAS interactions with the membrane. Looking forward, Cyro-EM will be used to analyze RAS on nanodiscs.

Dr. Fred Streitz, Director, High-Performance Computing Innovation Center, Lawrence Livermore National Laboratory, described the intent of the NCI-DOE Pilot 2 to gain a better understanding of the interactions of RAS with the plasma membrane using molecular dynamics. In the Pilot 2 model, the first step would be to study the behavior of the membrane and to develop and validate the methodology. Using this validated methodology, the RAS protein membrane interactions will be evaluated to answer critical questions about the activation of RAS, effector molecule behavior, and the signaling pathway. Machine learning will be used to guide automated hypothesis generation and dynamic validation. The goal of Pilot 2 is to develop a predictive molecular-scale model of RAS-driven cancer initiation and growth that can provide the needed insight to accelerate diagnostic and targeted therapy design. The pilot will develop an adaptive time and length scaling in dynamic multi-scaled simulations, an extended RAS-complex interaction model, and machine learning for dynamic validation of models. A major focus of Pilot 2 is to create a new computing capability.

The NIH and DOE laboratory collaboration team has been organized and comprises 20 members from various disciplines, including computer science, mathematics, physics, and biology. The communication plan, confidential data sharing agreement, and credentials for Argonne National Laboratory

(ANL) members to access NCI networks have been established. A 3-year technical road map is being developed, and demonstration projects are underway.

In the discussion, the following points were made:

- The NCI has a large computational science community of resident experts and their involvement would enrich the collaborative efforts.

- The computational methods are rigorously verified and validated to ensure that the simulations are providing the correct answer to the question.

- Possible outcomes for Pilot 2 would be the new computational capabilities in predictive oncology, an integration of the DOE into the cancer community, and better understanding of the RAS membrane interactions.

- Pilot 2 is an excellent collaboration for the NCI and the DOE, highlighting the strengths of both organizations and illustrating the level of interaction needed for computing and oncology. The scope of the project is extensive and offers future opportunities for engaging the rest of the biology community in the new computational capability.

- Pilot 2 can be thought of as a demonstration project to show how computing can be applied to cancer research and is relevant for the data being generated in the RAS Initiative.

- The NCI will consider ways for incorporating the computing power of the DOE into cryo-EM technology.

- The FNLCR is strategic for assembling a multidisciplinary team to determine a future focus of the NCI-DOE collaborations.

IV. RECOGNITION OF RETIRING MEMBERS—DR. DOUGLAS R. LOWY

Dr. Lowy recognized members of FNLAC whose tenure was ending and thanked them for their efforts and for the impact they have had on FNLCR. He commented that the program is vastly different from 4 years ago, and this is partly due to the input and efforts of FNLAC. Members retiring from the committee included: Dr. Alexandrea Joyner, Courtney Steel Chair in Pediatric Cancer, Memorial Sloan Kettering Cancer Center; Dr. Jill Mesirov, Associate Vice Chancellor for Computational Health Sciences, University of California, San Diego; and Dr. Joe Gray.

V. COMPUTATIONAL OPPORTUNITIES AT FNLCR (CONTINUED)— DRS. FRANCIS J. ALEXANDER, JAMES R. DOROSHOW, AND RICK L. STEVENS

Patient-Derived Xenograft (PDX) Patient Scale Pilot (Pilot 1). Dr. Doroshow began the discussion by referring to the resources the NCI has to support the DOE and NIH partnerships in predictive oncology. The partnership will provide a better understanding of how the use of targeted therapies and preclinical models to identify mechanisms of resistance would be translatable to the clinic. The two main categories of NCI resources for the DOE data sharing project include *in vitro* drug response data and the *in vivo* PDX models drug response and molecular characterization data. The *in vitro* data sets were derived from the following: Developmental Therapeutics Program (DTP) NCI-60 cancer cell line panel data; DTP Sarcoma and Small Cell Lung Cancer data; and the NCI ALMANAC (A Large Matrix of AntiNeoplastic Agent Combinations) and NCI-60 combination data. The *in vivo* data sets were derived from the FNLCR/NCI patient-derived models repository, which includes the model characterization data sets and the PDX drug response data sets. The predictive models for preclinical screening in oncology in collaboration

with the DOE will use molecular characterization data from both *in vitro* cell lines and *in vivo* PDXs, as well as drug response data in machine learning to build computational models of observed drug resistance.

