

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

12<sup>th</sup> Meeting  
Frederick National Laboratory Advisory Committee

**Summary of Meeting  
May 8, 2017**

**Conference Room 10, C Wing, 6<sup>th</sup> Floor  
Building 31  
Bethesda, Maryland**

**National Cancer Institute**  
**12<sup>th</sup> Meeting of the Frederick National Laboratory Advisory Committee**  
**to the National Cancer Institute**  
**May 8, 2017**

**Summary Minutes**

The Frederick National Laboratory Advisory Committee to the National Cancer Institute (FNLAC) convened for its 12<sup>th</sup> meeting on May 8, 2017, at 31 Center Drive, Building 31, C Wing, Conference Room 10, Sixth Floor, Bethesda, MD. The meeting was open to the public on Monday, May 8, 2017, from 9:00 a.m. to 3:10 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 (absent)  
 Dr. Lisa M. Coussens\*  
 Dr. Kevin J. Cullen\*  
 Dr. Levi A. Garraway (absent)  
 Dr. Angela M. Gronenborn (absent)  
 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 (absent)  
 Dr. Nilsa C. Ramirez-Milan\* (absent)  
 Dr. Cheryl L. Willman\* (absent)  
 Dr. Jedd D. Wolchok (absent)

**Ex Officio Members**

Dr. Stephen J. Chanock (absent)  
 Dr. James H. Doroshow  
 Dr. Paulette S. Gray  
 Dr. Warren A. Kibbe  
 Dr. Tom Misteli (absent)  
 Dr. Kristen Komschlies McConville  
 Dr. Donna Siegle  
 Dr. Dinah S. Singer

**Executive Secretary**

Dr. Caron A. Lyman

\*pending appointment

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## **I. OPENING REMARKS—DR. LAWRENCE J. MARNETT**

Dr. Lawrence J. Marnett, Chair, called to order the 12<sup>th</sup> meeting of the Frederick National Laboratory Advisory Committee to the National Cancer Institute and welcomed the Committee members, National Cancer Institute (NCI) staff, and guests. Dr. Marnett reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Caron A. Lyman, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

Dr. Marnett welcomed new FNLAC members: Dr. Kevin J. Cullen, Director, Marlene and Stewart Greenbaum Cancer Center, Professor of Medicine, University of Maryland School of Medicine; Dr. Lisa M. Coussens, Hildegard Lamfrom Chair in Basic Science, Professor and Chair, Cell, Developmental and Cancer Biology, Associate Director for Basic Research, Knight Cancer Institute, Oregon Health and Science University; Dr. Klaus Hahn, Thurman Professor of Pharmacology, Director, UNC-Olympus Imaging Center, Department of Pharmacology, The University of North Carolina at Chapel Hill; and Dr. Janet A. Houghton, Senior Research Fellow, Endowed Chair in Cancer Biology, Division of Drug Discovery, Department of Oncology, Southern Research Institute.

He noted that future meeting dates were listed on the agenda. A motion to confirm the 2018 meeting dates: July 18–19, 2018, and October 29–30, 2018 and the 2019 dates: May 13-14, 2019, July 24-25, 2019, and November 13-14 was unanimously approved. Given the short lapse of time between the May and July meeting, consideration may be given to changing future meeting dates.

## **II. REPORT FROM THE ACTING NCI DIRECTOR—DRS. DOUGLAS R. LOWY AND JAMES H. DOROSHOW**

Dr. Douglas R. Lowy, Acting Director, NCI, welcomed new and continuing Committee members and other attendees. Dr. Lowy expressed appreciation to Dr. Peter Wirth, Assistant Director, Division of Extramural Activities (DEA), for his excellent stewardship in serving as the FNLAC Executive Secretary, and welcomed new Executive Secretary, Dr. Caron A. Lyman, Chief, Research Programs Review Branch, DEA. Dr. Lowy provided an update on the NCI budget, appropriations, and other activities. Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, Division of Cancer Treatment and Diagnosis (DCTD), provided an update on NCI's Virtual Formulary, NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, and the Patient-Derived Models (PDMs) Repository.

**Frederick National Laboratory for Cancer Research (FNLAC) and FNLAC.** Dr. Lowy informed members that the next FNLAC regular meeting will be held October 30–31, 2017. Given that adequate time will not have elapsed between today's meeting and the July 18–19, 2017 meeting dates consideration may be given to holding a Virtual meeting in July. Members were told that the Federally Funded Research and Development Center (FFRDC) contract re-competition is postponed. This postponement is partly due to recommendations by the FNLAC during its May 2016 and subsequent meetings. The FNLAC offered three key points for postponing the full deployment of the re-competition. First, the re-competition was planned before the President announced the Cancer Moonshot<sup>SM</sup> Initiative at the January 2017 State of the Union Address and the National Cancer Advisory Board's (NCAB) Blue Ribbon Panel (BRP) had just begun to develop recommendations for the Cancer Moonshot<sup>SM</sup>. Second, the FNLAC needed adequate time to assess its vision for the new FNLAC in the context of NCI's larger mission. Third, the draft request for proposals (RFP) for the FFRDC contract re-competition and the statement of work needed further details and more clarity on the scope of the work and how the contractor would fill the mission of both the NCI and the FNLAC. The NCI listened and agreed with FNLAC's recommendations and is currently engaged in discussions on the future of the FNLAC. The NCI looks forward to sharing the results of these deliberations with the committee at a future meeting. As the re-

competition contract is being renegotiated, the NCI is limited in any discussions until this process is completed.

**The NCI Budget and Appropriations.** Dr. Lowy informed members that the fiscal year (FY) 2017 omnibus spending bill to fund the government for the remainder of the fiscal year was signed by the President on May 5, 2017, and includes a \$174 million (M) increase for the NCI and \$300 M for the Beau Biden Cancer Moonshot<sup>SM</sup>. He remarked that NCI's appropriations have steadily increased for FYs 2016 and 2017, partly due to the strong advocacy and bipartisan support of the House and Senate Appropriations Subcommittees on Labor, Health and Human Services, Education, and Related Agencies, which are chaired by Oklahoma Representative Thomas Cole and Missouri Senator Roy Blunt, respectively. Rep. Cole and Sen. Blunt are congressional leaders who have made strong commitments to the NIH and the 2 years of increase is reflected in their leadership. Dr. Lowy described a visit by the congressmen to the NIH and the NCI. At the May 2, 2017, early screening of the NIH Clinical Center's new documentary series, "First in Human," Rep. Cole and Sen. Blunt confirmed their commitments to sustained increased appropriations for the NIH and the NCI.

