Department of Health and Human Services
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National Institutes of Health (NIH)
National Cancer Institute (NCI)

9th Meeting of the Frederick National Laboratory Advisory Committee (FNLAC)
(Formerly NCI-Frederick Advisory Committee [NFAC])
September 30, 2015

Summary Minutes

Conference Room 10, C Wing, 6th Floor
Building 31
Bethesda, Maryland

National Cancer Institute
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The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 9th meeting on 30 September 2015, at 31 Center Drive, Building 31, C Wing, Conference Room 10, Sixth Floor, Bethesda, MD. The meeting was open to the public on Wednesday, 30 September 2015, from 8:30 a.m. to 2:47 p.m. The FNLAC Chairperson, Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Director, OHSU Center for Spatial Systems Biomedicine, Oregon Health & Science University, presided.

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

***Ex Officio* Members**
Dr. Lynn Austin
Dr. Stephen J. Chanock
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Lee J. Helman (absent)
Dr. Alan S. Rabson (absent)
Dr. Craig W. Reynolds

Executive Secretary
Dr. Peter J. Wirth

*pending appointment

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

Dr. Joe W. Gray, Chair, called to order the 9th meeting of the FNLAC and welcomed the Committee members. Dr. Gray reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Peter J. Wirth, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Dr. Douglas R. Lowy, Acting Director, National Cancer Institute (NCI), welcomed Committee members and other attendees.

Motion: A motion to accept changes to the FNLAC May 2017 meeting date was approved unanimously.

II. PRECISION MEDICINE INITIATIVE FOR ONCOLOGY, INCLUDING DEVELOPMENT OF IMPROVED PRECLINICAL CANCER MODELS—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, NCI, National Institutes of Health (NIH), provided an update on the Precision Medicine Initiative (PMI) with the focus on oncology and the related activities currently ongoing at the Frederick National Laboratory for Cancer Research (FNLCR). The NCI will receive a $70 million (M) increase in funding, earmarked for precision medicine as it relates to oncology, if the PMI budget is approved. If the funds are made available in 2016, the NCI would plan to increase the scope, scale, and speed of the PMI-Oncology efforts.

The role of PMI-Oncology is to combine all of the clinical tools available for research and standard-of-care practices with methods to analyze tumor tissues and other tissues to define their molecular characteristics to assist not only in assigning patients to appropriate therapies but also in monitoring the effects of the drugs: Are they on target, or not? When are the therapies effective, and when are they not? The goals include expanding the genomics-based clinical trials, understanding and overcome resistance to targeted drugs, developing drug combinations, supporting a mechanistic understanding of immunotherapy, building a repository of patient-derived preclinical models for evaluating targeted therapeutics, and creating a national cancer database to integrate genomic information with clinical response and outcome.

Dr. Doroshow reviewed the current status of precision oncology in regard to clinical trials. Within the past 1.5 years, the NCI has initiated several trials, including the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT), Lung Cancer Master Protocol (Lung-MAP), Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST), and the Exceptional Responders trial. In 2015, the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) trial was launched with the aim of assigning patients to appropriate therapies on the basis of their tumor's molecular abnormalities, as opposed to the tumor's origin. It is one of the largest trials to date and encompasses a regulatory umbrella and negotiations with more than 20 pharmaceutical companies for agreements for more than 40 drugs. Its unique signature is that it allows for multiple phase II trials with both standard agents and those not yet approved by the U.S. Food and Drug Administration (FDA). A major achievement is that the four clinical trial sites (MD Anderson, Yale University, FNLCR, and Massachusetts General Hospital [MGH]) participated in an intra-laboratory gene validation assessment or "lock down" assay and achieved a high level of accuracy. The NCI-MATCH enrollment began in August 2015, with 160 patients enrolled within 4 weeks. The NCI-MATCH process starts with a fresh biopsy from the patient, actionable mutation determination, and assignment to clinical studies based on the mutation; treatment continues as long as the patient has a stable disease or a response to the drug. The goal is to screen 3,000 patients, with 25 percent of the enrollment addressing rare tumor types.

