U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute

17th Meeting
Frederick National Laboratory Advisory Committee

Summary of Meeting
October 24, 2019

Auditorium E1600, Advanced Technology Research Facility, Frederick Campus
National Cancer Institute
National Institutes of Health
Frederick, Maryland

National Cancer Institute
17th Meeting of the Frederick National Laboratory Advisory Committee
October 24, 2019

Summary Minutes

The Frederick National Laboratory Advisory Committee (FNLAC) convened for its 17th meeting on October 24, 2019, in Auditorium E1600, Advanced Technology Research Facility, Frederick Campus, National Institutes of Health, Frederick, MD. The meeting was open to the public on October 24, 2019, from 8:45 a.m. to 4:00 p.m. The FNLAC Chairperson, Dr. Lawrence J. Marnett, Dean of Basic Sciences, Mary Geddes Stahlman Professor of Cancer Research, and Professor of Biochemistry, Chemistry, and Pharmacology, Vanderbilt University School of Medicine, presided.

FNLAC Members
Dr. Lawrence J. Marnett (Chair)
Dr. Catherine M. Bollard (absent)
Dr. Andrea Califano* (absent)
Dr. Lisa M. Coussens (absent)
Dr. Kevin J. Cullen
Dr. Raymond N. DuBois
Dr. Angela M. Gronenborn
Dr. Robert L. Grossman
Dr. Klaus M. Hahn
Dr. David I. Hirsh
Dr. Elizabeth M. Jaffee (absent)
Dr. Patrick Nana-Sinkam (absent)
Dr. Nilsa C. Ramirez-Milan
Dr. Lincoln D. Stein
Dr. Cheryl L. Willman (absent)

***Ex Officio* Members**
Dr. Stephen J. Chanock (absent)
Dr. James H. Doroshow
Dr. Paulette S. Gray
Dr. Sara Hook
Dr. Anthony Kerlavage
Dr. Tom Misteli (absent)
Ms. Donna Siegle
Dr. Dinah S. Singer

Executive Secretary
Dr. Caron A. Lyman

*pending appointment

TABLE OF CONTENTS

I. OPENING REMARKS—DR. LAWRENCE J. MARNETT

Dr. Lawrence J. Marnett, Chair, called to order the 17th meeting of the Frederick National Laboratory Advisory Committee (FNLAC) 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.

Motion. A motion to approve the minutes of the June 27, 2019 FNLAC meeting was approved unanimously.

Dr. Marnett called Committee members' attention to the confirmed future meeting dates listed on the agenda. He introduced a new FNLAC member, Dr. Lincoln D. Stein, Director, Informatics and Biological Computing Platform, Ontario Institute for Cancer Research, Professor, Department of Molecular Genetics, University of Toronto, who was attending his first in-person meeting.

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

Dr. Douglas R. Lowy, Acting Director, NCI, also welcomed the FNLAC members and attendees to the meeting. He provided updates on advances in cancer research, the NCI budget, and new and ongoing activities and also noted the full agenda focusing on FNLCR programs.

Cancer Research Advances. Dr. Lowy reported that NCI-supported researchers Dr. Gregg L. Semenza, Johns Hopkins University, and Dr. William G. Kaelin Jr., Dana-Farber Cancer Institute, shared the 2019 Nobel Prize in Physiology or Medicine with Dr. Peter J. Ratcliffe, University of Oxford, for their discoveries on cellular oxygen sensing: observations important to improving the research community's understanding of cancer. Another NCI-supported investigator, Dr. James P. Allison, MD Anderson Cancer Center, who shared the 2018 Nobel Prize in Physiology or Medicine with Dr. Tsauko Hunjo, Kyoto University, for their efforts in immune checkpoint inhibitor research, is the feature story of a 2019 documentary titled "Jim Allison Breakthrough," part of which highlights NCI's mission and accomplishments.

In addition to scientific breakthroughs, NCI investments have contributed to cancer research advances that have resulted in improved nationwide treatment-associated outcomes for many cancers, including multiple myeloma, non-small-cell lung cancer, and melanoma. NCI's Surveillance, Epidemiology and End Results (SEER) Program data on multiple myeloma revealed that since 2000, the U.S. Food and Drug Administration's (FDA) approval of drugs for treating multiple myeloma has steadily increased, especially for small-molecule targeted inhibitors. This increase in FDA-approved multiple myeloma medicines has resulted in improvements in patient survival, such that the mortality rates, which were once twice as high for African American men as for Caucasian men, are almost identical between these two groups. Similar results have been observed among African American and Caucasian women.

Dr. Lowy remarked that a cancer research advance in the area of prevention has been the human papillomavirus (HPV) vaccination program. The FNLCR HPV Serology Laboratory has led some of the program's efforts. The goals of an HPV vaccination program are to *directly r*educe the risk of infection and disease and *indirectly* reduce the risk by reducing the prevalence of HPV types in the general population. Following HPV vaccine approvals and implementation of national HPV vaccination programs, first in Australia in 2006 and subsequently the United States, the population immunity (i.e., herd immunity) has increased. In fact, the incidence of genital warts in heterosexual Australian men younger than age 21 decreased following female vaccinations in 2007. Although HPV vaccine uptake in the United States has been low, the Centers for Disease Control and Prevention (CDC) recently reported declines in vaccine-type (e.g., HPV-6/11/16/18) HPV prevalence in females across racial/ethnic groups compared to

non-vaccine HPV types. In this report, the National Health and Nutrition Examination Survey (NHANES) data on the prevaccine (2003–2006) and vaccine (2013–2016) eras showed a more than 80 percent reduction in HPV prevalence resulting from Gardasil® vaccinations in 55 percent of females 14 to 19 years of age. Dr. Lowy noted that Dr. Ligia A. Pinto, Director of the Vaccine, Immunity and Cancer Program at the FNLCR, would provide further details on the NCI/FNLCR HPV serology efforts later in the meeting.

NCI Budget and Appropriations. Dr. Lowy reminded the FNLAC members that from fiscal years (FYs) 2013 to 2018, the NCI competing R01 applications were 10 times higher than all other National Institutes of Health (NIH) Institutes and Centers (ICs). Congress has been generous in increasing the NCI budget (i.e., regular appropriations) by 20 percent during this time period, but those increases have not kept pace with the increase in applications, translating to reduced paylines. Since 2001, the funding success rates for NCI grant applications in the Research Project Grant (RPG) pool has been slightly lower than the other ICs' because of the additional support for Cancer Center Support Grants, Specialized Programs of Research Excellence, and Clinical Trials Cooperative Groups in the National Clinical Trials Network. The trend for NCI to receive regular appropriations increases, which mirror the NIH budget's increases, is continuing. The House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies FY 2020 spending bill markup includes a $310 million increase to the NCI, which is a 5-percent increase above the FY 2019 enacted budget.

Dr. Lowy explained that the government is operating under a continuing resolution until November 21, 2019 and is being funded at the FY 2019 level. He conveyed that a top priority of the NCI is to increase paylines, which he anticipates doing if the proposed congressional appropriations are any indication of the level of support that the NIH and the NCI will receive. In addition to the FY 2020 regular appropriations are the Cancer Moonshot℠ annual allotments and the annual appropriation for the new Childhood Cancer Data Initiative (CCDI).

Ongoing and New Activities. Dr. Lowy reported that from FYs 2014 to 2018, the NCI has made substantial increases in the number of grants awarded to support pediatric cancer research. In March 2019, Dr. Lowy and then-NCI Director Dr. Norman E. Sharpless attended a pediatric cancer stakeholder event convened by the White House; the Vice President, who organized the event, engaged with pediatric cancer patients who shared their stories. The NCI and its Center for Biomedical Informatics and Information Technology hosted a CCDI Symposium in July 2019, as a scientific planning session. The NCI CCDI goals focus on improving understanding of why some cancers develop resistance to treatment, generating new ideas for interventions, and identifying less toxic treatments and strategies for managing cancer therapy side effects.

