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Health and Medicine Division
Forum on Neuroscience and Nervous System Disorders

Therapeutic Development for Nervous System Disorders in the Absence of Predictive Animal Models of Disease: A Workshop

September 12–13, 2016

National Academy of Sciences Building
2101 Constitution Ave., NW | Room 120
Washington, DC 20418

Background: Although the prevalence and burden of nervous system disorders remains high, development of new therapeutics lags behind other disease areas. Current drug development from discovery to regulatory approval takes on average 12–15 years. Gaps in understanding of the underlying mechanisms of disease, a dearth of biomarkers, and limitations in the capacity of animal models to predict drug efficacy for human brain disorders have contributed to a high rate of late stage failures in drug development. As a result, many large pharmaceutical companies have decreased investment, or withdrawn entirely from their neuroscience research programs.

In 2012, the Forum on Neuroscience and Nervous System Disorders hosted a public workshop on *Improving the Utility and Translation of Animal Models for Nervous System Disorders* to discuss potential opportunities for maximizing the translation of effective therapies from animal models to clinical practice. During the workshop, several participants emphasized the utility of animal models for investigating basic neural processes, but their limitations for fully recapitulating nervous system disorders, and predicting therapeutic efficacy in human clinical trials. Given these concerns, the Forum hosted a second public workshop on *Improving and Accelerating Therapeutic Development for Nervous System Disorders* to explore opportunities and challenges in neuroscience research for accelerating entry of potential treatments into first-in-human trials. Workshop participants explored the potential usefulness of supplementing animal models of basic mechanisms with new technologies ranging from use of human induced pluripotent stem cells [iPSCs], to partially humanized animal models, to a greater emphasis on advancing human experimental biology. Much discussion was engendered about circumstances in which a therapeutic might be tested in patients (of different ages), in the absence of a predictive animal model so long as safety had been established. Among ethicists and regulators there were particular concerns expressed about proceeding to clinical trials in children, and about potential use of biologics. A larger concern within industry was the challenge of making a financial commitment to clinical trials, absent a predictive animal model, especially for common polygenic brain disorders where patient selection remains challenging.

Building on the discussions from these two activities, the Forum will host a public workshop to more deeply explore ways to motivate and accelerate drug development for nervous system disorders. The workshop will consider the evidence needed to bring compounds that appear to be safe into human efficacy trials both from an ethical and regulatory point of view and from a pragmatic and financial point of view in the absence of a predictive animal model. The workshop will bring together key stakeholders to discuss scientific, regulatory, and business challenges and

to identify potential opportunities in this domain to motivate and accelerate therapeutic development to address unmet medical needs.

Meeting objectives:

- Explore the utility of novel approaches to the process of target validation and biomarker development including human genetics, stem cell technologies, including use of iPS cells and human brain organoids, experimental human biology such as molecular imaging and neurophysiology, and computational modeling.
- Discuss future technological developments that would facilitate bringing compounds that appear to be safe into human dose finding and efficacy trials, even if an animal model of the human disease is not achievable.
- Discuss the regulatory landscape and what would be needed for regulatory agencies and institutional review boards to consider these approaches.
- Explore the private sector environment for proceeding with drug development approaches in situations that lack animal models to predict drug efficacy.
- Consider ethical issues, including for exploratory trials in pediatric populations.

Day One: September 12, 2016

1:00 p.m. *Opening Remarks and Review of Previous Neuroscience Forum Workshops*

STEVEN HYMAN, *Workshop Chair*
Director, Stanley Center for Psychiatric Research
The Broad Institute of MIT and Harvard University
Distinguished Service Professor
Professor of Stem Cell Biology and Regenerative Biology
Harvard University

1:15 p.m. *Where are we now? The utility and translation of animal models for nervous system disorders and novel advancements in the field.*

- Brief overview of the current drug development pipeline for nervous system disorders.
- Update on recent developments, both positive and negative, for the field.

DAVID MICHELSON
Vice President of Neuroscience and Ophthalmology Clinical Research
Merck & Co.

SESSION I: NEUROSCIENCE DRUG DEVELOPMENT IN THE ABSENCE OF PREDICTIVE ANIMAL MODELS OF DISEASE

Session Objectives:

- Discuss opportunities to move into human trials when compounds appear to be safe based on dose finding and efficacy trials.
- Consider the evidence and technological developments needed to decrease the translational gap between animal and human trials.
    - Using case studies, explore the utility of novel approaches and technology for target identification and validation (e.g., establishing predictive validity in proof-of-concept studies), and to identify biomarkers.
- Discuss the role of bidirectional translational endpoints and the relationship between preclinical endophenotypes and clinical outcome measures.
    - What are the clinical questions that could drive preclinical research?

1:30 p.m. *Overview and Session Objectives*

STEVIN ZORN, *Session Moderator*
President and CEO of MindImmune Therapeutics, Inc.
Ryan Research Professor of Neuroscience, George and Anne Ryan Institute for Neuroscience, University of Rhode Island
President, SH Zorn Consulting, LLC

Case Studies

1:40 p.m. Parkinson's disease (LRRK2)

TODD SHERER
Chief Executive Officer
Michael J. Fox Foundation for Parkinson's Research

JAN EGEBJERG
Vice President of Neurodegeneration and Biologics
H. Lundbeck A/S

2:15 p.m. Schizophrenia

STEVEN MCCARROLL (*via WebEx*)
Associate Professor, Department of Genetics, Harvard Medical School
Director of Genetics, Broad Institute's Stanley Center for Psychiatric Research