With additional funds, the NCI would expand PMI-Oncology efforts with such activities as

accelerating the launch of Pediatric NCI-MATCH trials, broadening the NCI-MATCH umbrella, performing randomized Phase II studies, applying genomics resources to define new predictive markers in novel immunotherapy trials, and expanding the study of "exceptional responders," with a focus on mechanisms of response and resistance. Other areas of interest include understanding and overcoming resistance to therapy, developing new models for preclinical studies, and developing a national cancer knowledge system to support precision medicine. The NCI has presented PMI-Oncology at a series of meetings and workshops to important scientific advisories soliciting input from the extramural community for the best utilization of additional funds.

Dr. Doroshow further updated the Committee on the progress of the NCI's Patient-Derived Models (PDM) Repository, which is designed to aid investigators who may not have access to a wide spectrum of clinically annotated tissue samples for their research. He described the development of the PDM repository since 2014, novel cancer models, and considerations for future use. The focus has been on diseases that are not as well represented in collections in the extramural community, such as small-cell lung, pancreatic, head and neck, ovarian, bladder, prostate, and kidney cancers, as well as sarcomas and melanomas. The goals of the repository are to have 50 unique models, comprehensive precompetitive molecular characterization of samples in the earliest passage patient-derived xenografts (PDXs), and all models with associated data made available. Dr. Doroshow gave a broad view of the specimen acquisition process for model development, which begins with receiving tissue (resections, biopsies) and blood samples from current procurement protocols and clinical centers. As of mid-September 2015, the facility has received 1,502 tissue and blood sample specimens from 1,083 patients. A substantial number of NCI-designated cancer centers, lead academic sites in the National Clinical Trials Network (NCTN) and the Experimental Therapeutics Clinical Trials Network (ETCTN), as well as NCI's in-core communities have supported this work.

Dr. Doroshow presented examples of how the FNLCR facility is being used now, as well as some anticipated uses. He discussed preclinical MPACT bladder cancer models (*in vivo*), specifically efforts by Dr. Paula Jacobs to enrich the repository with small-animal imaging of the bladder tumors to represent an *in vivo* arm. Other models and usages for the facility include the development of the rat PDX-tumors and enhancement of immunotherapy models. Dr. Doroshow closed by describing some future possibilities for the FNLCR and the expected launch of the NCI Patient-Derived Models Repository in the spring of 2016.

In the discussion, the following points were made:

- The FNLCR was encouraged to consider a subproject of multiple samples from the individual patient; a consideration of the rapid autopsy approach may be an option. This idea would be something to discuss in a workshop setting.

- Members encouraged the NCI to provide careful consideration to the scale of the National Repository and the shared resources with the extramural community.

- The consideration of the FNLCR as a site for performing the various types of screens should include a review of the critical requirements for centralizing and standardizing the process.

- Members encouraged the PMI-Oncology group to consider an alternative distribution system for the patient-derived models and FNLCR, in which the extramural community is leveraged to engage in a partnership model as satellite sites.

III. RAS INITIATIVE UPDATE—DRS. FRANK MCCORMICK AND LEVI GARRAWAY

Dr. Frank McCormick, Director, University of California, San Francisco (UCSF) Helen Diller Comprehensive Cancer Center, RAS Program Consultant, FNLCR, provided an update on the

accomplishments of the RAS initiative with highlights of the past 6 months. Dr. Levi Garraway, Associate Professor of Medicine, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, provided an update on the FNLAC RAS working group recommendations.

RAS Initiative Accomplishments. Dr. McCormick reminded the Committee that originally the initiative was focused on determining which cells containing mutant KRAS were most dependent on KRAS and which downstream pathways were most suitable for drug targeting. The wet laboratory portion is completed, but the data analysis is still pending. The siRNA methodology was used to assess the RAS dependency. The task involved interrogating 100 cell lines with KRAS mutations and the knock-down 40 KRAS effector nodes. The effector dependency profile for each cell line following knock-down included flow cytometry analysis for viability, proliferation, reactive oxygen species levels, apoptosis, and cell size. The results of the global gene assessment of the KRAS effector dependency show very heterogeneous responses downstream of RAS. As expected, the cell lines that showed the most dependency on RAS were those of the pancreatic, lung KRAS mutant, and lung KRAS-positive tumors. These data show that KRAS-mutant tumors are most dependent on KRAS and the downstream nodes as well. As the results suggest, the group focused on pancreatic cells as the group most likely to respond to KRAS therapy.

