Developing RNAi Approaches for Gain-of-Function Variants in KIF1A

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Ovid Therapeutics

+ **Our focus**

- Diseases with significant unmet medical need
  - AND
  - Opportunities to leverage academic/patient partnerships & patient data
  - AND
  - Potential to accelerate discovery & development of transformative medicines

+ **Building a leading neurotherapeutics company**

<table>
<thead>
<tr>
<th>+ Epilepsy franchise</th>
<th>+ Genetic seizure programs</th>
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<tr>
<td>• 2 programs with potential 1st-in-class or best-in-class medicines</td>
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<tr>
<td>• Novel mechanisms of action for the potential treatment of epilepsies &amp; seizures</td>
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<tr>
<td>• Building a pipeline of medicines for genetic seizure-related disorders</td>
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<tr>
<td>• Harnessing accelerated, replicable development approach using clear clinical endpoints</td>
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+ **Academic discovery & translation collaborations**

+ **3 INDs expected in next 3 years**
Ovid, Together with Our Patient Communities, is Transforming the Medical Landscape of Rare Neurogenetic Diseases

Ovid Therapeutics strives to develop potentially life-changing therapies based on our deep understanding of key biological pathways and their central role in rare neurological diseases.

We develop medicines using clinically relevant endpoints related to the underlying disease pathophysiology to capture the real-world patient benefits.

We do this with a deep understanding of the significant unmet therapeutic need in a sentinel indication.

We apply science-driven, patient-focused expertise to other syndromes where we can make a unique difference in the lives of patients and families.
Columbia collaboration is a research engine that enables a replicable approach for discovering & translating genetic CNS targets

- Discovery & research collaboration with Columbia University
  - Library of targets, PSCLs & animal models
- Screening Tools
  - Screening tools & assays help demonstrate blood brain barrier penetration
- “Trial Ready” Community Toolbox
  - Natural history and pathology mapping for rare CNS disorders
- Replicable approach for investigating similar genes/pathways
  - Partner targets with non-like modalities

Discover, translate & accelerate into human trials
Synergistic Development Plan for Genetic Therapies

- CNS Neuron Targeting
- RNAi Modality
- Clinical
- Patient Advocacy
- Patient Natural History
- Biomarker ID
- In Vivo/Biodistribution/Safety
- Translational Model
- Manufacturing and IND-enabling studies
- IND

Discovery
Hit POC
Delivery Development
Validation
Phenotypic Assay
Translational Model

18-24 months from Lead ID

Clinical Trial

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DNA sequencing is unlocking potential for therapies in genetic CNS medicines

RNAi as a gene silencing therapy shows promise for disorders associated with gain-of-function mutations

Advances in sequencing have accelerated the identification & characterization of underlying mutations

7,000+ rare, monogenic disorders
40% Neurological

SOURCES:
- Giannoni, Li et al. 2014, Cell Rep
Ovid seeks to reduce the amount of KIF1A variant protein

KAND is primarily an autosomal dominant, gain-of-function disorder with KIF1A mutations impacting the transport of synaptic vesicle precursors to the synapse

- Normally, KIF1A forms dimers, bind to synaptic vesicle precursors (SVPs) and transport cargo in a retrograde direction along microtubule filaments in neurons
- Mutant KIF1A proteins exert a dominant-negative effect and interfere with normal SVP transport
- When disrupted, patients do not maintain the proper synapses for neuronal function

OUR GOAL:
REDUCE EXPRESSION OF MUTANT FORM THAT INTERFERES THE FLOW OF SVP CARGO


Pairing the best modality to disrupt variant protein

Phenotypic screening
- Neurite outgrowth
- Neural differentiation
- Electrophysiological
- Kinesin aggregation
- SVP transport

Molecular screening
- Allele-specific qPCR

SOURCE: Research by Lia Boyle, Chung Lab
Missense variants result in more severe disease

Two normal alleles

Nonsense

50%

Missense

25%

50%

25%

Desired

Undesired

Lia Boyle, Chung Lab
Allele-specific knockdown as treatment for KAND

Ideal

Partial knockdown of both alleles
Reduction in mutant > reduction in wildtype

Heterozygous missense variants

Partial knockdown of mutant
No reduction in wild type

*Identified oligos that specifically reduce RNA from variant allele
*Continuing to investigate biology of delivery and functional rescue

Lia Boyle, Chung Lab
KIF1A variant targeting approaches

“Modality agnostic” (i.e. siRNA, shRNA, ASO)

One Oligo Per Variant

One Oligo Several Variants

Proof of concept
Functional return in models

Targeting a SNP in cis with several mutant variants as a “handle”

Charles Leduc, Chung Lab
C. elegans as a model for KIF1A variant function


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Learning from Advancements in Genetic Therapies

Bespoke Gene Therapies Consortium (BGTC)

• Partnership between NIH, FDA, many pharma companies, and non-profit organizations

• Goal is to build knowledge base and create resource to streamline development process for gene therapies in rare disease
  • AAV vector biology
  • Manufacturing/QC
  • Pre-clinical testing

Recent FDA Guidances

Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics
Guidance for Industry

Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases
Guidance for Sponsor-Investigators

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Summary

• Creating screening and functional models for multi-mutational, monogenic disorders
• Using models to screening for mutant-specific RNAi sequences
• Using active sequences for validation of phenotypic effect in models
• Leveraging genomic and patient-derived cell sequencing data to identify SNP Handles
• Apply this strategy and approach to other rare, monogenic disorders and kinesinopathies

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• Arne Gennerich
Thank you for including Ovid in the journey towards a cure for KAND.