The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Forum on
NEUROSCIENCE and
NERVOUS SYSTEM DISORDERS

# Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Blood-Brain Barrier: A Workshop

*September 8, 2017*
*Keck Center of the National Academies*
*500 Fifth Street, NW | Washington, DC*

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**Background:**
The blood-brain barrier (BBB) presents a special challenge to the development of therapeutics for many central nervous system (CNS) disorders. Far from acting simply as a physical barrier, the BBB is a complex dynamic system involving several cell types, passive and active transport mechanisms, and adaptive function to control the exchange of substances between the blood and the CNS. Few therapeutic agents readily traverse the BBB to reach the brain or spinal cord, including most small molecule drugs and the vast majority of large molecules such as proteins. Several research groups are exploiting intrinsic BBB transport mechanisms, such as molecular Trojan horses, and exploring technologies, such as chemical modifications and physical disruption, to test delivery of therapeutics to the CNS. Such strategies may greatly increase the armamentarium of potential drugs for treating psychiatric and neurological disorders. This public workshop will bring together key experts from academia, government, the biotechnology and pharmaceutical sector, disease-focused organizations, and other interested stakeholders to explore current development of novel methods for traversing the BBB to deliver therapeutics for nervous system disorders and identify potential opportunities for moving the field forward.

**Workshop Objectives:**
- Provide an overview of current knowledge on the role of the blood-brain barrier biology and delivery mechanisms examining gaps in our current knowledge that future research may address.
- Discuss brain-blood barrier passive and active mechanisms that challenge development and delivery of effective therapeutic interventions to central nervous system targets.
- Highlight current data and innovative approaches for delivery of therapeutics across the brain-blood barrier harnessing methods including chemical modifications, Trojan horse approaches, physical targeting and disruption, nanoparticles, ultrasound, and other technologies.
- Explore potential opportunities for catalyzing development of novel treatments that cross the blood-brain barrier--from the preclinical to clinical phase--with an emphasis on risks, levers, and potential collaborative efforts among sectors.

## September 8, 2017, Room 100

8:00 a.m. **Welcome and Overview of Workshop**
HUSSEINI MANJI, Janssen Research & Development, LLC (CO-CHAIR)
DANICA STANIMIROVIC, National Research Council of Canada (CO-CHAIR)

### OPENING TALKS

Session Objectives:

- Provide background information about BBB biology including its function in health and disease states and active and passive mechanisms challenging delivery of therapeutics to the CNS.
- Review different mechanisms and modes for traversing the BBB for the purpose of therapeutic delivery to the CNS.
- Highlight gaps in our understanding of BBB biology and transport mechanisms for delivery of therapeutics to the brain.

8:10 a.m. **Introduction**
HUSSEINI MANJI, Janssen Research & Development, LLC (MODERATOR)

8:20 a.m. **BBB Structure, Function, and Pathology**
BERISLAV ZLOKOVIC, University of Southern California

8:35 a.m. **Modes of Traversing and Overcoming the BBB**
WILLIAM PARDRIDGE, University of California, Los Angeles

8:50 a.m. **Discussion**

9:05 a.m. ***Break***

### SESSION 1: TRAVERSING THE BBB – MODALITIES AND TECHNOLOGIES FOR BRAIN DELIVERY

Session Objectives:

- Describe current understanding of modalities for traversing the BBB.
- Survey innovative technologies – including Trojan horse approaches, physical targeting and disruption, nanoparticles, and ultrasound – for delivery of therapeutics to the CNS.
- Discuss desirable characteristics for development of new technologies for traversing the BBB.

9:20 a.m. **Session Overview**
STEVEN PAUL, Voyager Therapeutics, Inc. (CO-MODERATOR)
ERIC SCHAEFFER, Janssen Research & Development, LLC (CO-MODERATOR)

9:30 a.m. **Presentations**
FRANK WALSH, Ossianix
VIVIANNA GRADINARU, California Institute of Technology
ROBERT THORNE, University of Wisconsin
ALEXANDER KABANOV, University of North Carolina at Chapel Hill
FONG-CHOI CHO, Brigham and Women's Hospital

10:30 a.m. **Discussion**

11:00 a.m. ***Break***

## SESSION 2: TRAVERSING THE BBB – PRE-CLINICAL TO CLINICAL TRANSLATION

Session Objectives:

- Discuss the translation – from late preclinical work to clinical trials – of delivery strategies for traversing the BBB, including delivery of synthetic molecules, biologics, and gene therapy.
- Describe the limitations of current methods for traversing the BBB and identify research and other potential next steps that would move the field forward.