Biophysical and Structural Analysis. Dr. McCormick further described the accomplishments of the structural analysis of KRAS4b. The FNLCR labored to produce and characterize fully processed KRAS protein using the baculovirus engineering techniques. This protein now is available to a federation of people in the academic community who have different angles on KRAS to further uncover new knowledge of its structural characteristics. One key collaborator, Dr. Stephen Sligar at the University of Illinois at Urbana–Champaign, has developed nanodisc technology. The processed KRAS4b binds to the nanodiscs in a phosphatidylserine-dependent manner, providing the correct nature of the lipid bilayer for insertion. The protein is behaving properly, and the FNLCR now is able to move forward with nuclear magnetic resonance and biochemical analysis and, in the future, cryo-electron microscopy (cryo-EM). The FNLCR has completed protein characterization of the lipid nanodiscs using biochemical assays to assess functionality; the next step will be to perform structural analysis. A workshop was convened in Frederick, Maryland, to discuss the biophysical properties of KRAS in the plasma membrane and was attended by many of the world leaders in the field. Several follow-up approaches were presented as ongoing efforts from the workshop.

Inhibitor Screens and Assays. Dr. McCormick summarized the FNLCR's efforts to characterize new and improved screens for compounds that interact with RAS directly or its downstream effectors. The first screen model system, Rasless-MEFs (mouse embryonic fibroblasts), is that originally developed by Dr. Mariano Barbacid's group. The wild-type $HRAS^{WT}$ and mutant $KRAS^{G12D}$ were selected as the screening pair cell lines. The goal is to find therapeutics that are specific for $KRAS^{G12D}$ and not $HRAS^{WT}$, drugs that are mutant-, translation-, and KRAS-specific. A pilot screen verifying specificity of the cell lines was completed in conjunction with the National Center for the Advancement of Translational Sciences (NCATS). The Rasless screening cell lines now are being shared with partners in the pharmaceutical industry and others to find KRAS-selective compounds. The FNLCR also has optimized an AlphaScreen® assay (protein-protein interaction assay) to examine direct binding of RAS to other proteins, such as the RAS-binding domain of RAF kinase. Library screens in partnership with another pharmaceutical company for compounds that prevent RAS-RAF interactions are underway. In addition to the assays for protein in solution, the FNLCR also has performed AlphaScreen® assays for KRAS on nanodiscs. The nanodiscs will be tested with various compounds. Novel approaches include the GFP-KRAS4b imaging-based assays that will look for compounds that displace and deactivate KRAS on the plasma membrane, as well as the HaloTag-KRAS fusion protein for the different states of KRAS.

Toward a "RAS Interactome." Dr. McCormick discussed the efforts of the FNLCR to build a community of people who interact with the laboratory in a "hub and spoke" model and to develop more interactions in the RAS research community. A first step has been to publish historical documents on the

Web at cancer.gov/ras, followed by establishing an interactive blog (the RAS Lab Discussion Forum) and a RAS reference reagents group. The FNLCR also is hosting RAS events, such as a RAS Initiative symposium that is planned for December 2015 in Frederick.

FNLAC RAS Working Group Recommendations. Dr. Garraway provided an update of the RAS Working Group recommendations to the FNLCR. The following areas of feedback from the most recent recommendations were highlighted: (1) science, (2) strategy, (3) interactions with the pharmaceutical industry, and (4) outreach and resources. The science recommendations include pursuing a detailed understanding of processed KRAS4b and continuing to study the biochemistry and structural biology of RAS complexes and RAS membrane interactions. The overall set of structures and reagents should present a concrete and useful set of deliverables from the RAS effort. The tools and resources for RAS researchers that were not previously available are significant. The framework for performing screens of compounds with RAS specificity is possible now. Strategically, developing a plan to augment industry partnerships, implementing a framework to lead compound development, generating ideas to harness deconvolution assays as an area of specialty, and increasing awareness and dissemination of information to the public were recommended. Dr. Garraway emphasized that interactions with the pharmaceutical industry should be centered on partnerships and blueprints to bring projects to completion. Dr. Garraway encouraged outreach to foster a bidirectional exchange of information, and a mechanism for visiting scientists would bring expertise in specific RAS assays or procedures at the Advanced Research Technology Facility.

