The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

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 Session overview

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

4:05pm Speakers

ANASTASIA KHVOROVA, University of Massachusetts Medical School

ASA ABELIOVICH, Columbia University Irving Medical Center

SARAH DEVOS, Denali Therapeutics

4:35pm Panel discussion among speakers above

5:00pm General discussion

Day One Closing Talk

5:30pm The vista for developing gene-targeting therapies for psychiatric and other circuit disorders

STEVEN HYMAN, The Broad Institute

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

LUK VANDENBERGHE, Harvard Medical School

JUNGHAE SUH, Rice University

9:15am Panel discussion

The speakers above will be joined by panelists:

VIVIANA GRADINARU, Caltech

JUDE SAMULSKI, University of North Carolina School of Medicine

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, *Session moderator*

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 Session overview

FRANCES JENSEN, Perelman School of Medicine at the University of Pennsylvania, *Session moderator*

1:35pm Gene mutations in autism and associate neurodevelopmental disorders

JOSEPH BUXBAUM, Icahn School of Medicine at Mount Sinai

1:50pm Novel, non-viral methods of gene therapy, tunable vectors, and AAV manufacturing capacity

ROBERT KOTIN, Generation Bio and University of Massachusetts Medical School

2:05pm Using a small molecule drug to modulate splicing

ANU BHATTACHARYYA, PTC Therapeutics

2:20pm Non-viral delivery nanoplatforms for brain-targeted genome editing

SHAOQIN SARAH GONG, University of Wisconsin-Madison

2:35pm Cost, access, and equity issues

HOLLY TABOR, Stanford

2:50pm Panel discussion

3:05pm General discussion

3:45pm Synthesis of key workshop themes and future directions

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

LAMYA SHIHABUDDIN, Sanofi, *Workshop Co-Chair*

4:00 p.m. ADJOURN WORKSHOP