



U.S. Department of Health and Human Services
National Institutes of Health
Division of Program Coordination, Planning, and Strategic Initiatives
Office of Research Infrastructure Programs
Division of Comparative Medicine

**Validation of Animal Models and Tools for Biomedical Research
Session VI. Validation of Nonhuman Primate Models for
Preclinical Research**

Tuesday, December 15, 2020
Virtual Meeting

Workshop Report

Table of Contents

Executive Summary	i
Workshop Report	1
<i>Opening Remarks</i>	1
<i>Naturally Occurring Primate Models of Human Genetic Diseases: An Under-Exploited Resource</i>	1
<i>Advances in Physiological Monitoring of Emerging Viral Diseases in NHPs</i>	1
<i>What Do We Need for the Validation of Disease Model Marmosets?</i>	2
<i>Development of Species-Specific Therapies and Reagents at the NHP Reagent Resource</i>	2
<i>NHP Models of Neurodegenerative Disease: Parkinson’s Disease, Multiple System Atrophy, and Alzheimer’s Disease</i>	3
<i>Challenges and Advances in NHP Models of Respiratory Infections</i>	3
<i>Group Discussion</i>	4
<i>Additional Comments</i>	5
<i>Summary and Suggestions</i>	7
Appendix A: Meeting Agenda	8
Appendix B: Discussants List	9

Executive Summary

The sixth of 10 sessions of the Virtual Workshop on Validation of Animal Models and Tools for Biomedical Research was held on December 15, 2020. This workshop is intended as a venue to discuss the status of and needs for the validation of animal models and tools used in biomedical research. The Office of Research Infrastructure Programs (ORIP) is seeking input from participants regarding current technologies and resources, as well as obstacles and gaps relevant to the validation of animal models and tools. Session VI focused on the validation of nonhuman primate (NHP) models for preclinical research. Important challenges of NHP research are (1) ensuring the robustness and reproducibility of studies using small numbers of NHPs and (2) accounting for the many external factors that can confound studies using NHPs. The participants were asked to consider the best practices for study design and opportunities for the National Institutes of Health (NIH) to support NHP model investigators. The following needs were identified: (1) coordination and resource sharing across institutions; (2) new tools to aggregate validation information on binding, affinity, function, and immunogenicity in NHPs; (3) expanded genomic sequencing of NIH-funded colonies to better understand the genetic basis of relevant phenotypes; and (4) support for colonies of specialized NHPs (e.g., aged macaques) for studies of relevant diseases in specific subpopulations. Several participants recommended involving the National Primate Research Centers (NPRCs) in the breeding, maintenance, and veterinary care of models with complex phenotypes.

Session Co-Chairs

John Morrison, Ph.D., University of California, Davis

David O'Connor, Ph.D., University of Wisconsin–Madison

Presenters

Deborah L. Fuller, Ph.D., University of Washington

Amy Hartman, Ph.D., University of Pittsburgh

Jeffrey H. Kordower, Ph.D., Rush University

Diogo Magnani, Ph.D., University of Massachusetts

Jeffrey Rogers, Ph.D., Baylor College of Medicine

Erika Sasaki, Ph.D., Keio University, Japan

ORIP Staff Members

Lola Ajayi
Susan Chandran
Michael Chang, Ph.D.
Miguel Contreras, Ph.D.
Bruce Fuchs, Ph.D.
Franziska B. Grieder, D.V.M., Ph.D.
Stephanie Murphy, V.M.D., Ph.D.
Desiree von Kollmar
Sige Zou, Ph.D.

Organizing Committee

Hugo Bellen, D.V.M., Ph.D., Chair, Baylor College of Medicine
Keith Cheng, M.D., Ph.D., Co-Chair, Penn State College of Medicine
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

External Experts

Alan Attie, Ph.D., University of Wisconsin–Madison
Stefania Forner, Ph.D., University of California, Irvine
Kent Lloyd, D.V.M., Ph.D., University of California, Davis
Cathleen Lutz, Ph.D., The Jackson Laboratory
John Morrison, Ph.D., University of California, Davis
Stacey Rizzo, Ph.D., University of Pittsburgh
William Talbot, Ph.D., Stanford University
Paul Territo, Ph.D., Indiana University
Douglas Wallace, Ph.D., Children’s Hospital of Philadelphia
Jill Weimer, Ph.D., Sanford Research