The number of new Research Project Grant (RPG) awards, solicited and unsolicited, have increased substantially since FY 2014, and this trend is expected to continue in FY 2017. The NCI has increased the number of investigator-initiated research awards (R01) given to early stage and new investigators. Specifically, one in four of the total awards is given to early stage and new investigators, with 50 percent being awarded to early stage investigators. Of the funded Exploratory/Development Grant (R21) awards, four in 10 have been awarded to new investigators.

The President's signing of the appropriations bill into law completes the NIH/NCI four-step budget process for regular appropriations and restarts at step 1 for FY 2018, which begins on October 1, 2017. The White House Office of Management and Budget released proposed appropriations for FY 2018, which include an 18 percent decrease in funds for the NIH. Although it is challenging to predict the outcome of the FY 2018 appropriations, the NIH and the NCI are optimistic, given the additional steps in the process where changes could occur before final approval of the Federal budget.

Dr. Lowy called attention to the 21<sup>st</sup> Century Cures Act, it is a 10-year appropriations bill, and funds are allocated annually for the first 7 years, but those funds are not evenly distributed across the funding period. For the Cancer Moonshot<sup>SM</sup>, the appropriated \$1.8 billion (B) is provided to the NCI in annual allotments, with the highest amounts distributed in the first 4 years. After careful thought and discussions, the NCI developed a plan for funding new awards that would be consistent with the Cancer Moonshot<sup>SM</sup> goals to accelerate progress. For FY 2017, more than 15 Funding Opportunity Announcements (FOAs) have been issued, committing \$140 M of the authorized funding for first-year awards. Implementation teams are working to develop initiatives and budgets, which Dr. Dinah Singer, Acting Deputy Director, NCI and Director, Division of Cancer Biology, will discuss later in the meeting. In addition, the NCI is planning to solicit input from stakeholders in the upcoming months and will convene a virtual meeting of the NCAB BRP, which developed the Cancer Moonshot<sup>SM</sup> recommendations, for its input.

**NCI Activities.** Dr. Lowy informed members of NCI's efforts to address a White House recommendation to organize an International Cancer Proteogenome Consortium (ICPC), which was strongly supported by then-Vice President Joseph Biden, and this support has continued into the new Administration. The ICPC consists of 18 participating institutions from 11 different countries, including NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC), and 10 other institutions who have signed Memorandums of Understanding (MOUs). These participating institutions will conduct genomics on cancers that are specific to their country using CPTAC's standard operating procedures, and they have made data-sharing pledges to make genomic and proteomic data sets available to the public through NCI's databases, including the CPTAC and the Genomic Data Commons. The ICPC met for its first meeting on

March 19, 2017, in San Diego, California. Dr. Lowy told members that the enthusiasm for the Beau Biden Cancer Moonshot<sup>SM</sup> remains strong in the United States and internationally, which is reflected in such initiatives as the ICPC.

**NCI Virtual Formulary.** Dr. Doroshow informed members of NCI's efforts to address the challenges of clinical and translational investigators at NCI-designated Cancer Centers to obtain clinical grade molecules (i.e., investigational new drugs [INDs]) for clinical trials, which resulted in the development of a Virtual Drug Formulary (NCI Formulary). The NCI Formulary establishes a rapid review system (i.e., 6 to 8 weeks) to facilitate the transfer of drugs from pharmaceutical companies to the clinical trial and pre-clinical trial communities. The investigators or institutions, not the Cancer Therapy Evaluation Program (CTEP), will hold the license for the INDs. NCI's role is to distribute the INDs, facilitate the transfer of requests for the letters of intent to the pharmaceutical companies, monitor clinical trial accruals, and ensure appropriate data are submitted for the INDs. Approximately 40 percent of studies conducted at NCI-designated Cancer Centers are investigator-initiated and some are funded indirectly by pharmaceutical companies, others by philanthropic organizations. Launched in January 2017, the NCI Formulary currently has seven companies that collectively have provided 26 agents, which are commercially and non-commercially available. The available agents, participating companies, and information for investigators can be accessed on the NCI Formulary website: [nciformulary.cancer.gov/default.htm](http://nciformulary.cancer.gov/default.htm). The NCI hopes that the Formulary will be a conduit for investigators to obtain quality compounds that can be used alone or as combinations for clinical and pre-clinical trials.

**NCI-MATCH Trial.** Dr. Doroshow reminded members that the NCI-MATCH trial opened August 12, 2015, with 10 treatment arms; its initial goals were to biopsy 3,000 patients, perform weekly accruals of 40–50 patients over a 3- to 4-year period, then expand to a total of 6,000 patients. The accrual rate far exceeded expectations after only 3 months, prompting a temporary pause in accruals on November 11, 2015, to conduct a built-in interim analysis. This analysis revealed the distribution of patients across the disease spectrum within more than 1,000 NCI-designated sites, and the trial re-opened on May 31, 2016, with 14 additional treatment arms, now totaling 24. As of April 30, 2017, accrual is almost complete, with biopsies of 5,451 patient tumors completed. The NCI-MATCH trial has proven to be the most rapidly accruing in NCI's 60-year history of conducting trials, with accrual rates of 115–125 patients weekly. The genomic analysis success rate of 94 percent and median turnaround time for results of 16 days also have exceeded expectations. Seven of the 24 arms have completed accruals and are undergoing initial efficacy evaluations; four others are nearing complete accruals. Six additional arms were recently added on March 13, 2017. There have been no reported adverse events or toxicities associated with initial treatments or biopsies.

