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

+ Epilepsy franchise

- 2 programs with potential 1st-in-class or best-in-class medicines
- Novel mechanisms of action for the potential treatment of epilepsies & seizures

+ Genetic seizure programs

- Building a pipeline of medicines for genetic seizure-related disorders
- Harnessing accelerated, replicable development approach using clear clinical endpoints

+ 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

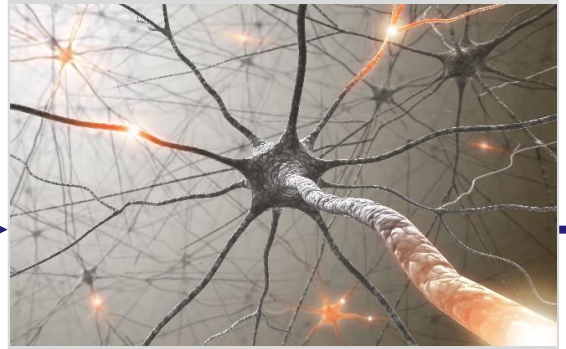
We apply *science-driven, patient-focused* expertise to other syndromes where we can make a unique difference in the lives of patients and families

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



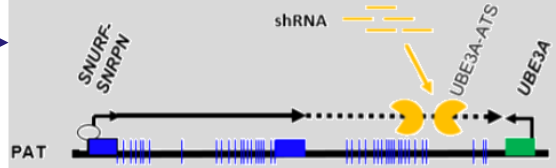
Screening tools & assays help demonstrate blood brain barrier penetration

"Trial Ready" Community Toolbox

KIF1A
KIF1A.ORG

Natural history and pathology mapping for rare CNS disorders

Replicable approach for investigating similar genes/pathways



Cassette style approach to targets and shRNA

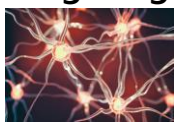
Partner targets with non-like modalities

Discover, translate & accelerate into human trials

Synergistic Development Plan for Genetic Therapies

Ovid Therapeutics

CNS Neuron Targeting



RNAi Modality

Clinical

Patient Advocacy

Patient Natural History

Biomarker ID

Discovery → Hit POC → Delivery Development → Validation → Phenotypic Assay → Translational Model → In Vivo/ Biodistribution/ Safety → Manufacturing and IND-enabling studies → IND

