



Transgenic and Chimeric Neuroscience Research: Exploring the Scientific Opportunities Afforded by New Nonhuman Primate Models—A Workshop

October 4, 2018

Keck Center of the National Academies
500 Fifth Street, NW | Washington, DC

Background:

The translational disconnect from preclinical studies with predominantly rodent animal models to human clinical trials remains a key challenge associated with lagging development of therapies for brain disorders. Since 2012, the Forum has hosted a series of workshops examining different aspects of this challenge, including maximizing the translation of effective therapies from animal models to clinical practice and exploring the evidence needed to bring compounds that appear to be safe into human efficacy trials. While no animal model will fully recapitulate human nervous system disorders, nonhuman primates—such as marmosets and macaques—have shown promise in their ability to serve as models for complex brain disorders, given the phylogenetic proximity and genetic similarity to humans, similarity of neuroanatomical organization (e.g., a well-developed prefrontal cortex) and associated cognitive and behavioral functions, social cognition, and the ability to study developmental phenotypes and prodromal disease states.

Workshop Objectives:

This one-day public workshop will bring together experts and key stakeholders from academia, government, industry, and non-profit organizations to examine the scientific opportunities and challenges, as well as bioethical considerations, of genetically engineered nonhuman primate models for neuroscience research.

Invited presentations and discussions will be designed to:

- Discuss the state of the science of transgenic and chimeric neuroscience research and emerging models for nervous system disorders, and explore the potential usefulness of such models to enhance understanding of behavior and higher cortical function, and advance therapeutic development.
- Examine current tools and technologies used in rodent models (e.g., transgenesis, chimera, AAVs [adeno-associated viruses], gene therapy, etc.) and explore how they would need to be modified for use in other animal models, such as nonhuman primates.
- Consider bioethical principles and issues related to genetic engineering of animal models for nervous system disorders, and discuss potential metrics for determining the models' readiness for nonhuman primate research.
- Discuss policies and infrastructure needed to advance research in this domain including, for example, training, recruitment of early career scientists, and the potential development of specialized research centers and international collaborations.

8:30 a.m. Welcome and Overview of Workshop
FRANCES JENSEN, University of Pennsylvania, Perelman School of Medicine (Chair)

Session I: Emerging Transgenic and Chimeric Nonhuman Primate Models for Neuroscience Research and Therapeutic Development for Nervous System Disorders

Objective:

- Discuss the state of the science of transgenic and chimeric nonhuman primate models for nervous system disorders, and explore the potential usefulness of such models to enhance understanding of behavior and higher cortical function, and in translational science to advance therapeutic development.

8:45 a.m. Session Overview
 SARAH CADDICK, Thalamic (Moderator)

8:55 a.m. Speakers
 GUOPING FENG, Massachusetts Institute of Technology
 HIDEYUKI OKANO, Keio University School of Medicine; RIKEN Brain
 Science Institute
 ANGELA ROBERTS, University of Cambridge
 YOLAND SMITH, Yerkes National Primate Research Center; Emory University

9:55 a.m. Discussion
 Discussant: WILLIAM NEWSOME, Stanford University

10:30 a.m. BREAK

Session II: Technology, Research Methodology, and Assessment Tools For Transgenic and Chimeric Nonhuman Primate Models

Objectives:

- Examine how current tools and technologies developed in rodent models (e.g., transgenesis, chimera, AAVs [adeno-associated viruses], gene therapy, in vitro fertilization, etc.) through the BRAIN Initiative and elsewhere, and might be modified for use in nonhuman primates.
- Consider potential logistical and feasibility issues unique to nonhuman primate models (e.g., cost).

10:45 a.m. Session Overview
 ROBERT WURTZ, National Eye Institute, Scientist Emeritus (Moderator)

11:00 a.m. Speakers
 MU-MING POO, Chinese Academy of Sciences
 KAREN PARKER, Stanford University
 JEAN BENNETT, University of Pennsylvania
 BEN DEVERMAN, Broad Institute of MIT and Harvard University

12:00 p.m. Discussion
 - Why and how do you make that leap from rodents to NHPs technically?
 - What are the logistical and feasibility issues in using genetic and chimeric technologies in NHP models for neuroscience research (e.g., cost)?
 - What tools and technologies are currently being used or needed to create these models?
 - What measures and assessment tools are needed (i.e., behavioral assessments)?