The NCI released its *Annual Plan & Budget Proposal for FY 2021* (also referred to as the Bypass or Professional Judgment Budget Proposal) in September 2019. Dr. Lowy shared an inspiring story about one pediatric fibrosarcoma patient, featured on the 2021 Annual Plan's cover, who benefited from targeted treatment with the FDA-approved larotrectinib (Vitrakvi®) and is now cancer free after being unresponsive to conventional therapies. The NCI, particularly the FNLCR researchers, supported larotrectinib's basic and clinical research, leading to its approval for adults and children with tumors harboring abnormal tyrosine receptor kinase fusion proteins. In its 2021 Annual Plan, the NCI is proposing an aggressive budget increase of 15 percent to enable raising R01 paylines to the 15th percentile.

Dr. Lowy remarked that Dr. Dinah Singer, NCI Deputy Director for Scientific Strategy and Development, has been actively leading implementation of the Cancer Moonshot℠ Initiative's Open Access and Data Sharing Policy to ensure that the data generated are shared with the cancer research community worldwide. The NIH Director, Dr. Francis S. Collins, also is assisting in open-access activities for Cancer Moonshot℠ publications by communicating with journal publishers. A recent report published in the August 2019 issue of *Science*—"Open Access Takes Root at the NCI"—is one product of those interactions.

Dr. Lowy noted a new topic of interest: intellectual property issues in academia and threats from foreign entities. Perspectives on this from university presidents vary. Dr. Michael Lauer, Deputy Director, Office of Extramural Research, NIH, will revisit his thoughts on how academic institutions can promote a culture of research integrity and will provide a balanced discussion of intellectual property issues at the December 3, 2019 Joint Board of Scientific Advisors/National Cancer Advisory Board meeting. He called attention to NCI's new blog—"NCI Bottom Line: A Blog About Grants & More"—featuring one or two posts per month focusing on NCI grants, funding policy updates, and research activities/priorities. Further details on subscribing to the blog can be accessed from the NCI website.

Leadership Appointments and Vacancies. Dr. Lowy announced that Ms. Joy Wiszneauckas has been named Director, Committee Management Office, and that Dr. Satish Gopal is selected as the top candidate for Director, Center for Global Health (CGH), pending NIH approvals. He noted the NCI's ongoing recruitment efforts for directors of the Division of Cancer Prevention (DCP) and Division of Cancer Biology (DCB) and for associate director of the Cancer Therapy Evaluation Program (CTEP). He expressed appreciation to Dr. Robert Croyle, Acting Director, CGH; Dr. Deborah Winn, Acting Director, DCP; Dr. Margaret Mooney, Acting Associate Director, CTEP; and Dr. Daniel Gallahan, Acting Director, DCB, for their support in filling these roles.

FNLCR Activities and Engagement. Dr. Lowy announced the third FNLCR-sponsored oncogenic ras sarcoma (RAS) Initiative Symposium planned for June 8-10, 2020 and invited FNLAC members to attend. He explained that the FNLCR task orders (TOs) awarded August 30, 2019 represent significant research support to the NCI and several other NIH ICs, including the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Neurological Disorders and Stroke (NINDS), and that this support extends beyond the NIH to other government agencies (e.g., the U.S. Department of Agriculture)**.**

NCI Vision for the FNLCR. Dr. Lowy explained that the FNLAC has been asked to provide input on ways that the unique capabilities of the FNLCR can best support the NCI mission and serve the broader NCI research community, both internally and externally. He noted that with input from Dr. Singer and the Scientific Program Leaders subgroup she led to discuss this topic, the NCI envisions the FNLCR offering support in three fundamental tasks: (1) providing NCI-supported investigators access to services, tools, and resources; (2) serving as a hub for technology; and (3) functioning as a nucleus for large-scale projects as necessary. Dr. Lowy pointed out that Dr. Marnett will lead a discussion later in the meeting on ideas for another national large-scale project.

In the discussion, the following points were made:

- Dr. Lowy noted that NCI discussions with other NIH ICs about funding cancer-related research projects are ongoing. Although some ICs, such as NIAID, have shown interest and are supporting cancer research within their respective purviews, the NCI is the primary funder and would be the IC to address increasing paylines. In fact, approximately 50 percent of the NCI's increases to regular appropriations/budget up to FY 2019 has supported raising funding in the RPG pool.

- Because NCI envisions the FNLCR as a hub for technology development, it would be prudent to add the qualifier that the FNLCR would complement—not compete with—existing intramural and extramural laboratories that are well established in this area.

- In response to a query about the status of and plans for recruiting a new NCI director, Dr. Lowy explained that the NCI Director is a Presidential appointee. The National Cancer Act passed in 1969 understood the NCI director position as having special status, rather than being tied to the Administration. The Acting NCI Director serves on an interim basis, indefinitely, and out of necessity he or she is someone onsite to the NCI and is appointed by the President without Senate confirmation. Dr. Sharpless, who is Acting Commissioner, FDA, could return to his role as NCI Director. Dr. Lowy conveyed that the NCI has a long history of successfully working with all of

its directors, and he is confident that this will continue, as will NCI's progress forward to help people with cancer.

III. FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR): CURRENT AND FUTURE WORK —DR. ETHAN DMITROVSKY

Dr. Ethan Dmitrovsky, Laboratory Director, FNLCR, President, Leidos Biomedical Research, Inc., (Leidos Biomedical Research) reviewed the FNLCR's advances since the last update, including progress in NCI and NIAID programs, and also discussed future directions. Dr. Dmitrovsky informed the FNLAC members that the NIH's legacy contract with Leidos Biomed ended and that all FNLCR work at the NCI and NIAID transitioned to a bridge contracting mechanism on September 30, 2019. Currently, five operational Task Orders (TOs) 95 non-operational (e.g., Cancer Moonshot^{SM}) TOs, and several subcontracting efforts with the extramural community are included in the contract portfolio. The FNLCR supports two types of projects: "operational TOs," which have annual appropriations, and "long-term projects," in which the benefits are received at the completion of the work.

Dr. Dmitrovsky remarked on FNLCR's broad research enterprise that spans across NIH ICs. He described the extensive support and funding patterns of the Clinical Research Directorate (CRD) Clinical Group that is under the direction of FNLCR's Chief Medical Officer, Dr. Barry Gause. The CRD Clinical Group consists of three other Directorates: Applied and Developmental Research, Biopharmaceutical Development Program (BDP), and Vaccine Clinical Materials Program. NIAID exclusively funds the Vaccine Clinical Materials Program, the Division of Cancer Treatment and Diagnosis (DCTD) largely funds the BDP, and the CRD is funded by multiple NCI Divisions, Offices, and Centers. With the CRD Clinical Group, the ICs can collaborate with the FNLCR in either the clinical or basic science domains, and 60 percent of the FNLCR funding supports subcontracts and procurement within the extramural community. NCI and FNLCR/Leidos Biomed researchers have published and continue to publish their key findings in high-impact journals.

Dr. Dmitrovsky highlighted NCI and NIAID projects that have made substantial progress since the last update. The FNLCR is supporting the NCI chimeric antigen receptor (CAR) T-cell clinical trials being organized by the DCTD. Their emphasis is on rare cancers, such as pediatric acute myeloid leukemia (AML). Initial efforts focused on developing the necessary infrastructure for conducting the trials, including performing dry runs using fresh Leukopaks in healthy donors. The first AML trial targeting cluster of differentiation (CD) 33 CAR T-cells will begin accruing patients in late 2019 or early in 2020 at two sites—the NCI Pediatric Oncology Branch and Children's Hospital of Philadelphia—and subsequently at four National Marrow Donor Program sites. The next series of trials will target the disialoganglioside GD2 CAR T-cells in neuroblastoma and osteosarcoma patients. The BDP will serve as a central CAR T-cell manufacturing site to support rare tumor clinical trials. The goal is to make the technology available to the public (i.e., democratize) by fulfilling an unmet need not currently being addressed in the academic or biopharmaceutical sectors.