Regarding the primary disease sites of patients enrolled for screening, as of October 2016, the distributions of breast and colorectal cancers of patients enrolled for screening are higher, but enrollments of patients with ovarian and uterine cancers and other disease sites have been reasonable over the duration of the trial. In addition, enrollment demographics show that patients enrolled range in age from 18 to 100 years, and 80 percent are Caucasian; 8 percent, African American; and 6 percent, Hispanic. States with enrollment of more than 30 patients per million of the population were not always the highly populated states. For example, Minnesota ranked second to California in enrollments.

Despite this progress, the 30 NCI-MATCH treatment arms may not robustly investigate low-frequency mutations (i.e., rare variants), which often occur with less than 1 percent penetrance. In May 2017—in collaboration with two major cancer centers, M.D. Anderson Cancer Center and Memorial Sloan Kettering Cancer Center, and two commercial laboratories, Foundation Medicine Inc. and Caris Life Sciences—the NCI will begin to transition the NCI-MATCH trial into the Rare Variant Initiative to identify patients who may have rare driver mutations detected from prior tumor sequencing analysis. Data will be verified with the NCI-MATCH assays retrospectively. Patients with confirmed targeted mutations will be enrolled. The NCI anticipates that data from this study will inform future trials, establish a standard clinical

practice, provide easier access to drugs for patients, and establish an interlaboratory quality control standard.

**Patient-Derived Models (PDMs) Repository.** The PDM repository, a national repository and easily accessible database, will launch soon with 100 clinically annotated models of molecular information for common (i.e., breast and colon cancers) and not-so-common cancers. The initial distribution groups will include models for colorectal adenocarcinomas, head and neck squamous-cell carcinomas, urothelial and bladder cancers, melanomas, pancreatic adenocarcinomas, lung squamous-cell carcinomas, adult soft-tissue sarcomas, renal cancers, and gastrointestinal cancers. The goal is for the FNLCR to house up to 1,000 models, comprising patient-derived xenografts (PDXs) and *in vitro* patient-derived cell cultures, including mixed cell populations, clonal cell lines, and fibroblast cell lines. The Repository will serve as a resource for both public-private partnerships and academic drug discovery efforts. All PDMs will undergo confirmatory functional and pathological validations and be available to the cancer research community at little to no cost.

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

- Because the proposed Federal budget for FY 2018 includes a substantial decrease in funding for the NIH, which will undoubtedly affect the NCI if approved, it is challenging to forecast any infrastructure changes that might result.
- The NCI-MATCH trial is providing opportunities to capture data related to immune-mediated drug resistance, which can be analyzed retrospectively. For example, a Southwest Oncology Group clinical trial focusing on rare diseases will enroll patients who are not matched to an actionable mutation into a separate immunotherapy trial if they choose to participate. In addition, NCI funds are set aside to biopsy patients at the time of disease progression for genomic analysis; biomarker consortia are established in NCI-Designated Cancer Centers to develop assays to measure drug resistance; and new FOAs for the Cancer Moonshot<sup>SM</sup> that focus on immunotherapies are expected to continue these efforts.

**III. NATIONAL CRYO-EM FACILITY, IMPLEMENTATION AND COMMUNITY DISSEMINATION—DRS. SRIRAM SUBRAMANIAM AND ULRICH BAXA**

Dr. Sriram Subramaniam, Senior Investigator, Laboratory of Cell Biology, Center for Cancer Research (CCR), NCI, detailed the scientific origin and history, mission and strategy, and infrastructure for launching a National Cryo-Electron Microscopy (Cryo-EM) Facility (NCEF). He was joined by Dr. Ulrich Baxa, Head, Electron Microscopy Laboratory, CCR, FNLCR, who explained the plan for executing the NCEF, including descriptions of personnel, the operational plan, user access, and data transfer. The cryo-EM field has experienced extraordinary growth and popularity partly because of its promising ability to resolve, at lower resolutions, complex protein structures and complexes, which has been challenging to do by other methods (e.g., X-ray crystallography, and nuclear magnetic resonance [NMR] spectroscopy). Applications in basic science and drug discovery are making use of cryo-EM's utility to resolve traditional targets and high-resolution structures, such as large viruses, as well as more diverse targets, including smaller dynamic molecular structures. Dr. Subramaniam was motivated by this rapid growth of cryo-EM and saw an opportunity for the NCI to assist the cancer community in resolving cancer research problems related to structural biology by establishing the NCEF. Initial discussions with the NCI and FNLCR leadership began in 2014, which included a presentation to the FNLAC and culminated in convening a workshop to bring together leading structural biology experts, the directors of NIH's Institutes and Centers (ICs), and other IC representatives. The workshop participants recommended establishing a national cryo-EM user facility that modeled those available for crystallography. In 2015, a proposal to establish such a facility at the FNLCR was submitted, refined, and unanimously approved by the FNLAC. Dr. Subramaniam and his team began a series of actions to establish the NCI-NCEF.

The mission of the NCEF is to provide a facility to accommodate three different groups of users: research groups already experienced in cryo-EM technology; structural biologists in adjacent disciplines (e.g., X-ray crystallography or NMR); and biologists with interest in important biomedical problems. The NCEF will initially focus on the first group, experienced cryo-EM users, because they are the most trained but may not have access to high-end technology. The NCI has budgeted \$5 M per year for FY 2016–2019 for equipping, staffing, and maintaining the NCEF. The FEI Titan™ Krios microscope has been purchased and installed; it is operational and the facility is expected to open for user access on May 15, 2017. Future directions include constructing a new microscope facility at the Advanced Technology Research Facility (ATRF) on the FNLCR campus by the summer of 2018; relocating the Krios microscope to the ATRF with the addition of a second Krios, or equivalent, in 2018; and adding a lower voltage microscope in FY 2017–18.