In the discussion, the following points were made:

- The members encouraged the RAS Initiative to consider using patient tissue models.
- The RAS Project will consider approaches to target KRAS directly.
- Dr. McCormick thought that future directions for the RAS Project should include using the developed tools to determine how RAS proteins actually activate RAF kinase, investigating why different RAS proteins engage different downstream effectors, and developing strategies to make KRAS tumor cells more antigenic.
- Members suggested that based on its success thus far, the RAS Initiative might provide insight into the context of mutations.

IV. 2016 FREDERICK NATIONAL LABORATORY ADVISORY COMMITTEE (FNLAC) REVIEW FOR RENEWAL PROCESS OF RAS INITIATIVE—DR. JOE W. GRAY

Dr. Gray described a proposal for a review process of the RAS Project. He reminded members that FNLAC is charged with overseeing the development and execution of "national cancer research projects" centered at the FNLCR, of which the RAS Initiative is the first. The RAS Project started in October 2013 with the goal of developing therapeutic strategies for the treatment of human cancers driven by mutated RAS. Progress has been monitored through a RAS Working Group chaired by Dr. Garraway, which meets annually in person and on quarterly teleconferences, as well as through FNLAC meetings.

Dr. Gray explained that the aim of the review plan is to determine whether funding for the Project should be extended for 5 more years. The FNLAC Evaluation Team will consist of the current FNLAC members with *ad hoc* reviewers as needed from the research community and private sector. The review will involve (1) a written report from the RAS Initiative Team, (2) oral presentations by the RAS Initiative leadership to the Evaluation Team, and (3) a formal recommendation report from the RAS Working Group. The evaluation is proposed to weight 80 percent focused on the progress during this first period and 20 percent on future plans.

Members were told that four components are proposed for the report. They include an overview that describes initial concept and goals, an assessment of progress (both successes and failures), and a description of the accomplishments and rationale for closing any projects. A second component involves a summary of work and a realistic assessment of a future path to clinical application for active research projects. In addition, an overview and assessment of interactions with the RAS research community (academia and industry) to include reagents and resources provided by the RAS Initiative would be required. Finally, the report would include a discussion of future plans, including any change in focus. Each section is limited to 12 pages; in the active research projects section, each specific research project will be allowed 12 pages. Dr. Gray stated that the FNLAC evaluation team will meet for 1 day on November 16, 2016, in Frederick, Maryland, to hear a series of presentations by the leadership of the RAS Initiative.

The RAS Working Group Report will inform the FNLAC evaluation and provide insight into any lessons learned for future development of new initiatives. The report will be limited to five pages and include a summary of progress and a recommendation to the FNLAC Evaluation Team. Comments on the scientific goals, direction, priorities, and timelines of the RAS research projects at the FNLCR will be incorporated, as well as the extent to which the Project engaged academia and industry through collaboration, sharing ideas, data, and reagents. Dr. Gray presented the timeline for the review, which would culminate in a formal recommendation from the FNLAC Evaluation Team to the Acting NCI Director in early December 2016.

In the discussion, the following points were made:

- The written report by the RAS Initiative Team will reflect the team's assessment of the Project's successes, as well as the start and cessation of activities that occurred during the life of the Project. The RAS Working Group Report should provide an impression of how the Project has performed and its future directions.

- Members noted that the evaluation review likely will serve as a template for future FNLCR projects and encouraged the RAS Initiative Team's report to highlight the depth and breadth of interactions at the FNLCR.

- Members suggested that the goal of the review plan be revised to determine whether funding for the RAS Project should be extended "for 5 years" rather than "for 5 more years."

- Recommendations should help the NCI and FNLCR leadership understand how best to support interactions with the extramural community and to prioritize resources for the National Laboratory's hub versus its components. Metrics that elucidate the benefits that the extramural community receive from the interactions would be of value.

- Members encouraged the Evaluation Team to consider the desired clinical endpoint(s) for the next 5 years of the project and to make clear why the FNLCR is the optimal place to conduct proposed RAS projects with the involvement of private-sector partners. NCI and FNLCR leadership are supportive of FNLCR efforts to develop specific therapies that can be shown to be clinically effective. The RAS Project would be considered successful from the clinical perspective if it results in increased private-sector activity to investigate RAS inhibitors or successful interventions against mutant RAS tumors.

- Members discussed the optimal balance in weighting progress achieved by the current phase of the RAS Project versus future plans and encouraged more even weighting (50/50) of these components,

noting that past performance can be a reflection of future direction and that proposal evaluations for other types of mechanisms (e.g., R01s) primarily focus on the proposed (future) work.