NIH Program Staff

Kristine Abraham, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases
Shreaya Chakroborty, Ph.D., National Institute on Aging (NIA)
Marc Charette, Ph.D., National Heart, Lung, and Blood Institute (NHLBI)
Miguel Contreras, Ph.D., ORIP
Bruce Fuchs, Ph.D., ORIP
Amelie Gubitz, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)
Lisa Schwartz Longacre, Ph.D., NHLBI
D.P. Mohapatra, Ph.D., NINDS
Lorenzo M. Refolo, Ph.D., NIA
Rebecca Roof, Ph.D., NINDS
Xiaoli Zhao, Ph.D., National Institute of General Medical Sciences

Workshop Report

Opening Remarks

Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine, ORIP
Sige Zou, Ph.D., Coordinator, Program Official, ORIP

Drs. Stephanie Murphy, Director, Division of Comparative Medicine, ORIP, and Sige Zou, Coordinator, Program Official, ORIP, welcomed the participants and offered thanks to the Organizing Committee and Session Chairs for their efforts in organizing the event. Dr. Zou explained that the meeting is the sixth in a series of 10 sessions. He also acknowledged the support of several NIH Institutes: the National Heart, Lung, and Blood Institute (NHLBI); National Institute on Aging (NIA); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institute of General Medical Sciences (NIGMS); and National Institute of Neurological Disorders and Stroke (NINDS). Dr. Murphy reminded the participants that validation of animal models and tools is a critical part of ORIP's trans-NIH efforts. She expressed appreciation for the participants' input. Dr. Zou introduced and thanked Drs. John Morrison and David O'Connor, Co-Chairs.

Naturally Occurring Primate Models of Human Genetic Diseases: An Under-Exploited Resource

Jeffrey Rogers, Ph.D., Baylor College of Medicine

Dr. Jeffrey Rogers began by highlighting his key messages that (1) rhesus macaques have greater genetic variation than humans, including more potentially functional variation, and (2) researchers can discover and validate spontaneously occurring models for human genetic disease by expanding the genetic and genomic information available for existing NHP colonies. He described a recently published study in which the genomes of 853 rhesus macaques from 10 research colonies were sequenced. The animals carried 85.7 million single nucleotide variants (SNVs). In contrast, a total of 67.3 million SNVs were found in a recently sequenced cohort of 929 humans from 54 diverse global populations. The level of genetic variation found among rhesus macaques is similarly high for baboons, African green monkeys, and other NHPs. Functionally significant genetic variation related to disease also was high in the rhesus macaques, with more than 400,000 missense variants and more than 20,000 likely gene-disruptive variants, affecting nearly all genes in the macaque genome. Many of these variants will be key to understanding the genetics of disease. Three approaches exist for discovering new primate models of human genetic disease—forward genetics, reverse genetics, and cross-species validation (i.e., testing hypotheses generated in human genome-wide association studies using NHP models). Dr. Rogers presented examples of studies that have identified and used spontaneous NHP models of human genetic diseases. He recommended performing genome sequencing (i.e., the reverse genetics approach) of all NHPs in NIH-funded research colonies of rhesus macaques, cynomolgus macaques, pigtail macaques, baboons, marmosets, and squirrel monkeys. These data are necessary because each species possesses a unique array of functional variation, and different species can provide optimal models for human diseases. A 2018 NIH report, *Nonhuman Primate Evaluation and Analysis, Part 2*, made similar recommendations. Dr. Rogers noted another study that found that whole-genome sequencing data for various NHPs could be valuable for distinguishing between benign and pathogenic disease-related mutations in humans.