Dr. Baxa described the organizational structure of the NCEF and acknowledged key personnel who will be responsible for daily operations: Dr. Subramaniam, Program Advisor; Dr. David Heimbrook, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos); and Dr. Dwight Nissley, Director, Cancer Research Technology Program, FNLCR, Leidos. As Senior Microscopist, Dr. Baxa will serve as the technical lead for the facility and will be supported by Junior Microscopist, Dr. Thomas Edwards, and Scientific Project Manager, Helen Wang. An *ad hoc* National Cryo-EM Facility Oversight Working Group will provide oversight on the technical aspects of the NCEF and provide recommendations to the FNLAC. The operational plan involves users completing a sample information form (SIF), which is linked to the NCEF website and asks the submitter for details on the sample type, imaging conditions, and a statement on the project's relevancy to cancer research. Once the SIF is approved, users are permitted to send prepared biological samples as frozen EM grids to the facility. User samples are properly stored until the scheduled date of analysis. Each user is allotted a maximum of 48 hours of imaging time. Data will be stored at the facility on a secure 100-terabyte server for 1 month and will be made available for download through Globus ([www.globus.org](http://www.globus.org)), a secure, reliable file transfer protocol service. The NCEF website will publish updates on performance and upgrades, and information also will be posted on NCI's social media outlets. Testing has been completed and benchmarks have been established for data collection with automated workflows and data transfer and downloads.

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

- The second and third user groups will be accommodated following the initial launch and assessment of demand for the services. The first objective is to establish that the facility services are needed among the experienced users and then address the demands of the other users. The projected expansion of the NCEF is expected to relieve the demand issues and reduce wait times.
- The NCEF will not charge users resolving molecular structures related to cancer, and the NCI has no expectations to fully recover the costs for operating the facility. As the use of the facility increases, a system to prioritize samples may be necessary.
- Several laboratories offer data processing and sample preparation services to structural biologists; access to instruments to analyze the samples has been limited, and the NCEF will fill this gap.
- The NCI will engage in community outreach efforts to increase awareness about the NCEF, including leveraging core facilities, posting to relevant microscopy websites and listservs, communicating with NCI grantees, using NCI media resources, and communicating with colleagues in academia.

**IV. THREE DEPARTMENT OF ENERGY AND FNLCR COLLABORATIONS: JOINT DESIGN OF ADVANCED COMPUTING SOLUTIONS FOR CANCER; RAS PILOT; AND ACCELERATING THERAPEUTICS FOR OPPORTUNITIES IN MEDICINE—DRS. WARREN KIBBE, EMILY J. GREENSPAN, FRANK MCCORMICK, ERIC A. STAHLBERG, AND FRED STREITZ**

Dr. Warren Kibbe, Acting Deputy Director, NCI and Director, Center for Biomedical Informatics and Information Technology, presented the background of the Department of Energy (DOE) and FNLCR collaborations. He was joined by Dr. Eric A. Stahlberg, Director, Strategic Data Science Initiatives, Data Science and Information Technology Program, FNLCR, Leidos, who provided an overview of the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C); Drs. Frank McCormick, Professor, Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco (UCSF), Scientific Advisor, NCI RAS Initiative, and Fred Streit, Director, High Performance Computing Innovation Center, Lawrence Livermore National Laboratory, DOE, who discussed the plans for the RAS Therapeutic Targets, Pilot 2; and Dr. Emily J. Greenspan, Program Director, Center for Strategic Scientific Initiatives, Office of the Director, NCI, who described the Accelerating Therapeutics for Opportunities in Medicine (ATOM) effort.

Dr. Kibbe reminded members of the key Presidential Executive Orders that lay the groundwork for the NCI-DOE collaborations: the January 2015 Precision Medicine Initiative, the July 2015 National Strategic Computing Initiative (NSCI), and the 2016 Vice President’s Cancer Moonshot<sup>SM</sup> Initiative, which was renamed the Beau Biden Cancer Moonshot<sup>SM</sup> Initiative in December 2016. The DOE is one of the lead agencies and the NIH is a broad deployment agency for the NSCI. Fostering public-private collaborations is a cross-cutting theme of these Federal initiatives. The DOE-NCI partnership to advance exascale development through cancer research was officially announced in June 2016 and a DOE-NCI Governance Review Committee routinely meet to discuss progress. The exascale partnership has evolved into the JDACS4C and comprises 3-year pilot projects that simultaneously push the frontiers of oncology and exascale computing with identified specific aims and clearly defined milestones. The pilots are jointly supported, managed, and planned by the FNLCR and four DOE National Laboratories: Argonne, Oak Ridge, Lawrence Livermore, and Los Alamos. In addition, the pilots align with the goals and objectives of other efforts, including NCI’s Precision Medicine Initiative for Oncology (PMI-O), the NSCI, and the Beau Biden Cancer Moonshot<sup>SM</sup>. Outreach efforts to increase awareness and engage the cancer research and computational communities in the DOE-NCI initiatives have included presenting at scientific meetings and conferences, such as the 2016 Frontiers of Predictive Oncology and Computing Meeting, the 2016 RAS Structures and Dynamics in Cellular Membrane Workshop, Supercomputing 2016, the 2017 International Strategic Initiative of Computing Systems and Applications Workshop, and DOE National Laboratory-Sponsored Computing Hackathons. Similar activities will continue throughout 2017.

**Joint Design of Advanced Computing Solutions for Cancer (JDACS4C).** Dr. Stahlberg pointed out that the motivation for a JDACS4C began with a prior initiative in the NCI to increase the high-performance computing capabilities to support the PMI-O and investigate whether such investments could accelerate cancer research. A 2014 initiative to prepare for “exascale cancer science” led to the generation of a timeline that extends from 2015 to 2020, containing considerations of infrastructure, training, applications, and collaborative pilot investigations. The JDACS4C collaboration consists of three pilot projects that unite the shared interests of the NCI and the DOE, to address scientific challenges in cancer research driven by advances in computing and advancing exascale technologies driven by cancer research advances. The three projects represent three distinct domains, which are integrated at the precision oncology and technology levels: Pilot 1, Improved Predictive Models, represents the preclinical domain; Pilot 2, Multiscale Biological Models, such as RAS-RAF interactions, represents the molecular domain; and Pilot 3, Precision Oncology Surveillance, represents the clinical domain. Cross-laboratory teams comprised of scientists and computational experts from the NCI and the DOE National Laboratories contribute their knowledge and insight to the projects and identify the challenges. The domain knowledge and challenges



addressed in the pilot projects will shape the priorities for the CANcer Distributed Learning Environment (CANDLE) project, a 4-year multi-laboratory DOE-supported Exascale Computing Project that focuses on creating a scalable, open, and deep-learning framework for the JDACS4C pilots, CANDLE began in September 2016. Reference benchmarks were released in January 2017, and the NIH has sponsored workshops to engage the computational community in this effort.

