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6th Meeting of the NCI-Frederick Advisory Committee (NFAC)
February 4–5, 2014

Summary Report

45 Center Drive, Natcher Building
Conference Rooms E1/E2
Bethesda, Maryland

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The NCI-Frederick Advisory Committee (NFAC) convened for its 6th meeting on 4–5 February 2014, at 45 Center Drive, Natcher Building, Conference Rooms E1/E2, Bethesda, MD. The meeting was open to the public on Tuesday, 4 February 2014, from 9:00 a.m. to 5:30 p.m., and on Wednesday, 5 February 2014, from 9:00 a.m. to 12:00 p.m. The NFAC Chairperson, Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, OHSU Center for Spatial Systems Biomedicine, Oregon Health and Science University, presided.

NFAC Members
Dr. Joe W. Gray (Chair)
Dr. J. Carl Barrett (absent)
Dr. David Botstein (absent)
Dr. Vicki L. Colvin
Dr. Levi A. Garraway
Dr. Beatrice H. Hahn
Dr. Monica J. Justice
Dr. Lawrence J. Marnett
Dr. Jill P. Mesirov
Dr. Garry P. Nolan (absent)
Dr. Kenneth J. Pienta (absent)
Dr. Jennifer A. Pietenpol
Dr. Steven T. Rosen (absent)
Dr. Cheryl Willman

***Ex Officio* Members**
Dr. Stephen J. Chanock
Mr. John Czajkowski
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Douglas R. Lowy (absent)
Dr. Alan Rabson (absent)
Dr. Craig W. Reynolds
Dr. Robert H. Wiltrout

Executive Secretary
Dr. Thomas M. Vollberg

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I. OPENING REMARKS

Drs. Joe W. Gray and Harold E. Varmus

Dr. Joe W. Gray, Chair, called to order the 6th meeting of the NFAC 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. Thomas M. Vollberg, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Dr. Harold Varmus, Director, NCI, welcomed everyone and thanked members for their service on this committee, especially Dr. Gray, who has extensive experience with National Laboratories. Dr. Varmus remarked on the NCI budget, noting a recent history of stagnation followed by a 5.5 percent reduction that was shared across the Institute. The NCI now has a 2-year budget plan, including an approved fiscal year (FY) 2014 budget which restores some of the reduction of the previous period. A challenge and goal of this situation is to foster an atmosphere in which scientists can focus on their scientific endeavors without too much preoccupation about future funding prospects. He expressed the NCI's commitment to maintain the same number of new R01/R21 awards provided in FY 2013 as well as to support new and novel research initiatives.

Dr. Varmus reviewed the 2-day meeting agenda and reflected on the progress made regarding the Frederick National Laboratory for Cancer Research (FNLCR) under the previous Chair, Dr. Zach Hall. Day 1 includes an overview of the FNLCR and its interactions with the NCI intramural research program, an update on the RAS Project, and discussion of potential projects for the FNLCR. On Day 2, members will hear perspectives and lessons learned from the Department of Energy (DOE) national laboratories. Dr. Varmus stated that the intent of the meeting format is to help the NCI to conduct more activities suited for a national research laboratory.

Dr. Gray encouraged members to consider how strategic direction should be set and the FNLCR enabled to respond to the strategic direction. He noted that the DOE divides those labors between the Office of Science, which sets the long-term scientific agenda for the DOE, and the national laboratories that respond with specific, competitive proposals. Drs. Gray and Varmus asked that the speakers diminish the amount of data presented to allow the NFAC to consider the broader perspective of tasks that are appropriate to a national laboratory.

II. OVERVIEW OF THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR) PROGRESS AND PROGRAMS

Drs. David C. Heimbrook and Robert H. Wiltrout

Dr. David C. Heimbrook, President, Leidos Biomedical Research, Inc., FNLCR, provided an overview of the operating principles and programs of the FNLCR. Dr. Heimbrook was joined by Dr. Robert H. Wiltrout, Director, Center for Cancer Research (CCR), who provided an overview of interactions between the NCI and the FNLCR.

Overview of FNLCR Process, Progress, and Programs. Dr. Heimbrook reminded members that the FNLCR is the only federally funded research and development center (FFRDC) that is dedicated exclusively to biomedical research. The FNLCR is operated in the public interest by Leidos Biomedical Research, Inc. (Leidos Biomed, formerly SAIC-Frederick), on behalf of the NCI. As an FFRDC with a broad charter and contractor staff, the national laboratory provides the NCI with flexible and efficient acquisition and response capabilities to meet changing needs that cannot be done effectively through other government mechanisms. Leidos Biomed is a wholly owned subsidiary of Leidos Holdings, Inc, and its sole purpose to operate the FNLCR, Leidos Biomed provides Leidos Holdings, Inc, with award fees as corporate revenue, and Leidos Holdings returns a good amount back to cover non-allowable costs (e.g. salary supplements, expenses during the government shutdown). Execution of the FNLCR contract supports

Leidos Holdings, Inc, in demonstrating capability to execute large contracts, and Leidos Biomed is a source of biomedical research and development expertise that is available to Leidos Holdings, Inc.. Leidos Holdings, Inc. supports Leidos through legal and financial oversight, and information technology (IT) and "big data" expertise.

Dr. Heimbrook provided details on the FNLCR operations and technical support contract, which has an overall value of $518 million (M), $300M of which is from NCI-appropriated funds. NCI Divisions, Offices, and Centers allocate funding for FNLCR science and services, with infrastructure, management oversight, and shared services funded by the Office of the Director. Projects that represent new work or a change in work are submitted as "Yellow Tasks" for approval, planning, and budgeting. A "Yellow Task" is initiated by a government "customer", the request is vetted for suitability for FNLCR by the NCI Project Officer and the NCI Contract Officer (both are NCI). The appropriate FNLCR program develops a budget and workplan with the customer. The plan and budget are approved by customer and the Administrative Officer (NCI), and the OTS contract is modified to reflect change in funding. In FY 2013, 195 Yellow Tasks—one of which was the RAS Startup Initiative—were submitted by 23 government entities, including NCI Divisions, NIH Institutes, and other agencies. In addition to the Office of the Director, the CCR and Division of Cancer Treatment and Diagnosis (DCTD) were the primary sources of FNLCR appropriations in FY 2013.

The FNLCR supports a wide variety of programs. The NCI Experimental Therapeutics (NExT) Program, led by the Division of Cancer Treatment and Diagnosis (DCTD), creates a coordinated cancer therapeutics discovery and development pipeline, including a molecular characterization laboratory and the Biopharmaceutical Development Program (BDP). The BDP provides expertise for complicated and difficult manufacturing efforts for small markets, and more than 60 products manufactured by the BDP since 1993 have entered clinical trials. An example is monoclonal antibody ch14.18, which following success of Phase III trials in patients with high-risk neuroblastoma has been transferred to a commercial vendor. The FNLCR provides project planning and management support to the Clinical Trials Reporting Program of the Center for Biomedical Informatics and Information Technology (CBIIT). The FNLCR's Cancer Genomics Research Laboratory provides core services, including genotyping, sequencing, and data analysis; conducts collaborative research; and develops new technologies. Collaborative research has produced a large number of publications, including in high-impact journals. The Antibody Characterization Laboratory tests and characterizes antibodies, resulting in more than 100 antibodies that have been proven useful. Facilities maintenance services also were provided. The Advanced Technology Program originally offered shared services, which facilitated access to new technologies on a fee-for-service basis, and dedicated laboratories and facilities. Dr. Heimbrook stated that most of the staff members who provided shared services now provide expertise to support the Cancer Research Technology Program and the RAS Project.

Overview of NCI/FNLCR Interactions. Dr. Wiltrout provided an historical context for the location of some CCR intramural laboratories at Frederick facilities. He told members that the CCR was formed in 2001 through the merger of two intramural NCI Divisions, the Division of Basic Sciences and the Division of Clinical Science. Prior to this merger, a portion of NCI intramural staff within the Division of Basic Sciences were positioned at Frederick in the context of a successful contractor operation. In the 1990's there was a fusion of the Frederick contractor program with the intramural NCI component in Frederick. Currently, almost 70 percent of the CCR laboratories are located on the NIH Bethesda Campus, about 30 percent in Frederick, and a small remainder at the Advanced Technology Center (ATC) in Gaithersburg, which is being phased out. CCR funding primarily supports basic research laboratories and clinical branches (approximately three-quarters of total funding), and the Office of the Director funds the CCR's animal model development activities. Current areas of research at CCR-Frederick laboratories include chemistry and structural biology, development of mouse models, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), RNA biology, and inflammation and immunology. Locating some of CCR's programs at the FNLCR allows flexibility in recruiting staff through the contractor mechanism, interactions with other FNLCR activities such as the DCTD's NCI Experimental Therapeutics (NExT) Program, and access to core resources. In the past, CCR laboratories have contributed

a strong scientific culture to the FNLCR campus, assisted with development and beta testing of new technologies, contributed to the NCI's drug development by interacting with the DCTD's NExT Program, developed IL-15 and IL-7 therapies in collaboration with the Biopharmaceutical Development Program (BDP), and contributed to drug development from natural products.

Dr. Wiltrout described the CCR's role in key product development and translational efforts. In immunotherapy, interleukin (IL)-15 and IL-7 were among the top agents selected for development at the BDP. IL-15 has great potential to enhance the effectiveness of therapeutic cancer vaccines. IL-7 is in clinical trials in the United States, Europe, and Asia. A large fraction of approved anticancer drugs are derived from natural products. CCR-Frederick has excellent resources for developing and screening natural products-derived therapeutics, including the world's largest storehouse of natural products.