 Discussants: ROBERT DESIMONE, Massachusetts Institute of Technology
 DAVID AMARAL, University of California, Davis

12:30 p.m. LUNCH

Session III: Bioethical Considerations for Transgenic and Chimeric Nonhuman Primate Models in Neuroscience Research

Objectives:

- Explore bioethical principles and issues related to the genetic engineering of nonhuman primate models or the creation of chimeric nonhuman primate models for neuroscience research.
- Consider key questions that will necessitate nonhuman primate models for basic and translational research.
- Discuss potential safeguards needed for transgenic and chimeric nonhuman primate models of nervous system disorders to ensure proper animal welfare.

1:30 p.m. Session Overview
HENRY T. GREELY, Stanford University (Moderator)

1:40 p.m. Speakers
STEFAN TREUE, German Primate Center; Georg-August University
MARGARET LANDI, GlaxoSmithKline
JEFFREY KAHN, Johns Hopkins University

2:25 p.m. Discussion

- As NHPs deserve greater or different consideration than other non-human animal species used in research generally, should there be particular considerations about their use in transgenic and chimeric neuroscience research? How should that be reflected in which research is carried out, and in the care of NHPs in research settings?
- What criteria must be met in order to justify the use of nonhuman primates in transgenic and chimeric neuroscience research, i.e., type and importance of research questions; unique aspects of nonhuman primates; data from other research models; clinical testing that cannot be performed in human subjects, etc.
- What are the possibilities that transgenic and chimeric neuroscience research in NHPs could confer some qualitatively different aspect of cognition on the NHP? How could that be assessed? What would be the significance if that were to happen?

Discussant: MARINA EMBORG, Wisconsin National Primate Research Center;
University of Wisconsin–Madison

3:00 p.m. BREAK

Session IV: Moving Forward: Policy and Infrastructure Needs to Advance Research

Objectives:

- Synthesize and discuss key highlights from the workshop presentations and discussions, including identifying next steps and promising areas for future action and research.
- Discuss policies and infrastructure needed to advance research in this domain including, for example, training, recruitment of early career scientists, and the potential development of specialized research centers and international collaborations.
- Consider the roles of national primate research centers, governments, private philanthropy, and other key stakeholders to advance this research.

3:15 p.m. Session Overview
FRANCES JENSEN, University of Pennsylvania, Perelman School of Medicine (Chair)

- 3:25 p.m. Keynote
 MU-MING POO, Chinese Academy of Sciences
- 3:40 p.m. Panel Discussion
 HIDEYUKI OKANO, Keio University School of Medicine; RIKEN Brain Science Institute
 JOHN MORRISON, California National Primate Research Center, University of California,
 Davis
 JOSHUA GORDON, National Institute of Mental Health
 MARK FRASIER, Michael J. Fox Foundation for Parkinson’s Research
 LOUIS REICHARDT, Simons Foundation Autism Research Initiative
 LISA STANEK, Sanofi
- 4:25 p.m. Discussion
- 5:15 p.m. Closing Remarks
 STEVEN HYMAN, Broad Institute of MIT and Harvard University
- 5:30 p.m. Adjourn Workshop

Workshop Planning Committee

Frances Jensen (Chair), University of Pennsylvania, Perelman School of Medicine
Susan Amara, National Institute of Mental Health
Sarah Caddick, THALAMIC
Marina Emborg, Wisconsin National Primate Research Center, University of Wisconsin–Madison
Guoping Feng, Massachusetts Institute of Technology
Joshua Gordon, National Institute of Mental Health
Hank Greely, Stanford University
Jeffrey Kahn, Johns Hopkins University
Walter Koroshetz, National Institute of Neurological Disorders and Stroke
John Morrison, California National Primate Research Center, University of California, Davis
William Newsome, Stanford University
Karen Parker, Stanford University
Michael Steinmetz, National Eye Institute
Andrew Welchman, Wellcome Trust
Stevin Zorn, MindImmune Therapeutics, Inc.