FNLAC members were reminded that the FNLCR Clinical Monitoring Research Program is supporting the NIAID-sponsored Ebola randomized controlled trial in the Democratic Republic of Congo (DRC), now called the Pamoja Tulinde Maisha (PALM) trial, which is Swahili for "Together Save Lives." PALM is evaluating four investigational new drugs—Zmapp, mAb114, REGN EB3, and remdesivir—and as of August 9, 2019, 671 patients have been enrolled. The interim safety and efficacy data review showed promising results in the mAb114 and REGN EB3 treatment arms, and the Data and Safety Monitoring Board recommended stopping the four-arm trial early and randomizing future patients to either of those two treatments. Dr. Dmitrovsky emphasized that the mAb114 used in this trial was manufactured at the FNLCR Pilot Plant and remarked on how this international, collaborative, team-science effort between the NIAID, FNLCR, World Health Organization (WHO), DRC, and other global health organizations brought about successful public health outcomes: a model that extends to other FNLCR programs (e.g., the HPV Serology Laboratory Program). In a model of partnership, the FNLCR also is supporting the NCI Division

of Cancer Epidemiology and Genetics' (DCEG) Cancer Genomics Research Laboratory in improving understanding of the viral genetic basis of HPV and in developing low-cost HPV genotyping assays for clinical applications.

Dr. Dmitrovsky detailed ongoing efforts under the direction of the FNLCR Chief Science Officer, Dr. Leonard P. Freedman, who oversees five Directorates: Laboratory Animal Sciences Program (LASP), Biomedical Informatics and Data Science (BIDS), Basic Science Program (BSP), Cancer Research Technology Program (CTRP), and AIDS and Cancer Virus Program (ACVP). The NCI-Frederick Office of the Director exclusively funds the ACVP, and the Center for Cancer Research (CCR) largely resources the BSP. The CTRP is funded by multiple NCI Divisions, Offices, and Centers. Forty percent of the FNLCR funding supports subcontracts and procurement within the extramural community for these five Directorates. Dr. Dmitrovsky highlighted recent major accomplishments. The ACVP received high marks on its quadrennial site visit and review and has gained recognition for its trailblazing publication demonstrating that early antiretroviral therapy (ART) can clear HIV infection in non-human primate models. The BSP published key findings that the immune response genotype determines survival in HIV-infected cells. The LASP, a core research animal facility that supports both intramural and extramural investigators, also contributes to highly visible FNLCR publications. He noted that detailed reports on these programs would be presented later in the meeting. In addition, the CTRP manages large-scale projects, including the National Cryo-Electron Microscopy Facility (NCEF). Launched in 2017, the NCEF is supporting extramural investigators with 300 cancer-related projects in 34 academic/research institutions, and data on solving high-resolution structures are being published in high-impact journals.

Dr. Dmitrovsky explained that as a Federally Funded Research and Development Center (FFRDC), FNLCR is mandated to maintain relationships with the broader research community to enhance the Laboratory's research relevance. The FNLCR BIDS directorate facilitates the outreach efforts to engage the extramural community in the Accelerating Therapeutics for Opportunities in Medicine (ATOM)—a public-private partnership consisting of four founders: NCI/FNLCR, Lawrence Livermore National Laboratory, GlaxoSmithKline (GSK), and the University of California, San Francisco. Activities have included hosting ATOM educational sessions at scientific conferences (e.g., American Association for Cancer Research Annual Meeting), delivering keynote presentations on ATOM at the National Academy of Sciences meetings, and reaching out to other national laboratories and research institutions. The NCI-Designated Cancer Center directors, NCI-funded academic program leaders, and pharmaceutical industry contacts attended these sessions aimed at encouraging potential collaborators to join ATOM. As a result of the outreach campaigns, Dr. Dmitrovsky noted that NVIDIA will be joining ATOM as a collaborator, and Argonne National Laboratory as a member.

In general, FNLCR's outreach efforts span the national, regional, and local communities. Education is a major focus, and energies are devoted to training the next generation of scientists, including undergraduate and graduate students and postdoctoral fellows, all via collaborations and at no cost to the FNLCR. Some of the FNLCR projects and collaborations provide sabbatical opportunities for senior faculty. The former Hood College–NCI meetings have been re-established and renamed the Leidos Biomedical Research–Hood College Cancer Science Symposium. The first meeting was held in June 2019; subsequent meetings are being scheduled every other year. The FNLCR Director's Distinguished Lecture Series was launched, and the sessions have been well attended. The FNLCR collaborates extensively with the extramural community; has 149 unique partners at universities, research institutions, and industry; and has 49 executed Contractor Cooperative Research and Development Agreements (cCRADAs).

In the discussion, the following points were made:

- The FNLCR uses the cCRADA mechanism to provide services and/or support to small- and medium-sized biotechnology companies that may not have specific capabilities. Making the RAS Initiative reagents publicly available is one example of enabling these companies.

- Although international collaborations with the FNLCR can be either technology or education based, most are educational. Few, if any, limitations exist to a specific organization's participation.

- FNLCR's research data/findings are widely disseminated among the cancer research community; however, codifying new information, lessons learned, and/or best practices in the core facilities regarding a process or implementation could be formalized.

IV. INVESTIGATOR-INITIATED AND EXTRAMURAL COLLABORATIVE RESEARCH IN THE AIDS AND CANCER VIRUS PROGRAM, FNLCR—DR. JEFFREY D. LIFSON

Dr. Jeffrey D. Lifson, Director of the AIDS and Cancer Virus Program (ACVP) at the FNLCR, provided an overview of the program, including selected investigator-initiated research projects and collaborations with non-ACVP NIH and extramural investigators. He noted that HIV, AIDS, and cancer overlap in the NCI research portfolio, particularly Kaposi sarcoma-related malignancies and lymphomas, and he summarized the history of the NCI and HIV/AIDS research. The NCI Laboratory of Tumor Cell Biology made important contributions to cancer-related retrovirology building on research on animal retroviruses leading to identification of the first human retroviruses (e.g., human T-cell lymphotropic virus I [HTLV-I] and II) and played a role along with French investigators in identifying HIV in the etiology of AIDS. NCI researchers Drs. Hiroaki Mitsuya, Samuel Broder, and Robert Yarchoan also contributed to the first active therapies for HIV. Following the discovery of HIV, the then-FNLCR contractor supported the large-scale propagation and purification of the new retrovirus to support ongoing research, and provided materials to licensees' of the NIH patent to facilitate development of first-generation HIV testing kits for screening the U.S. blood supply. NCI efforts later led to establishing the ACVP, which developed and preclinically evaluated a first-generation HIV vaccine candidate. Specimens from a never challenged but HIV seropositive chimpanzee identified through this work later were critical in identifying cross species transmission as the source of human HIV infection.