Advances in Physiological Monitoring of Emerging Viral Diseases in NHPs

Amy Hartman, Ph.D., University of Pittsburgh

Dr. Amy Hartman delivered an overview of her work at the University of Pittsburgh's Center for Vaccine Research using NHP models. The NHPs studied at the Center have been adapted to the Center's biosafety level 3 biocontainment facility. Dr. Hartman noted that work involving aerosol exposure to pathogens and physiological monitoring of the monkey models shows the greatest promise for validation of these models. The Center has technologies that facilitate research on mammal exposure to aerosol pathogens,

including respiratory inductive plethysmography and methods for accurate determination and adjustment of inhaled dose while measuring respiratory function. Physiological monitoring now is performed using implantable telemetry systems that collect data on temperature, activity, blood pressure, intracranial pressure, cardiac parameters, neurological parameters, electroencephalogram, and biopotential at regular, frequent intervals. The monitoring technology used at this facility is critical to ensuring reproducibility of all studies using NHPs. This technology offers the advantage of continuous remote collection of data on physiological processes of the study animals. Equipment setup, however, is technically challenging in a high-containment environment. The implants require specialized surgical techniques, and the generated data require substantial post-collection processing and storage. Additionally, the monitoring technologies do not allow the real-time assessments needed for euthanasia decisions. Nonetheless, advanced technologies have enabled the collection of more data from each NHP than was previously possible, increasing the information gleaned from each animal.

What Do We Need for the Validation of Disease Model Marmosets?

Erika Sasaki, Ph.D., Keio University, Japan

Dr. Erika Sasaki discussed what is needed for effective validation of disease model marmosets. She works at the Central Institute for Experimental Animals (CIEA), where a genetically modified disease marmoset model has been developed. Dr. Sasaki pointed out that marmosets are ideal models for behavior studies because of their many social behaviors that are similar to those of humans. The CIEA developed a transgenic marmoset model in 2009 and a targeted gene knockout marmoset model in 2016. The CIEA currently is working on a targeted gene mutant marmoset model of early-onset Alzheimer's disease (AD). To date, two mutant models of early-onset AD have been developed. The CIEA currently is attempting to validate these models. The mutations in these animals do not allow them to produce a mature PSEN1 protein. Magnetic resonance imaging (MRI) is performed every 6 months on the *PSEN1* mutant marmosets to detect abnormalities in brain development. Investigators are determining whether the *PSEN1* mutant marmosets exhibit dementia alone, behavior abnormalities without dementia, or both conditions. Challenges include (1) lack of behavioral analysis expertise at the CIEA and (2) inability to transfer the animals to other institutions because of the need to breed the animals while performing behavioral analyses. Collaborations between institutions working with NHPs and investigators studying the same phenotypes in humans are essential. Technical challenges are evident in this model; marmoset behavioral tasks are not well established. The CIEA is developing real-time behavioral analysis systems for freely moving marmosets. Social behaviors, sleep disorders, metabolic behaviors, motor functions, and any abnormal behaviors will be assessed across the marmosets' lifetimes using the system. The data collected by this system will be stored in an open-source database. Infrastructure is needed to support the collection and archival of large and expanding data sets, such as storage of video data.

Development of Species-Specific Therapies and Reagents at the NHP Reagent Resource

Diogo Magnani, Ph.D., University of Massachusetts

Dr. Diogo Magnani discussed the validation of monoclonal antibody (mAb) therapies for experiments with NHP models for disease. This form of therapy represents an expanding class of drugs with great success and potential. For example, hundreds of mAb therapies presently are being tested for COVID-19. Of particular interest are mAbs with demonstrated clinical utility and with regulatory approval, which would have an accelerated development path as medical countermeasures. While several U.S. Food and Drug Administration–approved mAbs are available for testing in NHPs, not all will work in NHPs because of species barriers to biological therapies. A valid therapy in an animal model ideally should replicate the outcomes of the same therapy in humans. Investigators must determine which reagents are appropriate and should be tested. For example, panels of antibodies used to profile immunity to COVID-19 must be developed, but not all clones that perform well in humans will work equally well in NHPs. Successful mAb therapy “back-translation” to animal models depends on several biological factors (e.g., epitope conservation, relatedness of targeted pathways to human pathways, antigen variability