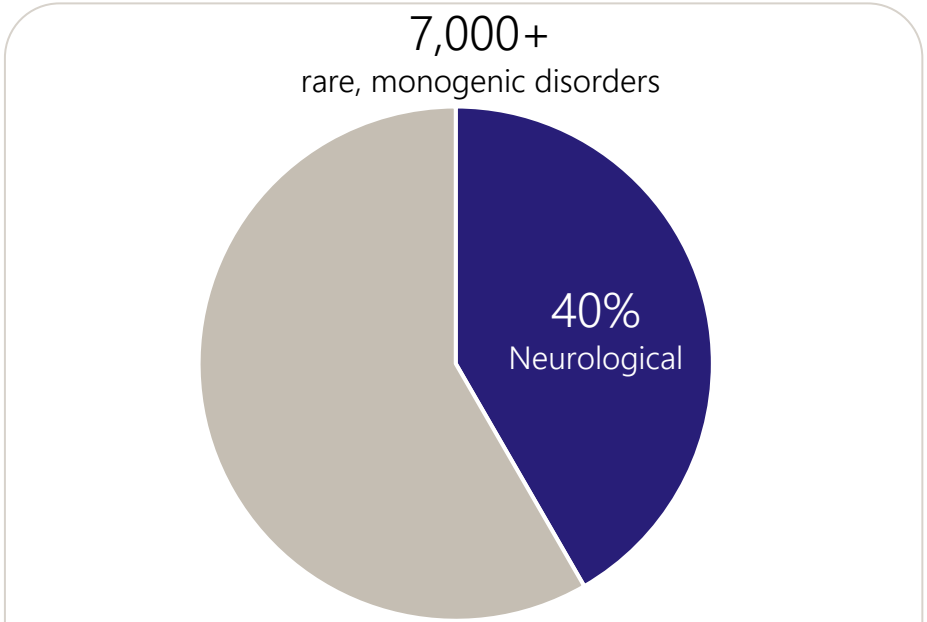
Lead ID

COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

Discovery → Clinical Trial

18-24months from Lead ID

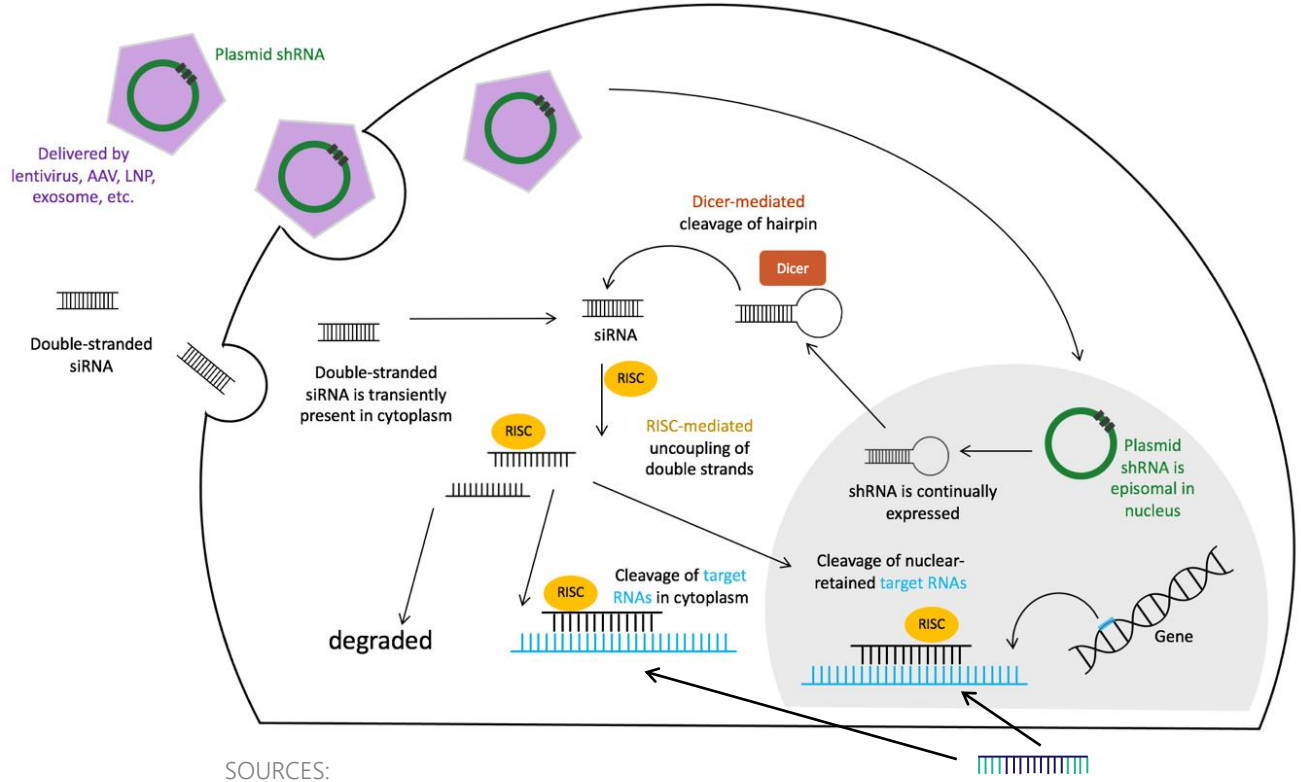
DNA sequencing is unlocking potential for therapies in genetic CNS medicines



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

SOURCE: Brooks et al., 2021, NINDS

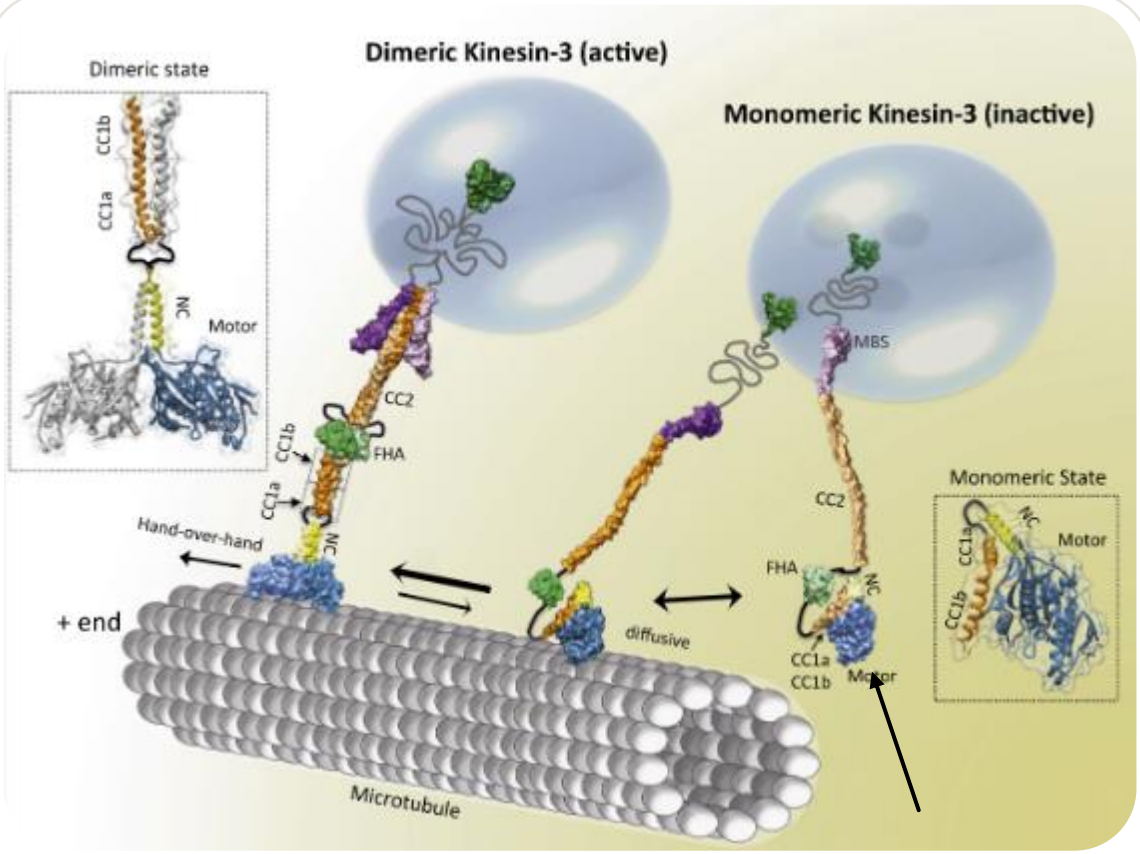
RNAi as a gene silencing therapy shows promise for disorders associated with gain-of-function mutations