- The proposed schedule will be revisited to ensure adequate time for response to comments and revision of the plan before submission to the Acting NCI Director, and changes to the timeline will be shared with the FNLAC.

V. REPORT FROM THE ACTING NCI DIRECTOR—DR. DOUGLAS R. LOWY

Dr. Lowy reflected on his experiences as Acting NCI Director for the past several months, acknowledged the support of NCI staff and extramural colleagues, and expressed appreciation for input received from NCI committees, including the FNLAC.

NCI Fiscal Year (FY) 2016 Budget and Beyond. Dr. Lowy reminded members that the NCI has operated under a flat budget for many years, with the same purchasing power as in 1999. The President's FY 2016 budget appropriation provides a $1 billion (B) increase for the NIH, which includes a $145 million (M) increase for the NCI, of which $70M is for PMI-Oncology. Each house of Congress has passed bills that support at least these proposed increases for the NCI and NIH. Members were told that the Federal government likely will operate under a Continuing Resolution (CR) through December 11, 2015, and the NCI will participate in a Senate Appropriation Committee hearing in October 2015. Dr. Lowy referred members to the recently released FY 2017 NCI Budget Proposal (www.cancer.gov/about-nci/budget/plan).

FNLCR and FNLAC. Dr. Lowy stated that as a Federally Funded Research and Development Center (FFRDC), the FNLCR provides a unique biomedical resource for the development of new technologies and translation of basic science discoveries into novel agents for prevention, diagnosis, and treatment of cancer and acquired immune deficiency syndrome (AIDS). It also provides exceptional acquisition and response capabilities (e.g., flexibility, rapid response, efficiency). Activities conducted at the FNLCR that are useful to the extramural community include the RAS Project, Nanotechnology and Antibody Characterization Laboratories, NCI Experimental Therapeutics (NExT) Program, Clinical Trials Reporting Program, molecular diagnostics, and the Biopharmaceutical Development Program (BDP). The BDP is one of two FNLCR sites capable of good manufacturing practice (GMP) production for materials, which has been important for intramural and extramural research; the site received an outstanding rating from the radiopharmacy in a recent evaluation. The BDP is the training site for the FDA, and produced the 1418 monoclonal antibody that has become the standard of care for neuroblastoma. In addition, seven Cooperative Research and Development Agreements (CRADAs) have been signed with academia and the private sector during the past 9 months, and five others are in negotiation.

Dr. Lowy described a new program to support Laboratory Directed Exploratory Research (LDER), which is modeled after the Department of Energy (DOE) FFRDC laboratory-directed research and development funds and provides up to $1 M for pilot projects. The goal is to enhance the innovation, creativity, originality, and quality of research activities; facilitate collaborations within the FNLCR; and engage academic institutions to encourage collaboration and strategic interactions. In addition, the LDER will enable the demonstration of exploratory proof-of-concept projects to lead to durable funding through contract or grant mechanisms. Members were told that the Laboratory Director of FNLCR is responsible for overall execution and performance of the Program. Initial strategic focus areas are improving therapeutic efficacy, AIDS and cancer-associated viruses, tumor microenvironment and heterogeneity, and immunotherapy. In the first year, 18 proposals were submitted, of which 12 were selected for oral presentations, and 5 approved for funding.

Members were reminded that the role of the FNLAC is to provide advice on the optimal use of the FNLCR to meet the most urgent needs of the NCI and to review the state of research at the FNLCR and

make recommendations for the best use of its capabilities and infrastructure. FNLAC also reviews major new projects proposed to be undertaken, evaluates productivity of the existing portfolio of projects, and helps to determine which projects should be transitioned to more conventional mechanisms of support and which should be considered for termination. Dr. Lowy provided information about the upcoming recompetition of the FFRDC and encouraged interested parties to attend a preproposal conference on October 1–2, 2015, at the NIH. FFRDCs are operated, managed, and/or administered by either a university or consortium of universities, other not-for-profit or nonprofit organization, or an industrial firm. The contract is anticipated as a single IDIQ (Indefinite Deliverable, Indefinite Quantity) award.