within the NHP colonies, antigen density equivalency across cells, antigen tissue distribution comparability to humans). Investigators also must determine whether the therapeutic molecule is specific, has a high affinity, and performs similar functions. Some of these properties can be determined *in silico* or *in vitro*. A significant challenge to mAb back-translation is the immunogenicity of non-native sequences to NHPs, which lacks efficient predictive tools and requires experimental validation. This challenge sometimes can be overcome by engineering human antibody sequences with higher NHP identity. Currently, this type of molecule engineering is based primarily on germline annotations of rhesus macaque genes. Engineering species-specific (i.e., “primatized”) antibodies for NHP use has been shown to reduce immunogenicity and result in sustained effectiveness in some, but not all, cases. Ultimately, validation of therapeutic mAbs still relies on *in vivo* testing, which is a low-throughput method. As the number of mAb-based therapies in clinical use expand, the need to validate therapies in NHP models will increase. Dr. Magnani concluded that the classification of clinically relevant therapies compatible with NHP testing will require new computing tools to predict and aggregate data on mAb validation, binding, affinity, function, and immunogenicity in NHPs.

NHP Models of Neurodegenerative Disease: Parkinson’s Disease, Multiple System Atrophy, and Alzheimer’s Disease

Jeffrey H. Kordower, Ph.D., Rush University Medical Center

Creating and supporting specialized NHP resources to study high-priority human diseases is a future priority. Dr. Jeffrey H. Kordower discussed research on Parkinson’s disease (PD), multiple system atrophy (MSA), and AD. These three diseases are age-related. As such, aged NHP models are needed. Dr. Kordower recommended supporting the purchase and maintenance of aged monkey colonies by the NPRCs. NHPs have been critical to the development and advancement of research on PD and associated therapies (e.g., deep brain stimulation is a highly potent therapy for motor PD and now is a treatment for over 200,000 individuals). For further study of therapies for PD, scientists need a model of the synucleinopathy that occurs in this disease. In Dr. Kordower’s laboratory, such models were developed with preformed fibril injections into cynomolgus monkeys to produce the Lewy body pathology associated with PD. Various imaging approaches have demonstrated that these NHP models exhibit a condition with high fidelity to human PD in its pathology and the degenerative process in the brain. Dr. Kordower and colleagues also developed a model of MSA through a vector that transduces cells to synthesize alpha synuclein—but only in oligodendroglial cells, as seen in human MSA. Scientists can demonstrate that the same effects (e.g., loss of neurons in the striatum and nigra, demyelination, inflammatory changes) occur with the parkinsonian form of MSA in NHP models 6 months after exposure to the vector. Some of these changes—but not neuronal loss—can be identified in the NHP models 3 months after exposure, thus presenting a period during which the NHP models can be treated with therapies to slow or halt these changes. Dr. Kordower also discussed an NHP model with neurofibrillary tangles and neuron loss caused by adeno-associated virus (AAV) double-mutant tau injections into the entorhinal cortex; this pathology spreads over time in a prion-like fashion. He presented MRI images showing the progression of the tangles and neuron loss, noting that MRI and other imaging approaches can help avoid the need to sacrifice the research animals. Dr. Kordower and colleagues have developed methods to demonstrate the CNS pathology produced in the NHP models and identified several biomarkers. Validation of the NHP models described in Dr. Kordower’s presentation is underway. Anatomical phenotype and prion-like propagation of pathologies also have been validated. Mechanisms of degeneration and behavioral and functional deficits still need to be validated.

Challenges and Advances in NHP Models of Respiratory Infections

Deborah L. Fuller, Ph.D., University of Washington

NHP resources can be prepositioned to respond effectively to such emergent threats as COVID-19. Dr. Deborah L. Fuller delivered an overview of challenges and advancements in the use of NHP models to study respiratory infections. NHPs have been used in the study of multiple respiratory infections that