SOURCES:
Robb, Brown et al. 2005, *Nat Struct Mol Biol*
Gagnon, Li et al. 2014, *Cell Rep*
Avivi, Mor et al. 2017, *Proc Natl Acad Sci U S A, Annu Rev Med*

Ovid seeks to reduce the amount of KIF1A variant protein

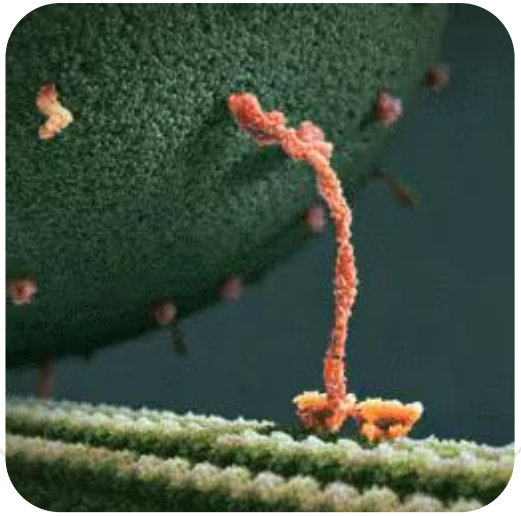
KAND is primarily an autosomal dominant, gain-of-function disorder with KIF1A mutations impacting the transport of synaptic vesicle precursors to the synapse