Dr. Stahlberg discussed highlights of Pilot Projects 1 and 3. The goal of Pilot 1 is to improve predictive capabilities for preclinical screening through advances in machine learning and integrated modeling. The specific aims are to build (1) reliable machine learning-based predictive models of drug response using data from the NCI and other sources (e.g., NCI-60 Cell Lines, NCI Sarcoma Project, NCI PDM, and the Broad-Novartis Cancer Cell Line Encyclopedia); (2) uncertainty quantification and improved experimental design; and (3) hybrid predictive models. The envisioned impact will be to expand the range of treatments for cancer precision medicine and a design of architectures that integrate learning systems and simulation. Progress to date includes development of early-stage shallow and deep predictive models; quality assurance clustering and mapping of studies using current data; and completion of initial molecular network-based convolution experiments. Early insights reveal that many model types have predictive capabilities on response problems similar to cancer, but efforts have been constrained due to the limited data to capture the response distributions, especially in clinically relevant cases. Pilot 3 focuses on improving cancer surveillance. Aim one in particular focuses on increasing the use of computational methods to automate data collection using natural language processing for pathology reports extending the depth and breadth of the information resource can be developed in detail and affordably. The Surveillance, Epidemiology and End Results (SEER) registry data from Georgia, Kentucky, Louisiana, and Washington will be the initial inputs. Progress to date includes establishing the annotation framework, text comprehension, and text synthesis.

Dr. Stahlberg summarized that the JDACS4C is building, motivating, and expanding interdisciplinary collaborations and partnerships and, in so doing, is piloting cross-disciplinary activities to enable precision oncology. The collaboration is delivering insight combined with new computational capabilities, thus enabling open team science to rapidly achieve goals in precision oncology.

**Pilot 2: RAS Therapeutic Targets.** Dr. McCormick described RAS therapeutic targets, the scientific basis for Pilot 2. The focus is to increase understanding, at the molecular or atomic levels, of how RAS proteins activate the RAF kinase and the mechanisms that are associated with the resulting malignant transformation. Approximately 20 percent of human cancers can be attributed to uncontrolled RAS activation of RAF. He reminded members of the goals of the RAS Initiative: to discover small molecules that bind RAS directly or disrupt RAS/effector interactions and to provide insight on how RAS functions in the plasma membrane, with considerations for imaging and biophysical, biochemical, and computational analyses. Although much is known about the biophysics, biochemistry, and function of the RAS protein, much is yet to be discovered about the mechanisms associated with its interactions with the plasma membrane; the DOE computational effort will increase the field's understanding of these interactions. The collaboration involves a multilevel approach to investigating KRAS-RAF membrane interactions, which includes use of high-tech imaging processes to measure RAS proteins in live-cells, followed by biochemical and biophysical analysis of recombinant RAS proteins on synthetic lipid bilayers, and culminating with *in silico* modeling. These iterative processes are expected to build models that accurately depict RAS interactions in the plasma membranes. Dr. McCormick remarked that the RAS Biochemistry and Biophysics Group and Image-Based Screens Group scientists presented at the 2017 American Association for Cancer Research (AACR) meeting, and feedback from the cancer community was encouraging. Data from the RAS activation experiments performed in collaboration with subject-matter experts in academia who have specialized biophysical techniques will inform the computational modeling, which will concentrate on NMR, neutron reflectivity, and protein footprinting methods.

Dr. Streitz presented DOE's computational approach to addressing RAS membrane interactions. The goal is to develop a predictive simulation capability to better understand the RAS protein membrane interactions. These efforts will require generating a new computing capability, which the DOE is undertaking enthusiastically. This novel approach, adaptive sampling molecular dynamics (MD) simulation codes, will connect a phase-field model, coarse-grain MD (i.e., atomistic), and classical MD and will leverage DOE's existing efforts in giant computing, in which simulations have been used instead of experiments to answer important questions. To build reliable, validated predictive simulations, team science is necessary to work seamlessly across the two agencies. The DOE National Laboratories and the FNLCR have worked as such since the project began. The adaptive sampling MD model will access biologically relevant time and length scales using free-energy calculations. The challenge will be to build a framework where the three models—phase field, coarse grain MD, and classical MD—are consistent internally and externally. Simulation of not just one RAS protein/membrane but a full system of hundreds of RAS protein/membrane interactions will incorporate many smaller simulations, close to 100,000 simultaneous atomic simulations. Unlike biologists, physicists need this scale and magnitude to better understand the correct distribution of RAS on the membrane statistically. Dr. Streitz reported that initial coarse-grain MD simulations of KRAS depicted in an average complex human plasma membrane, comprising 64 KRAS proteins incorporated into a membrane measuring  $70 \times 70$  nanometers, revealed that the RAS proteins readily cluster and rapidly associate with aggregated charged lipids in the plasma membrane. These simulations will continue to be developed and validated.

Building the predictive models for RAS membrane interactions from simulations will require close collaboration between computational biological system modelers, computer programmers and coders for large complex systems, and experimentalists who understand the RAS biology to integrate the data. Simulations of KRAS in biologically relevant lipid environments are currently in progress. The pilot will focus on developing three new computational capabilities: multiresolution, machine learning-optimized resolution, and automated hypothesis exploration. These capabilities will be broadly applicable to the NCI and DOE missions and are anticipated to drive the next generation of computing.