occur in humans, including COVID-19 and influenza. The NPRCs currently are collaborating to establish harmonized protocols that can be applied to other NHP models for respiratory infections. NHP models have presented several challenges in COVID-19 studies; for example, NHPs experience a relatively mild form of the respiratory effects of COVID-19, compared to humans. The mechanism underlying this mild form of disease requires further exploration. Dr. Fuller's laboratory is working on a model of exacerbated disease. More research on COVID-19 in aged NHPs is needed because insufficient numbers of these animals are available. Another important area of study involves the use of NHPs in examining co-infection of SARS-CoV-2 with influenza, HIV, and other diseases. Other critical COVID-19 research areas that will benefit from the use of NHP models include immune correlates, durability of vaccine effects, biotherapeutics, and improved second-generation vaccines. Lessons learned from COVID-19 research likely will be applicable to the research response during the next pandemic. Influenza continues to pose a risk as a future pandemic virus, and the NHP influenza A infections closely mirror symptoms experienced by humans. As work progresses toward developing universal influenza vaccines, researchers will need a reliable influenza B model of infection, further testing of the Group 2 influenza A NHP model, and studies of influenza in vulnerable populations (e.g., aged, pregnant women, children). A better understanding of the mechanisms of respiratory disease in NHP models will require definition of mild, moderate, and severe disease, as well as the identification of the earliest events leading to severe pathology. Another important research gap is the definition of the role of mucosal immunity in protection from respiratory infections, which will require consistent evaluation tools. Lung mucosa could be a promising target for vaccines. Additional research opportunities in NHPs include (1) the role of respiratory infections in individuals with chronic lung and immune diseases and (2) the biodistribution and safety of inhaled drugs and antivirals, which cannot be determined in smaller animals.

Group Discussion

John Morrison, Ph.D., University of California, Davis

David O'Connor, Ph.D., University of Wisconsin–Madison

Dr. Kordower stated that he is willing to share NHP brain sections. He suggested that one of the NPRCs oversee the collection and distribution of resources. Dr. Morrison offered to share plasma and cerebrospinal fluid. Dr. Guoping Feng said he would like to see more sharing of live animals to test the efficacy of gene therapy. Drs. Morrison and Feng recently co-authored a paper published in *Proceedings of the National Academy of Sciences of the United States of America* on the challenge of distributing genetically edited NHP models and recommended involving the NPRCs in the breeding, maintenance, and veterinary care of these myriad models with complex phenotypes.

Dr. Jon Levine explained that many NPRCs sell NHP postmortem biological materials and support a service to provide stem cells to researchers. The NPRCs are responding to the demand for more marmosets for neuroscience research through a National Institute of Mental Health U24 initiative to double marmoset populations in the NPRC colonies and distribute them through a coordinating center. Dr. Kevin Wells stated that the challenges associated with the collection and sharing of rare biological samples are shared across taxa. He suggested considering other species (i.e., rather than NHPs) for studies of aging.

Dr. Betsy Ferguson commented that because genetic models are discovered based on variants, small numbers of animals initially are available as potential breeders. The fastest way to create a colony from two or three new models is through *in vitro* fertilization. The Oregon NPRC has this capability, but many other NPRCs do not. Dr. Rogers added that spontaneously occurring models also are expensive and time-consuming to expand—taking years to move from variant discovery to a relevant NHP model—but can serve as unique models that are not possible in rodents or other non-primates. Dr. Feng's laboratory has identified spontaneous mutations linked to human diseases in marmosets.

Dr. Rogers also is working on whole-genome and whole-exome sequencing of breeding animals; the information will be made available to researchers. Dr. Levine suggested that investigators advocate for a similar effort to expand and sequence rhesus macaque colonies. Dr. Rogers reiterated the importance of full-exome and full-genome sequencing of the NHPs of all ages at the NPRCs. Dr. Levine added that these approaches should be a priority for animals used in longitudinal cognitive studies. Dr. Rogers highlighted the importance of considering the best approaches for matching genotypes and phenotypes. Dr. Keith Cheng expressed particular interest in tumor suppressor genes in NHPs. Dr. Ferguson noted that genomes of NHPs across all seven NPRC breeding colonies will be released in January 2021 through the macaque genotyping and phenotyping resource (mGAP). This resource will provide an opportunity to identify alleles relevant to research on COVID-19 and diseases of aging.

Dr. Suhas Kallapur commented that rhesus macaques are good models of pregnancy and fetal immunology. She asked Dr. Fuller whether the COVID-19 vaccines were tested in pregnant NHPs. Such testing was not performed, but some women enrolled in the Phase 3 clinical trials became pregnant during the study. These women experienced no problems, but the sample size was small.

Dr. Steven Bosinger noted that he and his colleagues found that early inflammation was an effective outcome when testing COVID-19 therapeutics and vaccines. Models of pathogenesis could take years to develop, but models of inflammation could be used for quick assessments. Dr. Fuller added that COVID-19 vaccination and therapeutics evaluation groups are working to harmonize protocols across the NPRCs.