Dr. Rick L. Stevens, Associate Laboratory Director, Computing Environment and Life Sciences, Argonne National Laboratory (ANL), described the DOE and NCI partnerships in Predictive Oncology. He recognized the co-lead investigator for Pilot 1, Dr. Francis J. Alexander, Acting Division Leader, Computer, Computational and Statistical Sciences Division, Los Alamos National Laboratory (LANL). The aims for the preclinical screening pilot are to: build reliable machine learning-based predictive models of drug response; utilize uncertainty quantification and optimal experimental design to assert quantitative limits on predictions; and improve modeling paradigms. The predictive models for preclinical screening Pilot 1 model will integrate data from the NCI and other sites into an integrated data environment that will be shared within the ANL and also to the broader community to build machine learning-based predictive models and to design experiments. In addition, integrated data will be used for hypothesis formation and mixed models.

Goal 1 of the pilot project is to build machine learning models of drug response beginning with the NCI-60 data and later expanding to the PDX data sets. To date, more than 50,000 models have been built and cross validated. Goal 2 is to catalog molecular signatures for each agent or class of agents and perform analysis to gain insight into the potential mechanisms. Goal 3 is to test signatures and agents in PDX models and other *in vitro* models to develop a framework for high-throughput predictions with uncertainty quantification. Goal 4 is to develop deep learning-based model formulations that combine information about the drug, the drug target, and the PDX cell lines. Goal 5 is to develop advanced architecture. The overarching goal of the DOE-NCI collaboration is to more thoroughly understand the architectural requirements for integration of simulation, scalable data analysis, and deep learning.

In the discussion, the following points were made:

- Some members of the computational science community are already working in this arena and could be engaged in the NCI-DOE efforts. One strategy would be to sponsor focus workshops, which would spur conversations about the opportunities. The NCI leadership could provide ideas for how to engage the NCI computing community in the NCI-DOE collaboration.

- The Pilot 1 project is a move in the positive direction and has implications for the NCI MATCH clinical trial to identify a predicted match to a genome-targeted therapeutic for the patients. Including molecular signatures to predict response against the microenvironment would enhance the robustness.

- One strategy to compensate for a lack of data would be to develop a parallel activity that would fill the gap, and apply the computational expertise in an intelligent manner.

- Consider ways for the FNLCR to be the model and serve as the interface of the cancer research community to create partnership models, whereby the NCI and all of the extramural community could work with the DOE on computational challenges as applied to cancer.

VI. ANTIBODY TECHNOLOGY RESEARCH CENTER (ATRC)—DRS. CHARLES CRAIK, JAMES D. MARKS, AND JIM WELLS

Dr. James D. Marks, Professor and Vice Chair of Anesthesia, UCSF, described the capabilities of the ATRC and stated that the facility was awarded the NCI Research Programs Projects and Centers P41 grant. The goal of the ATRC is to develop technologies that support robust approaches for generating high-quality recombinant antibodies (rAb) to the proteome, focusing on secreted extracellular and membrane proteins and protein posttranslational modifications (PTM). The technologies used at the ATRC include

phage antibodies, automation and high-throughput screening, in vitro antigen and antibody (Ab) expression, and automatable cell selection. The ATRC is trying to solve a two-fold problem: Functional Abs are not available for more than 90 percent of the proteome; and more than half of the available Abs are nonspecific, show a lot-to-lot variability, are expensive, are not renewable (i.e., not cloned), and are typically of the immunoglobulin G (IgG) type. The recombinant Abs are specific to the target, are renewable, and can be generated as alternative antibody constructs, or with any fragment crystallizable region.