There are multiple areas of potential interaction for the CCR with the FNLCR. These include co-located cores at the Advanced Technology Research Facility (ATRF), some of which have pivoted and others which have expanded with CCR funding; computational support from the NCI-Frederick Advanced Biomedical Computing Center (ABCC); the Center for Advanced Preclinical Research; and other FNLCR projects or technologies. Pre-pivot, the CCR made extensive use of Advanced Technology Program (ATP) shared services, expending $2.2M; post-pivot, these services were provided primarily by CCR-dedicated cores, with Yellow Tasks used to transfer full-time equivalents to the dedicated cores. The advantages of co-located cores are shared instrumentation and reduced duplication in some cases, potential rapid access to additional resources in urgent situations, and a critical mass of specialized expertise. Experience has shown that a strength of the FNLCR cores lies in responding to specific tasks with close oversight. The main challenge in operating core laboratories is a tendency for "mission drift" and reduced efficiency, particularly when core leaders' interests do not coincide with NCI's needs. In regard to computational resources, the ABCC currently provides support to the CCR in several areas, including informatics, and the CCR benefits from computational support in genomics, proteomics, and metabolomics for drug development. The CCR and Center for Advanced Preclinical Research are partnering with the Lustgarten Foundation on preclinical studies of pancreatic cancer therapeutics, the majority of which are RAS-related. Progress is being made on collaborations on RAS-related research, including RAS biology, siRNA interrogation of RAS signaling, and RAS inhibitors, and collaborative efforts between ATRF investigators and intramural researchers continue as well as the sharing of reagents and technologies to avoid redundancy. Dr. Wiltrout suggested several areas of strategic emphasis in NCI-FNLCR interactions, including with mouse models, screening for natural products, structural biology and chemistry, and communication and interaction on RAS-related projects and reagents.

In the discussion, the following points were made:

- Small molecules formulation in the NExT program is carried out through contract research organizations.

- The shifting of support from shared services to services in support of the RAS Project has been undertaken with care to ensure that users of the shared services have access externally or through dedicated laboratories to needed services that are not integral to the RAS Project.

- In response to a question about whether Leidos Holdings, Inc. might provide services to the FNLCR, such as engineering and fabrication capability, it was noted that Leidos Holdings, Inc. has engineering expertise with experience in arranging and managing subcontracts for engineering capabilities rather than providing direct access to these services from dedicated employees.

- Members encouraged leadership to provide funds in the FNLCR core service laboratories for intellectual pursuit in development and evaluation of new technology platforms and for activities that improve and make the technologies and methods more efficient and cost-effective. It was noted that an oversight group at the CCR meets regularly with the core leaders and promising new

technologies are identified (e.g., laser capture microdissection) and brought to the attention of the FNLCR leadership to foster deployment to the broader community.

- In response to a member's question about the source of NCI's natural products collection, NCI leadership indicated that budget constraints have halted new plant collection, marine collection is continuing, and bacteria and fungi are the current focus of the NCI's natural products collection efforts; in addition, several large collections that recently were donated to the NCI have been curated and are in development.

- Members commended NCI and FNLCR leadership in recognizing the value of the distinct roles of core and individual researchers as well as economies through sharing resources. Standardized expectations for core facilities are needed, and opportunities lie in improvements to platforms, centralization sequencing, and informatics resources. NCI leadership acknowledged the critical role of oversight groups in identifying opportunities to share resources, as seen through collaborations between the sequencing center in Frederick and the Division of Cancer Epidemiology and Genetics (DCEG).

- The FNLCR structure helps optimize the investment of funds, allowing the closure of core facilities that are not on the forefront of research so as to be able to reinvest in new science. Core services are reviewed over time and can be adapted based on needs and feedback from user groups.

- Members expressed concern about objectivity in core service oversight that includes users on committees that oversee funding as well as decisions of cost effectiveness of providing access to the newest technologies as an internal core service versus obtaining service through outside sources. FNLCR leadership noted that using the FNLCR contract to supply dedicated core services through Leidos Biomed, allows termination within 60 days and facilitates adaptation to new technologies. Rapid changes in technologies, such as in the field of proteomics, drives users to seek new technology platforms and capabilities that are needed to move research forward. In addition, the high-quality expertise of individual investigators who are developing cutting-edge technology can be made accessible on a fee-for-service basis before the technology is transitioned to a core service.

- The continual, close interactions between FNLCR and NCI staff ensure productive outcomes for cancer research at the National Laboratory and in NCI's intramural research program.

III. RAS PROJECT UPDATE

Drs. Frank McCormick and Atsuo Kuki

Dr. Frank McCormick, Director, University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, and RAS Program Consultant, FNLCR, provided an update report of the RAS Project. Dr. McCormick was joined by Dr. Atsuo Kuki, Chief Technology Officer, Leidos-Frederick, FNLCR, who described how FNLCR resources have been deployed to assist with RAS research.

RAS Project Progress Report. Dr. McCormick reminded members that RAS mutations are frequent in human cancers, as seen in pancreatic cancers, 71 percent of which have a Kirsten RAS (KRAS) mutation. Because RAS proteins currently cannot be targeted directly, there are no ways to treat RAS-driven cancers effectively with therapy, representing a significant clinical need. The number of patients affected by these mutant alleles exceeds the number of those affected by epidermal growth factor receptor (EGFR) mutations and ALK mutations combined.

There are four primary KRAS mutant alleles—G12C, G12D, G12V, and G13D—that each have different biological effects. The G13D allele responds to EGF receptor therapy, but the other alleles do not. The G12C allele is observed most frequently in lung cancers caused by smoking tobacco. There are different RAS proteins, including KRAS 4A and KRAS 4B. The KRAS 4B protein is a major driver of

human cancer, but it is possible that 4A is required for tumor initiation. More subtleties have been found in the various functions of the KRAS proteins. RAS and RAF protein structures remain unknown, as well as how RAS activates RAF, which may involve a complex dimerization process. Solving the structure of the RAS-kinase may lead to the discovery of potential targets that have not been exploited yet.

A RAS workshop in 2013 defined five projects, with a precursor project (Project Zero) identified later. Project Zero's goal is to obtain a better understanding of the mechanisms of resistance. It focuses on the validation of KRAS as a therapeutic target and the definition of subsets of KRAS cancers that are most likely to be vulnerable to KRAS attack. The project involves a large-scale screen of siRNA knockdowns to determine KRAS-dependent cell lines. Extramural researchers at Harvard, Massachusetts General Hospital, and UCSF have moved forward with this work, focusing on lung cancer cell lines. To leverage resources and avoid replication of effort, the FNLCR will contribute by characterizing pancreatic cancer cell lines. Clustered regularly interspaced short palindromic repeats (CRISPR) technology is better suited to this project than siRNA methods.

Project 1 addresses the structural biology of KRAS proteins to identify new binding sites, thus identifying potential drug targets to inactivate RAS. The goals of Project 1 are to conduct a structural and biophysical analysis of four KRAS mutants bound to key effectors and regulators such as RAF and calmodulin. KRAS proteins will be expressed in *Escherichia coli* cells or insect cells and analyzed quantitatively using amino acid analysis and high-performance liquid chromatography. The KRAS-calmodulin interaction will be characterized by SEC and Western blots. The binding kinetics of calmodulin to wild-type KRAS also will be characterized and the role of cofactors (e.g., GDP and CA2+) identified.

Dr. McCormick explained that Project 2 focuses on cell-based screens for compounds that target KRAS. Developing screens and assays will help to identify drugs and their targets in the KRAS pathway. Mutant alleles are dependent on different downstream pathways, and collaborations with National Center for Advancing Translational Sciences (NCATS) will enable the analysis of the different gene expression profiles associated with KRAS mutant alleles.

Project 3 is based on the discovery that KRAS forms dimers. Complexes containing KRAS has potential as a target of therapeutic action and a readout for assay development. Dimers are detectable by imaging, split luciferase screens and other methods. Disruption of these complexes may attenuate the oncogenic signaling and therefore represent a target of drug discovery. Additionally, oncogenic signaling driven by KRAS is mediated by KRAS dimers and higher order structures in the cell membrane. Cells cultured on micropatterns are more homogeneous in the subcellular localization of cellular structures and improve the ability to quantify changes. Protein biosensors, based on fluorescence resonance energy transfer (FRET) signals can be used to observe protein-protein interactions locally. Protein biosensors will be used as a follow-up for the cell-based screen as well as to identify compounds that disrupt interactions between RAS and RAF.

Members were informed that the goal of Project 4 is to identify proteins on the surface of KRAS cancer cells for targeting nano-particles or immunotherapy, or for use as biomarkers. Using mass spectrometry (MS) methods, such as cell surface proteome mapping, chemical tagging of cell surface proteins in live cells, liquid chromatography–MS analysis of cell surface proteins, and cell surface protein labeling, surface proteins will be isolated and characterized. Bioinformatics tools also will be employed to identify genes differentially expressed on the surface of KRAS mutant cells relative to normal cells of the same tissue.

Project 5 focuses on synthetic lethal screens. Participants from a previous workshop on lethal screens concluded the following: previous whole-genome RAS synthetic lethality screens were substantially underpowered; CRISPR technology is probably superior to RNAi technology; heterogeneity matters (the more cell lines, the better); *in vivo* screens require cells that form tumors very efficiently, and this imposes selective pressure; combining knockdown or knockout of genes with inhibition of specific

(druggable) pathways can reveal new susceptibilities. There are synthetic lethal interactions that are not understood, but if even one KRAS mutant allele in a major human cancer could be targeted as the result of a new synthetic lethal screen, thousands of lives could be saved.