Dr. Peter Nghiem asked whether any efforts are underway to inform the public about the importance of NHPs in the development of the COVID-19 vaccine. Dr. Fuller expressed interest in collaborating with NPRCs and other NHP facilities to develop a story about this topic. Dr. Bosinger suggested that scientists who have gained significant popularity on Twitter during the COVID-19 pandemic could communicate the importance of NHP models. Dr. Morrison added that the participants should consider how scientists can work with Congress to better support NHP research. He encouraged all participants to proactively communicate about the value of their work with NHPs.

Dr. Morrison stated that attempts have been made to standardize brain albums across laboratories, but these resources tend to be low resolution. Standardization of NHP brain section images is needed. Drs. Cheng and Morrison agreed to speak offline about the approaches for responding to this gap. Dr. Amy Arnston noted the importance of coordinating brain harvesting to capture phosphorylation state and perfusion fixation. A participant replied that many laboratories section the brain so that it can be shared between investigators, providing views of a complete lesion or the full brain.

A participant asked who would be responsible for expanding NHP colonies and for what species. Dr. Morrison responded that he has obtained NIH support for a geriatric colony at the California NPRC. The Center will be accepting requests for minimally invasive studies. Invasive studies will not be disallowed, but investigators must meet specific criteria. Dr. Manuel Moro is the contact for this resource. Dr. Kordower expressed interest in obtaining NHPs 22 years and older from the NPRCs. Another participant emphasized that the NPRCs maintain health records and pedigrees for aged NHPs. Multiple NPRCs have aged NHP colonies, but the participants agreed that these colonies should be expanded.

Given the difficulty of accessing Chinese-origin animals at this time, Dr. Morrison wondered whether these animals should be validated and compared to the NHPs of Indian origin.

Additional Comments

In the Zoom chat, Dr. Elliot Mufson asked whether any attempts have been made to perform RNA sequencing or single-cell neuron analysis within or across primate species for comparison with humans.

Dr. Morrison responded that some work of this type has been performed in the retina, but he was not certain that this involved a direct comparison to humans. Dr. Moore indicated that her laboratory has begun RNA sequencing in aged rhesus monkeys; details about this effort will be available soon. Dr. Feng's institution has an ongoing NIH Brain Research through Advancing Innovative Neurotechnologies Initiative project to perform single-cell RNA sequencing for most regions of the marmoset brain (biccn.org/teams/u01-feng). Dr. Mufson also wondered about single cortical neuron profiling, which is performed in humans with certain conditions.

Dr. Kathleen Engelman asked Dr. Rogers how genetic heterogeneity compares between New and Old World primates. Fewer data are available for New World primates, but the available data suggest that the genetic heterogeneity is more similar between New and Old World monkeys than to humans. New World primates appear to have high levels of functional variation.

Dr. Mufson asked Dr. Sasaki how the presenilin mutation affects the development of amyloid pathology in the marmoset. Dr. Sasaki responded that her group still is investigating this issue and is planning to perform positron emission tomography scans. Dr. Mufson asked whether Dr. Sasaki's group has brain tissue for amyloid antibody immunohistochemistry. She asked Dr. Sasaki to collect and fix the brain tissue of any young animals that die. Dr. Sasaki agreed to keep in touch with Dr. Mufson.

Dr. Bosinger asked Dr. Hartman in what tissues investigators were able to detect Rift Valley fever virus viremia. Dr. Hartman responded that they found febrile responses in all lethally infected animals and in most survivors. The fever was biphasic in marmosets and monophasic in African green monkeys. Dr. Kallapur asked whether Dr. Hartman was aware of any telemetry system for monitoring uterine contractions during labor. She responded that she was not aware of any such system, but some likely exist.

Dr. Mufson asked Dr. Kordower if tangle-like brain cells that he found in his study have a flame-like appearance. Dr. Mufson also asked about the appearance of labeled cells when the cells are Nissl stained. Dr. Danielle Beckman responded that she has found that tangles in NHP brains are flame-like, especially the thioflavin-positive tangles. She visualized axonal transport by combining multiple labeling for sites of tau phosphorylation. Dr. Mufson asked whether Dr. Beckman also observed anterograde transport. Dr. Beckman noted that she has been focusing on confocal microscopy; she could not confirm that anterograde transport was occurring. Dr. Cheng asked about capabilities for performing high-resolution fluorescence and light-microscopy scans. Results of these scans can be made available.