The dual mission of the ACVP is to conduct investigator-initiated basic and applied research to improve diagnosis, treatment, and prevention of HIV/AIDS and infections with cancer-associated viruses and to develop and proactively share novel research methods, analytical techniques, and reagents with the broader research community. Established in 1987, the ACVP is 100 percent contractor staffed (currently 60 full-time employees) and has expanded its scope and research focus from solely HIV/AIDS to include research on viral-associated cancers, including Kaposi sarcoma-associated herpesvirus (KSHV). Five principal investigator-led multidisciplinary Research Sections organized by interest/expertise and eight Research Support Cores comprise the ACVP organizational structure. Distinctive capabilities include NHP model development, NHP and KSHV studies, viral quantitation and sequencing, tissue-based analysis, and scaled virus production and purification. Although not formally part of the NCI Intramural Research Program and funded through the Office of the Director, the ACVP undergoes quadrennial Site Visit reviews, hosted by the CCR, including a review in 2019 [in which the program was rated Outstanding] in connection with which the program received more than 150 letters of support from diverse collaborators testifying to program's enabling contributions to facilitating their research.

Dr. Lifson highlighted key frontier areas of unresolved need in AIDS research in 2019 involving prevention, non-AIDS morbidity and mortality, and residual virus during ART. He and his colleagues are credited with developing one of the first polymerase chain reaction–based assays able to rigorously quantify levels of HIV in blood ("viral load" test), which they showed could be correlated with disease status and used to evaluate response to treatment interventions—a discovery that revolutionized the field. This development captured the attention of NIAID researchers focusing on HIV vaccine studies in nonhuman primates (NHPs), and resulted in the development of similar viral load assays for use in NHP studies. After moving to the FNLCR to join the ACVP Dr. Lifson has focused much of his research on NHP model development and application to AIDS related studies. He emphasized that NHP models are powerful systems to address key HIV/AIDS research question because of the experimental control in virus identity, the dose, route and timing of inoculation, longitudinal sampling options, and interventional

latitude. The ACVP works closely with the FNLCR Laboratory Animal Sciences Program to conduct experiments, which have resulted in the development of innovative viruses and new NHP models.

Dr. Lifson reviewed selected examples of different aspects of the ACVP's research activities, including investigator-initiated research. Dr. Brandon Keele, Principal Investigator for the Retroviral Evolution Section of the ACVP, developed two robust approaches for molecular tracking of AIDS viruses in rhesus macaques. In the first approach, Dr. Keele utilized naturally occurring silent mutations as molecular tags to track distinct chains of infection events. Using a well-characterized infectious molecular clone—SIVmac239-- he generated a synthetic swarm comprised of wild type virus and nine distinct silent mutation tagged variants to track local sites of initial mucosal infection and subsequent spread of distinct viral lineages. For the second approach, he generated robust sequence-tagged synthetic swarms consisting of otherwise isogenic infectious molecular virus clones containing approximately 10,000 distinct randomized short insert sequences (barcodes). Such barcoded viruses are useful for tracking the behavior of distinct chains of infection events in infected macaques during virus establishment and tracking those that persist during suppressive ART, features relevant to viral reservoir and "HIV cure" research. Barcoded virus stocks are made available to other investigators in the field.

Dr. Lifson reviewed previous studies, in which he and others showed that SIV can persist in immune privileged tissue sanctuaries, even in "elite controllers" (i.e., individuals capable of substantial spontaneous control of virus replication through natural immune responses) and in infected macaques receiving ART. B-cell follicles in lymphoid tissues represent such a sanctuary site. In follow up studies they showed that CD8+ T cells, engineered to express SIV specific T cell receptors, along with the CXC chemokine receptor type 5 (CXCR5) to allow localization to B cell follicles did indeed localize to this tissue site, and exerted antiviral activity, reflected in reduced numbers of virus positive cells in lymph node tissue sections and decreased reduced plasma viremia. In collaboration with CCR senior investigator Dr. George N. Pavlakis Dr. Lifson is combining this approach with the novel cytokine heterodimeric IL-15 pioneered by Dr. Pavlakis.

Among ACVP collaborations with NIH investigators, Dr. Lifson highlighted work with Dr. Stephen H. Hughes, Senior Investigator, HIV Dynamics and Replication Program, CCR. Building on work by Dr. Hughes and his colleagues in HIV infected humans, Dr. Lifson is working with him to develop an NHP model to study the role of expanded clones of CD4+ T cells in maintenance of persistent viral reservoirs despite ongoing ART. The aim is to better understand the biology of expanded clones and their contributions to viral persistence and recrudescence, to enable development of more definitive HIV treatments. Having established that integration patterns on SIV infected macaques recapitulate observations in HIV infected humans, and demonstrated the presence of expanded clones of virus positive cells in SIV infected macaques receiving ART, follow up efforts are focused on using this model in mechanistic studies to determine the contributions of antigen driven and homeostatic proliferation to the establishment, expansion, and persistence of these clones.

The ACVP also collaborated with Dr. Anthony Fauci, Director, NIAID, and Dr. H. Clifford Lane, Deputy Director, Clinical Research and Special Programs, NIAID, on deciphering controversial reports of sustained virologic control in SIV-positive NHPs after short-term ART and integrin alpha (α) 4 beta (β) 7 antibody therapy. Subsequently, clinical trials began evaluating the FDA-approved α4 β7 therapeutic for inflammatory bowel disease, Vedolizumab (Entyvio®). Acting as a neutral honest broker, ACVP assisted the NIAID with follow-up studies to evaluate these data. Using the same challenge virus, obtained from the original study investigators, Dr. Lifson noted that characterization of that virus in the ACVP demonstrated that the virus was not SIVmac239, as stated in the manuscript, but rather an attenuated virus-- SIVmac239 Nef-stop-- with a stop codon in the viral protein Nef. Using this virus, the NIAID/ACVP study obtained results different than the original published report, with no treatment associated evidence of viral control. Variability in the kinetics and pathways of mutational repair of the stop codon in Nef required for full virulence of the virus were in turn associated with differences in viral dynamics that had lasting impact on long term viral replication patterns, regardless of antibody treatment. Differences in the details of repair of the stop codon in Nef may have contributed to differences in the results observed in the

two studies. These results, along with negative results in the clinical study, helped the field interpret and contextualize the observations reported in the original publication and appropriately prioritize proposed follow up studies.

Exemplifying ACVP collaborations with extramural investigators, Dr. Lifson noted a longstanding collaboration with Dr. Louis Picker, Oregon Health & Science University, on using cytomegalovirus vectors engineered to express SIV proteins in HIV vaccine development. The NHP vaccination preclinical studies showed an unconventional major histocompatibility complex (MHC)-class E-restricted CD8+ T-cell response to the vaccine is critical for protection along with activation of Interleukin 15 (IL-15) signaling pathways. In addition, attenuated variants developed to maximize vaccine safety demonstrated immunogenicity and protective efficacy comparable to the less attenuated vector. The first in-human study is planned for 2020. Highlighting enabling contributions of ACVP Research Support Cores, Dr. Lifson described how Dr. John R. Mascola, Director, Vaccine Research Center, and Dr. Malcolm A. Martin, Chief, Viral Pathogenesis and Vaccine Section, NIAID, have utilized the Quantitative Molecular Diagnostics Core (QMDC) of the ACVP to conduct viral load testing for NHP models for evaluating passive immunoprophylaxis with broadly neutralizing monoclonal antibodies (bNAbs) against HIV. With virologic monitoring support from the ACVP, these researchers demonstrated that a single bNAb injection can protect against repeated viral challenges over extended periods, correlating with the antibody clearance half-life. Extramurally, Dr. Michael Farzan, Professor, Scripps Research Institute, has worked with the QMDC for virologic monitoring in his prophylactic and therapeutic NHP studies of a novel engineered HIV-neutralizing molecule-- eCD4-Ig-- that incorporates both CD4 and CCR5 sequences. The Vaccine Research Center, U.S. Military HIV Research Program, and the Thai Red Cross, Bangkok, Thailand, all collaborate with the ACVP HIV Monitoring Core on HIV viral load monitoring in support of clinical trials.

