Accelerating Therapeutic Development for Nervous System Disorders towards First-in-Human Trials: A Workshop

April 8 and 9, 2013

National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., N.W., Washington, DC

Background: In March 2012, the Forum on Neuroscience and Nervous System Disorders hosted a public workshop *Improving Translation of Animal Models for Nervous System Disorders.* This workshop explored strategies for improving the processes of discovery and development of effective therapies for nervous system disorders with a focus on translation of results from animal models to clinical practice. Two themes that emerged from the workshop were that many have lost confidence in the ability of animal models to predict efficacy and that current animal models may, in fact, be screening out potentially effective compounds. Another theme was the need to combine animal models with emerging translational tools and technologies in therapeutic development. Following on these themes, the goal of this workshop is to explore opportunities to accelerate the pathway from discovery to approval of new therapeutics for nervous system disorders.

Meeting Objectives:

- Examine opportunities and challenges in neuroscience research for facilitating faster entry of potential treatments into first-in-human trials.
    - Discuss the role of new and emerging tools and technologies in accelerating therapeutic development.
    - Identify avenues for developing integrated strategies that utilize both animal and non-animal models.
    - Discuss potential benefits and risks of such an approach.
- Explore how emerging neuroscience technologies and techniques may improve the efficiency of research and facilitate a more effective and efficient pathway to first-in-human trials (e.g. iPSCs, *in vitro* neuronal circuits, connectomics, brain imaging, etc.)
- Consider regulatory mechanisms that may facilitate faster entry of potential treatments into first-in-human trials.
    - Discuss how new and emerging tools and technologies may accelerate progress towards first-in-human trials.
- Consider mechanisms for integration and proliferation of new technologies and techniques to facilitate drug development and discovery.

DAY ONE

Note: Breakfast will be available at 8:00 a.m.

8:30 a.m. Opening Remarks

JOHN DUNLOP, *Co-chair*
FRED GAGE, *Co-chair*

8:40 a.m. Review of workshop "Improving Translational of Animal Models for Nervous System Disorders"

RICHARD HODES
Director
National Institute on Aging

SESSION I: CURRENT THERAPEUTIC DEVELOPMENT PRACTICES

Session Objectives: Discuss the benefits and risks of accelerating therapeutic development into first-in-human clinical trials. Consider the need for new molecular targets for nervous system disorders. Examine therapeutic development practices with a focus on challenges presented by current tools and technologies.

8:55 a.m. Overview and Session Objectives

DAVID MICHELSON, *Session Chair*
Vice President
Clinical Neuroscience and Ophthalmology
Merck Research Laboratories

9:00 a.m. The therapeutic development pathway: From the lab to the clinic

WILLIAM POTTER
Senior Advisor
Office of the Director
National Institute of Mental Health

9:15 a.m. Meeting the medical need: The benefits and risks of aggressively moving compounds forward

JASON KARLAWISH
Professor of Medicine, Medical Ethics and Health Policy
Perelman School of Medicine
University of Pennsylvania

9:30 a.m. Evolutionary conservation and divergence: The utility of animal models in development of therapeutics

DANIEL GESCHWIND
Gordon and Virginia MacDonald Distinguished Professor
Center for Autism Research and Treatment
UCLA School of Medicine

9:45 a.m. Developing new molecular and clinical targets for nervous system disorders

SAMUEL GANDY
Professor of Neurology and Psychiatry
Associate Director
Mount Sinai Alzheimer's Disease Research Center

10:00 a.m. Therapeutic development practices: Challenges and limitations of current tools and technologies

CHAS BOUNTRA
Professor of Translational Medicine
Head of Structural Genomics Consortium
University of Oxford

10:15 a.m. Panel Discussion with Participants

DAVID MICHELSON, *Moderator and Session Chair*

10:45 a.m. BREAK

SESSION II: OPPORTUNITIES AND CHALLENGES FOR NEW AND EMERGING TOOLS AND TECHNOLOGIES

Session Objectives: Examine the role of new and emerging tools and technologies in accelerating the development of therapeutics for nervous system disorders. Discuss the readiness of these tools and technologies for integration into therapeutic developmental pathways. Examine the utility of specific new and emerging tools and technologies in relation to nervous system disorders.

11:00 a.m. Overview and Session Objectives

RAJESH RANGANATHAN, *Session Chair*
Director
Office of Translational Research
National Institute of Neurological Disorders and Stroke

Speakers will focus on the following questions

- How could this area of research speed therapeutic development?
- What would the qualification process look like for this area?
- How long would it take for integration into therapeutic development pathways?

