



## Advancing Gene-Targeted Therapies for Central Nervous System Disorders— A Workshop

April 23-24, 2019

National Academy of Sciences Building | Lecture Room  
2101 Constitution Avenue NW, Washington, DC

### Workshop Objectives:

This public workshop will bring together experts and key stakeholders from academia, government, industry, and non-profit organizations to explore approaches for advancing the development of gene-targeted therapies for central nervous system (CNS) disorders, including approaches that target nucleic acids, such as adeno-associated viruses (AAVs), antisense oligonucleotides (ASOs), and RNA interference, as well as gene product-targeted therapies.

Invited presentations and discussions will be designed to:

- Provide an overview of the current landscape of gene-targeted therapies approaches for nervous system disorders.
- Discuss lessons learned from recent advances in gene therapy and ASO development for retinal dystrophy and spinal muscular atrophy.
- Compare features of different gene-targeted therapy approaches in development for CNS disorders, and discuss approaches to matching the approach to specific diseases, addressing their respective administration, distribution, and dose challenges, and potential long-term effects.
- Explore clinical development—including biomarker and clinical endpoint selection, trial design to demonstrate disease modification, and the regulatory path—for gene-targeted therapy approaches for rare genetic disorders that have more variable onset and slower progression.
- Discuss what it would take to move beyond rare genetic disorders to develop gene-targeted therapy approaches for more common, heterogeneous disorders such as Alzheimer's and Parkinson's diseases.
- Explore opportunities for catalyzing development of gene-targeted therapy approaches for nervous system disorders, including potential collaborative efforts among sectors and across disorders.

### Workshop Planning Committee

**Story Landis**, Co-Chair, Forum on Neuroscience and Nervous System Disorders, *workshop co-chair*

**Lamya Shihabuddin**, Sanofi R&D, *workshop co-chair*

**Zeshan (Shanny) Ahmed**, Eli Lilly and Company

**David Bredt**, Janssen R&D

**Daniel Burch**, PPD Biotech

**Joseph Buxbaum**, Icahn School of Medicine at Mount Sinai

**Beverly Davidson**, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine

**Joshua Gordon**, National Institute of Mental Health

**Frances Jensen**, University of Pennsylvania School of Medicine

**John Krystal**, Yale University School of Medicine

**Maryann Redford**, National Eye Institute

**Todd Sherer**, Michael J. Fox Foundation for Parkinson's Research

**Hao Wang**, Takeda

**Clinton Wright**, National Institute of Neurological Disorders and Stroke

**April 23, 2019**

1:30pm Welcome and Overview of Workshop

STORY LANDIS, *Co-chair*, Forum on Neuroscience and Nervous System Disorders and  
*Workshop co-chair*

LAMYA SHIHABUDDIN, Sanofi, *Workshop co-chair*

### Session I: Current Landscape and Lessons Learned

Objectives:

- Provide an overview of the current landscape of gene-targeted therapies approaches for central nervous system disorders.
- Explore lessons learned from gene and ASO therapies that have achieved FDA approval—including translation plans and which animal models were used in preclinical studies, use of dog model for RPE65, role of natural history studies for spinal muscular atrophy (SMA) therapy, and other lessons learned in translation to clinical development.
- Examine lessons learned from gene therapy efforts that were not successful, including neurotrophins for neurodegenerative diseases.

1:40pm Session overview

LAMYA SHIHABUDDIN, Sanofi, *Session moderator*

1:45pm RPE65 gene therapy

KATHLEEN REAPE, Spark Therapeutics

2:00pm ASO therapy for SMA

C. FRANK BENNETT, Ionis

2:15pm Gene therapy for SMA

PETRA KAUFMANN, AveXis

2:30pm Lessons learned from unsuccessful gene therapy trials of neurotrophins for neurodegenerative diseases

JEFFREY KORDOWER, Rush University

2:45pm Panel discussion: preclinical studies, delivery methods, clinical trial issues focused on these cases with the intent to identify general issues that will and will not apply to other applications/diseases

*The speakers above will be joined by panelists:*

RONALD CRYSTAL, Weill Cornell Medicine

CHRISTOPHER HENDERSON, Biogen

3:25pm General discussion

3:45pm BREAK

## Session II: Selecting Gene-Targeted Therapy Approaches for CNS Disorders

### Objectives:

- Discuss the promise and potential pitfalls of gene-targeted therapies specifically for CNS disorders.
- For CNS disorders, compare features of different therapies that target nucleic acid, including adeno-associated viruses (AAVs), antisense oligonucleotides (ASOs), and RNA interference, as well as gene product targeted therapies.
- Explore what makes a CNS disorder potentially amenable to treatment via gene-targeted therapies and how to match therapy modality and mechanism of action to specific diseases.
- Discuss when uncontrolled overexpression is appropriate.