ACVP's Tissue Analysis Core pioneered next-generation RNAscope and DNAscope technologies for in situ HIV and SIV detection in tissue sections and is working the FNLCR BIDS Advanced Biomedical Computing Center in machine-learning efforts, developing artificial intelligence algorithms for quantitative image analyses of tissue sections from infected individuals. The Retroviral Protein Chemistry Core continues to produce and purify virus for various applications and is one of the few groups worldwide capable of producing sufficient amounts of material of sufficient purity to enable evaluation of site specific glycosylation patterns of virion derived viral envelope glycoproteins, important data for informing vaccine design efforts. The Viral Oncology Section is supporting the NCI HIV and AIDS Malignancy Branch by developing serologic and molecular assays for KSHV, including CLIA certified assays.

In closing, Dr. Lifson summarized that the ACVP is a unique program, with unique capabilities, and the dual mission of conducting original investigator initiated research and also providing extensive collaborative support to other investigators, seeking to advance the overall AIDS research enterprise, consistent with the mission of the NCI and the FNLCR.

In the discussion, the following points were made:

- In HIV-related cancers, the effects of aggressive treatments to eradicate cancer and HIV simultaneously must be balanced regarding quality of life and benefit of a cure. Recognizing that totally eradicating each replication-competent provirus in the body may not be achievable for all patients, a more realistic approach in the field is to reduce the viral reservoirs to a minimum. When combined with other treatments (e.g., immunotherapy and/or vaccine), this approach would increase potential for achieving sustained antiretroviral drug free virologic remission.

- NHP models to further understand HIV morbidity and mortality to assess the cumulative toxicity of ART may be needed. More than 30 FDA-approved drugs for HIV currently are available, and the trend has been to develop less toxic drugs and focus on combination therapy; however, the long-term side effects of chronic treatments are not well understood. Immune system activation

still occurs in patients with viral suppression, which is likely attributing to excess morbidity and mortality from non-AIDS-related events.

- Investigators are encouraged to review the existing ACVP Task Orders and scope of current research available on the FNLCR/NCI website.

V. DISCUSSION ON STRATEGIES FOR DEVELOPING RAS-LIKE PROJECTS—FNLAC MEMBERS

Dr. Marnett echoed Dr. Lowy's comments regarding the NCI's vision for the FNLCR and noted that most national laboratories routinely conduct large-scale projects. He reminded FNLAC members that subsequent to the establishment of the NCI-Frederick Advisory Committee (NFAC; subsequently renamed the FNLAC) in 2012 were initial discussions with then-NCI director Dr. Harold E. Varmus about the NCI-Frederick Cancer Research Center's (FCRC, subsequently renamed the FNLCR) existing capabilities and how best to use and mobilize them. The Department of Energy (DOE) system of national laboratories was viewed as a model for conducting large-scale projects not being addressed in the extramural community, especially in an FFRDC setting. The outcome of those discussions was a set of recommendations from the NFAC, including renaming the FCRC the FNLCR and refocusing efforts to establish the Center as a national laboratory. The FNLAC began discussing the type of large-scale projects that the FNLCR could consider and viewed a series of presentations from FNLCR/NCI staff on the laboratory's capabilities. After further discussions and deliberations, the decision was made to begin the RAS Initiative project to interrogate RAS biology in depth, which would provide the knowledge to develop new cancer therapeutics, translating into therapeutic opportunities for RAS-driven cancers. Dr. Marnett remarked that the RAS Initiative, a hub-and-spoke model of research and drug design, leveraged the unique capabilities of the FNLCR and mobilized the cancer research community to participate in ongoing projects. He noted another large-scale project—the NCI–DOE Joint Design of Advanced Computing Solutions for Cancer (JDACS4C)—that also combines the unique capabilities of FNLCR as the only FFRDC with the ability to answer biological questions, particularly about cancer, with DOE computational resources.

Dr. Lowy stated that the NCI is requesting that the FNLAC provide input on a potential new project and the vetting process of such a project. He called attention to potential approaches currently being investigated in the cancer research community that, if additional resources were available, could advance progress, such as developing interventions against the c-Myc oncogene, the undruggable genome, and the loss of tumor suppressor genes. Dr. Singer added that the FNLAC first would need to establish criteria for evaluating a new large-scale project and then would need to establish a process to identify a potential new project.

Dr. Marnett opened the discussion to ideas on a next RAS-like project for the FNLCR and ways to engage the extramural community in the decision-making process.

In the discussion, the following points were made:

- Developing and/or providing technology and resources not readily available or affordable for smaller research groups, such as artificial intelligence, would be valuable. Also, compensation for drug therapy development that is successful should be considered.

- Leverage the clinical data and molecularly characterized residual specimens of other NCI initiatives and programs, including the National Clinical Trials Network (NCTN) and The Cancer Genome Atlas, that could be further evaluated with new technologies.

- Consider a model similar to the former NCI Academic Public-Private Partnership Program that would engage the strengths of FNLCR, the academic community, and industry.

- Create processes and an infrastructure that provides the flexibility to address scientific categories and problems that have long-term benefit to the cancer research community, such as targeting undruggable transcription factors and/or rapid modifiers.

- Reviewing examples of successful initiatives and merging enabling technologies with unmet intervention needs would be one way the FNLCR could make a difference.

- The NCI could conduct a portfolio review to determine the programs that will be ending soon and consider investing resources into two or three projects that the FNLCR would pursue.

- The NCEF, which is providing technologies to the cancer community to address scientific needs relevant to their respective institutions, is not competitive to the RAS Initiative, which is addressing a specific biological question.

- A mechanism to reach out to the broader cancer research community for their input on significant opportunities (e.g., big ideas) and challenges that could be parlayed into a new project is needed. For example, the RAS Initiative started as an idea that was an outcome of FNLAC and NCI discussions, and it was further deliberated in a larger working group meeting of experts in the field. The opportunity exists to solicit input on what was not ideal about the RAS Initiative and take that feedback into consideration for new projects.

- The NCI Provocative Questions Initiative, established in 2011, is a forum that could be leveraged to generate a list of ideas for the next collaborative project, and it could be prioritized in a workshop setting. The Provocative Questions could speak to the FNLCR's strengths and resources.

- One way for the NCI to clearly democratize the process of soliciting ideas from the broader research community is to issue a request for information (RFI) similar to the approach used in the Cancer Moonshot[SM].

- Dr. Marnett explained that the initial steps for generating an RFI for input on a new FNLCR large-scale project would be to compile the ideas from today's discussion and circulate them to the FNLAC for comments. Persons attending today's meeting via NIH videocast are welcome to send their ideas to Dr. Lyman. Dr. Singer added that after the proposals are vetted and shortlisted, the NCI would likely convene a workshop to further discuss the ideas/responses.

VI. ROLE OF FNLCR IN NCI'S NEW PRECISION MEDICINE INITIATIVES—DR. JAMES H. DOROSHOW

Dr. James H. Doroshow, Deputy Director, Clinical and Translational Research, and Director, DCTD, reminded the FNLAC members that the NCI clinical trials program is grant funded, primarily via the cooperative agreement mechanism. He pointed out that the NCI precision medicine clinical trials—Adult NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) and Pediatric MATCH—are not funded through the FNLCR, but the laboratory plays a significant role in their activities. The Adult NCI-MATCH trial, which began in 2015 and rapidly accrued 6,000 patients who are now randomized to 40 Phase II clinical trials, has stopped accepting new treatment arms. Treatments that have not yet reached their accrual goals, including the rare tumor variants, are continuing. Thirty different commercial and academic Clinical Laboratory Improvement Amendments (CLIA)–certified laboratories are directing patients to NCI-MATCH using a mechanism to leverage the genomic tumor testing ordered by oncologists during routine clinical care of cancer patients at academic cancer centers and community hospitals for the Rare Variant Initiative part of the trial.