Dr. McCormick stated that the FNLCR has established high-quality standardized reference reagents for the RAS extramural community, including CRISPR reagents and RAS clones. Other reagents are in the process of being developed. Using mechanisms such as the Small Business Innovation Research (SBIR) program, small businesses could contribute to progress on the RAS Project.

FNLCR Resource Deployment Onto RAS. Dr. Atsuo Kuki discussed the contractor resources and staff dedicated to the RAS Project at the FNLCR. Launch of the RAS project occurred through the redeployment of FNLCR resources and manpower, largely in the Cancer Research and Technology Program Directorate. Members were informed that the recruitment of Dr. McCormick to a leadership role in the RAS Project 8 months prior was critical for moving this large-scale effort forward. The RAS Project comprises several technology core laboratories, including protein expression and characterization, genomics, and microscopy, which involve 55 employees who work exclusively on the RAS Project. The FNLCR has an annual budget of $12.3M for the RAS Project. The character of the FNLCR is mainly as a center for storing and sharing reagents, and coordinating large-scale efforts and "team science." The goal of the FNLCR is to be embedded in the research and development community and enable RAS research efforts in the community. Dr. Kuki explained that additional expertise is critical, and recruitment is planned for a senior structural biologist, a senior cancer biologist, and other senior RAS Project leadership roles. The RAS Project is an example of pivoting existing technology, teams, and expertise to address a scientific problem. The RAS Project leverages and shares talent and investments across NCI initiatives.

In the discussion, the following points were made:

- The FNLCR will interact with the therapeutic development community of academic laboratories and industry on several levels, including: providing materials, qualified proteins and reagents to researchers, solving the structures of critical complexes and sharing that information to accelerate drug discovery efforts, and forming formal relationships with companies to develop and utilize drug development screens and identify candidate compounds. Members encouraged interaction and engagement of the NCI Chemical Biology Consortium. Material transfer agreements (MTAs), technical service agreements (TSAs) and contractor- cooperative research and development agreements (CRADAs) are available to FNLCR in facilitating these interactions.

- Members encouraged the FNLCR to share with the extramural community cell lines that are characterized in depth under the RAS Project and the data from those characterizations. This resource would be useful for developing screens, and the integrated data associated with the cell lines (e.g., proteomic, genomic, and biomarkers) would be valuable to researchers. HUBzero®, a platform developed at Purdue University, allows researchers to blog, share information, and upload tools for data visualization within that Web platform; it could serve as a useful data resource tool for the RAS Project.

- The NCI's commitment to the RAS Project encompasses a 3- to 5-year timespan, at which point progress will be evaluated, new directions assessed, and some work possibly transferred to industry or academic investigators. FNLCR leadership recognized the importance of establishing a mechanism to allocate or re-distribute resources appropriately following project evaluation.

- The FNLCR can accommodate possibly three additional new big projects of a similar size to the RAS Project. Conversations with other Yellow Task owners and a balancing of their needs would be a required step in the initiation and management of a new project if the new project is a reprioritization rather than an addition of resources.

- Members noted that projects, such as complex screens, may require different kinds of expertise that could be obtained by partnering with experts in the community. The FNLCR's role might be that of a clearinghouse to enable access of reagents and dissemination of information to the community.

IV. DISCUSSION OF NEW PROJECT IDEAS FOR FNLCR

Dr. Gray introduced the goal of this session, which is to propose potential projects and explain why they would be particularly suited to the FNLCR.

Tumor Heterogeneity—Drs. Joe W. Gray and Jennifer Pietenpol

Dr. Jennifer Pietenpol, Director, Vanderbilt-Ingram Cancer Center, and B.F. Byrd Professor of Oncology, Professor of Biochemistry, Vanderbilt University Medical Center, explained that tumor heterogeneity was discovered in the late 1800s and has been studied for 150 years. Dr. Pietenpol stated that tumor heterogeneity poses a significant challenge in cancer treatment, with a larger issue being how best to leverage NCI's ongoing research efforts in the area. The Tumor Cell Heterogeneity Think Tank, which convened on December 2–3, 2013, made three key observations about tumor heterogeneity:
(1) Heterogeneity arises from epigenomic and genomic events intrinsic to tumors as well as signals from diverse microenvironments. (2) Tumor heterogeneity is a fundamental driver of therapeutic resistance in most human cancers. Understanding this is an urgent and unmet need in cancer treatment. (3) Recent advances in measurement technology, data analytics, and biological models enable new approaches to studies of tumor heterogeneity that can advance progress, particularly if results of high-throughput experiments are shared with the community.

Genomic aberrations are well-established as mechanisms of therapeutic resistance. Understanding tumor heterogeneity and how the clonal frequency of alleles changes over time will help in the design of appropriate therapies. Intra-tumor heterogeneity is visible by abrupt boundaries of gene expression. The degree of heterogeneity can vary substantially between tumors and has therapeutic implications. Targeted molecular therapies select certain clonal populations, and thus lead to more resistant tumors depending on the order and sequence of treatment. Model systems displaying intrinsic heterogeneity can be used to study multi-drug steering strategies and mechanisms. Quantitative dynamic imaging can be used to study the proliferative dynamics of a cell population to heterogeneous single-cell fates in response to drug treatment. Extrinsic signals from the microenvironment also drive heterogeneity, and selected microenvironment proteins influence the therapeutic response.

Advances in measurement technology, microscopy, and bioinformatics allow the exploration of the clonal evolution of tumors. New experimental tools to facilitate the study of heterogeneity include: vital imaging to study dynamic changes in population composition, mass cytometry for high-dimensional assessment of heterogeneity, multi-color super resolution fluorescence microscopy, nanometer resolution 3-dimensional (3-D) electron microscopy, and single-cell sequencing. New computational tools and models also are important for analyzing the data collected from new tools. Critical needs include developing methods to characterize the functional state of cells within a solid tumor as well as cells in the microenvironment; identifying the mechanisms that account for the differences in cancer drug metabolism and toxicity at various stages of life; and developing methods to assign patients to subgroups who will benefit from more specific, defined cancer therapies.

The role of the FNLCR could be to integrate and enable the ongoing efforts to understand heterogeneity, coordinate clinical trials to enable analysis of mechanisms that influence heterogeneity-mediated resistance, establish a national clearinghouse to collect, organize, and disseminate clinical and basic science data applicable to the study of heterogeneity, and facilitate collaborative, pre-clinical and clinical studies across the national cancer program aimed at deciphering and targeting heterogeneity-based resistance.

In the discussion, the following points were made:

- An indepth study of specific tumor types in the context of tumor heterogeneity likely would be more efficacious than a broader heterogeneity program. The deliverable (e.g., tools, core facility) for a program on tumor heterogeneity should be clearly defined. Other potential projects include understanding the role and the mechanisms of heterogeneity, or conducting a comprehensive analysis of two cancers, such as leukemia and kidney cancer.

- The FNLCR could provide a unique value to the community in IT and "big data" arenas. The data from whole genome analysis of tumors should be made available to the community to accelerate discoveries as the cost of conducting this level of analysis is prohibitive at individual laboratories and academic centers.

- A deeply characterized system is highly valuable as researchers do not need to generate the required ancillary information. The FNLCR could serve as a place both to coordinate and integrate data collections and to design clinical trials, collect materials, and analyze data onsite or via partners; in this manner, the FNLCR could enable the comprehensive study of clinical trials to understand both the mechanisms by which the targeted agents act and the mechanisms for resistance that allow tumors to escape them.

- Tools are available to study the evolution of tumors, but few researchers with access to those data are developing models to study it. The FNLCR could support and enable such projects that are not possible to complete through other mechanisms of funding.

- Members agreed that tumor heterogeneity is an important problem that will require the coordination of many different activities, and the FNLCR could have a coordinating role.

Multiscale Imaging of Tumor Architecture and Dynamics—Drs. Atsuo Kuki and Andrew Quong

Drs. Kuki and Andrew Quong, Director, Partnership Development Office, FNLCR, presented a project focused on multiscale imaging technologies. Dr. Kuki said that the FNLCR has the potential to move the field of cancer research forward in critical areas, such as: (1) understanding the molecular and cellular events in the tumor microenvironment that determine whether a tumor at the earliest stages of malignant transformation is eliminated or stimulated for further development; (2) characterizing the functional state of individual cells within a solid tumor; and (3) developing methods to portray the "cytotype" of a tumor (the identity, quantity, and location of each of the different cell types that comprise a tumor and its microenvironment).

Scientists have isolated tumor-initiating stem cells circulating in the blood that are the root of resistance and metastasis. There is a need to identify and study them to understand mechanisms of resistance to therapy. It is possible to clone them *in vitro* and study the malignant transformation of "organoids" derived from these cancer-initiating stem cells. Dr. Kuki proposed to launch a systematic program to study tumor organoids using 3-D models at FNLCR. Such models would be important to fields such as regenerative medicine, bioengineering, and embryonic development. Building a 3D model would entail developing sets of molecular probes and antibodies to allow a comparative and functional study of developmental processes. After testing and validating high-performance molecular probe toolsets, the FNLCR could open this resource to the extramural research community, thereby functioning as a platform for access and partnership.

Dr. Quong explained that the FNLCR is an ideal host for developing multiscale imaging capabilities. Multiscale imaging starts at the subcellular level (i.e., molecular architecture of a single cell), up to the scale of organoids and even whole animals. The strategy to launch this research program would

begin by leveraging existing FNLCR capabilities in sequencing; mass spectroscopy (MS); various imaging techniques (electron microscopy, optical, magnetic resonance imaging [MRI], ultrasound, positron emission tomography [PET]); computation (image analysis, data warehousing, pathway modeling); and animal models. These capabilities should be expanded, and partnerships and collaborations should be formed to develop novel tumor equivalent models and imaging probes.