**Accelerating Therapeutics for Opportunities in Medicine (ATOM).** Dr. Greenspan described a new public-private partnership, ATOM, which has emerged from the DOE-NCI collaborations. In January 2017, the NCI, GlaxoSmithKline (GSK), and the DOE signed a memorandum of agreement to establish a public-private partnership. The goal of the partnership is to accelerate preclinical drug design and development through use of advanced computational and *in silico* technologies. This process is expected to generate relevant research tools, models, and data; establish an environment of parallel activities; and shorten the U.S. Food and Drug Administration (FDA) process for approving INDs designed for known cancer-related targets. ATOM aligns with the overall interests of the NCI and FNLCR to provide open data, tools, and capabilities to the broader cancer research community and will leverage existing expertise. The next step will be to expand, over 3 years, this large team effort into an ATOM Consortium that will include additional partnerships with qualified pharmaceutical and biotechnology companies, academia, and governmental agencies; the FNLCR, GSK, Lawrence Livermore National Laboratory, and UCSF are founding members. The first year of the 3-year timeline will focus on selecting a location, recruiting staff, establishing workflows, engaging new partners, and identifying problems. The NCI is planning to locate the Consortium near UCSF's Mission Bay Campus in time for a spring 2017 launch; the FNLCR will provide onsite and remote research expertise, and the NCI will provide onsite and remote subject-matter expertise and program management. The second year will involve process refinements, skill building, and model testing. In the third and final year, the proof-of-concept experiment will be conducted using the models and tools developed in the prior years to identify compounds that modulate the selected cancer-relevant target. Safety, efficacy, and bioavailability testing will also be performed. The process is aiming to yield a viable cancer therapeutic that is linked with an approved IND application from the FDA. The NCI anticipates that the ATOM Consortium would have accelerated the process leading to a FDA IND application from 5 years to 1 year or less. The ATOM workflow model is being developed, FNLCR

technical and research contributions are being evaluated, and ideas to increase engagement across the broader research community are being discussed.

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

- Pilot Project 1, Preclinical Models, will focus on some of the models (e.g., cell lines and PDXs) for which the NCI already has data. Although humanized animal models (e.g., transgenic mouse models) do capture *de novo* tissue remodeling and other aspects of immunobiology, they will not be included at this iteration and could be models to consider in the future.
- The recommendation was made to consider providing a list of the achievements and benchmarks for the Pilot Projects, or examples of prior successes of similar collaborations. When available resources have been evaluated and the number of full-time employees needed has been determined, the NCI and the DOE can consider sharing resources to support the projects.
- Although the JDACS4C pilot projects will not answer every dynamic question about RAS, this work has tremendous potential to provide relevant biological answers, which can be tested as hypotheses and either verified or refuted experimentally.
- The extramural computational community could be directly engaged in the exascale efforts.
- Committee members would like more specific information on the state of Pilot Project 3 and its scope and metrics.
- The SEER Data Management System (DMS) is a controlled HIPAA-exempt environment, which is hosted through Information Management Services, Inc. (IMS). The rules are explicit on data reporting from participating registries and the NCI is working to determine how this would affect the ability to share data from the Pilot 3 project publicly with the broader cancer community.

**V. FNLCR UPDATE: PROGRESS AND PROGRAMS—DR. DAVID C. HEIMBROOK**

Dr. Heimbrook provided an update on the progress and programs of the FNLCR. The FNLCR, a Federally Funded Research Development Center (FFRDC) dedicated exclusively to biomedical science, is operated by Leidos Biomedical Research (Leidos Biomed) on behalf of the NCI, and the main campus is in Fort Detrick, Maryland. Leidos Biomed employees are co-located with NCI researchers and other contractors at the Frederick National Laboratory. The two-fold mission is to provide a unique resource for developing new technologies and to translate basic science discoveries into novel agents for the prevention, diagnosis, and treatment of cancer and AIDS. As an FFRDC, the FNLCR is flexible and efficient and responds rapidly to meet NCI's changing needs in a unique manner. He acknowledged the Leidos Biomed leadership and key groups in the organization and remarked on the cadre of talented professionals at the FNLCR who oversee a staff of 2,000 Leidos Biomed employees.

Dr. Heimbrook provided details on FNLCR operations and its technical support contract and the FY 2016 obligated funding. The government obligated \$669 M to support FNLCR operations; 73 percent (\$489 M) supported NCI-related work and 27 percent (\$180 M) supported non-NCI-related work, primarily that of the National Institute of Allergy and Infectious Diseases (NIAID). The NCI-appropriated funds are distributed across the NCI Divisions, Offices, and Centers. The Office of the Director, the CCR, and DCTD were the primary sources of FNLCR appropriations in FY 2016.

Dr. Heimbrook also updated members on FNLCR programs and projects. The FNLCR's support to the Zika outbreak response has been primarily through the manufacture of vaccine drug products and supporting vaccine clinical trials for the NIAID. The clinical development cycle begins with the basic

science at the Vaccine Research Center (VRC), where vaccines are identified and tested for *in-vitro* activity against the Zika virus. Promising candidates move to the next phase, process development, at the VRC's Vaccine Production Program Laboratory and, upon completing this phase, products are delivered to the Vaccine Clinical Materials Program at the FNLCR, a Current Good Manufacturing Practice (cGMP) facility. Once produced and manufactured, the vaccine products are entered into clinical trials and immune responses are assessed within NIAID's Vaccine Immune T-Cell and Antibody Laboratory. On June 15, 2016, 60 days from the receipt of the initial plasmid from the VRC, vaccine drug manufacturing was completed—quality control and sterility testing of 664 vials were completed mid-July 2016, meeting the target release date. Phase 1 clinical trials began on August 2, 2016, and the FNLCR continues to support the NIAID in these efforts.

Dr. Heimbrook then provided status updates on a number of programs that had previously been reviewed and endorsed by FNLAC. Dr. Heimbrook reminded members that a detailed review of the RAS Initiative (or RAS Program) was completed in November 2016, and he expressed appreciation to the FNLAC and the RAS *ad hoc* Working Group for their feedback. Because of the review, the FNLAC provided strategic recommendations for the long-term vision of the FNLCR: Emphasize partnerships that might provide the RAS Program significant influence on RAS inhibitor development priorities; develop medicinal chemistry capabilities in-house; develop *in silico* screening capabilities; and develop models for RAS activation of downstream effectors. The RAS Program has made progress to address these recommendations. For example, recent collaborations focusing on shared intellectual property, including the Beatson Institute for Cancer Research collaborations, are steps to move forward on RAS inhibitor development priorities. The FNLCR recently hired a medicinal chemist to join the RAS Program. The DOE-NCI collaborations are expected to assist in developing *in silico* screening capabilities and models of RAS activation. The strategies for implementing the RAS Initiative recommendations will be presented in detail following discussions with the expanded RAS *ad hoc* Working Group.