NIELS PLATH
Head of Department on Synaptic Transmission
H. Lundbeck A/S

2:50 p.m. Discussion among Speakers and Workshop Participants

3:30 p.m. BREAK

3:45 p.m. Stem cells and Organoids

LEE RUBIN
Professor, Department of Stem Cell and Regenerative Biology
Harvard University
Director of Translational Medicine, Harvard Stem Cell Institute

STEVE FINKBEINER
Associate Director and Senior Investigator
Gladstone Institute of Neurological Disease

4:20 p.m. Engineered Primate Models

GUOPING FENG
Poitras Professor of Neuroscience, Department of Brain and Cognitive Sciences
McGovern Institute for Brain Research
Massachusetts Institute of Technology

4:40 p.m. Computational Quantitative Systems Pharmacology Modeling of Brain Circuits

HUGO GEERTS
Chief Scientist
In Silico Biosciences

5:00 p.m. Discussion among Speakers and Workshop Participants

5:50 p.m. Day One Wrap-up
STEVEN HYMAN, *Workshop Chair*

6:00 p.m. Adjourn Day One

Day Two: September 13, 2016

8:30 a.m. *Day Two Opening Remarks*

STEVEN HYMAN, *Workshop Chair*

SESSION II: PRIVATE SECTOR THRESHOLDS FOR INVESTMENT IN NEUROSCIENCE CLINICAL TRIALS

Session Objectives:

- Discuss the decision-making process within the private sector for proceeding with drug development approaches in situations that lack predictive animal models of disease.
- Consider potential incentives that might encourage industry to reinvest or increase investments in CNS trials.

8:45 a.m. *Overview and Session Objectives*

RITA BALICE-GORDON, *Session Moderator*
Head, Neuroscience Research,
Sanofi, Inc.

Perspectives from the Private Sector

8:55 a.m. Pharmaceutical Company

KIM ANDERSEN
Senior Vice President and Head of Research
H. Lundbeck A/S

9:10 a.m. Biotechnology Company

BILL MARTIN
Head of Research and Development
BlackThorn Therapeutics, Inc.

9:25 a.m. Venture Capital

DOUG COLE
Managing Partner
Flagship Ventures

Public-Private Partnerships

9:40 a.m. Understanding the Role of Public-Private Partnerships to De-risk the Development Process and to Facilitate Data Sharing

JOHN MICHAEL SAUER
Executive Director of the Predictive Safety Testing Consortium
Critical Path Institute
Adjunct Research Professor, Department of Pharmacology
University of Arizona, College of Medicine

9:55 a.m. Discussion among Speakers and Workshop Participants

Discussant:

FRANK YOCCA
Senior Vice President of CNS Research and Development
BioXcel Corporation

10:30 a.m. BREAK

SESSION III: ETHICAL AND REGULATORY CONSIDERATIONS FOR HUMAN TRIALS

Session Objectives:

- Consider the ethical implications of bringing compounds that appear safe to human efficacy trials without preclinical data from animal models.
  - What are the risks and potential benefits to patients?
  - What do patients consider to be tolerable risks?
- Discuss the unique challenges for trials in vulnerable populations.
- Discuss the regulatory landscape and the evidence needed for regulatory agencies to consider trials in humans in the absence of predictive animal models of disease.
- Explore areas within the drug development pipeline where new and emerging tools, technologies, and techniques might be subject to regulatory processes.

10:45 a.m. *Overview and Session Objectives*

NITA FARAHANY, *Session Co-Moderator*
Professor of Law & Philosophy and Director of Duke Science & Society
Duke University School of Law

LINDA BRADY, *Session Co-Moderator*
Director, Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health

Ethical Considerations

10:55 a.m. Incorporating Safeguards into Preclinical Research and the Ethics of First-in-Human Trials

JOHNATHAN KIMMELMAN
Associate Professor, Biomedical Ethics Unit/Social Studies of Medicine
McGill University

11:10 a.m. Considerations for Conducting Trials in Vulnerable Populations

REBECCA DRESSER
Daniel Noyes Kirby Professor of Law
Professor of Ethics in Medicine
Washington University

11:25 a.m. Discussion among Speakers and Workshop Participants

Discussant:

LUCIE BRUIJN
Chief Scientist
The ALS Association

12:15 p.m. LUNCH

Regulatory Considerations

- What evidence is needed to conduct efficacy trials in humans? What constitutes a feasible outcome measure and what is the role of surrogates?
- Discuss how accelerating to human trials would alter the drug development pipeline. Consider potential challenges to such approach.

1:15 p.m. Perspectives from the U.S. Food and Drug Administration

ROBERT TEMPLE
Deputy Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

1:30 p.m. Perspectives from the European Medicines Agency

MARIA ISAAC (*via WebEx*)
Senior Scientific Officer
European Medicines Agency

1:45 p.m. New Approaches to Establishing Safety and Conducting Toxicology Studies

THOMAS HARTUNG
Professor and Chair for Evidence-based Toxicology
Johns Hopkins University Bloomberg School of Public Health

2:00 p.m. Discussion among Speakers and Workshop Participants

2:45 p.m. BREAK

SESSION IV: MOVING FORWARD

Session Objectives:

- Highlight workshop key themes.
- Identify opportunities and key stakeholders necessary for bringing compounds that appear to be safe into human efficacy trials for nervous system disorders.

3:00 p.m. Overview and Session Objectives

STEVEN HYMAN, *Workshop Chair*

3:05 p.m. Session Synopsis and Potential Next Steps
Session Moderators

3:45 p.m. Discussion among Speakers and Workshop Participants

4:25 p.m. Final Comments
STEVEN HYMAN, *Workshop Chair*

4:30 p.m. ADJOURN