Translating science into therapies for one or for many

Omid Karkouti, MS
Chief Operating Officer
omid@rarebase.org

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Patient organizations are the hub

- Engage families, strengthen patient community
- Build networks of disease area experts
- Disseminate findings to community
- Bridge learnings across researchers
- Awareness, outreach, and public education
- Fundraise

Patient organizations like KIF1A.org are emerging as research hubs
The R&D landscape is complicated

- Therapeutic discovery
- Preclinical efficacy
- Safety Pharm & Tox Studies
- cGMP manufacturing
- IND Submission
- Clinical trial recruitment
- Clinical trial

Models
Assays
Unbiased data
Biospecimens
Screens
Targets
Drug candidates

Retrospective clinical research
Prospective clinical endpoints/biomarkers
Patient organizations as biotech seeds

- Access to hundreds of labs and researchers ready to work on each disorder
- In-house, creative translational science team to develop therapeutic roadmap
- Ability to identify synergies with other disorders
- Ability to build networks of disease area experts
- Ability to create and distribute research materials at cost
- Fundraise for awareness, outreach, and public education
- Disseminate findings to community
- Bridge learnings across researchers
- Future revenue sharing and venture philanthropy to reinvest in research
- Cutting edge technology through biotech partnerships

The future we want to build together
Clinical features of KAND

Spectrum of symptoms
- Encephalopathy
- Neurodegeneration
- Epilepsy
- Autism
...

Spectrum of genetics
- Autosomal dominant
- Autosomal recessive
- Wide range of variants and severity
KIF1A deficient iPSC-neurons exhibit degenerative phenotype

The Kampmann lab at UCSF used CRISPR to knock down KIF1A as part of a CRISPR interference (CRISPRi) screen using human iPSC-neurons.

KIF1A deficient iPSCs exhibit less growth, KIF1A deficient neurons have impaired survival, shorter neurites, and fewer branches. [Blue= Decrease; Red= Increase]

Adapted from (Tian et al, Neuron, 2019).
Targeting KAND neurodegeneration

Rarebase identified a target relevant to KAND neurodegeneration and hereditary spastic paraplegias, and began in-house development of antisense oligonucleotides (ASOs) against this target in Q4 of 2020.

In March 2021 we partnered with KIF1A.org to further develop these potential therapies.

- **Target identification**
- **Novel ASO design and synthesis**
- **Validated assay for target**
  - **Q4 2020**

- **Neurodegeneration cell-based assay development**
- **KAND iPSC-neuron differentiation and phenotyping**
- **Optimize target knockdown**
  - **In progress**

- **Efficacy study in cell-based assay**
- **Lead optimization**
- **Planning further efficacy studies**
  - **Q3-Q4 2021**
KIF1A deficient iPSC neurons exhibit potential mitochondrial dysfunction

Mitochondria cytochrome C oxidase genes MT-CO1, MT-CO2, and MT-CO3 are upregulated in KIF1A-deficient neurons suggesting a link between KIF1A deficiency and mitochondrial dysfunction - a known mechanism of neurodegeneration.

Adapted from (Tian et al, Neuron, 2019).

Mitochondria dysfunction has been observed clinically in a pediatric PEHO syndrome patient with a heterozygous de novo mutation in KIF1A.

PEHO syndrome: KIF1A mutation and decreased activity of mitochondrial respiratory chain complex

Debopam Samanta a,*, Murat Gokden b (J. Clin Neurosci, 2018).
Investigating mitochondrial function in KIF1A deficient cells

- We plan to measure mitochondrial function in KAND patient-derived iPSC neurons using assays for cellular energy production, respiration, and reactive oxygen species.

- Depending on the dysfunction, we will determine whether compounds we’re investigating for mitochondrial disorders can rescue the bioenergetic phenotype and/or improve KIF1A-deficient neuron survival.

- Successful compounds may be further evaluated in additional KAND models, e.g. mouse studies.
Function is our screening and computational drug discovery platform

Prediction  Validation  Learning

Function is our CNS drug discovery platform that integrates the latest methods in stem cell biology, laboratory automation, next-generation sequencing, computational biology and machine learning.

To learn more, contact us at: function@rarebase.org
Screening for drugs and targets that upregulate gene expression

**Screening Pipeline A**

1. **Compound screen**
2. **Drug action**
   - Neurons
3. **Gene expression signatures**
4. **Computational pipeline**
5. **Efficacy + tox predictions**
Small molecule upregulation of KIF1A gene expression

Analysis of a pilot study of a small compound library in a neuronal cell line to identify drugs that upregulate KIF1A gene expression

Preliminary data require additional validation but suggest the potential for small molecule upregulation of gene expression

We intend to reproduce these data in KAND patient-derived iPSC neurons and will also perform larger scale screens

These methods may lead to additional potential drugs or drug targets, especially for haploinsufficient KAND cases

Redacted pending further validation in disease relevant context. To learn more, contact us at: function@rarebase.org
Summary and next steps

- We have partnered with KIF1A.org to develop ASOs targeting KAND neurodegeneration.

- We’re investigating additional paths to therapeutic discovery including:
  - Mitochondrial dysfunction
  - Upregulation of KIF1A gene expression
We're hiring: rarebase.org/careers

Research

Head of Computational Biology

- Full-time
- CA

Senior Scientist (Neuroscience Drug Discovery)

- Full-time
- US

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Thank you from our dedicated team of patients, advocates, scientists, and engineers

Onno Faber  
Co-founder and  
CEO

Omid Karkouti  
Co-founder and  
COO

Hayley Brooks  
Chief of Staff

Elizabeth Iorns,  
PhD  
Scientific Advisor

Nicole Perfito, PhD  
Director of Research  
Operations

Lynsey Chediak  
Head of Partnerships

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