Auto-inhibited Form

SOURCE: Al-Bassam, et al. 2018.
www.pnas.org/cgi/doi/10.1073/pnas.1818758115

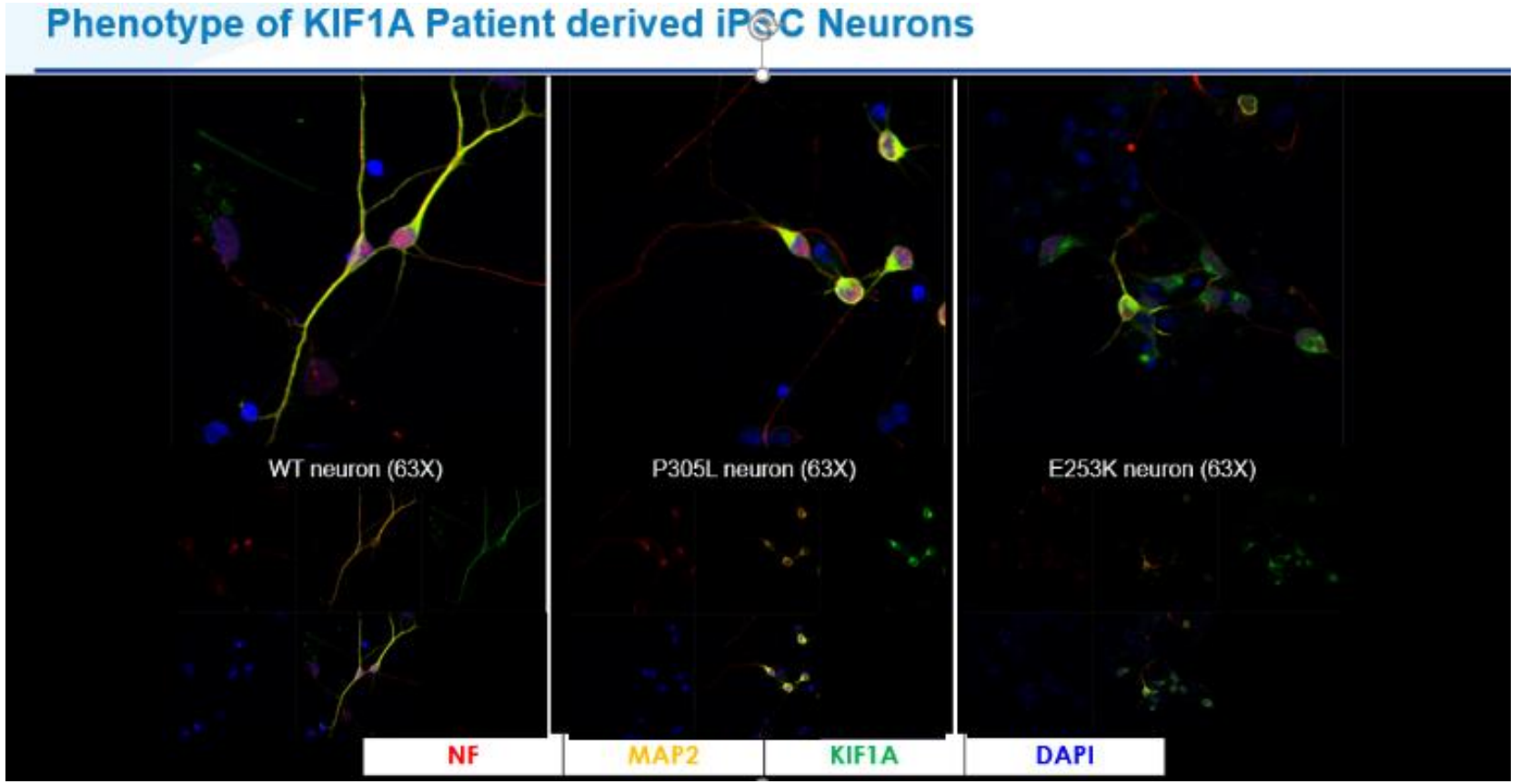
- Normally, KIF1A forms dimers, bind to synaptic vesicle precursors (SVPs) and transport cargo in a retrograde direction along microtubule filaments in neurons
- Mutant KIF1A proteins exert a dominant-negative effect and interfere with normal SVP transport
- When disrupted, patients do not maintain the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



SOURCE: Lieber, J. Life of the Cell (2006)

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

Pairing the best modality to disrupt variant protein



NF = Neurofilament MAP2 = Microtubule associated protein 2 KIF1a = KIF1A protein DAPI = nuclear stain