The FNLCR has a strong capability in electron microscopy, but electron microscopy does not allow tracking of changes through time. In contrast, high-resolution optical microscopy allows visualization of very fine structures and tracking of cells during embryonic development. Light sheet microscopy would allow less-invasive analysis, enabling the study of dynamics. Higher field instruments for animal imaging will provide functional molecular imaging in longitudinal studies. This would extend the FNLCR's existing strengths in sequencing and proteomics to improve capabilities to view biological samples dynamically and non-destructively. The FNLCR would provide a unique value to the community by functioning as a clearinghouse for validated probes; many groups in the extramural community are developing probes, but the costs of sharing are high.

Members were told that the National Laboratory could collaborate with the HUB Foundation for Organoid Technology to develop organoid models. These models could be used to understand the response to external stimuli, conduct molecular profiling within the organoid architecture, determine the molecular and cellular features that may be correlated with metastatic potential, and monitor dynamics of the organoid as it changes. Organoids already have been established from pancreatic ducts and cancers, which mimic the original tissue architecture. Orthotopic xenografts of samples metastasize to distant sites.

Dr. Quong explained that the FNLCR could launch a program to study select 3D model systems and their implantation, build a facility for testing and validating high-performance molecular probe toolsets, and share the 3D models with the research community. The focus should be on large-scale team science, developing reproducible protocols for 3D culture and molecular imaging, and developing new probes for imaging. Multiscale Imaging of Tumor Architecture and Dynamics (MITAD) could be used as a system for comparative functional and architectural analysis of candidate 3D tumor models and their dynamics. Dr. Quong stated that this foundation would enable future comparative characterization projects and provide the basis for strategic technology partnerships and entrepreneurial activity.

In the discussion, the following points were made:

- The concept of organoid culture around which to build imaging capabilities might not extend to systems that investigators are already studying. For this to be a FNLCR project, imaging and modeling capabilities would have to extend to other systems. The key is to develop analytical capabilities that are not available anywhere else, so as to draw researchers to use the facilities and resources unique to the FNLCR.

Implementation of Guiding Preclinical Platforms for Precision Cancer Therapies—
Dr. Terry Van Dyke

Drs. Wiltrout and Terry Van Dyke, Head, Cancer Pathways and Mechanisms, and Director, Center for Advanced Preclinical Research (CAPR), CCR, described potential projects focused on tumor immunotherapies in the preclinical context. Dr. Wiltrout introduced the concept of immunotherapy, a field that was selected as *Science*'s "Breakthrough of the Year" in 2013. Immunotherapy is not just a treatment for a few specific cases (e.g., melanoma) but has generalized applications in cancer treatment. Clinical trials have shown that there is a low frequency of exceptional responders who have a long-term response. In contrast, molecular target therapies tend to have a higher frequency of shorter term responses. Thus, one promising avenue of research is to strategically combine molecular targeting agents with immunotherapy. Understanding the mechanisms leading to the durable immune-induced response may provide useful insights for the development of cancer therapeutics. Focused strategies that exploit adaptive antigen-specific

immunity show promise in modulating tumor immunity. Dr. Wiltrout said that as research advances in the development of molecularly targeted agents based on genomic anomalies in human cancers, the community also should study the mechanisms by which immunotherapy produces more frequent and durable responses.

Dr. Van Dyke informed members that antibody antagonists of suppression elicit durable responses in subsets of patients. There would be value in doing comprehensive genomic analyses of the tumor and its microenvironment, and observing its responses to immunotherapy. These analyses would inform the development of rational treatments. Progress in understanding immunomodulation of cancer response will require a major effort in integrated team science.

The FNLCR could be a resource "hub" for conducting these types of studies and build the necessary technologies and infrastructure. The mission would be to facilitate the development of guiding preclinical workflows for clinical research and effective cancer management. The CAPR would generate mouse models to conduct clinical and basic research, which could be used for biomarker discovery, development of imaging technologies to monitor disease and treatment, and development of preclinical or clinical interactive data management systems. One mouse model that already has been developed is the mouse for Pathway-Specific Serous Epithelial Ovarian Cancer (SEOC), which mirrors human responses to treatment. Other cancers of interest for which there are mouse models include cutaneous melanoma and pancreatic ductal adenocarcinoma.

The CAPR within the FNLCR will have internal projects, but the anticipated mode of operation is to interface and partner with investigators on the outside. Dr. Van Dyke expressed enthusiasm about collaborating with foundations and combining subject matter experts with the necessary technologies to develop successful cancer drugs. The projects would focus on the mechanisms and optimization of therapeutic responses by targeted immunomodulation. The development of robust preclinical technologies will provide a reproducible bridge between basic and clinical investigators. The FNLCR could facilitate collaborations and partnerships, including with the private sector. As a hub, the FNLCR could provide resource optimization through economy of scale, team science, and the sharing of technologies.

In the discussion, the following points were made:

- Members appreciated the phenomenal technology and infrastructure for models systems that are available but were unclear about the questions that the project would address using these technologies. The response was that one important question is to understand why some patients respond to therapy whereas others do not. Other questions could arise from the research community.

- Dr. Varmus stated that the intent of these proposed projects is to discover the next direction for the FNLCR. The RAS Project is an example of a productive FNLCR activity but should not be perceived as the template for future National Laboratory projects.

Immunologic Approaches—Dr. Beatrice Hahn

Dr. Beatrice Hahn, Professor of Medicine, Division of Hematology/Oncology, University of Pennsylvania, informed members that she communicated with Dr. Jeffrey Lifson, Director, AIDS and Cancer Virus Program (ACV), FNLCR, to explore project ideas that might be translated from the infectious disease research to the cancer arena. Dr. Lifson's laboratory is designing chimeric antigen receptors for targeting T cells to combat simian immunodeficiency virus (SIV) in a Macaque model. Immune cell modulators that are discovered through the study of infectious diseases such as in AIDS vaccine research might have potential use in cancer therapy. Dr. Hahn proposed an approach in which stakeholders are queried about the most important questions related to use of immune modulators and cancer, with the goal of better understanding how the FNLCR could assist in a combined national effort. If there is interest, a think tank workshop could be convened to discuss the issues. Dr. Hahn indicated that pursuit of a think tank

approach would need input for a list of who should be involved and for questions which should be asked. Members were told that Dr. Hahn contacted Dr. Carl June, University of Pennsylvania, who indicated that pharmaceutical companies have been engaged in related efforts during the past 5 years. Opportunities exist, however, in the areas of vector development and production as well as good manufacturing protocol (GMP) production for clinical trials. Although immunotherapy has progressed in the infectious disease arena, additional research is needed, and there is an opportunity to bring together the related efforts in infectious disease research and in cancer to find common ground. Dr. Hahn noted that at the FNLCR the AIDS and Cancer Virus Program already brings together the fields to some extent.

In the discussion, the following point was made:

- There is a lot of interest in identifying the determinants of response and distinguishing between immunotherapies. A workshop in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) to determine whether certain elements of shared interest coalesce into an initiative could be advantageous.

- A workshop could offer additional advantages in raising awareness in the cancer immunology research community for resources and capabilities at FNLCR that might be put to use.

Synergistic Therapeutic Combinations for Molecularly Defined Cancers—Dr. Levi Garraway

Dr. Levi A. Garraway, Associate Professor, Department of Medicine, Harvard Medical School, and Assistant Professor of Medicine, Medical Oncology Service, Dana-Farber Cancer Institute, proposed the idea of positioning the FNLCR to conduct systematic studies of anticancer therapeutic combinations through a preclinical cell line screening project. Although immunotherapies have made significant advances in recent years, achieving durable control of many types of advanced cancers likely will require effective combinations of therapies. Current understanding of the spectrum of therapeutic combinations, including the efficacy in specific genetic and molecular contexts, has been limited by issues of multiplicity and existing infrastructure. The FNLCR provides an ideal platform to overcome several of these challenges by leveraging advances in robotics, cell line characterization, screening throughput, and tool compound ability to launch a large-scale effort to conduct *in vitro* preclinical combination screens.

The FNLCR has proven success with large-scale screens, as demonstrated by the NCI-60 pharmacologic screening effort conducted over the past 3 decades by NCI's Developmental Therapeutics Program (DTP). The NCI-60 Program introduced a paradigm for systematic screening efforts across multiple cell line models, and although the genetic spectrum of diseases addressed was narrow, the concept introduced new experimental opportunities.

Dr. Garraway presented several scenarios for the proposed project. The first scenario, 1A, would utilize a FNLCR-centered effort similar to the RAS Project. The FNLCR could begin by partnering with the American Type Culture Collection (ATCC) and other established cell line collections and then augment the cancer cell line resources through community outreach efforts to increase representation of particular lineages and genetic contexts. In parallel, the FNLCR would acquire, through purchase or synthesis, a robust collection of chemical compounds and focus on a set of mechanistically validated or highly relevant probes. The FNLCR also would need to develop the capacity to perform synergy screens at a minimum of 50 drug combinations across 100 cell lines per year. Dr. Garraway displayed an example of a scalable screening format to demonstrate how synergistic cell growth inhibition can be assessed in the presence of therapeutic combinations. In addition, assays in the presence of different cell growth conditions (e.g., 2-dimensional [2-D] growth on plastic versus 3-D matrices) could provide added complexity.

A second scenario, 1B, would entail a distributed effort partly housed at the FNLCR, but also involving partnerships with the extramural research community. An RFA could be issued to perform combinatorial screening efforts, and grant recipients would convene at an initial workshop to establish

streamlined approaches, protocols, and standards. This would generate a network of connected investigators with a vested interest in the project and allow the development of innovative assays to study complicated topics, such as intermittent dosing, in preparation for clinical pilot studies. One example of a proof-of-concept innovation that vastly increases assay capacity involves DNA barcoding of cell lines to allow for multiplex analysis. This technique, known as PRISM, was developed by Dr. Todd Golub, The Broad Institute, to recover genotype-phenotype relationships.