Dr. Heimbrook described programs that are aligned to ensure that the FNLCR resources have an impact on the broader biomedical community. The contractor partnering authorities were approved in 2012, and the Contractor Cooperative Research and Development Agreements (cCRADA) have expanded access to FNLCR resources and are foundational to many of the programs that are supported, including the RAS Program. The cCRADAs enable research collaboration involving intellectual and material contributions by FNLCR scientists, who are not government personnel, and external partners. A total of 28 cCRADAs have been executed since FY 2013 with \$6.8 M in total partner investments, resulting in six employee invention reports and two patent applications to date. In addition, three material cCRADAs and two collaboration agreements were completed. FY 2017 is likely to be the most active year regarding signed agreements, which are widely dispersed across the FNLCR Directorates, including Cancer Research Technology and the Basic Science Program. In addition to cCRADAs, the Technical Service Agreement (TSA) is a streamlined agreement executed under the same statute; it allows the FNLCR to provide well-defined and validated research services to the scientific community. To date, partner contributions from TSAs total approximately \$6.7 M, with more than 200 agreements and 85 partners. Of the 23 preapproved technical services available within the FNLCR, those offered by the AIDS and Cancer Virus Program and the Laboratory Animal Services Program are the most sought after.

The Nanotechnology Characterization Laboratory (NCL) was established in 2004 by the NCI in collaboration with the FDA and the National Institute of Standards and Technology to accelerate the development of promising nanotechnology therapies and diagnostics. The NCL, known for its assay cascade, has evaluated more than 350 nanomedicines and enabled 13 therapeutic candidates to transition into the clinic. The assay cascade services of the NCL accessed all the capabilities of the FNLCR to help nanotechnology inventors better understand their products and the necessary safety and efficacy evaluations. As the nanomedicine field expanded, capabilities and demand increased; thus, NCL 2.0 emerged, concentrating on reformulation, non-oncology nanomaterials, metrology and new materials, basic research and grand challenges, informing regulatory agencies, and transnational collaboration. Reviewed by the

FNLAC in 2015, implementation of NCL 2.0 has been ongoing and includes collaborations with pharmaceutical companies, new publications, toxicity assessments, cross-agency communications, and international collaborations to address the increased activities. In addition, the NCL is a partner in a multinational “mirror” NCL in Europe, EU-NCL, which is a consortium of eight laboratories across seven countries formed to expand access to nanomaterial characterization for nanotech developers. The FNLAC provided training for EU-NCL’s Core Expert Team, assay qualification support, and systems testing. This collaboration benefits both the NCI and the EU-NCL by providing access to resources that would not have otherwise been available to either party separately.

The Laboratory-Directed Exploratory Research (LDER) Program at the FNLAC emulates DOE’s FFRDC Laboratory-Directed Research and Development (LDRD) Fund, which has been a cornerstone of success for the DOE. New creative and innovative projects at the DOE National Laboratories are supported by the LDRD Fund, which itself is financed through an appropriation-enabled tax on all funding. After discussions in the NCI and with the FNLAC on whether a similar program, using an appropriate funding mechanism, would foster development of new innovative projects at the FNLAC, the following emerged as probable objectives that could be addressed, if such a fund existed: enhance the innovation, creativity, originality, and quality of research activities; facilitate collaborations within the FNLAC; engage local universities; and enable demonstration of exploratory proof-of-concept projects. Also, the FNLAC Laboratory Director would be responsible for the overall execution and management of the program. In FY 2016, the NCI committed \$1 M to establish the FNLAC LDER Program; that commitment has been renewed for FY 2017. Five projects, selected through a peer-reviewed process, were funded for FY 2016, three of which were renewed for FY 2017. Four new projects were funded for FY 2017, and solicitations for proposals for FY 2018 are in progress.

Dr. Heimbrook congratulated Dr. Claudia Haywood, Director, Intellectual Property and Strategic Agreements, Leidos, on receiving the 2017 Excellence in Technology Transfer Award, and Dr. Stahlberg on being selected as one of *Federal Computer Week’s* 2017 Federal 100.

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

- There is a large amount of variation in the FNLAC-supported projects for both the NCI and the NIAID. Given the scale of the rapid-response projects, NIAID’s projects are probably more expensive to conduct, but there are fewer NIAID projects.
- The FNLAC supports the VRC Drug Development process in the operation of the cGMP manufacturing facility and supports NIAID clinical trials in the identification of clinical sites for the studies. All other aspects of the work are performed by government personnel. Also, with joint NCI-NIAID projects, the activities of the individual Institutes are performed separately.
- Although the unique features of the FNLAC—flexibility, capability for rapid response, and increased efficiency—would suggest that the laboratory engages in smaller short-term projects rather than long-term robust projects, the RAS Program benefited from the flexibility to move resources to where they could be most productive. Also, recruiting and hiring talented researchers for the RAS Program was able to be expedited and flexibility has allowed for seamless support for NIH’s ICs.
- Some of the FNLAC programs and projects may be ambitious and high-risk, including leading-edge and innovative technologies; however, rapid application of these technologies to critical scientific problems is a win-win situation on all levels. Guaranteed success is not a requirement for supporting a project.

## **VI. IMPLEMENTATION OF THE CANCER MOONSHOT BLUE RIBBON PANEL RECOMMENDATIONS—DR. DINAH SINGER**

Dr. Singer reminded members that in January 2016, then-President Barack Obama launched the Cancer Moonshot<sup>SM</sup> and articulated three primary goals: accelerate progress in cancer, encourage greater cooperation and collaboration, and enhance data sharing. The NCI focused on identifying those areas of cancer research that could be accelerated and established a 28-member BRP of external experts from relevant scientific disciplines to identify major scientific opportunities that were poised to be accelerated with additional emphasis and funding. The BRP worked over 4 months, engaged the support of more than 200 participants, and organized seven Working Groups, which culminated in 10 high-priority scientific recommendations that were summarized and published in a BRP report. This report is available on the NCI website. Several themes cross-cut the recommendations, including health disparities, technology development, prevention, data sharing, and partnerships.