Dr. Rochelle Buffenstein asked Dr. Kordower whether other physiological organs and systems (e.g., voice box, respiratory system) were affected in the models and whether they responded to treatments. She also asked whether the animals exhibited any signs of tangles or tau proteins with different subcellular localizations (e.g., nucleus, cytosol). Dr. Rogers responded that he still does not know if there is a difference in distribution in the cells, but tau expression is altered between the entorhinal cortex and the hippocampus after the AAV injection.

Dr. Courtney Glavis-Bloom wondered whether there exists a method for sequencing marmosets that does not require 3 milliliters of blood. At the Salk Institute, she is conducting a longitudinal aging study with marmosets by testing cognitive function and examining biomarkers across the lifespan.

Dr. Cheng noted that it would be useful to determine whether aged NHPs show a higher fraction of cells with random mutations across model systems. This question could be investigated through the use of paired-end sequencing.

Summary and Suggestions

Because NHPs carry a high degree of functional genetic variation, researchers can discover and validate spontaneously occurring models for human genetic disease by expanding the genetic and genomic information available for existing NHP colonies. The participants discussed and provided the following areas that require new or continued support from ORIP and the NIH:

- NHP resources to effectively anticipate and respond to the next potential infectious disease pandemic
- Expanded breeding colonies at the NPRCs, with improved documentation of pedigrees
- Characterized genetics of all monkeys at the NPRCs, potentially using multiple technologies (e.g., genomics, transcriptomics, proteomics, metabolomics, microbiome analysis) at multiple times throughout the lifespan
- Further development of specialized colonies (e.g., aged monkeys) and increased availability to collaborative teams
- Enhanced capacity for the evaluation of complex phenotypes based on human disease phenotype and encouragement of phenotype experts (i.e., researchers who are not using primates presently)
- Enhanced mechanisms for tissue sharing and digitized primate pathology for remote validation within the NHP community and cross-validation with human and other model system pathologies
- Expanded capacity for breeding and sharing live animal models and support for large, collaborative teams to develop and study gene-edited models
- NPRC involvement in the breeding, maintenance, and veterinary care of gene-edited NHP models with complex phenotypes developed in university laboratories
- Identification and breeding of NHPs with spontaneous disease-causing mutations for disease gene discovery and modeling, as well as expanded sharing of information about those animals
- Development of in-cage voluntary behavioral testing facilities that do not require transport or restraint
- Standardization of NHP brain and section preparation and digitization of section images
- Public communication describing the importance of NHP models

Appendix A: Meeting Agenda

Session VI. Validation of Nonhuman Primate Models for Preclinical Research

2:00–4:00 p.m. EST

December 15, 2020

Chairs

John Morrison, Ph.D., University of California, Davis

David O'Connor, Ph.D., University of Wisconsin–Madison

2:00–2:05 p.m.

Opening Remarks

Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine,
Office of Research Infrastructure Programs (ORIP)

Sige Zou, Ph.D., Coordinator, Program Official, ORIP

2:05–3:30 p.m.

Presentations

Jeffrey Rogers, Ph.D., Baylor College of Medicine

Naturally Occurring Primate Models of Human Genetic Diseases:

An Under-Exploited Resource

Amy Hartman, Ph.D., University of Pittsburgh

*Advances in Physiological Monitoring of Emerging Viral Diseases in Nonhuman
Primates*

Erika Sasaki, Ph.D., Keio University

What Do We Need for the Validation of Disease Model Marmosets?

Diogo Magnani, Ph.D., University of Massachusetts

*Development of Species-Specific Therapies and Reagents at the Nonhuman
Primate Reagent Resource (NHPRR)*

Jeffrey H. Kordower, Ph.D., Rush University

*Development of Species-Specific Therapies and Reagents at the Nonhuman
Primate Reagent Resource (NHPRR)*

Deborah L. Fuller, Ph.D., University of Washington

*Challenges and Advances in Nonhuman Primate Models of Respiratory
Infections*

3:30–4:00 p.m.