SOURCE: Research by Lia Boyle, Chung Lab

Molecular screening

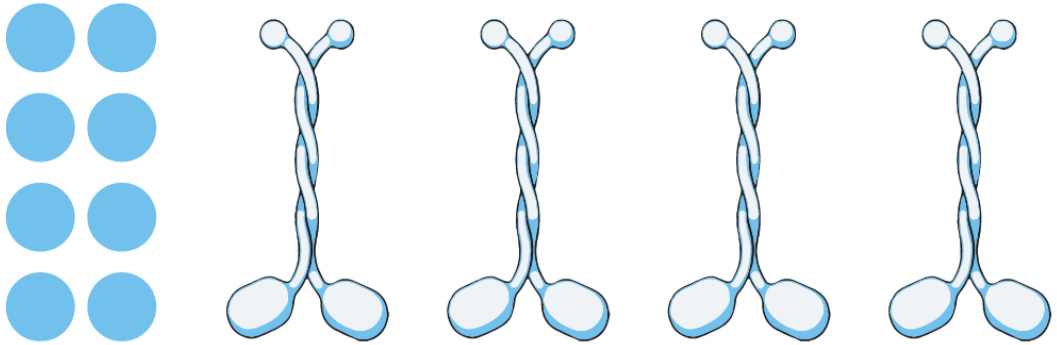
- Allele-specific qPCR

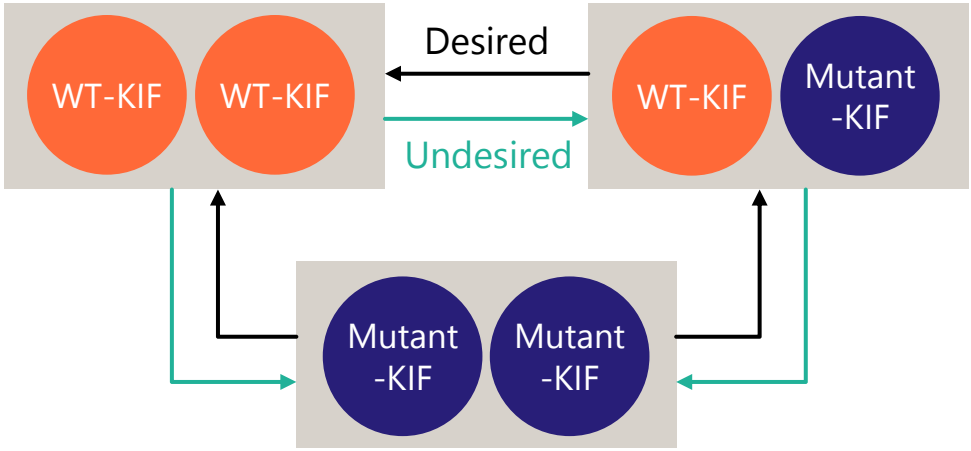
Phenotypic screening

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

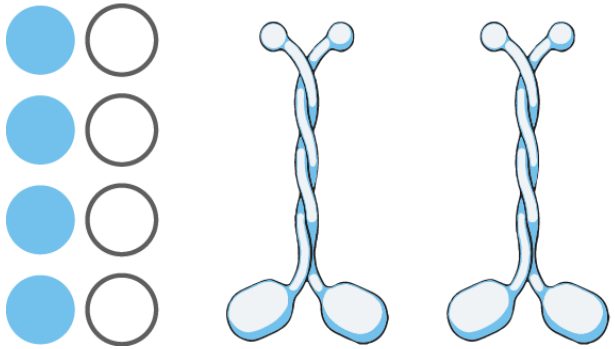
Missense variants result in more severe disease