On December 13, 2016, Congress passed the 21st Century Cures Act authorizing \$1.8 B in funding to broadly support cancer research through the Beau Biden Cancer Moonshot<sup>SM</sup>. The funds will be allocated over 7 years, and \$300 M have been allocated for FY 2017. Although \$1.8 B is the total authorized funding, the allocations will not be distributed evenly over the 7-year period; higher amounts are allocated for FYs 2017–2019 and drop off sharply for the remaining 4 years, which poses a challenge to the implementation plan. The NCI has developed approaches for accelerating research using the 21st Century Cures funding that involves initiating a large amount of new research in FYs 2017–2019; a portion of the grant awards will use multiyear funding mechanisms. In addition, contracts with the cancer community will be managed through the FNLCR, and core resources will be established. The NCI anticipates funding new grants each year of the Cancer Moonshot<sup>SM</sup> except for FY 2020 and FY 2021, when the allocations drop precipitously. Funding of new awards is expected to resume in FY 2022.

Although funds were not authorized until near the end of FY 2017, the NCI was able to launch initiatives that will lay the groundwork for implementing the broader initiatives in FY 2018 and FY 2019. Initiatives addressing six of the 10 BRP recommendations—Fusion Oncoproteins in Pediatric Cancer, New Enabling Technologies, Cancer Immunotherapy, Therapeutic Target Identification to Overcome Drug Resistance, Prevention and Early Detection, and Symptom Management Research—have been developed. The FY 2017 FOAs have been issued, and applications are being reviewed.

For FY 2018 and FY 2019, the NCI has developed a more coherent implementation process for the BRP recommendations that is designed to be well managed and sustainable. Twelve Cancer Moonshot<sup>SM</sup> Implementation Teams (CMITs) are aligned with the 10 BRP recommendations; cancer immunology has both adult and pediatric CMITs, and prevention and early detection has both cancer screening and prevention CMITs. These 12 CMITs, comprising more than 250 representatives from NCI's intramural and extramural communities and other Institutes, are charged with developing initiatives that will achieve the goals of each recommendation. The CMITs will identify gaps and opportunities in the existing initiatives; seek input from others, including the NCAB, advocacy groups, and associations; and leverage existing partnerships. In addition, the CMITs are charged to provide oversight and coordination of the funded initiatives. The CMITs were encouraged to use, and have used, different outreach strategies for obtaining input from the broader community on how best to implement the BRP recommendations, including issuing requests for information, convening parallel sessions with stakeholders at the 2017 AACR meeting, discussing recommendations with BRP Working Groups, and organizing workshops. To address communications across CMITs, which will be critical to the success of the implementation plan, the NCI has established an Implementation Coordinating Committee (ICC) that convenes bimonthly meetings with coordinators who are assigned to each CMIT to share ideas and cross-cutting information and to discuss concepts. In parallel, an Implementation Partnership Committee engages the appropriate partners for research initiatives as they are being developed. Information on high-priority concepts is forwarded to an Implementation Steering Committee for review, budgetary consideration, prioritization and approval. The

approved concepts will be presented to the Board of Scientific Advisors (BSA) at the June 2017 joint BSA-NCAB meeting. The implementation plan is moving rapidly—the CMITs meet weekly, and the ICC meets biweekly—and FY 2018 FOAs are expected to be released July–August 2017. The Implementation Partnership Committee has been approved to begin developing partnerships with other members of the cancer community.

Dr. Singer informed members that the NCI is planning to issue contracts through the FNLCR to support the following Cancer Moonshot<sup>SM</sup> projects: human tumor atlas pilot, molecular markers of drug response and resistance, cancer data ecosystem pilots, and the human papillomavirus trial. In addition, core resources will be established at NCI-Frederick for several of the initiatives, including support for the pediatric fusion oncoprotein research, tumor and tissue characterization repository PDX development, and data ecosystem pilots.

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

- The FNLCR protein purification facility supports the RAS Initiative and should be scalable to meet the demands of the Cancer Moonshot<sup>SM</sup>.
- The NCI estimates that a third of the Cancer Moonshot<sup>SM</sup> funding will be allotted to contracts and two-thirds will be committed to grants.

**VII. ONGOING AND NEW BUSINESS—DR. LAWRENCE J. MARNETT**

Dr. Marnett requested input from the committee members regarding any remaining issues for discussion.

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

- The discussions and questions after each presentation benefit both the speakers and the committee. Presenters and speakers might consider providing to the committee specific questions to be addressed prior to the meeting.
- Communicating to colleagues and the academic community about the opportunities for collaborations that are available at the FNLCR is one way the committee could help increase awareness and be strong advocates for the Laboratory.
- The FNLCR looks forward to leveraging its role as an FFRDC, as well as its special capabilities to provide services to the broader biomedical community, by continuing to seek and support new opportunities, national missions, and programs (e.g., RAS Initiative, JDACS4C, and LDER), while sustainably supporting NIH's ICs. The Beau Biden Cancer Moonshot<sup>SM</sup> might be one way to launch new national mission-like projects.
- Consider ways to convey the uniqueness of the FNLCR, which sets it apart from other NIH ICs or organizations that engage in large-scale projects that benefit the biomedical community. Efforts that directly engage the extramural community would be one place to start.
- The DOE-NCI collaborations are still young and many details will need to be addressed. In the future, a new FNLCAC working group will be convened to provide scientific evaluation of programs, projects and collaborations formed in support of or relevant to NCI-DOE collaborations. The working group will be composed of various NCI Advisory board/committee members and individuals representing a spectrum of oncology, computational biology, advanced computing, machine learning, data science, precision medicine experts and other ad hoc members as needed.

- The extensive review of the RAS Program in 2016 clearly indicated that efforts should continue focusing on basic research and biology and expanding capabilities to develop putative RAS inhibitors, either in-house or through outreach to other academic institutions.

**VIII. ADJOURNMENT—DR. LAWRENCE J. MARNETT**

Dr. Marnett thanked the Committee members and other invitees for attending. There being no further business, the 12th meeting of the FNLAC was adjourned at 3:10 p.m. on Monday, May 8, 2017.

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Date

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Lawrence J. Marnett, Ph.D., Chair

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Date

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Caron A. Lyman, Ph.D., Executive Secretary