National Cancer Institute
1st Virtual Meeting of the Frederick National Laboratory Advisory Committee (FNLAC)
October 21, 2016

Summary Minutes

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 1st virtual meeting on 21 October 2016. FNLAC members attended virtually, and National Cancer Institute (NCI) staff attended in Conference Room TE406, East Wing, Shady Grove Campus, National Institutes of Health (NIH), Rockville, MD. The meeting was open to the public on Friday, 21 October 2016, from 2:00 p.m. to 4:00 p.m. The FNLAC Chairperson, Dr. Lawrence J. Marnett, Dean of Basic Sciences, University Professor, Mary Geddes Stahlman Professor of Cancer Research, and Professor of Biochemistry, Chemistry, and Pharmacology, Vanderbilt University, presided.

FNLAC Members
Dr. Lawrence J. Marnett (Chair)
Dr. Gail A. Bishop
Dr. Lisa M. Coussens
Dr. Levi A. Garraway
Dr. Joe W. Gray
Dr. Angela M. Gronenborn
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. David I. Hirsh
Dr. Janet A. Houghton
Dr. Elizabeth M. Jaffee (absent)
Dr. Sanford D. Markowitz (absent)
Dr. Piermaria Oddone
Dr. Kenneth J. Pienta (in person)
Dr. Nilsa C. Ramirez-Milan (absent)
Dr. Cheryl L. Willman
Dr. Jedd D. Wolchok (absent)

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

Executive Secretary
Dr. Peter J. Wirth

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Dr. Lawrence J. Marnett, Chair, called to order the 1st virtual meeting of the FNLAC and welcomed the Committee members, NCI staff, and guests. Dr. Marnett reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Peter J. Wirth, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

He called Committee members’ attention to future meeting dates listed on the agenda. The Committee confirmed the July 18–19, 2017, and November 7–8, 2017, meeting dates. The May 8–9, 2017, meeting date was confirmed in a prior meeting. The Committee was informed that the FNLAC will now begin conducting its business in three regular meetings per year.

**Motion:** A motion to confirm the July 18-19, 2017 and November 7-8, 2017 meeting dates was approved unanimously.

Dr. Marnett welcomed new members: Dr. Lisa M. Coussens, Hildegard Lamform Chair in Basic Science, Professor and Chair, Cell, Developmental, and Cancer Biology Department, Associate Director for Basic Research, Knight Cancer Institute, Oregon Health and Science University; Dr. Angela M. Gronenborn, University of Pittsburgh Medical Center (UPMC) Rosalind Franklin Professor and Chair, Department of Structural Biology, Professor, Department of Bioengineering, Swanson School of Engineering, Director, Pittsburgh Center for HIV Protein Interactions, University of Pittsburgh; Dr. Klaus M. Hahn, Thurman Professor, Department of Pharmacology, Director, University of North Carolina (UNC)-Olympus Imaging Center, Department of Pharmacology, UNC at Chapel Hill; Dr. Janet A. Houghton, Senior Research Fellow, Endowed Chair in Cancer Biology, Division of Drug Discovery, Department of Oncology, Southern Research Institute; Dr. Sanford D. Markowitz, Markowitz-Ingalls Professor of Cancer Genetics, Department of Medicine, Case Western Reserve University School of Medicine, Head, Cancer Genetics Program, Case Comprehensive Cancer Center; and Dr. Nilsa C. Ramirez-Milan, Medical Director, Biopathology Center, Pathology Operations Director, Biospecimen Core Resource, The Research Institute at Nationwide Children’s Hospital, Director, Autopsy Pathology, Department of Pathology and Laboratory Medicine, Nationwide Children’s Hospital. Drs. Markowitz and Ramirez-Milan did not attend the meeting.

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

Dr. Douglas R. Lowy, Acting Director, NCI, welcomed new and continuing Committee members and other attendees. He stated that part of the reason for increasing the number of times the FNLAC meets from two to three is because the NCI recognizes the importance of the Committee’s input in the recompete of the Frederick National Laboratory for Cancer Research (FNLCR) and in defining the role of the FNLCR in implementation of the Cancer Moonshot recommendations. Dr. Lowy reviewed the agenda for today’s meeting and stated that Dr. Dinah Singer, Acting Deputy Director for the Moonshot and Director, Division of Cancer Biology, NCI, would provide an overview of the Cancer Moonshot, and Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research and Director, Division of Cancer Treatment and Diagnosis, NCI, would update the Committee on the President’s Precision Medicine Initiative for Oncology (PMI-O).