The ATRC has three Technology Research and Development (TR&D) projects that partner with Driving Biomedical Projects from the academic research community to produce Abs to high-quality antigen submitted by investigators. The investigators provide feedback on the utility of the new Ab and suggest ways the technology might be improved at the ATRC. TR&D 1 is focused on next-generation phage Ab libraries and is led by Dr. Marks; TR&D 2 is focused on generating Abs to secreted Type-2 transmembrane (TM) serine proteases and is led by Dr. Charles Craik, Director, Chemistry and Chemical Biological Graduate Program, and Professor, Department of Pharmaceutical Chemistry, UCSF; and TR&D 3 is focused on generating renewable Abs for PTM in protease modifications in signaling and is led by Dr. Jim Wells, Professor, Department of Pharmaceutical Chemistry, UCSF. Additional information is provided below.

TR&D 1. Dr. Marks described the in vitro rAb generation for secreted extracellular and membrane proteins using the phage display methodology that involves cloning a gene repertoire into a phage vector display. Phage-display libraries are generated, and antibodies are selected against the antigen. The antibodies will be conformation-specific, a desired feature. The rAb generation pipeline begins with the investigator-generated high-quality antigen and includes phage selection, competition assays, sequencing, and expression and validation. The ATRC has an alternative yeast-display method for generating high-quality antigen when it is not supplied. TR&D 1 activities include designing next-generation phage libraries, such as the nature-inspired synthetic antibody libraries; developing therapeutic antibodies; and developing antibodies to multipass membrane proteins, such as 7-TM.

TR&D 2. Dr. Craik described the ongoing work of TR&D 2 to identify and characterize rAbs against select protease targets. Proteases are associated with all cancers, and there are more than 600 proteases in the human body, making them high-value targets. Currently, 17 anti-proteolytic therapeutics are on the market, leaving many proteases with unexplored biology. Dr. Craik and others discovered a class of membrane-anchored proteases known as Type-2 membrane anchored serine proteases; one in that class, matriptase, is involved in prostate and colon cancer. An Ab activity-based probe to matriptase designed at the ATRC is providing diagnostic information in colon cancer and also may be important for disease staging. In addition, technology is being developed to design a matriptase Ab-imaging probe. The group has designed conformational selective fragment antigen-binding (Fab) fragments to other challenging targets, including the ABC transporter, the dimeric chloride channel, and the membrane-anchored serine protease TMPRSS6 to aid in their structural (both Cryo-EM and X-ray) and functional characterization.

TR&D 3. Dr. Wells described the TR&D 3's work, which includes the automated industrialized Ab pipeline. The industrialized Ab pipeline is a high-throughput platform for rAbs and is performed in collaboration with the University of Chicago and the University of Toronto—forming the rAb network. The robot performs all of the steps of phage display, including selection, competition assays, sequencing, and expression. The rAbs network has used the automated platform to generate more than 3,000 Fabs, 346 transcription factors, and 211 epigenetic factors. The TR&D 3 group also has been focused on generating conformationally selective Abs that act as functional reagents capable of toggling the function of proteins, as well as DNA barcoding for multiplex detection for proteomics. A major project is the collaboration with the FNLCR to generate high-resolution Abs that can be used for selecting and detecting different mutant forms of RAS. In addition, Dr. Wells and his group have demonstrated how KRAS remodeled the cell surface. Dr. Wells discussed possible opportunities for the ATRC to collaborate with the FNLCR, including

protein antigen production at a scale of 100 per year; IgG conversions, expressions, and distribution at a scale of 100 per year; and access to high-purity targets and collaborations.

In the discussion, the following points were made:

- Much of the RAS investment is in protein production, which is supported by about 15 full-time employees. IgG conversion is not a specialty for FNLCR. Generating 100 antigens per year is doable at the FNLCR, but additional investments and demand for space will need careful consideration.

- The ATRC has a proven record of producing high-quality Abs. The scalability would be rate-limiting if the demand is high. One strategy to filling an unmet need would be to leverage existing NCI-funded projects.

- Much of the discovery technology at ATRC is off patent and available to the community. Specialized Abs produced at the ATRC range from $1,500 to $2,100, compared to commercially supplied Abs at a cost of $5,000.