Group Discussion

Appendix B: Discussants List

Session VI. Validation of Nonhuman Primate Models for Preclinical Research

2:00–4:00 p.m. EST

December 15, 2020

Kristin Abraham, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases
Lola Ajayi, Office of Research Infrastructure Programs (ORIP)
James Andersen, M.D., Ph.D., Division of Program Coordination, Planning, and Strategic Initiatives
Amy Arnsten, Ph.D., Yale Medicine School
Danielle Beckman, Pharm.D., Ph.D., University of California, Davis
Hugo Bellen, Ph.D., Baylor College of Medicine
Erwan Bezar, Ph.D., University of Bordeaux, France
Rudolf (Skip) Bohm, D.V.M., Tulane National Primate Research Center
Steven Bosinger, Ph.D., Emory University
Rochelle Buffenstein, Ph.D., Calico Life Sciences
Michael Chang, Ph.D., ORIP
Marc Charette, Ph.D., National Heart, Lung, and Blood Institute (NHLBI)
Keith Cheng, M.D., Ph.D., Pennsylvania State University
Miguel Contreras, Ph.D., ORIP
Kathleen Engelman, University of Massachusetts
Guoping Feng, Ph.D., Massachusetts Institute of Technology
Betsy Ferguson, Ph.D., Oregon National Primate Research Center
Scott Fraser, Ph.D., University of Southern California
Deborah Fuller, Ph.D., University of Washington School of Medicine
Michael Gale, Ph.D., University of Washington
Courtney Glavis-Bloom, Ph.D., Salk Institute
Franziska B. Grieder, D.V.M., Ph.D., ORIP
Amelie Gubit, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)
Renzhi Han, Ph.D., The Ohio State University
Matthew Harris, Ph.D., Harvard Medical School
Amy Hartman, Ph.D., University of Pittsburgh
R. Paul Johnson, M.D., Emory University
Amitinder (Miti) Kaur, M.D., Tulane University
Suhas Kallapur, M.D., University of California, Los Angeles
Deepak Kaushal, Ph.D., Southwest National Primate Research Center
Jeffrey H. Kordower, Ph.D., Rush University Medical Center
Jens Kuhn, M.D., Ph.D., National Institute of Allergy and Infectious Diseases
Jon Levine, Ph.D., University of Wisconsin–Madison
Zhandong Liu, Ph.D., Baylor College of Medicine
Diogo Magnani, Ph.D., University of Massachusetts
Jennifer Manuzak, Ph.D., Tulane National Primate Research Center
Tara Moore, Ph.D., Boston University School of Medicine
Manuel Moro, D.V.M., National Institute on Aging
John Morrison, Ph.D., University of California, Davis
Elliot Mufson, Ph.D., Barrow Neurological Institute
Stephanie Murphy, V.M.D., Ph.D., ORIP
Peter Nghiem, D.V.M., Ph.D., Texas A&M University
David O’Connor, Ph.D., University of Wisconsin–Madison
Megan O’Connor, Ph.D., University of Washington
Afam Okoye, Ph.D., Oregon Health & Science University

Randall Prather, Ph.D., University of Missouri
Jay Rappaport, Ph.D., Tulane National Primate Research Center
Crystal Rogers, Ph.D., University of California, Davis
Jeffrey Rogers, Ph.D., Baylor College of Medicine
Rebecca Roof, Ph.D., NINDS
Erika Sasaki, Ph.D., Keio University
Manfred Schartl, Ph.D., University of Würzburg, Germany
Lisa Schimmenti, M.D., Mayo Clinic
Lisa Schwartz Longacre, Ph.D., NHLBI
Leonard Shultz, Ph.D., The Jackson Laboratory
Elly Tanaka, Ph.D., Research Institute of Molecular Pathology
Sara Thomasy, D.V.M., Ph.D., University of California, Davis
Sally Thompson-Iritani, D.V.M., Ph.D., Washington National Primate Research Center
Koen Van Rompay, D.V.M., Ph.D., California National Primate Research Center
Francois Villinger, D.V.M., University of Louisiana
Kevin Wells, Ph.D., The University of Southern Mississippi
Xiaoli Zhao, Ph.D., National Institute of General Medical Sciences
Sige Zou, Ph.D., ORIP