In contrast to the 1A/B approaches that rely on experimental serendipity, scenario 2 applies a targeted combinatorial screening strategy that anchors one compound on the basis of known mechanistic efficacy while interrogating additional compound(s). For example, a MYC inhibitor could serve as an anchor in K-RAS mutant cell lines to permit screening a larger collection of potential therapeutics or explore compound synergy screens with two or more additional compounds. This approach would begin with a hypothesis for an efficacious compound in a particular genetic context.

Scenario 3 utilizes a synthetic lethality approach that combines a drug with a genetic perturbation, such as a shRNA or CRISPR library. The goal is to utilize large numbers of cell lines that share a common genetic or molecular feature to reduce individual cell line or off-target effects, a scope that could be accomplished at the FNLCR. Dr. Garraway noted that this strategy has been proposed to support the RAS Project.

A combinatorial cell line screening effort is on the critical path to durable cancer control and represents a natural extension of the existing FNLCR capabilities through the NCI-60 Program. Leveraging coordinated extramural research efforts could provide synergistic research opportunities and envelop new technologies into the FNLCR, such as PRISM multiplexing or robotics.

In the discussion, the following points were made:

- Members expressed support for the proposed combinatorial screening project.

- NCI leadership told members that a manuscript in preparation for publication demonstrates the efficacy of screening 100 drugs in 60 cell lines for a total of 5,000 combinations. Many unexpected synergistic combinations, several of which are now being studied using *in vivo* models, were uncovered through this effort. As a result, the NCI released a request for information (RFI) to query the research community about needs for combinatorial screening because it is such an important yet intensive technique. A large library of investigational agents is available at the FNLCR in quantities appropriate for tissue culture as well as animal models. Although the library must be used at the FNLCR facility, investigators could send postdoctoral fellows to access the resources.

- Combinatorial screening is expensive and requires an adequate scale to achieve success, which can be provided by the FNLCR.

- Cell lines themselves are heterogeneous, which must be considered in the assays. Secondary screens can be employed during validation.

Functional Assessments of Cancer Genome Aberrations—Dr. Cheryl Willman

Dr. Cheryl L. Willman, Director and CEO, Cancer Research and Treatment Center and Maurice and Marguerite Liberman Distinguished Chair in Cancer Research, University of New Mexico, reminded members of the importance of applying advances in technology and engineering for real-time sampling of a tumor within its microenvironmental context. The “holy grail” of cancer medicine would involve *in vivo* measurement of tumor mutation spectrums and functional therapeutic responses to enable effective treatment of human cancer.

A large collaboration coordinated through the NCI's Children's Oncology Group (COG) has resulted in the sequencing of approximately 1,200 pediatric acute lymphoblastic leukemias (ALLs) in collaboration with the NCI The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiatives. This project has been completed through a large consortium including COG, TARGET, the St. Jude Children's Research Hospital-U Washington, St Louis Pediatric Genome Project, the University of New Mexico, the University of Colorado, and the University of California-San Francisco. The analysis has revealed many novel mutations. Notably, therapeutically resistant leukemias in children are populated by RAS mutations in up to 30 percent of cases. RNA-seq data from another set of cases revealed 100 variants of cryptic translocations involving seven genes encoding tyrosine kinases, which is a large amount of genetic complexity. Currently, mutations can be identified through gene expression-based screening tools and RNA-seq. Importantly national clinical trials are in design in both pediatric and adult ALL to integrate these findings and target these ALL patients to treatments incorporating tyrosine kinase inhibitors. Although these initial findings are exciting, there is no certainty that exposure to a single tyrosine kinase will yield a durable response. Next year, 3,000 children in a pediatric clinical trial (COG AALL 1131) will be screened and biologic samples will be collected. Although that clinical trial is investigating tyrosine kinase inhibitor response with or without traditional chemotherapy, members were told that those samples could be subjected to a combinatorial, unbiased functional screen to identify compounds that in combination will give the children a durable response. This project would be ready for implementation immediately.

Members were told that the project could begin with a study focused on developing and applying methods to primary human cancer cells *ex vivo* or *in vivo* to determine the heterogeneity of the clonal subpopulations, as most of the children with leukemia possess as many as 12 subclones and understanding the functional consequences of those mutations is important. Functional genomic characterization of a sample set would require cancer cell genomic data, which could be procured from TCGA and TARGET datasets. Approximately 40 patient-derived xenografts (PDX) have been collected, which represent virtually all of the targetable mutations that would be treated in clinical trials. The response of cancer cells to a screen is an important indicator of efficacy, but the host genomic polymorphic factors are another important consideration in a patient's ultimate response to therapy and must be captured in the overall assessment of therapeutic response. The suggested approach involves unbiased, high-throughput functional screening of compounds (individual or in combination) using existing drug libraries and repurposed drugs as well as siRNA and CRISPR approaches. The clonal heterogeneity of response could be addressed using this approach.

Dr. Willman also described the current efforts that could be scaled up to leverage the initial investment. For example, Dr. Louis Staudt, CCR, has begun to perform a similar study in lymphoma, performing unbiased drug and siRNA screening in samples that have undergone extensive genomic analysis. The objective is to combine detailed structural and functional genomic analyses in a cancer cell to identify the essential targeted pathways. Dr. Staudt's work enabled the discovery of novel mutations in the immunoglobulin receptor and NF-kappa B signaling pathways in B-cell lymphoma (BCL), which have been identified as two of the most important signaling pathways in BCL and are being targeted in clinical trials. In a related effort, Dr. William Hahn, The Broad Institute and Harvard University, is constructing 3,000 cDNAs containing mutations identified in TCGA to perform gain-of-forward screens and perform combinatorial sequencing. Similarly, NCI's Cancer Target Discovery and Development (CTD^2) project leverages the expertise of 13 research groups to perform focused functional analyses.

A study at the Knight Cancer Institute funded by the Leukemia and Lymphoma Society is also taking a similar approach, analyzing primary human tissue cancer samples in real time, focusing on acute myeloid leukemia (AML). The research group is employing a combination of detailed sequencing (e.g., whole-genome sequencing and RNA-seq); functional analyses (e.g., RNAi, kinase inhibitors); informatics (e.g., integration of data on every patient, pathway analysis, machine learning); target validation; and immediate enrollment of the patient into an appropriate clinical trial. A large heterogeneity in response to different treatments has been shown during the analysis phase. The project has been successful in procuring

human samples, analyzing them expediently, and targeting patients to trials. Because each patient is very different, designing clinical trials in the context of a large variety of targets will be challenging.

In closing, Dr. Willman reiterated the ultimate goal of obtaining and using primary human cancer cells and tissues for unbiased, functional drug screens, rather than established cell lines. Methodologic improvements are essential to assure one can perform detailed genomic profiling along with combinatorial functional screening on primary patient samples to perform truly personalize medicine and personalized therapeutic targeting in the future. Specifically, translating the TCGA and TARGET studies to national clinical trials provides an opportunity to leverage samples in unbiased screening approaches. She emphasized that the FNLCR has the capability for this type of project.

In the discussion, the following points were made:

- Members expressed support and excitement for the proposed project.

- Solid tumors present a challenge with a slow rate of growth following biopsy. A valuable technique development solution would include miniaturization of the process to reduce the number of cells required for the experiments.

- TCGA might be difficult to use for this project because information about the genetic architecture of cell lines is unavailable.

- Partnerships with clinical trial and health care networks is critical to access all of the patient data related to medications and comorbid conditions in relating the information to the available outcomes and considering the heterogeneity of treatment response. A comprehensive set of clinical and epidemiological data, along with the tumor characteristics and functional screens, would be ideal.

- Members discussed the opportunity to focus on pediatric cancers but observed that the vast majority of cancers in the United States develop after age 50. Pediatric cancers are more facile to study because they develop within a short period of time, comorbid conditions are restricted, and up to 92 percent of children are accrued to clinical trials. Integration of genomics and RNA-seq will begin in July 2014, for 3,000 children in a COG clinical trial (AALL1131), providing an opportunity for prospective thought about how to perform the study correctly. Members also suggested performing two sets of projects to address pediatric cancer as well as adult disease as a comparative opportunity to appreciate the extremes of complexity.

- The Knight Cancer Institute study involves numerous partnerships. Due to the lack of clinical infrastructure and resources, the FNLCR might not be the best place to perform the similar suggested study. The FNLCR, however, possesses large-scale, unbiased combinatorial screening capacity that is unavailable elsewhere. Developing such a project in academia is a time- and labor-intensive endeavor that requires significant coordination, which the FNLCR could undertake. Screens could be run at the FNLCR and technology could be developed to screen minute amounts of *ex vivo* samples, which would be transformative. NCI's Chemical Genomics Center could be a partner in the screening effort because of its better robotics infrastructure.

Biology Coordinated Clinical Trials—Dr. James H. Doroshow

Dr. Doroshow explained how the NCI has been using human tumor tissue to transform experimental therapeutics. One major challenge is collecting tissue from patients, which is then subjected to an iterative process involving molecular characterization to develop new preclinical models specific for the individual and ultimately are used to treat the patient. Within the context of the NCI, the FNLCR allows

access to clinical trials networks that are not available to single centers, allowing the collection of tissues nationally at a scale that is difficult to duplicate elsewhere.