**The Fiscal Year (FY) 2017 Budget.** Dr. Lowy informed members that the budget outlook for the NIH and the NCI remains positive. Although Congress has not budgeted allocations for the Cancer Moonshot, Vice President Joseph Biden is confident that it will be funded, and the NCI looks forward to that being a high probability. Dr. Lowy stated that the federal government is operating under a continuing resolution (CR) until December 9, 2016. It is anticipated that an omnibus appropriation, which would include funds for the NIH, will be made during the lame-duck session of Congress. The Senate passed a bill to increase funding to the NIH by $2 billion (B) and to the NCI by $216 million (M); the House passed a
bill to increase funding to the NIH by $1.25 B and to the NCI by $124 M. House appropriators will more than likely make further attempts to achieve the $2 B increase approved by the Senate. Dr. Lowy told members that the President’s budget for fiscal year (FY) 2017 recommended a $680 M increase for the NCI; the $200 M increase passed by the Senate falls short of the President’s recommendations.

**NCI Research Beyond the PMI-O and the Cancer Moonshot.** Dr. Lowy stated that the NCI is continuing to strongly support investigator-initiated research and other meritorious research. Although the PMI-O and the Cancer Moonshot are high priorities for the NCI, it is of utmost concern that the cancer community understands that the NCI is committed to its ongoing efforts; he provided an update on one of those efforts. Members were informed that from FY 2013 to FY 2015 there was a 25 percent increase in the funding for the Research Project Grant (RPG) pool for new (Type 1) and competing (Type 2) awards. This represented an increase from $400 M to $500 M per year, and the amount for FY 2016 is expected to be slightly higher. Maintaining this award rate will require adding a total of $300 M to the RPG pool in the next few years. Increased appropriations for the NCI will enable increases in funding to the RPG pool; however, if the budget remains stable, maintaining the RPG pool funding rate will be challenging. The NCI is cautiously optimistic for an omnibus appropriation in FY 2016 to continue to support the growth of the RPG pool.

**Precision Medicine Initiative for Oncology.** Dr. Doroshow reminded members of the January 2015 State of the Union Address in which President Barak Obama announced the PMI-O; the NCI was allocated $70 M to initiate the PMI-O. These funds are being used primarily to expand accrual to an adult NCI-Molecular Analysis for Therapy Choice (NCI-MATCH); launch the NCI Pediatric MATCH trial; develop more preclinical models to advance predictive oncology; and develop biomarkers in immunotherapy. In addition, 20 percent of the allotted funds are being used to develop a Genomic Data Commons (GDC), a large annotated database of cancer patients.

Dr. Doroshow told members that more than 60 percent of the allocated funds received in FY 2016 were disbursed in a series of Administrative Supplements that were issued in April 2016 and May 2016. In the scientific area of improving preclinical models for evaluating targeted therapeutics and immunotherapy, the NCI funded eight projects to support research in canine immunotherapy via collaboration among NCI-designated Cancer Centers and veterinary medical colleges, as well as 10 projects to support collaborative research efforts to enhance preclinical drug development and preclinical clinical trials using patient-derived xenograft models. In the scientific area of expanding support for developing immunotherapy trials, the NCI funded 13 projects to support biomarker development and correlative studies associated with clinical trials on immunotherapy, nine to support studies on the tumor microenvironment of pancreatic ductal adenocarcinoma and immunotherapy, and three to support projects on improvement and optimization of T-lymphocyte (T-cell) therapy products targeting solid tumors. In the scientific area of employing clinical materials from drug-resistant patients for molecular analysis leading to rational studies of target combinations, the NCI funded 10 projects to support studying mechanisms of cancer sensitivity and resistance to therapy utilizing samples and information from human clinical trials. In addition, supplements to create a repository on molecularly analyzed samples of resistant disease (pre- and post-treatment pairs) will be issued in the fall of 2016 to NCI Community Oncology Research Program (NCORP) sites.

**The Vice President’s Cancer Moonshot Blue Ribbon Panel (BRP) 2016.** Dr. Singer updated members on the Cancer Moonshot and the BRP. The final recommendations of the BRP, submitted to the National Cancer Advisory Board (NCAB) in September 2016, are included in the final report of the Cancer Moonshot Task Force (Task Force). The President’s memorandum that established the Cancer Moonshot and the Task Force also charged the NCI, through the auspices of the NCAB, to establish a BRP to provide expert advice on the vision, proposed scientific goals, and implementation of the National Cancer Moonshot. The 28-member BRP considered those areas of cancer research that were poised to be accelerated by the additional funding promised through the Cancer Moonshot. The BRP, through its seven Working Groups (WGs), submitted a total of 14 recommendations that were discussed at the July 2016
face-to-face meeting of the BRP. Of these, 13 were approved as Moonshot recommendations and one was converted to a demonstration project. The BRP’s report to the NCAB summarizes these recommendations of exceptional research opportunities that could lead to powerful advances in our understanding of cancer. This report can be accessed from the NCI website: www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel. In addition, the BRP identified policy issues that are barriers to the recommendations’ progress; these policy issues have been forwarded to the Task Force to address.