Two normal alleles

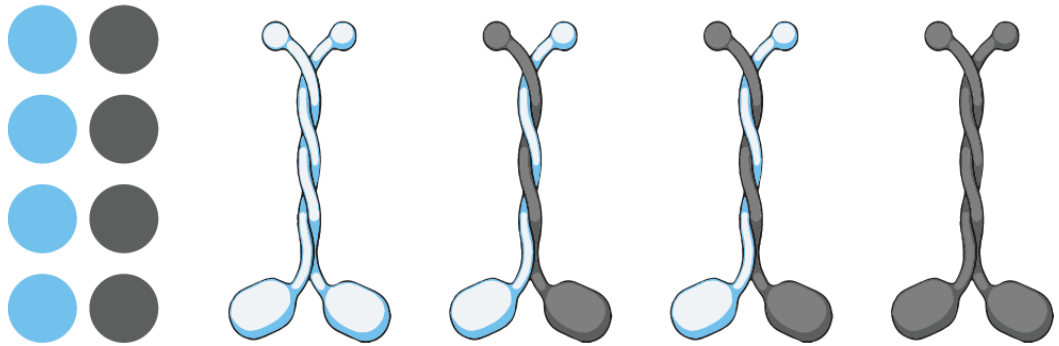




Nonsense 50%



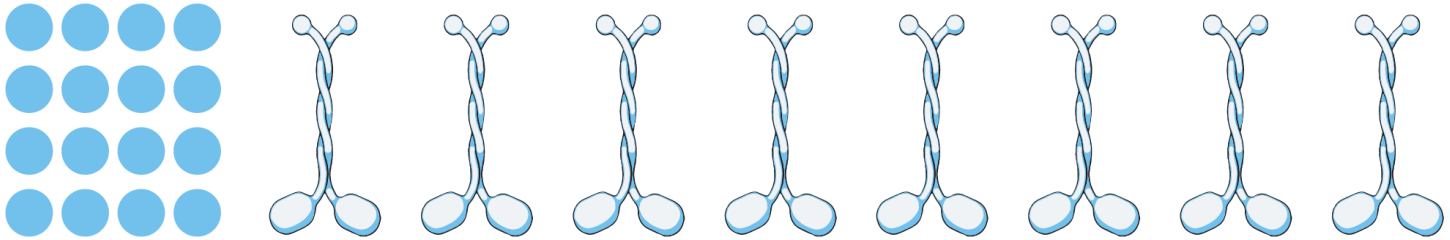
Missense 25% 50% 25%



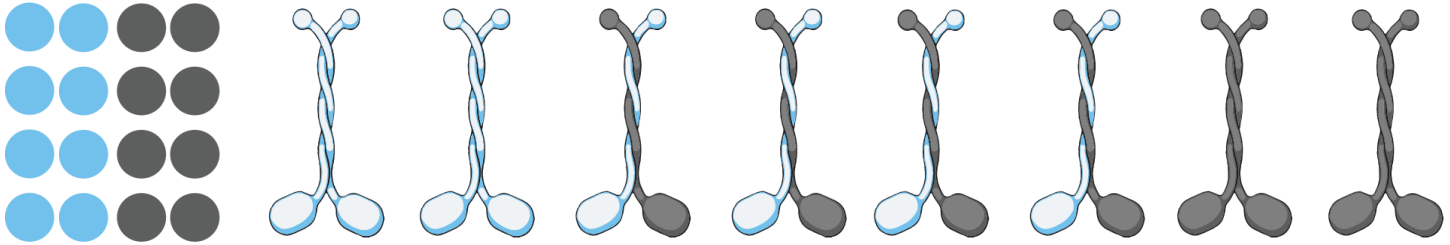
Lia Boyle, Chung Lab

Allele-specific knockdown as treatment for KAND

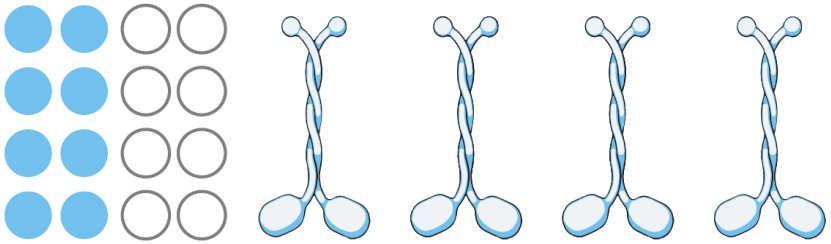
Ideal



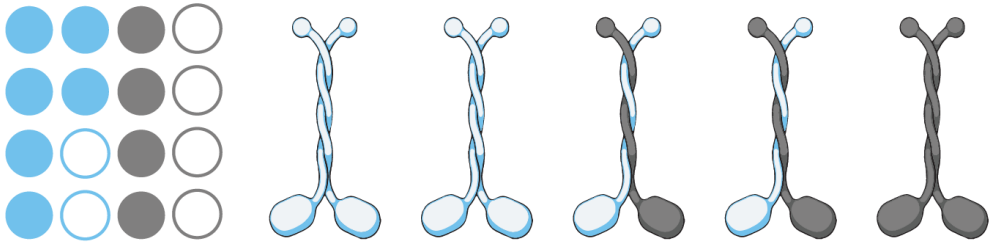
Heterozygous missense variants



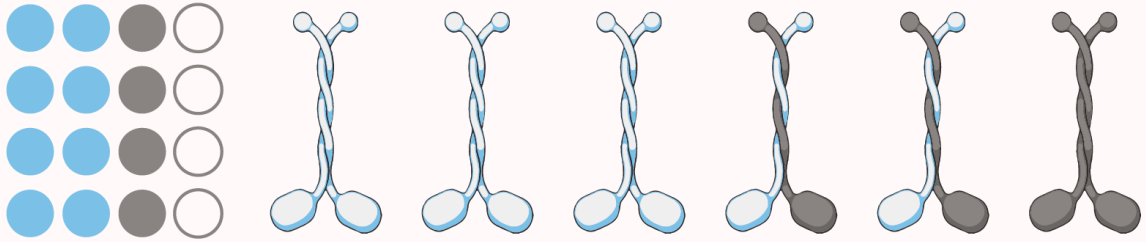
Allele-specific knockout



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



Partial knockdown of mutant
No reduction in wild type

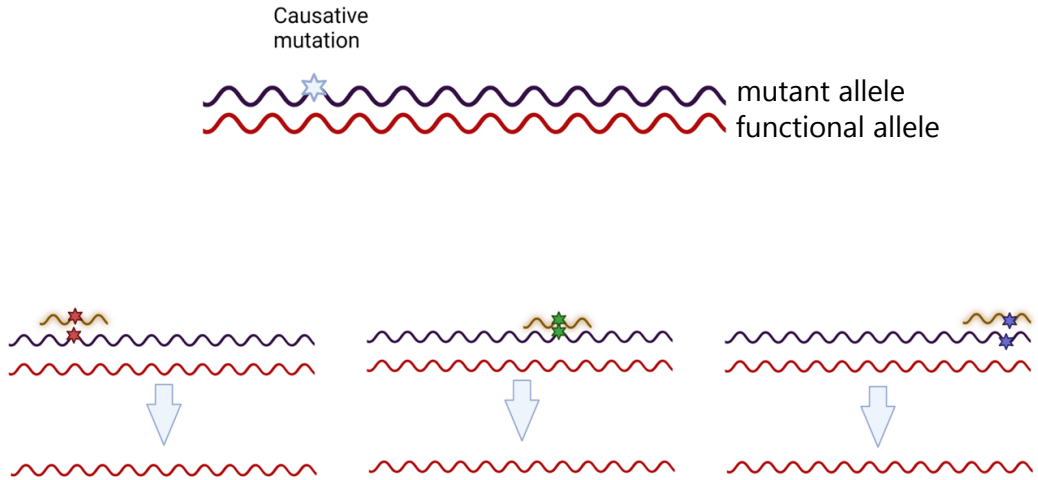


*Identified oligos that specifically reduce RNA from variant allele
*Continuing to investigate biology of delivery and functional rescue