The PDX Repository was created to store the hundreds of models produced from primary tissues and blood with circulating tumor cells supplied by 15 NCI-designated Cancer Centers or developed from NCI-supported clinical trials. One such trial that will be generating material is the newly initiated Molecular Profiling-based Assignment of Cancer Therapeutics (M-PACT) trial. The objective of M-PACT is to assess whether matching mutations to therapy (using a limited number of drugs and combinations) enhances the response rate and progression-free survival in a randomized, prospective trial in which patients directly receive their matched therapy or receive it at a time when they progress from a limited group of drugs. Solid tumors from adults are being interrogated with four drug protocols targeted to 22 genes within three specific cellular pathways.

One critical component of the protocol development is the robust, early phase network that collects biopsies from metastatic sites. M-PACT was approved by the U.S. Food and Drug Administration (FDA) in December 2013, opened 2 weeks ago at the NIH Clinical Center, and will be available at 30 different sites that will provide fresh tumor biopsies fixed for genomic assessment. Biopsy material will be used to create PDX samples to perform a variety of different experiments and develop models. Accessing fresh tissue samples is among the most expensive components of the M-PACT trial. Approximately 1,000 patients will be screened, and the crossover study design from rebiopsy at the time of progression will be of immense clinical interest.

M-PACT will provide fully characterized, clinical trial grade tissue biopsies from sites of recurrence and blood samples for the use of genomic analysis, PDX, and cell line establishment. A proof-of-mechanism preclinical trial was performed to determine whether the results of the M-PACT trial can be predicted with respect to actionable mutations. Each “patient model” was treated with all matched and unmatched agents (singular and in combination) to increase statistical power and allow for assessment of pharmacodynamics. For each model, 250 samples were generated for use by extramural investigators in other studies. Planned analyses include growth curves, mutation assay, gene expression, and histology; materials will be available at the FNLCR for distribution on request. Depending on the success of the pilot preclinical trial, the continuation of the study with patient-generated PDXs from M-PACT could be assessed using a retrospective correlation of preclinical results with the therapeutic outcome of M-PACT.

The M-PACT preclinical trial demonstrated the feasibility of generating PDXs from biopsy samples of metastases and showed that passaging PDX tissues successfully expands the available material while maintaining genetic stability and reconstitution ability. Preliminary results indicate that treatment of models with genomically matched and unmatched agents can produce clinical outcomes consistent with the type of targeted therapy used. The available materials provide a unique opportunity for the extramural community to study the mechanisms of targeted agent sensitivity and response heterogeneity.

The PDX Repository can be optimized further for extramural investigators by developing a method for prioritized distribution of clinically annotated PDX tumors, inviting the community to contribute data to the PDX Repository, performing preclinical studies for the extramural community, and considering the use of annotated model development for Phase II trials if the feasibility of the preclinical M-PACT study is confirmed.

In the discussion, the following points were made:

- This project provides a hypothesis-generating platform to address issues of tumor heterogeneity through basic research. The renewable resource adds translational capacity.

- One limitation of the project is the small size given the genomic heterogeneity in the tumors. The FNLCR has the capacity to increase the scope of the project to analyze additional samples from other clinical trials.

- The largest component of the project cost is the needle biopsy, which costs up to $3,000; the animal and observational costs are much lower. The analysis easily and inexpensively could be appended to other trials that provide biopsy samples.

- NCI-designated Cancer Centers will provide surgical samples from untreated patients as well as those who have progressed.

V. SUMMARY OF THE DAY'S DISCUSSIONS

Dr. Joe W. Gray

Dr. Gray provided a summary of the day's discussions about the direction and potential activities for the FNLCR. He noted that many of these activities are needed by the community, would be difficult to obtain funding to complete, and may require new resources or redeployed funding. Ideas included expansion of the laboratory's capabilities that have been built for the RAS Project to guide the development of drugs against other important targets. In addition, the FNLCR could serve as a coordinating center for a community of research on a complex question, such as heterogeneity, play a pivotal role in advancing biology-coordinated clinical trials, or help develop better biological models. The laboratory could provide services as a center for either advanced technology development, collaborating with local universities that have a substantial physics department, or for projects requiring industrial-scale biology. Another possibility is for the FNLCR to act as a user facility, such as for PDX models or multiscale imaging, before making available certain advanced technologies. The FNLCR should hold meetings or a series of workshops to develop concepts and engage the research community in these areas.

Dr. Varmus remarked on the hierarchy of possible activities, including holding a workshop to consider one or more of these topics discussed; expanding existing FNLCR capabilities; or an activity related to the NCI's large-scale clinical trials that can be conducted most effectively and efficiently only at the National Laboratory. He added that an opportunity might reside in an intermediate stage between a project and a core function.

VI. PERSPECTIVE FROM DEPARTMENT OF ENERGY (DOE) NATIONAL LABORATORIES

Introduction of Speakers—Dr. Joe W. Gray

Dr. Gray told members that the purpose of this session is to learn from the structures and experiences of DOE National Laboratories to better understand how to develop the FNLCR into a true National Laboratory-like enterprise. He welcomed and introduced colleagues from DOE National Laboratories: Drs. Sharlene Weatherwax, Associate Director of Science for Biological and Environmental Research, DOE; Thom Mason, Director, Oak Ridge National Laboratory; Reinhold Mann, Associate Laboratory Director, Environmental, Biological, and Computational Sciences Directorate, Brookhaven National Laboratory; and Kathy A. Yelick, Associate Laboratory Director for Computing Sciences, Lawrence Berkeley National Laboratory.

Dr. Varmus welcomed DOE constituents on behalf of the NCI. He said that the NCI has had its FFRDC for 40 years and is striving to balance support of the FNLCR with its intramural and large extramural research grant programs to ensure that the most interesting and productive activities are supported. Changes in management and research have been implemented at the FNLCR, and leadership continues to seek new ideas and processes that are compatible with best fiscal and intellectual configuration at the Frederick facility.

Office of Science, DOE—Dr. Sharlene Weatherwax

Dr. Weatherwax discussed the management of the DOE's Office of Science National Laboratory, which is a complex and ever-evolving process. The DOE is led by Secretary Dr. Ernest J. Moniz, who directs three major areas focused on national nuclear security, science and energy, and management and performance. Science and energy are combined to ensure cross-fertilization of ideas between fundamental research and applied technology offices. The Office of Science and applied topics (e.g., renewable energy, electricity delivery, and energy reliability) fall under the purview of the Office of the Under Secretary for Science and Energy.

The DOE owns 17 national laboratories distributed across the country, which together comprise a system intended to accomplish several major goals. The most important objective is to execute long-term government missions and the National Laboratories are stewards of that mission and first responders when an urgent national need arises. The DOE's National Laboratory system was created to develop unique scientific capabilities beyond the scope of academic and industrial institutions to benefit the scientific and technological communities. The development of unique capabilities is encouraged while maintaining a spirit of collaboration and partnerships. The National Laboratories are responsible for developing and sustaining scientific and technical capabilities, which was an initial objective related to weapons production.

The DOE's National Laboratory system is distinguished by five major elements: laboratories must be mission driven, perform science at a large scale, be comprised of multidisciplinary teams, consist of distinctive, powerful research facilities, and provide safe and secure operating environments. The majority of Federally Funded Research and Development Centers (FFRDC) are government-owned, contractor-operated laboratories; this management model necessitates a unique legal relationship by a Management and Operation (M&O) contractor. The M&O contractor can be a university, nongovernmental organization (NGO), or industrial entity, which recruits the best contractor personnel and research management practices for the National Laboratories while ensuring the flexibility necessary to engage academia and the private sector. National Laboratory contractors are selected competitively under a policy designed to address many performance criteria and balance the DOE's interest in obtaining the best value with the benefit of a long-term relationship. The individual science elements may evolve over time, but they are shepherded by the management of the M&O contractor in collaboration with the DOE headquarters, which provides federal oversight along with the federal site offices. DOE headquarters provides strategic planning and scientific direction, and the site offices coordinate local management. Most DOE laboratories receive funding from multiple sources, including DOE, NIH, and U.S. Department of Homeland Security (DHS) as well as private funding. This balance provides a rich environment for the researchers.

Members were informed that three DOE National Laboratories support the National Nuclear Security Administration (NNSA) mission, four perform applied technology, and 10 support the Office of Science. Some laboratories are focused on a particular technology office, such as the National Renewable Energy Laboratory (NREL). Together, the laboratories carry out the missions of the DOE. The Office of Science is the primary fundamental research granting office within the Agency with a total budget of $5 B, which is divided evenly between research and facility operations. Acting Office Director Patricia Dehmer leads three lines: Field Operations, Science Programs (e.g., Advanced Scientific Computing Research, Basic Energy Sciences), and resource management. Each program office has its own strategic goals, disciplinary strengths, and distinct culture for engaging with the academic community. Cross-office initiatives promote transdisciplinary efforts. The Office of Science supports Nobel prize-winning research projects in the physical and energy related sciences; graduate students, postdoctoral fellows, undergraduates, and engineers at more than 300 institutions; and the largest collection of scientific user facilities to engage the external community and provide a signature role in leading a community of science.

The Office of Science's user facilities are open to all interested potential users, with resource allocation being determined by merit review of the proposed work. In general, user fees are not charged for

non-proprietary work to multiply the impact of the effort. The facilities are designed not to compete with private-sector resources, underscoring the unique role of the DOE laboratories in addressing unmet needs. Two types of research funding modalities are applied at the National Laboratories: limited term projects are funded by merit in response to targeted Funding Opportunity Announcements (FOAs), and scientific focus areas (SFAs) provide a block of sustained funding to support integrated teams.