NCI Priorities. Dr. Lowy provided an update on several areas of interest, including NCI funding mechanisms, health disparities activities, and the Institute's commitment to basic research. The NCI's Outstanding Investigator Award provides long-term support to experienced investigators with outstanding records of cancer research productivity who propose to conduct exceptional research and allows them the opportunity to take greater risks. In the first round of awards, the NCI has made 40 awards in FY 2015 and will make 24 additional awards with FY 2016 funds. The award solicitation has been reissued with minor changes. Other types of awards under discussion will support research specialists and the transition from graduate student to postdoctoral fellow. Dr. Lowy also stated that the NCI is working toward increased funding for NCI-Designated Cancer Center P30 core grants, with full funding contingent on an increased NCI appropriation for FY 2016.

Dr. Lowy told members that precision oncology research is as equally important in cancer screening and prevention as in drug development. This has been shown in cervical cancer screening in which, although cytologic (Pap) screening is sensitive in the detection of squamous cell cancer precursors, a study of pooled cervical cancer incidence from four randomized controlled trials in Europe has shown that human papillomavirus (HPV) testing can prevent more cervical cancers, especially adenocarcinomas. HPV methlyation can achieve high-risk stratification that alters clinical management, and methlyation testing is possible from the HPV DNA sample, thus enabling self sampling. Next-generation HPV sequencing can become highly cost-effective for cervical cancer screening and have major implications for screening in low- and middle-income countries, as well as provide new insights into the molecular pathogenesis of HPV-induced cancer. Dr. Lowy shared an example of precision oncology in cancer prevention in the use of aspirin, which has been shown to reduce the risk of colorectal and other cancers, with the idea of using molecular understanding to risk-stratify those patients who would derive the most benefit. A study described in an earlier presentation to the National Cancer Advisory Board (NCAB) found that high 15-hydroxyprotaglandin (15-HPGD) in the normal colon is associated with reduced risk of colorectal cancer in regular aspirin users.

Dr. Lowy highlighted the NCI's focus on specific cancers with health disparities, such as colorectal, liver, breast, prostate, and multiple myeloma cancers, with an emphasis on identifying the risk factors (e.g., biological, lifestyle, health care access/utilization) and their relative contribution to the disparities. A study by Dr. Sandy Markowitz of novel recurrently mutated genes in African American colon cancers noted an important difference in the mutational landscapes of colorectal cancers arising in different ethnic groups. The NCI is holding a workshop on cancer health disparities on November 11–13, 2015, under the leadership of Co-Chairs Drs. Edith Mitchell, Thomas Jefferson University; Lisa Richardson, Centers for Disease Control and Prevention (CDC); and Sandy Markowitz, Case-Western Reserve University, with assistance from Dr. Michelle Bennett, NCI, who is leading the new Center for Research Strategy. Dr. Lowy stated that the NCI's clinical trials system has done reasonably well in minority enrollment and confirmed as follow up to a comment made at the June 2015 Joint Boards meeting that the PDX models also will include underrepresented populations. He stated that the NCI is watchful of the engagement of early-stage investigators in basic research, because attendance trends at the NCI Division of Cancer Biology (DCB) new grants workshops have decreased over time.

In the discussion, the following points were made:

- The NCI has seen a progressive increase in applications related to translational research because of the greater opportunities available, but it remains equally supportive of basic research.

- Members encouraged the NCI to consider the K24 mechanism as an opportune way to enhance the quality of mentoring and training.

- The NCI supports point-of-care analysis but recognizes the cost-effectiveness of using next-generation sequencing technologies during the long term. In addition, self-sampling of patients is feasible in many locations and important for cervical and other cancer screenings.

- Molecular imaging remains an important technology for the cancer research setting, but it is less popular in the identification of high-risk populations because of harm-benefit ratios seen in some areas of cancer screening.

VI. PROPOSAL TO LAUNCH A NATIONAL CRYO-EM USER FACILITY AT FREDERICK NATIONAL LABORATORY (FNL)—DR. SRIRAM SUBRAMANIAM

Dr. Sriram Subramaniam, Senior Investigator, Laboratory of Cell Biology, Center for Cancer Research, NCI, NIH, reiterated that the use of cryo-EM to elucidate protein structures has become very popular and that it has the potential for yielding the results usually obtained by x-ray crystallography, with higher resolution. The main objective is to make this technology broadly available to both the extramural and intramural NCI communities. The recent excitement for structural and cell biologists around cryo-EM is based on the following: (1) structure determination at high resolution without three-dimensional (3-D) crystals, (2) structural analysis of dynamic protein assemblies, (3) mapping conformational states of integral membrane proteins, (4) localization of drug binding sites, and (5) a potential for a high degree of automation in data collection and processing. The idea to establish a National Cryo-EM User Facility at the FNLCR and to disseminate this technology to the extramural community began in the spring of 2014 and culminated with a workshop recommendation that NIH fulfill the need for a national user facility similar to those available for crystallography.