KIF1A variant targeting approaches

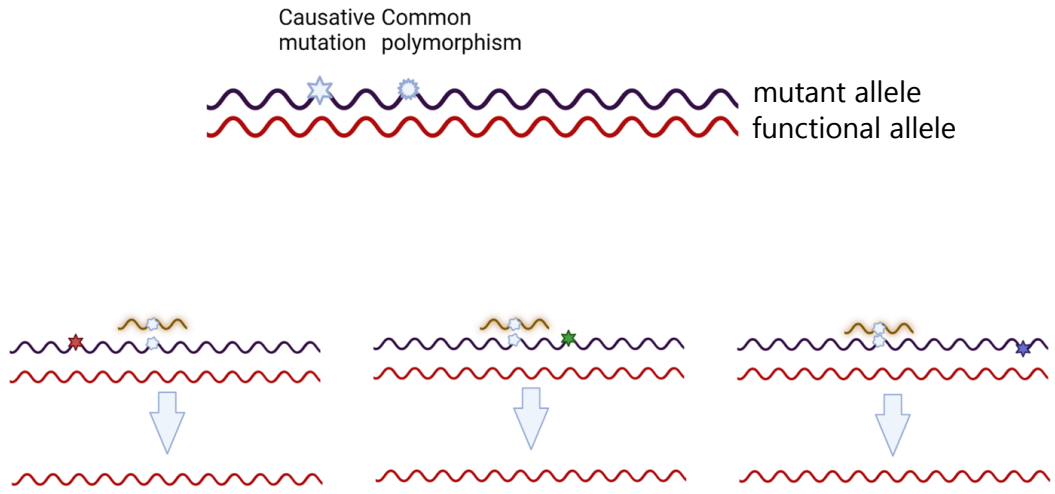
"Modality agnostic" (i.e. siRNA, shRNA, ASO)

One Oligo Per Variant



Proof of concept
Functional return in models

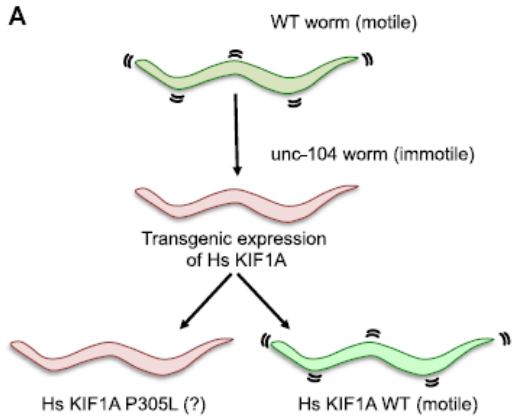
One Oligo Several Variants



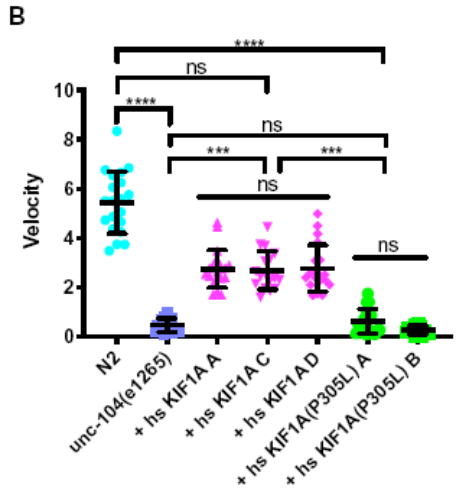
Targeting a SNP in *cis* with
several mutant variants as a "handle"