VII. FUTURE OF THE FNLCR—DRS. CRAIG W. REYNOLDS AND KRISTIN KOMSCHLIES

Dr. Craig Reynolds, NCI Associate Director, provided an overview of the NCI at Frederick and the FNLCR. The laboratory was established in 1971 by President Nixon, in the War on Cancer initiative, by converting a part of Fort Detrick's biodefense laboratory to a leading center for cancer research. In 1975, the contract component of the NCI at Frederick, now known as FNLCR, was designated as a Federally Funded Research and Development Center (FFRDC). The NCI at Frederick is a government-owned facility that is operated by a contract company, currently Leidos Biomedical Research, Inc. The NCI at Frederick hosts 2,600 employees, 70 percent of whom are contract staff; the remaining 30 percent are government employees.

Dr. Kristin Komschlies, Deputy Director, Office of Scientific Operations, NCI, discussed the operations of the FNLCR. Funds are obligated to the FNLCR from federal agencies, and most of the funding comes from the NCI and the National Institute of Allergy and Infectious Diseases (NIAID). Projects are initiated using the obligated funds. Ideas for new research come from the NCI Divisions, Offices, and Centers, as well as other NIH Institutes and Centers (ICs). The governmental groups are responsible for obtaining concept approval and for funding the projects. Continuous project oversight is provided by the funding agency, and the frequency and type of oversight varies according to the project. Complicated projects may include integrated efforts of government and contractor staff.

The FY 2015 funds to the FNLCR obligated from all federal agencies was $579.5 M, with 59 percent coming from the NCI, 40 percent from the NIAID, and 1 percent from other ICs and government agencies. Two thirds of the research being conducted at FNLCR during this period was primarily concentrated in HIV/AIDS, drug development, vaccine development, and clinical trial support. Support also was provided to efforts in bioinformatics, biodefense, genomics, and infectious diseases. The NCI-obligated funds for FY 2015 totaled $334 M and is appropriated from intramural programs, the Office of the Director at NCI, and extramural programs. The RAS projects and others are funded from the extramural obligation.

In the discussion, the following points were made:

- The ability to do independent research develops strong staff. Providing a mechanism for staff-initiated projects also plays a role. There is more instability than with academics due to the

dependence on projects. The logistics for the peer-review process for staff-initiated projects will need to be addressed.

- The Laboratory Directed Exploratory Research (LDER) funds ($1 M) are used for staff-directed research. Five have been awarded at an average of $120,000, and some have been awarded for multiple years. The LDER can be used to provide preliminary results that would feed into larger projects. The opportunity exists to perform a different kind of research than the intramural or extramural communities.

- The FNLCR can provide a service to the community through commitments and investments or independent research that is proposed.

- The FNLCR mission is tightly linked to the mission of the NCI. The FNLCR can act as an independent idea generator to secure its own funding and serve as a higher advanced technological center. The NCI intramural program would provide projects that cannot be done at other ICs.

- There should be a two-way dialogue for FNLCR-driven research and the freedom and incentive for the staff to have big ideas. Both the NCI and the FNLCR would drive the science to produce the best projects. There could be joint project development as well.

- The NCI should develop joint appointments with faculty and the FNLCR to encourage initiative-driven research; the FNLCR staff can prepare new concepts and have them reviewed by the NCI.

- The current portfolio of the FNLCR can be used to fill gaps in research.

- The future of the FNLCR will depend on how it elevates the scientific community in decreasing mortality and morbidity of cancer. The RAS project is one example where $10 M was redirected from other projects. Also, the cryo-EM is a core project. The goal is to develop measures to identify the science that will push the laboratory forward. The FNLCR could play a key role in the VPCI to either provide a service or a specialization.

- The NCI should develop initiatives to engage the extramural community in the activities of FNLCR. The quality of work the laboratory is doing will attract attention to the FNLCR. The nanotechnology laboratory and the Cryo-EM facility are good examples.

- The FNLCR is not allowed to apply for grants under its current authority.