Members were told that potential users of the cryo-EM Facility can be divided into three broad groups: research groups already experienced in cryo-EM technology, structural biologists in adjacent disciplines, and biologists with interest in important biomedical problems. Dr. Subramaniam proposed that the project focus on the experienced cryo-EM users, initially because this user community has the experience, but may not have access to high-end technology. A possible model for user access includes plans for proposed fees, instrument time, and overall capacity. Starting the cryo-EM facility at the FNLCR has been jumpstarted by the NIH intramural program. A new Titan Krios microscope arrived late September 2015 and will be available to the FNLCR. Dr. Subramaniam proposed a budget plan for FY 2016–2019 with costs of approximately $5M per year. The initial cost would be allocated for the NCI intramural program loan of the Titan Krios microscope to the FNLCR, additional microscope upgrades, and personnel, with equipment add-ons proposed for later years. The cryo-EM Initiative's structure will include an organizational team, a steering committee, and a funding and evaluation group (similar to the RAS Working Group). Finally, the cryo-EM at the FNLCR execution plan would occur in two phases. In closing, Dr. Subramaniam highlighted his prior experience in establishing and serving as Director for other microscopy facilities, including the NIH-FEI Living Lab for Structural Biology and the Center for Molecular Microscopy. The next logical progression is to establish a facility that focuses entirely on supporting the extramural community and capitalizing on the growth of these technologies in the United States.

Motion. A motion to support the launch of a National Cryo-EM User Facility at the FNLCR, with the advisement of a Steering Committee of experts and an evaluation in the second year, was approved unanimously.

VII. THE NCI-DOE PILOT AND PRECISION MEDICINE INITIATIVE (PMI) IN ONCOLOGY—DR. WARREN KIBBE

Dr. Warren Kibbe, Director, NCI Center for Biomedical Informatics and Information Technology (CBIIT), updated the members on the PMI involving informatics and the initiative between the DOE and the NCI. From an informatics perspective, the PMI involves creating a knowledge network and a taxonomy of disease. Dr. Kibbe outlined the PMI-Oncology informatics and computational goals. They include the development of a cancer knowledge system, signatures that predict therapeutic response, and multiscale predictive computational models for understanding cancer. High-performance computing (HPC) and computational modeling require sophisticated computer models to understand patient response, methods of resistance, and integration of preclinical model data. The amount of genomic data is forecasted to exceed the available resources, and a vast majority of the data will come from cancer patients. The NIH HPC working group and the NCI HPC group already are addressing this problem. The key points for the NCI's future computing efforts include three phases: (1) prepare foundations for high-performance computational science data management, storage, and networking HPC system access; (2) access the training, education, and expertise of FNLCR, DOE, and others; and (3) catalyze global collaborations to advance science. The NCI's forward thinking to prepare for "Exascale Cancer Science" has led to the generation of a timeline that extends from 2015 to 2020, containing considerations of infrastructure, training, applications, and collaborative pilot investigations. Dr. Kibbe commented that in addressing the HPC problems, the NIH has initiated discussions with the DOE. The DOE is the leader in computing and has expertise that the NIH does not have and would be a leader for the exascale computing initiative. Dr. Kibbe further noted that the DOE has made strides in computing, which the NIH wants to leverage for cancer research. One DOE initiative that was launched a few prior is the Biological Applications of Advanced Strategic Computing (BAASiC). BAASiC is a multi-institutional initiative led by the Lawrence Livermore National Laboratory (LLNL) that applies the power of extreme computing, data analytics, and revolutionary sensor technologies to enable a new era of predictive biology. This framework serves as a starting point for the NCI and DOE to work together more effectively.