Dr. Doroshow described three NCI-MATCH successor trials that are in development and made possible partly due to the efforts of the FNLCR. Providing central support for these trials are the Molecular and Immunologic Diagnostics Network (MDNet) and Precision Medicine Analysis and Coordinating Center (PMACC). MDNet is a network of laboratories (NCI and FNLCR) providing CLIA and non-CLIA services for the three trials. PMACC is an FNLCR-hosted data center providing information coordination and warehousing. Patient enrollments are anticipated to begin in 12 to 18 months, and all trials will be conducted either in the NCTN or Experimental Therapeutics Clinical Trials Network (ETCTN).

The AML/Myelodysplastic Syndromes (MDS) Basket Trial is a national program focusing on matching AML molecular subtypes to targeted therapies in different age and fitness groups. The Myeloid Malignancies Precision Medicine Initiative® structure is composed of a senior leadership council composed of NCTN cooperative groups; two working groups—the Agents and Genes Working Group and the Laboratory Assays Working Group; initial and final screening protocols consisting of four categories of AML/MDS—Older Less Fit, Older More Fit, MDS, and Younger/Fit; and a data commons. Each of the disease categories will contain specific molecular characteristics and protocols. The overall clinical trial design mirrors the AML/MDS treatment regimen.

The Combination (Combo) MATCH trial is evaluating drug combinations versus single agents in the NCI-MATCH, and a match will constitute sufficient evidence for further evaluation of the combination. The ComboMATCH protocol is coordinated through the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG ACRIN) Cancer Research Group and consists of four substudy treatment-specific cassettes organized by an NCTN cooperative group.

ImmunoMATCH (iMATCH) aims to establish an immuno-oncology precision medicine framework to support immunotherapy trials and will be a cross-NCTN effort. Unlike NCI-MATCH, iMATCH currently has no marker-regimen matches for immune-oncology combinations and will stratify patients based on tumor microenvironment and potential mechanisms of immune invasion. The iMATCH central screening protocol consists of CLIA assay platforms, markers and classifiers, and potential subgroups.

Dr. Doroshow introduced the NCI CTEP's new centralized biomarker resource—the National Clinical Laboratory Network. This resource will establish a U.S. laboratory network capable of providing centralized, genomic characterization and pharmacodynamic biomarker assays for the ETCTN early-phase trials. Technologies developed in the FNLCR for genomic characterization and pharmacodynamic biomarkers have been transferred to MD Anderson Cancer Center–subcontracted network laboratories and the Molecular Pathology Laboratory Network, Inc. The NCTN core technologies include next-generation sequencing panels, whole-exome and RNA sequencing, a targeted gene panel for circulating tumor DNA, and a broad range of pharmacodynamic assays. Further details can be accessed from the NCI website.

In the discussion, the following points were made:

- The DCTD is starting to focus on using the technologies developed in the Clinical Proteomic Tumor Analysis Consortium (CPTAC) to perform targeted proteomics and phosphoproteomics on some immunological targets, first in the Patient-Derived Xenograft (PDX) models, integrating them into *in vivo* studies, and then clinical studies.

VII. BASIC SCIENCE PROGRAM —DR. MARY N. CARRINGTON

Dr. Mary N. Carrington, Director of the Basic Science Program at FNLCR, stated that the mission of the program is to conduct investigator-initiated research in immunology, genetics/epigenetics, cell biology, and computational biology to gain a more thorough understanding of the processes involved in human disease, with emphasis on cancer and HIV. The BSP, which is closely integrated with NCI's CCR

in expertise and physical location, has 80 full-time staff. Of the 80 staff members, 6 are principal investigators; 17 support the principal investigators' research; 48 are located in and provide research support to CCR laboratories; and 8, including the program manager, operate the BSP Office to provide logistical and operational support to FNLCR and CCR government employees. All BSP staff are reviewed annually on the same review cycle as the FNLCR staff. The BSP principal investigators and their CCR laboratory/program colleagues are reviewed every 4 years. The CCR funds the BSP principal investigator laboratories, and support is contingent on the results of site visit reviews.

Dr. Carrington described the scope of the research of the six BSP principal investigators, highlighted recent published findings, and noted that each laboratory has four or five full-time staff. Dr. Stephen K. Anderson, Head, Molecular Immunology Section, and his laboratory are focusing on understanding the mechanisms controlling the stochastic processes governing MHC class I receptor expression in a subset of natural killer (NK) cells. The primary goal is to delineate gene regulation in the immune system. Dr. Anderson's discovery of probabilistic promoter switches in both the human *KIR* gene family and the mouse *Ly49* gene family produced a novel paradigm for the selective activation of genes. The Anderson laboratory recently reported that the human leukocyte antigen (HLA)-C transcript profile (a classic molecule expressed in NK cells) varies across the distinct stages of NK cell differentiation. Dr. Jonathan R. Keller, Head, Hematopoiesis and Stem Cell Biology Section, is investigating the cellular and molecular regulation of hematopoietic stem cell (HSC) quiescence, survival, self-renewal, and cell fate and the role of the inhibitor of DNA-binding/differentiation (ID) proteins in normal and malignant hematopoiesis. Dr. Keller and his laboratory recently reported that ID1 ablation protects HSCs from stress-induced exhaustion and aging.

Dr. Kathrin Muegge, Head, Epigenetics Section, studies the molecular mechanisms that alter chromatin structure and function during development using the murine model. The primary goals are to: (1) delineate the impact of epigenetic changes on mammalian development; and (2) determine the role of a chromatin remodeler—lymphoid-specific helicase (LSH) homolog—in human immunodeficiency, centromeric instability, facial anomalies (commonly called ICF) 4 syndrome. Dr. Muegge and her group demonstrated that LSH regulates nucleosome occupancy and chromatin accessibility during development. Dr. Ruth Nussinov, Head, Structural Biology Section, researches key signaling proteins in the cellular network (e.g., RAS) and their signaling pathways and allosteric structural regulation. The primary goals are to untangle KRAS4B oncogenic signaling at the membrane and to determine how microbes alter host signaling and evade immune surveillance through protein crosstalk. Dr. Nussinov and her group developed the first computational structural method to predict how microbiota can hijack host signaling, which revealed that oncoviruses can drive cancer by rewiring signaling. Dr. Cheryl Winkler, Head, Molecular Genetic Epidemiology Studies Section, and her laboratory investigate the influence of host factors that contribute to infectious and other complex diseases, such as kidney disease and cancer, with the aim of identifying drug targets and improving diagnosis. The primary goal is to interrogate the impact of genetic variation on global health disparities and chronic diseases, particularly the Apolipoprotein L1 (*APOL1*) gene in African and African American populations. Dr. Winkler and her colleagues conducted a study that concluded that living kidney donors with *APOL1* high-risk genotypes are at greater risk of decreased kidney function and end-stage renal disease. Implementing the process of screening African American living kidney donors for the *APOL1* gene was an outcome of this study.

Dr. Carrington, Head, HLA Immunogenetics Section, and her laboratory focus on understanding the impact of genetic variation on resistance or susceptibility to human disease using whole-genome sequencing, genotyping, and bioinformatics. The goals are to identify immunogenetic polymorphisms that associate with human disease and to determine the functional significance of these genetic associations. The Carrington laboratory recently reported that elevated levels of HLA-A associates with lower CD4 cell counts consistently over time and also correlates to increased NK inhibitory receptor NKG2A-expressing cells, translating to impaired HIV control.

In the discussion, the following point was made:

- The BSP principal investigators interact and collaborate across programs around which there is a shared interest, such as hematopoiesis and NK cells.