11:05 a.m. iPSCs

LARRY GOLDSTEIN
Distinguished Professor, Department of Neurosciences
Director, UC San Diego Stem Cell Program
UCSD School of Medicine

11:25 a.m. Humanized Animal Models

IRVING WEISSMAN
Director, Institute of Stem Cell Biology and Regenerative Medicine
Professor of Pathology and Developmental Biology
Stanford University

11:45 a.m. Biomarkers/Imaging

SCOTT SMALL
Herbert Irving Professor in Neurology
The Neurological Institute of New York
Columbia University Medical Center

12:05 p.m. Human models/Experimental medicine

JOHN KRYSTAL
Robert L. McNeil, Jr., Professor of Translational Research
Chair, Department of Psychiatry
Yale University School of Medicine

12:25 p.m. Computational neuroscience

READ MONTAGUE
Director, Human Neuroimaging Laboratory
Director, Computational Psychiatry Unit
Virginia Tech Carilion Research Institute
Professor, Wellcome Trust Centre for Neuroimaging, University College London

12:45 p.m. Panel Discussion with Participants

- How would these new and emerging tools and technologies complement or replace current methods including animal models?
- How could these new and emerging tools and technologies aid in the identification of new molecular and clinical targets?
- What are potential challenges for incorporation into current developmental pathways?

RAJESH RANGANATHAN, *Moderator*

1:15 p.m. LUNCH (*Will be provided for all participants*)

2:00 p.m. Opportunities and challenges around incorporation of new and emerging tools and technologies into current research programs

- Which tools and technologies show the most promise for the particular disease area?
- How could these tools and technologies best be positioned to positively bolster current research programs?

1) Neurodevelopmental disorders: Autism and schizophrenia

KEVIN EGGAN
Associate Professor
Harvard Stem Cell Institute
Harvard University

2) Mood disorders: Depression

WAYNE DREVETS
Scientific Vice President
Disease Area Leader in Mood Disorders
Janssen Pharmaceuticals Companies of Johnson & Johnson

3) Neurodegenerative disorders: Alzheimer's and Parkinson's

PAUL AISEN
Director, Alzheimer's Disease Cooperative Study
Professor, Department of Neurosciences
University of California, San Diego

4) Traumatic brain injury

RAMON DIAZ-ARRASTIA
Director of Clinical Research, Center for Neuroscience and Regenerative Medicine
Professor of Neurology
Uniformed Services University of the Health Sciences

3:00 p.m. Panel Discussion with Participants

RAJESH RANGANATHAN, *Moderator*

3:30 p.m. BREAK

SESSION III: EVALUATING THERAPEUTIC DEVELOPMENT PATHWAYS

Session Objectives: Explore mechanisms by which evidence is evaluated in decisions to commit to therapeutic development approaches. Discuss ways in which new and emerging tools and technologies could increase confidence in decision making.

3:45 p.m. Overview and Session Objectives

MAGALI HAAS, *Session Chair*
Chief Science & Technology Officer
One Mind for Research

3:50 p.m. Decision processes for committing to a therapeutic development approach

- What evidence is required for research programs to commit resources?
- How is evidence evaluated in the decision process? What evidence is given greater weight?
- When and how are decisions made to switch to a different approach?

1) Industry perspective

KALPANA MERCHANT
Chief Science Officer
Tailored Therapeutic, Neuroscience
Eli Lilly and Company

2) Government perspective

STORY LANDIS
Director
National Institute of Neurological Disorders and Stroke

3) Academic perspective

REISA SPERLING
Director, Center for Alzheimer's Research and Treatment
Professor of Neurology
Harvard Medical School

4:35 p.m. The contribution of animal models within the therapeutic development pathway

- What is the spectrum of animal models used in the therapeutic development pathway?
- How are research programs currently supplementing animal models in the development pathway?

NICK BRANDON
Senior Director, Neuroscience iMED
AstraZeneca

4:50 p.m. Panel Discussion with Participants

- How can these tools and technologies help identify and validate molecular and clinical targets?
- Which of these tools and technologies show the best promise to help groups make these commitments?
- What combinations of new and emerging tools, technologies and animal models have the potential to accelerate therapeutic development?

MAGALI HAAS, *Moderator*

5:20 p.m. Day One Wrap-Up

JOHN DUNLOP, *Co-chair*
FRED GAGE, *Co-chair*

5:30 p.m. ADJOURN

DAY TWO

Note: Breakfast will be available at 8:00 a.m.

8:30 a.m. Welcome

JOHN DUNLOP, *Co-chair*
FRED GAGE, *Co-chair*

SESSION IV: THE REGULATORY PATHWAY

Session Objectives: Examine the current regulatory processes and the use of new and emerging tools and technologies in applications. Discuss common mistakes in applications as guidance for developing accelerated pathways into first-in-human trials.

8:35 a.m. Overview and Session Objectives

WILLIAM POTTER, *Session Chair*
Senior Advisor
Office of the Director
National Institute of Mental Health

8:40 a.m. Lessons learned: Accelerating therapeutic development through a look at current regulatory applications

- What are key components of successful applications? What are common mistakes?
- What uses of new and emerging tools and technologies are subject to regulatory processes across the phases of drug development: IND/Phase 1; Phase 2; Phase 3; and NDA?
- Are there mechanisms for moving into patients, children/adolescents faster? First?