National Strategic Computing Initiative (NSCI). Dr. Kibbe updated the members on the backdrop for the NCI and DOE pilot project. In July 2015, President Barack Obama issued an executive order to create a cohesive multi-agency, strategic vision and federal investment strategy in HPC. The lead agencies identified were the DOE, Department of Defense (DOD), and National Science Foundation (NSF). The deployment agencies are the NIH, National Aeronautics and Space Administration (NASA), Department of Homeland Security (DHS), and the National Oceanic and Atmospheric Administration (NOAA). These agencies will participate in shaping future HPC systems to meet the aims of their respective missions and support workforce development needs. The NCI will work with DOE and others to expand the use of HPC to advance research and clinical applications related to cancer. In considering how to create this initiative, Dr. Kibbe identified three candidate pilot projects: (1) preclinical model development and therapeutic evaluation (Dr. Doroshow); (2) improving outcomes in RAS-related cancers (Dr. McCormick); and (3) information integration for evidence-based cancer precision medicine (Dr. Penberthy). The plan is to definitively frame the NCI-DOE NSCI initiative by mid-October or early November 2015. These projects will be instrumental in collaboratively developing project plans with the DOE computational scientists. The NCI-DOE partnership will extend the frontiers of DOE non-defense-directed computing capabilities in the areas of simulation, data analytics, and new computing architecture.

Genomics Data Commons (GDC) and Cancer Genomics Cloud Pilots (CP). Dr. Kibbe reiterated the PMI-Oncology Informatics goals: (1) develop a cancer knowledge system, thereby

establishing a national database that integrates genomic information with clinical response as a resource; (2) develop molecular imaging, pathology, and clinical signatures that predict therapeutic response, outcomes, and tumor resistance; and (3) build multiscale, predictive computational biology models for understanding cancer biology and informing therapy. The GDC is an existing effort to standardize and simplify submission of genomic data to the NCI, and it follows the principle of "FAIR": Findable, Accessible, Interoperable, and Reusable. The objective is for the GDC data to be accessible as a public resource. The GDC Project was started in the spring of 2014 in a contract awarded to Dr. Robert Grossman, University of Chicago, and is expected to go live in mid-2016. Dr. Kibbe also presented an update on the NCI Cancer Genomics CP. The rationale for the CP is understanding how to meet the research community's need to analyze large-scale cancer genomic and clinical data without downloading massive datasets. The three Cloud Pilots will use a cloud-based architecture, where researchers can use existing as well as novel algorithms to analyze and visualize TCGA data all in the cloud infrastructure. The NCI CPs (The Broad Institute, Institute for Systems Biology, Seven Bridges Genomics) are working jointly with each other, the GDC and the Global Alliance for Genomics and Health to define shareable, interoperable cloud components. The first CP will be open for public access in December 2015, and the remaining ones will be available by March 2016.

Dr. Kibbe shared with the members the informatics problems that the PMI-Oncology Informatics Initiative intends to solve. The most important goals are to establish a sustainable infrastructure for cancer genomic data through the GDC; provide a data integration platform to allow multiple data types, multi-scalar data, and temporal data from cancer models and patients; and support precision medicine-focused clinical research. In closing, Dr. Kibbe stated that the overarching goal of this work is to bridge cancer research and cancer care by making clinical research relevant in the clinic, supporting the virtuous cycle of clinical research informing care, and providing decision-support tools for precision medicine.

In the discussion, the following points were made:

- Members recommended that the PMI-Oncology Informatics Initiative consider the importance of high performance data intensive computing in the NCI-DOE Pilots, given the growing importance of large-scale genomic datasets.

- Members encouraged the PMI-Oncology Informatics Initiative to crystalize the role of the FNLCR role in the NCI-DOE Pilot Exascale Model as a computing core.

- The NCI-DOE Pilot should be discussed in depth in subsequent FNLAC meetings to include DOE computational scientists.

VIII. NEW BUSINESS—DR. JOE W. GRAY

Dr. Gray requested input from the committee members regarding the central focus of the next meeting. The members agreed on a computationally oriented meeting with NCI (Dr. Kibbe) and DOE colleagues for the May 2016 meeting.

IX. ADJOURNMENT—DR. JOE W. GRAY

Dr. Gray thanked the Committee members and other invitees for attending. There being no further business, the 9th meeting of the FNLAC was adjourned at 2:47 p.m. on Wednesday, September 30, 2015.

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Date Joe W. Gray, Ph.D., Chair

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Date Peter J. Wirth, Ph.D., Executive Secretary