4:00pm	<p>Session overview</p> <p style="text-align: center;">BEVERLY DAVIDSON, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, <i>Session moderator</i></p>
4:05pm	<p>Speakers</p> <p style="text-align: center;">ANASTASIA KHVOROVA, University of Massachusetts Medical School ASA ABELIOVICH, Columbia University Irving Medical Center SARAH DEVOS, Denali Therapeutics</p>
4:35pm	Panel discussion among speakers above
5:00pm	General discussion

### **Day One Closing Talk**

5:30pm	<p>The vista for developing gene-targeting therapies for psychiatric and other circuit disorders</p> <p style="text-align: center;">STEVEN HYMAN, The Broad Institute</p>
5:45pm	Discussion
6:00pm	ADJOURN DAY ONE

**April 24, 2019**

8:30am Welcome and overview of day one

STORY LANDIS, Co-chair, Forum on Neuroscience and Nervous System Disorders,  
*Workshop co-chair*

LAMYA SHIHABUDDIN, Sanofi, *Workshop co-chair*

### Session III: Gene-Targeting Therapy Technologies for CNS Disorders

Objectives:

- For different therapy modalities, and with a focus on general issues rather than specific disease indications:
  - Discuss approaches to addressing their respective administration challenges,
  - Explore CNS fluid dynamics and barriers, as well as delivery routes and distribution, and dose,
  - Examine what is known about clinical and nonclinical safety, as well as potential long-term effects.
- Consider how previously successful approaches for spinal muscular atrophy and retinal dystrophy would need to be adapted for monogenetic disorders that have more variable onset and slower progression, and discuss timing of interventions.
- Discuss what it takes to move beyond monogenetic disorders to develop gene therapy approaches for common, heterogeneous disorders such as Alzheimer's and Parkinson's diseases.
- Examine key challenges such as:
  - CNS cell type-specific transduction.
  - Regulation of viral gene expression to optimize safety and efficacy
  - Capsid engineering to improve tissue-specific targeting and BBB penetration.

8:40am Session overview

DAVID BREDT, Janssen R&D, *Session co-moderator*

HAO WANG, Takeda Pharmaceuticals, *Session co-moderator*

8:45am Speakers

BEVERLY DAVIDSON, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine

JUNGHAE SUH, Rice University

VIVIANA GRADINARU, Caltech

JUDE SAMULSKI, University of North Carolina School of Medicine

9:25am Panel discussion

9:45am General discussion

10:15am BREAK

## Session IV: Clinical Trial Design and Regulatory Pathways

### Objectives:

- **Translation and treatment paradigm** – explore issues with preclinical models, delivery, considerations for FIH, immune response, dose response, and dose and dose regimen selection. What unique challenges do neuropsychiatric diseases present?
- **Patient access** – discuss recruitment challenges, natural history studies, and opportunities with registries/ patient advocacy.
- **Regulatory pathway** – address ethical considerations, issues with standards and harmonization, and overall level of proof required.
- **Risk/benefit and value to patients** – consider how to define meaningful, clinically relevant endpoints, and how to demonstrate efficacy, safety and overall effectiveness over the long run.
  - Specific questions may include, should long term toxicity studies be required (6 months or more)? Should biodistribution and rationale be considered for each gene product or can biosimilars be cross-referenced? What is a biosimilar?

10:30am	Session Overview DANIEL BURCH, PPD Biotech, <i>Session moderator</i>
10:35am	Translation AKSHAY VAISHNAW, Alnylam
10:45am	Clinical MICHAEL PANZARA, Wave Biosciences CRISTINA SAMPAIO, CHDI Foundation
11:05am	Regulatory pathway PETER MARKS, Food and Drug Administration RUNE KJEKEN, Norwegian Medicines Agency
11:25am	Ethics HOLLY TABOR, Stanford
11:35am	Patient Advocacy TIM COETZEE, National MS Society
11:45am	General discussion
12:30pm	LUNCH

## Session V: Moving Forward

### Objectives:

- Discuss new technologies on the horizon, for example, non-viral approaches, small molecules targeting RNA (e.g., ExpansionRx, Arrakis, Skyhawk), chaperones, targeted protein degradation (many companies), and cell penetrant stapled peptide therapeutics (e.g., Fog Pharma).
- How can these approaches be used for psychiatric disorders and other circuit disorders?
- What else do we need to know that we don't know? For example, precision medicine for low incidence disorders, developing a strategic pipeline for treatments, Timothy syndrome, neuregulins.
- Briefly discuss issues related to cost, access, and health equity, as well as AAV manufacturing capacity.

1:30pm	<p>Session overview</p> <p style="margin-left: 40px;">FRANCES JENSEN, Perelman School of Medicine at the University of Pennsylvania, <i>Session moderator</i></p>
1:35pm	<p>Gene mutations in autism and associate neurodevelopmental disorders</p> <p style="margin-left: 40px;">JOSEPH BUXBAUM, Icahn School of Medicine at Mount Sinai</p>
1:50pm	<p>Novel, non-viral methods of gene therapy, tunable vectors, and AAV manufacturing capacity</p> <p style="margin-left: 40px;">ROBERT KOTIN, Generation Bio and University of Massachusetts Medical School</p>
2:05pm	<p>Using a small molecule drug to modulate splicing</p> <p style="margin-left: 40px;">ANU BHATTACHARYYA, PTC Therapeutics</p>
2:20pm	<p>Non-viral delivery nanoplatfoms for brain-targeted genome editing</p> <p style="margin-left: 40px;">SHAOQIN SARAH GONG, University of Wisconsin-Madison</p>
2:35pm	<p>Cost, access, and equity issues</p> <p style="margin-left: 40px;">HOLLY TABOR, Stanford</p>
2:50pm	<p>Panel discussion</p>
3:05pm	<p>General discussion</p>
3:45pm	<p>Synthesis of key workshop themes and future directions</p> <p style="margin-left: 40px;">STORY LANDIS, Co-Chair, Forum on Neuroscience and Nervous System Disorders, <i>Workshop Co-Chair</i></p> <p style="margin-left: 40px;">LAMYA SHIHABUDDIN, Sanofi, <i>Workshop Co-Chair</i></p>
4:00 p.m.	<p>ADJOURN WORKSHOP</p>