Dr. Weatherwax stated that each laboratory performs specific activities in a number of scientific areas that all address DOE missions. Many decisions about strategic directions are performed at the Laboratory Director level. The Office of Science engages the National Laboratories in strategic planning each year to ensure progress and address challenges. To ensure adequate contractor support, the National Laboratories receive annual performance evaluations addressing eight elements: (1) mission accomplishment; (2) design and operations of research facilities; (3) program management; (4) competent leadership and stewardship; (5) integrated safety, health, and environmental protection; (6) business systems; (7) operating facility and infrastructure portfolio; and (8) integrated safeguards. Success is measured differently for the National Laboratories and universities. The 10 Office of Science Laboratories have demonstrated steady growth in external users for the unique facilities, ultimately transforming the original focus of the laboratories.

In the discussion, the following points were made:

- More than 50 percent of Office of Science funding is for the National Laboratories; the remaining 50 percent is directed toward universities for multidisciplinary research projects in response to an FOA. A competitive relationship between the National Laboratories and the extramural research community is not ideal. Currently, funded academic projects have a limited duration and narrower scope. Collaborations between academia and the National Laboratories is encouraged but not mandated; most principle investigators (PIs) have a relationship with the associated National Laboratory. Regular investigator and user facility meetings are designed to stimulate cross-fertilization between projects.

- The research performed by the DOE National Laboratories is large scale. A field component might be accompanied by a high-performance computing component and integrated scientific expertise; this breadth of proficiency exceeds the capacity at most academic research institutions.

- The larger Office of Science vision is set through a process initiated by the Secretary of Energy. Strategic planning cascades through the DOE hierarchy, and both Office and stakeholder input help inform a 5-year strategic plan.

- The Laboratory Director plays a critical role in setting the agenda and direction for the research. Most Directors come from a respected academic background.

- Investments in user facilities and extramural DOE national laboratory research are critical to reach the goals of the Office of Science.

Oak Ridge National Laboratory—Dr. Thomas E. Mason

Dr. Mason explained the distinction between the contractor and the laboratory using the Oak Ridge National Laboratory logo, which emphasizes the Laboratory but indicates that it is "managed by UT-Battelle for the U.S. Department of Energy." As Laboratory Director, Dr. Mason also is the President and CEO of UT-Battelle, LLC, which is a company designed specifically to manage Oak Ridge National Laboratory. Dr. Mason explained that most of the National Laboratories have transitioned to this model, although exceptions—such as the management of Berkeley National Laboratory by the University of California—do exist. The LLC has a Board comprised of representatives from UT and Battelle as well as a Science and Technology Committee with representatives of regional core universities. The allegiance of

laboratory staff is for the Oak Ridge National Laboratory. Changes in contractor support result in profound changes at the senior management level, but do not affect most of the staff. The DOE Office of Science deliberately avoids a profit-motivated contract model through reduced fees.

Dr. Mason reiterated that the DOE is a major supporter of research and development, particularly in the physical sciences. Approximately 80 percent of the Oak Ridge National Laboratory's funding derives from the DOE; the remaining 20 percent constitutes work for other federal agencies, such as the Nuclear Regulatory Commission. Privately funded research represents a small fraction of the Laboratory's budget. Program funds are taxed to generate overhead resources to operate the National Laboratory.

DOE National Laboratories are distinguished by sustained support aligned with the DOE mission, delivering large-scale, long-term programs with the talent needed to address the Nation's energy, environmental, and nuclear challenges through transformative multidisciplinary science and technology. Stewardship of powerful, distinctive research facilities with safe and secure operating environments are important features of the National Laboratories.

The Oak Ridge National Laboratory is DOE's largest science and energy laboratory with 4,400 employees, an operating budget of approximately $1.5 B, and significant high-performance computing, materials research, and energy portfolios. The diverse energy portfolio is focused on energy generation, distribution, and end use, including projects on energy efficiency, vehicle technology, buildings, fission, and fusion. The Oak Ridge National Laboratory contributes to DOE's mission by conducting basic research to understand materials and improve computational tools. The Laboratory's most challenging project is managing the United States' contribution to the International Thermonuclear Experimental Reactor (ITER). Guest scientists come to the user facilities to conduct their research programs. Recent efforts to modernize the facilities represent a sizeable investment for the Laboratory.

The mission of the Oak Ridge National Laboratory is to deliver scientific discoveries and technical breakthroughs that will accelerate the development and deployment of solutions in clean energy and global security, and in doing so create economic opportunity for the Nation. Science is the largest focus, followed by global security and energy technology; signature strengths of the Laboratory include computational science and engineering, materials science and engineering, neutron science and technology, and nuclear science and technology.

Each program within the of Office of Science—including the basic energy sciences, advanced scientific computing, and high energy physics, among others—has a Federal Advisory Committee Act (FACA) Committee to help direct long-term planning. The National Laboratories conduct their own review processes to guide the organization as well as annual strategic planning exercises to establish targets for discretionary funds and identify emerging opportunities. At times, a breakthrough in technology can provide the foundation for novel basic research, as in the case of the Linac Coherent Light Source (LCLS). Other times, the scientific question is apparent and tools are developed to address the demand. The strategic planning cycle product is a concise DOE Laboratory Plan for the Oak Ridge National Laboratory, which is influenced by national research and development priorities, National Academy of Science (NAS) studies, and the DOE Strategic Plan. The Laboratory Agenda identifies critical outcomes and initiatives to accomplish the strategic objectives of excellence in science and technology, laboratory operations, and community engagement for the coming year. The Laboratory Agenda also guides annual business and initiative plans.

Dr. Mason described the development of the Spallation Neutron Source (SNS) as an example of a large-scale project conducted by the Oak Ridge National Laboratory. The process that led to the SNS, which included a $1.4 B capital investment, was initiated in 1980 with a report of the review panel on neutron scattering (Brinkman Panel Report), which indicated that leadership of the topic had transitioned to Europe. A National Academy of Sciences (NAS) study then recommended the development of an advanced neutron source facility in the United States to recover prominence. In 1993, the advanced neutron reactor

specifications were developed into a proposal that was subsequently waylaid due to political and budgetary challenges. Tremendous progress in accelerator technology, however, provided the opportunity for an accelerator-driven neutron source proposal that was approved in 1998. The first neutrons were produced at the SNS in 2006, and target operating levels of the facility were reached in 2010. The DOE Office of Science maintains rigorous control over projects. National Laboratories maintain excellence in project and risk management that is overseen by a federal Project Director.

In the discussion, the following points were made:

- There are more than 150 joint appointments between UT-Knoxville and Oak Ridge National Laboratory. Joint appointments also exist with Vanderbilt University, North Carolina State University, and Duke University.

- Dr. Mason joined the Oak Ridge National Laboratory prior to the UT-Battelle contract in 1998 when the SNS was under construction.

- The Federal Government owns all of the land and almost all of the facilities at the Oak Ridge National Laboratory.

- A change in contract management replaces the senior management and is an option to increase efficiency in operating a National Laboratory if the current management is inadequate. A structural reorganization within the Oak Ridge National Laboratory led to the launch of UT-Battelle, LLC. Now that UT-Battelle, LLC, is nearing the end of the contract term, the benefits of competition for a new contractor will be weighed against the potential disruption in deciding on a contract extension.

Brookhaven National Laboratory—Dr. Reinhold Mann

Dr. Mann informed members that regional context matters for the DOE National Laboratories; the Brookhaven National Laboratory is the only multiprogram National Laboratory in the northeast. A snapshot of FY12 indicated that Brookhaven is a $700 M laboratory, with three-quarters of the funding applied to research in basic energy sciences, nuclear physics, and high-energy physics. Work for non-DOE customers comprises more than 10 percent of the budget. Annual planning efforts strategize whether the mix of research best positions the Laboratory to accomplish its mission.

National Medal of Science and other award-winning research can be traced back to Brookhaven, demonstrating the Laboratory's research leadership. Recent research awards related to the National Synchrotron Light Source (NSLS) include ribosome structure and ion channel impulse generation, and several others relied on the Alternating Gradient Synchrotron (AGS). Joanna Fowler was awarded the National Medal of Science for pioneering the development of radiotracers for positron emission tomography (PET) imaging, which was a multidisciplinary project that exemplified all of the strengths of a National Laboratory.

Dr. Mann explained that National Laboratory facilities are evaluated by their scientific merit and whether they fulfill a justifiable unique niche that cannot be addressed with traditional academic research facilities. The NSLS is funded in part by the NIH, providing a hub that enables many technical advances from multidisciplinary teams. The Brookhaven National Laboratory includes computational facilities that are intended to promote interactions with small and medium-sized businesses and a new initiative to study renewable energy in the northeast through the Long Island Solar Farm. The Brookhaven National Laboratory utilizes a collaborative approach that spans basic science to research applications. Partnerships with Brookhaven's four frontier energy research centers, industry, state agencies, and Stony Brook University focus on superconductivity, catalysis, and other topics.

Brookhaven National Laboratory is owned by the Federal Government and managed by Brookhaven Science Associates, LLC, with a structure that mirrors closely the organizational structure at Oak Ridge National Laboratory. Brookhaven Science Associates, LLC was formed through a partnership with Stony Brook University and Battelle. A Science and Technology Steering Committee is convened three times per year to provide feedback to the Board on scientific direction and quality of the research, which influences the annual performance review. Performance feedback from the DOE is formally conveyed once per year. Management goals for each year are derived from the strategic planning documents. In addition, official performance review grades are published on the Internet.

The annual planning process at Brookhaven National Laboratory is initiated with a formal strategy retreat that involves key scientists and department chairs. The challenge with the process is to provide a solid bottom-up component with a top-down element. Approximately $30 M is allocated for laboratory-directed research development and program development. Any ideas that require sustained investments are formulated as initiatives with an associated business plan because the capacity to sustain large annual investments is limited and funds must be allocated judiciously. As an example, if Brookhaven's current focus on data-centric computing is developed into an initiative, a certain investment would be required on an annual basis.