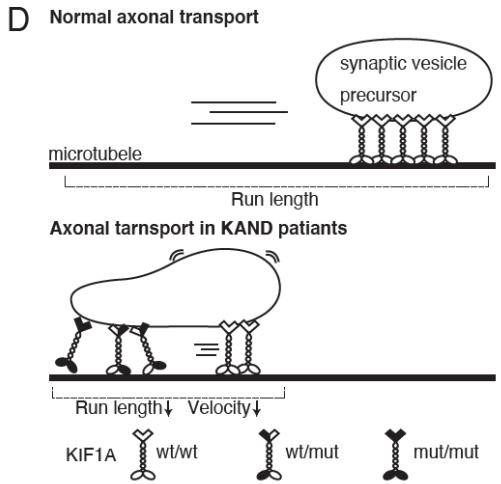
Charles Leduc, Chung Lab

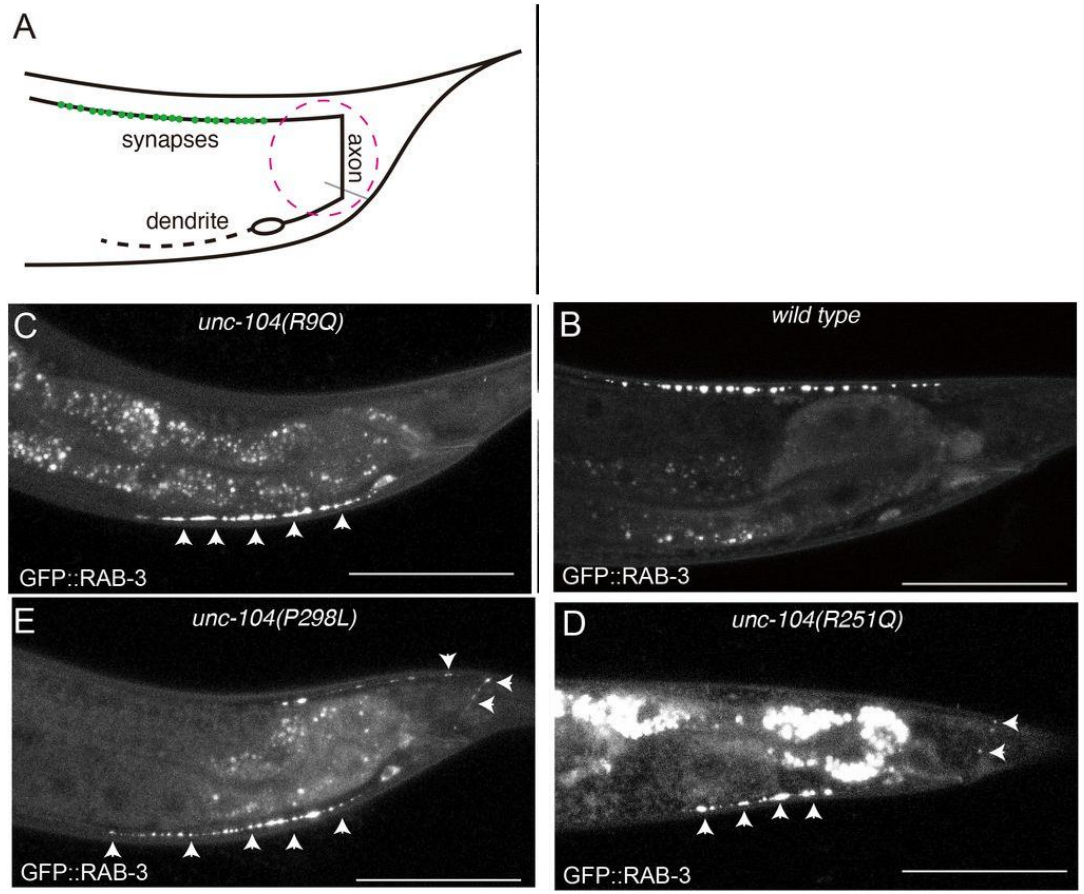
C.elegans as a model for KIF1A variant function



Lam *et al., Sci.* Adv. 2021; 7







SOURCE: Anazawa et al. *BioRxiv* 2021.07.22.453457

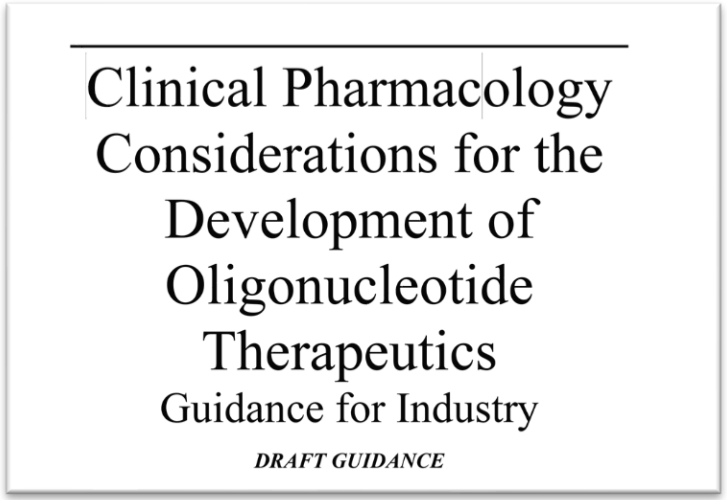
Learning from Advancements in Genetic Therapies

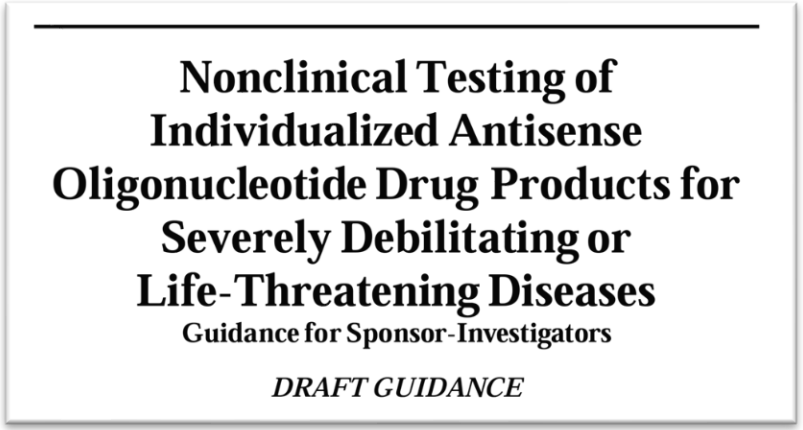
Bespoke Gene Therapies Consortium (BGTC)

- 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





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

Acknowledgements:

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- Charles Leduc
- Jiangyuan Hu
- Michael Zuccaro

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- Arne Gennerich

Ovid™ Therapeutics

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