VIII. RE-COMPETE OF FEDERALLY FUNDED RESEARCH AND DEVELOPMENT CENTER (FFRDC) CONTRACT —DR. LYNN AUSTIN AND MR. STEPHEN C. DAVIS

Dr. Lynn Austin, Deputy Director of Management, Executive Officer, NCI, discussed the logistics on the draft request for proposals (RFP) for the FFRDC contract re-competition. She stated that the committee's comments and any public comments would be collected and used to inform the NCI of any changes needed to the RFP before it is released in late June 2016. Questions would not be answered to maintain the integrity of the procurement process.

Mr. Stephen C. Davis, Chief, Management Operations Support Branch, NCI, discussed the details of re-competition process. The draft RFP was released on April 15, 2016, and the schedule of acquisition has established key milestones through to the award in June 2017. The FNLAC is responsible for reviewing the state of research at FNLCR and making recommendations on the best use of its capabilities and infrastructure to meet the urgent needs of the NCI. Comments can be submitted via NCI's website through the end of May 2016. Dr. Austin said that the committee had received a statement of work (SOW) along

with the draft RFP. The SOW is inclusive to contain the current work of the FNLCR and gives an open-ended view of its ability to carry out a multiplicity of opportunities.

In the discussion, the following points were made:

- The goal of the RFP is to help the potential competitors for the contract present the best proposals to the NCI. The SOW is essential to providing a good proposal and currently is too high level and does not best describe enough of the work of the FNLCR. Details on the business model, interactions with the NCI, and the current state of the flow of money should be conveyed. What the NCI hopes to accomplish with the re-competition needs to be clarified and competitor roles need to be defined.

- The proposal should reflect the vision of how the contractor would fill the mission of both the NCI and the FNLCR in a way that goes beyond business-as-usual to proposing the creation of new technologies. A proposal also should include ideas for organizing activities and working with the research community.

- The SOW should clearly define the services needed (i.e., administrative or scientific and clinical), and provide criteria and scoring details by which the proposals will be judged. Also, the NCI needs to clearly define what it considers to be marks of success.

- Consider the role of FNLCR in the VPCI and the timing of the re-competition. Members cautioned against changing management in the middle of a major NCI initiative and to consider slowing down the final RFP release date. In addition, the FNLCR could engage in long-term planning to offset the distraction with the Moonshot.

- Members suggested that input from the BRP for the VPCI may help in setting a better vision of the FNLCR in the context of NCI's larger mission.

IX. NEW BUSINESS—DR. JOE W. GRAY

Dr. Gray requested input from the committee members regarding the central focus of the next meeting. Members agreed on a site visit to the FNLCR for the November 2016 or the May 2017 meeting.

Dr. Lowy pointed out that Dr. Lawrence J. Marnett, Associate Vice Chancellor for Research, Vanderbilt University School of Medicine, would be assuming the chair position starting with the next meeting, and he thanked Dr. Gray for his service to the FNLAC and for being a model chair for others. Dr. Gray reflected on his involvement with the FNLCR and the Committee's role in helping to set the stage for future development at the FNLCR.

FNLAC members voted via mail ballot for the establishment of the Cryo-EM Facility Oversight Subcommittee of the FNLAC. The purpose of this ad hoc subcommittee is to provide oversight to the Frederick National Laboratory Advisory Committee (FNLAC), Associate Director, Frederick National Laboratory for Cancer Research (FNLCR), and the Director, NCI on the operation of the National Cryo-EM Facility (NCEF), which is hosted by the FNLCR. The subcommittee will evaluate the goals, scientific priorities and scope, technical and operational aspects, and equipment and staffing needs of the NCEF in support of the Cryo-EM community.

X. ADJOURNMENT—DR. JOE W. GRAY

Dr. Gray thanked the Committee members and other invitees for attending. There being no further business, the 10th meeting of the FNLAC was adjourned at 4:25 p.m. on Wednesday, 11 May 2016.

Date	Joe W. Gray, Ph.D., Chair
Date	Peter J. Wirth, Ph.D., Executive Secretary