11:15 a.m. **Session Overview**

DANICA STANIMIROVIC, National Research Council of Canada (CO-MODERATOR)
E. ANTONIO CHIOCCA, Harvard Medical School (CO-MODERATOR)

11:25 a.m. **Presentations**

BALU CHAKRAVARTHY, National Research Council of Canada
ALEXANDRA GOLBY, Brigham and Women's Hospital
RUBEN BOADO, Armagen
DAHAVALKUMAR SHAH, State University of New York at Buffalo

12:25 p.m. **Discussion**

12:55 p.m. ***Lunch***

## PANEL 1: REGULATORY CONSIDERATIONS IN DEVELOPMENT OF METHODS FOR TRAVERSING THE BBB

Session Objectives:

- Discuss approaches, tools, and lessons learned from other regulatory domains that may advance the development and translation of novel methods to traverse the BBB.
- Identify specific barriers and opportunities in the regulatory domain related to the development and application of methods for traversing the BBB.
- Explore issues related to critical attributes and potency assays; safety, including immunogenicity and CNS toxicity; and animal models, including appropriate species selection.
- Explore best practices and strategies to facilitate regulatory consideration of novel technologies for traversing the BBB.

1:40 p.m. **Session Overview**

FRANCESCA BOSETTI, National Institute of Neurological Disorders and Stroke, (MODERATOR)

1:50 p.m. **Panel Remarks**

DOUGLAS HUNT, Armagen
VIKRAM PATEL, Food and Drug Administration
*Additional panelists to be announced*

2:20 p.m. **Discussion**

2:40 p.m. **Break**

## PANEL 2: ACCELERATING RESEARCH AND CLINICAL TRANSLATION – CONSORTIA AND PUBLIC PRIVATE PARTNERSHIPS

Session Objectives:

- Identify specific barriers and opportunities for increased coordinating among ongoing efforts in academia, the private sector, and the federal agencies.
- Brainstorm potential collaborative projects that could be submitted through current or planned mechanisms.
- Explore novel mechanisms for catalyzing innovative technologies for traversing the BBB through new public-private partnerships and consortia, including discussion of potential practical next steps.

2:55 p.m. **Session Overview**
SARAH H. LISANBY, National Institute of Mental Health (MODERATOR)

3:05 p.m. **Reflecting on the Workshop: Challenges and Emerging Opportunities for Development of Innovative Methods to Traverse the BBB**
ERIC SCHAEFFER, Session 1 Co-Moderator
E. ANTONIO CHIOCCA, Session 2 Co-Moderator
FRANCESCA BOSETTI, Panel 1 Moderator

3:30 p.m. **Panel Remarks**
BERND STOWASSER, Sanofi
BARBARA TATE, Dementia Discovery Fund / SV Life Sciences
ANDREW WELCHMAN, Wellcome Trust
EDMUND TALLEY, National Institute for Neurological Disorders and Stroke / BRAIN Initiative
KATJA BROSE, Chan-Zuckerberg Initiative
GRANT CAMPANY, X-prize Foundation

5:00 p.m. **Discussion**

5:30 p.m. ***Adjourn Workshop***

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**Workshop Planning Committee**

**HUSSEINI MANJI,** Janssen Research & Development, LLC (co-chair)
**DANICA STANIMIROVIC,** National Research Council of Canada (co-chair)
**FRANCESCA BOSETTI,** National Institute of Neurological Disorders and Stroke
**E. ANTONIO CHIOCCA,** Harvard Medical School
**VIVIANA GRADINARU,** California Institute of Technology
**CHENGHUA GU,** Harvard Medical School
**JIM KOEING,** National Institute on Neurological Disorders and Stroke
**SARAH H. LISANBY,** National Institute of Mental Health
**ROGER LITTLE,** National Institute on Drug Abuse
**WILLIAM PARDRIDGE,** University of California, Los Angeles
**STEVEN PAUL,** Voyager Therapeutics, Inc.
**ERIC SCHAEFFER,** Janssen Research & Development, LLC
**AJAY VERMA,** United Neuroscience