VIII. HUMAN PAPILLOMAVIRUS (HPV) SEROLOGY AT FNLCR: PROGRESS TO DATE AND FUTURE DIRECTIONS—DR. LIGIA A. PINTO

Dr. Ligia A. Pinto, Director, Vaccine, Immunity, and Cancer (VIC) Program at FNLCR, informed the FNLAC members that the VIC Program is sponsored by the NCI DCEG, DCP, and Center for Strategic Scientific Initiatives, as well as the Bill and Melinda Gates Foundation (Gates Foundation). The Program consists of three laboratories—HPV Immunology, HPV Serology, and Cancer Immunoprevention—and has a mission to provide scientific leadership and laboratory infrastructure to study immune responses to HPV vaccines and other cancer preventive strategies in the context of clinical and preclinical studies.With the overall goal of translating laboratory findings into public health, the Program investigates immune responses to vaccines, infections, and cancer; develops and validates new methods for evaluation of markers of protection; monitors immunity in both clinical trials and preclinical studies; and provides evidence to inform new trials and create tools to enable decision making and public health changes. The Program supports NCI vaccine trials and epidemiological studies and collaborates with the extramural HPV community through cCRADAs.

To put the VIC Program's work in perspective, Dr. Pinto reminded the group that HPV, a non-enveloped double-stranded DNA virus, is the most common sexually transmitted infection worldwide. More than 200 types of HPV exist; 40 are sexually transmitted, and 13 of the 40 are high-risk oncogenic types—HPV-16 and HPV-18 contribute to 70 percent of cervical cancer cases. Low-risk types—HPV-6 and HPV-11—are associated with more than 90 percent of anogenital warts. Globally, an estimated 5 percent of total new cancer cases are attributable to HPV. Cervical cancer accounts for ~ 83% of HPV attributable cancers globally with over 500,000 cervical cancer cases diagnosed annually; one woman dies of cervical cancer every 2 minutes. In the United States, HPV-associated cancers account for approximately 35,000 new cases—60 percent in women and 40 percent in men. The U.S. incidence of oropharynx cancers is increasing.

Dr. Pinto emphasized that HPV and HPV-associated cancers are preventable. Three licensed HPV prophylactic vaccines were approved by the FDA for both females and males ages 9 to 26 years as three-dose regimens. The quadrivalent vaccine, Gardasil® (Merck), was FDA-approved in 2006 and protects against HPV-6/11/16/18; the bivalent vaccine, Cervarix® (GSK), was approved in 2009 and protects against HPV-16/18. In 2014, the FDA approved a nonavalent vaccine, Gardasil®9 (Merck), that protects against nine HPV types, HPV-6/11/16/18/31/33/45/52/58, which are responsible for about 90 percent of cervical cancer cases and 90 percent of genital warts. In October 2016, FDA approved a two-dose schedule with Gardasil®9 and the CDC Advisory Committee on Immunization Practices recommended a two-dose schedule with Gardasil®9 for adolescents who initiate the vaccine series before 15 years of age. In October 2018, FDA approved Gardasil®9 for adults up to age 45 years. The HPV vaccines demonstrated high efficacy in clinical trials in females with no genital HPV infection at the trial start, with more than 96 percent protection against precancerous lesions and genital warts.

Because HPV neutralizing antibodies are the main mechanism of protection against infection induced by prophylactic vaccines, Dr. Pinto pointed out that vaccine immunogenicity is a critical parameter in HPV vaccine trials. HPV serology is a tool to assess vaccine immunogenicity and is a key parameter in addition to the clinical efficacy. The FNLCR HPV Immunology Laboratory has supported HPV vaccine trials and immunogenicity studies, including the NCI Costa Rica Vaccine Trial, a Phase III trial evaluating the bivalent vaccine in nearly 7,500 healthy young adult Costa Rican women ages 18 to 25 years. The laboratory developed and optimized assays for measuring markers of protection against infection using trial specimens, monitored duration of antibody responses to the vaccination, and

demonstrated long-term antibody responses for a single dose. Dr. Pinto described the HPV serology assays used to measure quantity and function developed at the FNLCR and highlighted that the ELISA antibody assay, which showed strong correlation to the neutralization assays, detected HPV-16 and HPV-18 IgG levels after vaccinations in the Costa Rica trial. The assay has been optimized and validated for serum and subsequently, in collaboration with the Moffitt Cancer Center, in saliva specimens.

Dr. Pinto explained that the NCI (Dr. Aimee Kreimer, DCEG) further evaluated whether a single dose of vaccine would provide durable protection against cervical cancer in the Costa Rica trial. The HPV Immunology Laboratory supported the project with the optimized assays and compared the antibody responses between one- and two-dose regimens, which led to the conclusion that the bivalent HPV vaccine induces durable antibody in one-dose vaccine recipients. In the 11-year follow up, 100 percent of one-dose recipients remain seropositive, suggesting that one-dose vaccine schedules may induce long-term immunity and could dramatically reduce health care costs.

Dr. Pinto called attention to the current HPV vaccination status and the global demand/supply imbalance. As of June 2019, only 50 percent of countries have national immunization programs, and the introductions of such programs are lowest in low- and middle-income countries, primarily due to costs. The HPV vaccine uptake globally is low: only 5 percent of youth in the recommended age group have received vaccination. The WHO calls for action toward a global cervical cancer elimination that will increase vaccine demand over the next 10 years. Per the 2018 WHO Global Market Study on HPV, a demand/supply imbalance is projected to last for 3 to 5 years. To alleviate these challenges, several new one-dose HPV vaccine trials to evaluate immunogenicity and non-inferiority have been initiated: two in Costa Rica, two in Africa, and one in the United States. The FNLCR will be supporting these trials with serology and immunogenicity testing. The goal is to accelerate policy recommendations for 2020–2025. In addition, an increasing number of prophylactic HPV vaccines are in development in China, which the FNLCR will likely be supporting as well.

Dr. Pinto elaborated on the transition from clinical to serology endpoints in vaccine trials and how it impacts the increased demand for standardized serology testing in light of no commercially available validated assays. To address this issue, the NCI and the Gates Foundation sponsored the HPV Serology Standardization Initiative in 2017, which is led by the FNLCR HPV Serology Laboratory. The mission is to work in partnership with the international HPV serology community to promote further standardization, harmonization, and proficiency of HPV serology assays. Further details can be accessed from the FNLCR website. Dr. Pinto noted the progress to date, the accomplishments, and the impact and highlighted future plans, including establishing a Center of Excellence for HPV Serology and HPV Vaccine Trial Network.

In the discussion, the following points were made:

- Although the different distributions of serum type vary by populations worldwide, the nonavalent vaccine protects against 90 percent of HPV types related to cervical cancer.

- Mathematical modeling of herd immunity estimations combined with the biological/clinical data predicts 85 percent vaccine uptake in one sex to have an effect on the unvaccinated opposite sex; or 75 percent uptake in both sexes. The CDC NHANES data suggest that 75 percent of a vaccinated sex, in this case females, results in strong immunity in males, which far exceeds any model predictions.

- Lessons learned from the HPV vaccine program pipeline of standardization as well as the technologies is a platform that could be applicable to other infectious diseases (e.g., Ebola virus).

- The HPV vaccines are prophylactic and no evidence of a therapeutic benefit to cervical cancer has been reported by the NCI or other research groups.

- Moving forward, the FNLCR VIC Program could consider supporting HPV natural history studies in the population with persistent HPV infection and their potential for developing cancer.