Dr. Mann said that the laboratories within Brookhaven are organized into directorates that align with program offices in the DOE. Each of the Brookhaven laboratory directors have three major functions: capability stewardship, customer relations, and horizontal integration to ensure connectivity between programs. Oversight and review is provided at all levels within the organization.

In the discussion, the following point was made:

- A business plan provides a strategy to expand an existing effort or develop a new initiative. It addresses the scientific opportunities and challenges as well as funding prospects, both internal and external to the DOE. The business plan describes resource requirements (including leadership) and feasibility for the proposed project to ensure success. The DOE Laboratory Director makes the ultimate decision about funding initiatives.

Lawrence Berkeley National Laboratory—Dr. Kathy Yelick

Dr. Yelick stated that the Lawrence Berkeley National Laboratory (Berkeley) was founded in 1931 on the principles of team science and is the oldest of the National Laboratories. Berkeley excels at interdisciplinary research, which is difficult to conduct in the university setting, and the scientific quality of its research is shown through 13 associated Nobel Prizes. The Laboratory is operated by the University of California (UC) at Berkeley with an $800M annual budget and is used robustly by the UC science complex. Approximately two-thirds in UC nurse computing use Berkeley facilities, and many FOAs in the computing field call for joint activities involving the university and laboratory. Being one of many DOE National Laboratories presents a healthy competition. This influences Berkeley's entrepreneurial style of bottom up science, and requires a visionary leadership team with capability to synthesize ideas that are arising from the bottom and articulating them as a coherent story.

Members were informed that the Lawrence Berkeley National Laboratory uses a strategic planning process. Usually, strategic plans do not change significantly from year to year but rather morph, or transform, over time. This year's strategic planning process, which involved the Laboratory Director and Associate Laboratory Directors, shifted focus from a large facility that was moved to another site to the creation of an energy technologies area. Focus areas at the laboratory level are: microbes to biomes; extreme science data initiative; diffraction-limited ALS (light source) for materials and biology; energy innovation; diversity and inclusion; and service technologies for science. A previous initiative on community relations was completed.

Berkeley's organizational structure has changed over the years and now includes several Assistant Laboratory Directors who report to the Laboratory Director instead of the previous 23 direct reports. The National Laboratory uses the Laboratory Directed Research and Development (LDRD) vehicle with an annual budget of $20M. The management culture is that of influence rather than direct implementation, and investigators work on problems together, help define a scientific vision to discuss with DOE, and develop projects that fit within DOE's priorities. Dr. Yelick said that Berkeley has achieved notable successes from the LDRD, such as the Joint Bio Energy Institute.

Members were informed that Berkeley is building a site to handle extreme data for science. This has been driven by both the availability of technology and DOE concerns about the placement of user data, which has grown exponentially. The building is underway, with financing covered by bonds issued by UC as the contractor, and will house a DOE-specific network to facilitate the movement of large datasets between the laboratories and user facilities. This effort is the result of dialogues among the laboratories, DOE, and UC.

Berkeley prides itself on the impact it has had in various areas, including industry and technologies licensed by industries. One example is the work of Berkeley scientist Dr. Rosenfeld on the standards of energy efficiencies in refrigerators and the impact on energy savings. Dr. Yelick told members that 30 Berkley laboratory spinoffs contribute $695 M to the Bay area and $2.8 B nationally each year. A visionary leadership, the right funding model, and attention to intellectual property rights are critical components to Berkeley's success.

Discussion

NFAC members engaged in a general discussion with the speakers about the experiences and models used by DOE National Laboratories. In the discussion, the following points were made:

- Projects initiated through the LDRD vehicle have greater risk than other projects, and benefits of scientific capabilities result even if the projects are unsuccessful. Funding for most LDRD projects is small ($200,000-300,000 each, per year), and LDRD management varies by the National Laboratory; for example, Berkeley offers laboratory-initiated and division-initiated LDRD projects, and Brookhaven uses the LDRD as a startup package for recruits and evaluates performance, productivity, and impact to determine the basic return on investment.

- DOE imposes rules on how the National Laboratories can spend the LDRD funding, including a 2-3 year limit for funding. This can be used to facilitate strategic hires and allow recruited investigators the time to integrate into the programmatic funding structure. Return on investment is difficult to capture, but LDRD-funded projects are approximately three-fold more productive than the core funding in terms of intellectual property rights, and generally attract more attention from venture capitalists and private companies who visit. Congress sets the LDRD budget level and recently reduced the cap from 8 to 6 percent.

- The DOE has an SBIR commitment that is managed by its Programs. The National Laboratories do not have the same commitment but support companies that have received SBIR awards.

- The energy and cancer communities differ in size but experience the same dynamics in meetings and generating research ideas.

- Leadership of the DOE National Laboratories interact with the political side of the funding process, and Congress has legislated line item in appropriations for some activities. For example, Oak Ridge's advanced neutron source project inclusion in the budget for 2 consecutive years is attributable to Mr. Al Gore being U.S. Vice President during that time. In addition, the SNS project successfully secured funding because contractors from Oak Ridge, Brookhaven, Los Alamos,

Berkeley, and Argonne National Laboratories worked together in advocacy efforts with their congressional representatives.

- The DOE generally receives guidance for allocated funds and can receive an unfunded mandate. Additional funds have not been forthcoming in the current fiscal environment, but the constrained budget is insufficient reason to postpone advancements in the research portfolio. The DOE Office of Science budget historically has grown by investments in new facilities, with funds segregated for operations and new activities.

- The number of funding streams varies for National Laboratories and across DOE Divisions, with emphasis currently placed on the hub-like model that favors larger, team-science projects. The hub model is an important factor in distinguishing a National Laboratory from the university research context.

- Dr. Varmus expressed appreciation to the speakers for coming to the NFAC and sharing their perspectives and experiences in managing and working within the DOE National Laboratories.

VII. WRAP-UP DISCUSSION

Dr. Joe W. Gray

Dr. Varmus stated that the discussion should focus on a process to allow ideas to be brought forward for a scientific community-wide discussion about what might be conducted at the FNLCR, as well as how best to implement the process. He noted that the RAS Project has been carried out through a redeployment of resources and said that budget neutral approaches were optimal at this time. Members were referred to a recent communication by Dr. Willman that raised the question of whether the emphasis should be to identify projects that are amenable to the FNLCR's current capabilities versus projects that are important or needed but would require a change in laboratory capabilities for successful execution. Dr. Varmus indicated that, for the proposed projects discussed earlier, changes in laboratory direction that require staff reductions-in-force, retooling, and new instrumentation may present challenges. He encouraged members to provide general comments on projects that the laboratory should take on and share their thoughts on comparisons of the DOE national laboratories and the competitive environment in which they thrive.

After a period of discussion, Dr. Heimbrook summarized three opportunities that he heard in terms of bringing new programs forward within the FNLCR context: (1) Combining components of several of the proposed projects could form a successful program, particularly one that builds on existing expertise at the laboratory. The engagement of broader scientific community, including crowd-sourcing, could help define such a program. (2) The focus should remain on conducting cancer research that is important, not simply on what is convenient. The emphasis on "big science" could help target opportunities that are not possible in other settings. (3) The long-term future of the FNLCR should be considered in a 5–10 year timeframe. Strategic plans for proposed projects or programs should be developed with this longer perspective in mind. Dr. Heimbrook said that future funding increases would seem most likely to be incremental. Implementation of new big projects could require a rebalancing of resources that include support service. So, achieving the bold vision of where the FNLCR will be in 10 years should include an assessment of the type and amount of direct support that FNLCR provides in service to the intramural and extramural community..

In the discussion, the following points were made:

- Members expressed support for using a number of mechanisms, such as workshops, on-line discussion forums and bulletin boards, to engage the broader scientific community in defining cancer research questions for FNLCR. In addition, using the FNLCR as a strategic place to gather experts who help decide the scope of the laboratory's research effort helps promote the role of the FNLCR in the community. Dr. Varmus remarked on the value of workshops in vetting topics, as

seen by the RAS Project, and the possibility of the FNLCR campus as a meeting place for specific issues.

- The focus should be on interdisciplinary research that cannot be accomplished in the academic setting. Discussions should consider how the FNLCR can attract experts to come to the laboratory and focus attention on the 5–10 year goal as well as accelerate the science toward that vision. This will necessitate a transformation of the FNLCR from its longstanding history as a service organization, shifting the mindsets of staff toward a more entrepreneurial environment.

- A process similar to that which led the Provocative Questions (PQ) Initiative could help to advance the FNLCR vision. The PQ process (e.g., building questions and holding workshops) has been successful, but the PQ structure involves the extramural community answering questions in the shorter term, whereas the FNLCR would require a different framework. It was noted that having the community think in terms of formulating questions is powerful and establishes an effective structure for research. Dr. Varmus agreed with the idea of having several provocative questions that can be answered only in a national laboratory setting.

- The DOE national laboratories benefit from a tradition of understanding among physical scientists and computational and quantitative tool developers. Members encouraged leadership to ensure that the FNLCR selects projects appropriate for a national laboratory to avoid replicating activities that can be completed by the extramural community.

- Scientific projects and challenges should drive the technologies that are used or developed. Capabilities needed for projects could be consolidated, and there is potential to work with technologies developed by the extramural community. The FNLCR could enhance or develop technologies at a scale not possible outside a national laboratory.

VIII. ADJOURNMENT

Dr. Joe W. Gray

Dr. Gray thanked the Committee members and other invitees for attending. There being no further business, the 6th meeting of the NFAC was adjourned at 11:22 a.m. on Wednesday, February 5, 2014.