Dr. Singer highlighted the Cancer Moonshot recommendations that the FNLCR might play a role in implementing: a network of direct patient engagement, a cancer immunotherapy translational science network, development of therapeutic target identification to overcome drug resistance, development of a national cancer data ecosystem, and development of a human tumor atlas. The NCI is considering approaches to implementing the Moonshot recommendations. The first approach will identify those recommendations that can be implemented in FY 2017 and develop a longer timeline for the more complicated and complex recommendations. The NCI is relying on its advisory boards, including FNLAC, to provide insight during this process. The goals are to establish public-private partnerships, as well as partnerships with other federal agencies. Dr. Singer reaffirmed the NCI’s commitment to investigator-initiated research and stated that areas of research that extend beyond the scope and activities of the BRP remain a high priority for the NCI.

In discussion, the following points were made:

- The recommendations are extensive in scope and the total resources needed will be determined as the NCI moves further into the implementation phase. Supporting the Cancer Moonshot will require sustained investments. The President’s request for $680 M for FY 2017 would be a good place for the budget to start.

- The BRP and its WGs prioritized those areas of cancer research (non-overlapping) that could be accelerated, which is reflected in the final Moonshot recommendations; the NCI considers all the recommendations as high priority. The cancer research community will have a role in assisting the NCI in further prioritizing the Moonshot projects and establishing requests for applications (RFAs).

- Dr. Lowy stated that the NCI plans to focus on those recommendations whose implementation can be started quickly with limited funds by leveraging research that is related, but differs qualitatively. Two examples include drawing on experience with The Cancer Genome Atlas (TCGA) to build a human tumor atlas and the modeling the recommendation to develop enabling technologies through the Small Business Innovation Research for Innovative Molecular Analysis Technology (SBIR-IMAT) program. The NCI has a strong foundation in many areas of cancer research, and Dr. Lowy sees the ability to build on that foundation as a strength.

- Implementing the Moonshot recommendations at the level and speed that the NCI is proposing will become increasingly challenging if the government continues to operate under a CR without specific budget appropriations.

- Members encouraged the NCI and FNLCR to consider establishing discussion groups and designating discussion leaders (e.g., expert leadership) to navigate the process of incorporating the Cancer Moonshot recommendations into the FNLCR programs. Engaging the extramural community at this junction will be a key step to enable the NCI and FNLCR to strengthen existing collaborations and develop new partnerships around the Cancer Moonshot ideas. The RAS Initiative program and the expert leadership of Dr. Frank McCormick, Director, University of
Consultant, FNLCR, would be a good model to emulate.

III. RAS WORKING GROUP REPORT—DR. LEVI A. GARRAWAY

Dr. Levi A. Garraway, Associate Professor of Medicine, Harvard Medical School; Director, Center for Cancer Precision Medicine, Dana-Farber Cancer Institute and Brigham and Women’s Hospital; and Institute Member, Broad Institute, gave the report from the RAS ad hoc Working Group (WG) on the FNLCR RAS Initiative. He reminded members of the mission of the RAS WG: to advise on the strategic, technical, and scientific aspects of the NCI RAS Initiative and to present findings and recommendations to FNLCAC. The WG met seven times between July 2014 and August 2016 to provide feedback and suggestions to Dr. McCormick and the RAS Team at FNLCR. The feedback included assessments of research strategies that were working and those needing improvements. In addition, the RAS WG ensured optimal connectivity between the FNLCR RAS Initiative and the extramural community.

Dr. Garraway pointed out that the RAS project initially focused on five objectives that later converged into four major areas, which FNLCR developed: biophysical characterization, structural biology, assay development and screening, and interactions with the scientific community. He highlighted the key scientific advances of these areas. Fully processed RAS proteins, wild-type and mutant, are bound to the plasma membrane, which enables them to carry out their effector functions. There had not been, however, a great deal of progress in generating large quantities of fully processed or membrane-bound RAS proteins for biological studies. Regarding biophysical characterizations, the RAS laboratory groups have successfully purified fully processed (i.e., farnesylated and methylated) wild-type KRAS protein; characterized guanosine triphosphate hydrolase (GTPase) activity; and characterized effector binding, such as RAF, on lipid nanodiscs, which mimic membranes. The fully processed KRAS protein and RAS reagents have been widely distributed to extramural collaborators in academia and industry settings.