IX. OVERVIEW OF THE BIOPHARMACEUTICAL DEVELOPMENT PROGRAM — DR. DOUGLAS GAUM

Mr. Douglas Gaum, Director of Quality Assurance for the Biopharmaceutical Development Program (BDP) at FNLCR, explained that the NCI established the BDP at the FNLCR Advanced Technology Research Facility in 1993 to provide specialized and unique technical expertise and services not available in the commercial market. In a structured process, the BDP performs feasibility studies, develops manufacturing processes and assays, generates and submits regulatory filings, and transfers technology to commercial entities. Mr. Gaum pointed out that because the BDP is not allowed to compete commercially, it typically develops products for rare diseases or when a company wants known efficacy data from a clinical trial before making an initial investment. Typical projects involve small markets, novel technologies, or technologies with regulatory challenges. Federal regulations allow project originators to retain the intellectual property rights. Example applications include monoclonal antibodies, recombinant proteins, oncolytic viruses, gene therapy vectors, and cell therapy.

Funding for intramural projects comes from indefinite delivery/indefinite quantity TOs. Competitively selected extramural projects are funded by the NCI Experimental Therapeutics Program. Other ICs and other federal agencies can access underused BDP resources upon NCI approval, with full cost recovery. Companies partner with the BDP through cCRADAs. The BDP's extensive training programs include joint workshops with the FDA, international collaborations, and trainings on good manufacturing practices. The BDP hosts and trains interns and long-term volunteers, and the program's website freely offers more than 300 standard operating procedure documents, manufacturing and testing procedures, facility quality system documents, and additional training resources, all of which have been vetted and audited. In terms of infrastructure, the BDP contains a virus production facility, manufacturing areas for products derived from mammalian subculture and bacteria, and an area for fill-finish processing. Resources include aseptic column chromatography, liquid chromatography, cell-based assays, and a high-resolution mass spectrometer.

Since 1998, the BDP has manufactured more than 130 distinct products. More than 60 products have been or are currently undergoing human clinical trials. More than 14 products are currently nearing licensure. Two products have been licensed and are commercially available: (1) HA22, an immunotoxin that targets cancer cells with certain surface receptors, and (2) dinutuximab, a monoclonal antibody that targets surface receptors on neuroblastoma cells. Additional highlighted products manufactured by the BDP and currently in development include a vaccine for Epstein-Barr virus, and a treatment for Fuchs' endothelial corneal dystrophy.

In the discussion, the following points were made:

- The BDP is beginning to use disposable bags for its bioreactors and fermenters. Because these bags are laminates containing three different types of bonded plastic, they are difficult to recycle.

- Because any government agency can work through the NCI to bring its project into the BDP, the facility also develops products for illnesses and molecules other than cancer.

- Principal investigator projects arrive at the BDP in various stages of initial development. In challenging project cases, the BDP and principal investigator collaborate toward a solution for successful product development.

X. DISTINCTIVE CAPABILITIES OF THE LABORATORY ANIMAL SCIENCES PROGRAM —DR. STEPHEN N. JONES

Dr. Stephen N. Jones, Director of the Laboratory Animal Sciences Program (LASP) at the FNLCR, pointed out that LASP operates animal facilities and provides animal husbandry services for NCI investigators at the NIH-Bethesda and NCI-Frederick campuses. With 344 staff members, LASP manages 27 rodent and one NHP vivaria, maintains more than 350,000 research animals, coordinates animal shipments, and provides board-certified veterinary care for all animals. The program currently supports 231 investigators in 587 active study protocols and other NIH ICs in addition to NCI researchers, as well as other federal agencies on occasion. The LASP has 10 core facilities with distinctive capabilities supporting research in cancer and AIDS, including the ACVP and PDX Model Repository. The program also provides technology development for the NCI Office of the Director and the Office of Scientific Operations.

Dr. Jones described the research capabilities of several LASP cores. The Animal Diagnostic Laboratory and Genotyping Core perform viral serology, parasitology, and bacteriology for rodents and NHPs, molecular-based assays for pathogens, and high-throughput genotyping. The Genome Modification Core provides technical guidance and expertise for genetic and epigenetic modifications in primary cells and cell lines, including libraries for performing genetic screens. The Mouse Modeling and Cryopreservation Core (MMC) makes transgenic and CRISPR-modified mice using pronuclear injections, generating 50–100 models annually. The MMC supports the NCI Mouse Repository by cryopreserving and distributing frozen sperm and embryos for popular mouse models.

The Animal Research Technical Support (ARTS) program provides expert consultation services to investigators on a plethora of animal life systems analyses, data collection, and surgical procedures. The ARTS Gnotobiotic Facility develops and monitors germ-free mouse colonies and examines the role of microbiota in inflammation and cancer. Its distinctive capabilities include germfree strain derivations, administration of investigational compounds, fecal transplants, and assessment of immunologic and metabolic functions during disease progression. The Small Animal Imaging Program (SAIP) monitors mouse models of cancer using *in vivo* imaging techniques and develops new molecular imaging probes. Dr. Jones explained how SAIP's hyperpolarizer enabled researchers to observe the course of treatment for a PDX model of human bladder cancer injected into a mouse.

In addition to basic histology tissue processing and assays, the Molecular Histopathology Laboratory performs advanced distinctive capabilities, such as laser capture microscopy, combined immunofluorescent and *in situ* hybridization, and digital pathology quantification of metastatic tumor burden. Dr. Jones discussed a preclinical mouse model for pediatric brain cancer that was developed by three LASP cores, exemplifying the collaborative nature of many innovative LASP projects. Dr. Jones conveyed that researchers interested in collaborating with or accessing LASP resources should contact the FNLCR Partnership Development Office.

In the discussion, the following points were made:

- The LASP is not a certified Biological Safety Level 3 (BSL-3) laboratory but performs BSL-2 and BSL-3 procedures for SIV research in primate facilities. The U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick contains BSL-3 facilities.

- SAIP core capabilities include photoacoustics, ultrasound, volume imaging, gamma well counters, bioluminescence, and hybrid technologies that incorporate positron emission tomography with computed tomography or magnetic resonance imaging. The SAIP can fuse multiple imaging modalities on a single imaging project and the LASP animal facilities contain Xenogen cameras for *in situ* bioluminescent imaging.

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

Establishing a FNLAC NCI–DOE Collaborations Task Force. Dr. Marnett stated that the Committee will need to concur on establishing a FNLAC NCI–DOE Collaborations Task Force. The mission statement was provided in the Committee folder. He noted that the NCI–DOE JDACS4C is in Year 3 of its 3-year pilot project and that an *ad hoc* NCI–DOE Collaborations Working Group was constituted to provide scientific evaluation of the project. The Working Group recommended establishing a Task Force to evaluate formally the collaborative arrangements and determine whether and how the collaborations will go forward in Years 4 and 5.

Motion. A motion to establish a FNLAC NCI–DOE Collaborations Task Force was approved unanimously.

Engaging with the FNLCR. Dr. Marnett reflected on the massive amount of technology and resources at the FNLCR that may not be well known in the research community. He suggested: (1) planning a presentation on the existing FNLCR internal and external communication mechanisms that could be discussed at a future FNLAC meeting and (2) identifying any problems in communicating with large consortia, for example, that the FNLAC can help to address. Dr. Marnett also asked the FNLCR leadership to consider highlighting NCI-supported investigators who have used the range of FNLCR capabilities to advance a research program. Dr. DuBois suggested including details about the FNLCR in the NCI Director's updates at conferences and meetings, such as the American Association for Cancer Research's annual meeting.

XII. ADJOURNMENT—DR. LAWRENCE J. MARNETT

Dr. Marnett thanked the Committee members and other invitees for attending. Members were reminded to send potential agenda topics for future FNLAC meetings to Dr. Lyman. The next FNLAC meeting is scheduled for February 19, 2020 and will be a virtual meeting. There being no further business, the 17th meeting of the FNLAC was adjourned at 4:00 p.m. on Thursday, October 24, 2019.

_____ _____

Date Lawrence J. Marnett, Ph.D., Chair

_____ _____

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