IMRAN KHAN
Pharmacologist & Toxicologist
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration

9:00 a.m. Potential challenges facing integration of new and emerging tools and technologies into the regulatory process

- What potential challenges do these new and emerging tools and technologies face in the approval process?

ROBERT CONLEY
Distinguished Lilly Scholar
Regulatory Leader, Biomedicines
Eli Lilly and Company

ERIC BASTINGS
Deputy Director
Division of Neurology Products, Center for Drug Evaluation and Research
Food and Drug Administration

NI KHIN
Medical Team Leader
Division of Psychiatry Products, Center for Drug Evaluation and Research
Food and Drug Administration

9:30 a.m. Panel Discussion with Participants

WILLIAM POTTER, *Moderator*

SESSION V: ACCELERATING THERAPEUTIC DEVELOPMENT

Session Objectives: Explore mechanisms by which evidence is evaluated to make commitments to invest in clinical trials. Discuss ways in which therapeutic development paradigms can be optimized and accelerated. Identify potentially innovative methods to accelerate development of new therapeutics.

10:00 a.m. Overview and Session Objectives

DANIEL BURCH, *Session Chair*
Global TA Head Neurosciences – GPD
PPDi

10:05 a.m. Investment decisions in preclinical development and movement into clinical trials

- What is the level of proof needed to justify investment in a preclinical project for IND enabling or a phase 1 activity?
- From an investment point of view, how attractive are neuroscience research areas when compared to other therapeutic areas? What could make it more attractive at the preclinical stage?
- How important is it to fully understand mechanisms and molecular pathways of action prior to initiation of the IND enabling package?

KIRAN REDDY
Principal
Third Rock Ventures

STEVE ELMS
Managing Partner
Aisling Capital

KAZUMI SHIOSAKI
Managing Director
MPM Capital

10:35 a.m. Panel Discussion with Participants

- How would new and emerging tools and technologies affect the decision process? Would they increase confidence in decisions?

DANIEL BURCH, *Moderator*

11:05 a.m. BREAK

11:20 a.m. Improving current therapeutic development approaches

- How could new and emerging tools and technologies provide solutions for challenges currently facing development of drugs for nervous system diseases?
- How could new and emerging tools and technologies be used in place of, or in addition to, animal models?

1) Discovery/Basic research

DAVID GOLDSTEIN
The Richard and Pat Johnson Distinguished University Professor
Director, Center for Human Genome Variation
Duke University

2) Target ID/Validation

DANIEL WEINBERGER
Director and CEO
Lieber Institute for Brain Development

3) Screening/Optimization

ADRIAN IVINSON
Director, Harvard NeuroDiscovery Center
Harvard University

4) Pre-clinical development

MARK BEAR
Picower Professor of Neuroscience
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology

12:20 p.m. Panel Discussion with Participants

- What balance between emerging tools and technologies and current methods (e.g. animal models) would be needed to increase confidence in selection of a particular development pathway?

DANIEL BURCH, *Moderator*

12:45 p.m. LUNCH (*Will be provided for all participants*)

SESSION VI: NEW APPROACHES TO THERAPEUTIC DEVELOPMENT

Session Objective: Discuss workshop concepts in the context of nervous system disorders. Identify tangible next steps by which identified mechanisms might be rapidly incorporated into current practices.

1:45 p.m. Overview and Session Objectives

STEVEN HYMAN, *Session Chair*
Director, Stanley Center at the Broad Institute
Distinguished Service Professor
Professor of Stem Cell Biology and Regenerative Biology
Harvard University

1:50 p.m. Imagining new therapeutic development pathways (w/ Q&A)

CHRISTOPHER AUSTIN
Director
National Center for Advancing Translational Sciences
National Institutes of Health

2:10 p.m. Next steps with workshop co-chairs and individual session chairs

- How could workshop concepts be rapidly incorporated into current therapeutic development practices?

JOHN DUNLOP, *Workshop Co-chair*
AstraZeneca

FRED GAGE, *Workshop Co-chair*
Salk Institute

DAVID MICHELSON, *Session I Chair*
Merck Research Laboratories

RAJESH RANGANATHAN, *Session II Chair*
National Institute of Neurological Disorders and Stroke

MAGALI HAAS, *Session III Chair*
One Mind for Research

WILLIAM POTTER, *Session IV Chair*
National Institute of Mental Health

DANIEL BURCH, *Session V Chair*
PPDi

3:30 p.m. Final comments

JOHN DUNLOP, *Co-chair*
FRED GAGE, *Co-chair*

3:45 p.m. ADJOURN