The RAS Initiative has yielded significant progress in structural biology. The crystal structures of wild-type KRAS and 6 oncogenic mutants (G12C, G12D, G12V, G13D, Q61L, and Q61R) have been solved. These structures revealed how oncogenic mutations affect the conformation of regions that interact with regulatory and effector proteins and perturb GTP hydrolysis. Also, the crystal structure of the Q61 mutants in complex with the GTPase-activating protein (GAP) protein, RASA1, as well as that of the fully processed KRAS in complex with the chaperone PDEδ, were solved. These structures for the first time revealed the hypervariable region of KRAS and the sequences involved in the interaction with PDEδ. Assay development and screening efforts include developing cell-based assays to monitor RAS dimerization, membrane localization, effector activation, and cell proliferation. In vitro assays were developed to measure RAS GTPase activity, lipid interactions, and effector interactions. The capability of these assays has sparked interest and enthusiasm from the pharmaceutical and biotechnology industries, resulting in establishing new collaborations for the NCI and the FNLCR.

Interactions between the RAS Initiative and the scientific community have focused on facilitating connections between and among academic and industry researchers, both within the United States and abroad. Outreach elements include providing RAS reference reagents to the community; establishing collaborations with the research community; disseminating RAS-related information through a dedicated website (www.cancer.gov/ras); hosting workshops and meetings; and identifying and promoting funding opportunities. The RAS Pathway Clone Collection 2.0 (R777), consisting of 180 genes, was deposited into the Addgene plasmid repository, and reagents for producing fully processed KRAS have been requested by researchers from 23 countries. Formal collaborations extend to the Pancreatic Cancer Action Network, the Defense Advanced Research Projects Agency’s Big Mechanism Program, the Department of Energy’s Molecular Level Pilot Program, and KRAS Synthetic Lethality Grant awardees, as well as 53 individual scientists and companies.
Dr. Garraway attributes the success of the RAS Initiative to the expert direction from Dr. McCormick, the clear definition of a world-class set of project objectives early in the program’s implementation, and the recruitment of talented staff. He remarked on the considerable success achieved in each of the four objectives, as demonstrated by the new insights in RAS biology and the reagents and assay platforms made available to the cancer community. This research has catalyzed interest in RAS research and increased awareness of the importance of RAS biology. The RAS Initiative model is well positioned to serve as a robust platform for current and future collaborations and accelerate the development of RAS-directed therapies.

The RAS ad hoc WG offers the following recommendations for consideration during the next stage of the RAS Initiative:

- Use industry collaborations established in the RAS Initiative to identify lessons learned that will guide development of a generalizable framework for future FNLCR initiatives.
- Continue developing large-scale approaches to identify and validate new compounds that selectively inhibit wild-type or mutant RAS.
- Prioritize further augmentation of the biochemical advances.
- Consider efforts to resolve RAS-effector complexes using cryo-electron microscopy.

These recommendations have been fully outlined in the report. In summary, Dr. Garraway conveyed the WG’s appreciation of the progress of the RAS Initiative and how it has proven to be an example that demonstrates the leveraging of resources at FNLCR.

**Motion:** A motion to accept the report of the RAS ad hoc WG was approved unanimously.

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

- The results that have come from the RAS Initiative are quite impressive and numerous, involving a range of collaborations. In assessing the RAS Initiative’s impact, it would be of interest to the cancer community to know the paths taken, lessons learned, and barriers encountered in achieving these significant scientific advances.

- Copies of the progress report and the 5-year plan of the RAS Initiative will be circulated to Committee members for comments; the plan will provide new members with background on the program. New members also are encouraged to reach out to former Committee members at their respective institutions who may provide details on the early inception of the RAS program.

- One key decision for the NCI is to determine the role of the RAS program in establishing and directing a systematic lead compound validation and structure activity relationship iteration around those promising drug candidates that could become tool compounds (i.e., chemical probes) for the cancer community.

- The degree of interest of pharmaceutical companies in the RAS Initiative and the number of resulting collaborations with the companies have far exceeded expectations. A goal for the NCI would be to determine whether the FNLCR might serve as a model system to maximize these types of relationships in the future. Assessing the financial investments of these collaborations has yet to be determined.
• The opportunity exists for leveraging the NCI’s Experimental Therapeutics (NEXT) program and the Chemical Biology Program within the Division of Cancer Treatment and Diagnosis to expand the drug screening of promising candidates from the RAS Initiative.

• Members encouraged the FNLCR to investigate the commonalities (e.g., effector molecule interactions) of the biology of the KRAS oncogenic mutants, which could provide new insights into drug discovery for different tumor types.

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

Dr. Marnett requested that members send RAS Initiative discussion topics for the November 16–17, 2016, meeting to Dr. Wirth. The Committee will likely tour the Advanced Technology Research Facility at FNLCR on the second day of the meeting.

Dr. Lowy expressed his appreciation to the new members of the Committee for agreeing to participate and for their active engagement with the FNLCAC.

V. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other invitees for attending. There being no further business, the 1st virtual meeting of the FNLCAC was adjourned at 3:37 p.m. on Friday, 21 October 2016.