Rarebase

Translating science into therapies for one or for many

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

Rarebase

Engage families, strengthen patient community

Patient organizations are the hub

Awareness, outreach, and public education

Fundraise

Build networks of disease area experts

Bridge learnings across researchers

Disseminate findings to community

Patient organizations like KIF1A.org are emerging as research hubs

Rarebase

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

Rarebase

Patient organizations as biotech seeds

Engage families, strengthen patient community

Access to hundreds of labs and researchers ready to work on each disorder

Awareness, outreach, and public education

In-house, creative translational science team to develop therapeutic roadmap

Fundraise

Cutting edge technology through biotech partnerships

Build networks of disease area experts

Ability to identify synergies with other disorders

Bridge learnings across researchers

Disseminate findings to community

Create and distribute research materials at cost

Future revenue sharing and venture philanthropy to reinvest in research

The future we want to build together

Rarebase

Clinical features of KAND

Spectrum of symptoms

- Encephalopathy
- Neurodegeneration
- Epilepsy
- Autism

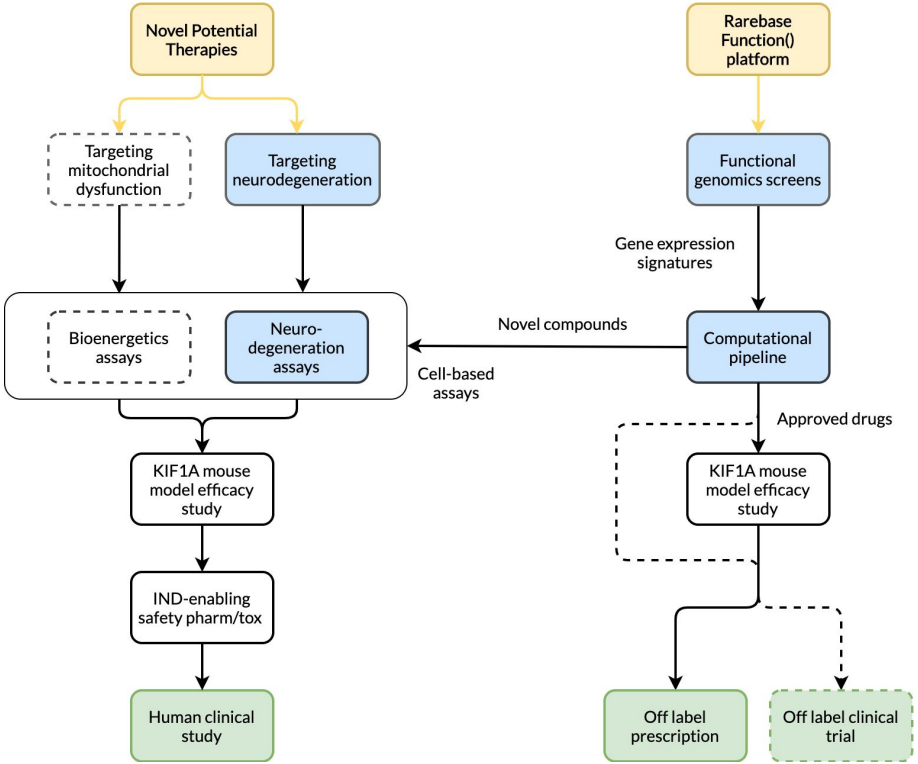
...

Spectrum of genetics

- Autosomal dominant
- Autosomal recessive
- Wide range of variants and severity

Rarebase

Therapeutic Discovery Roadmap

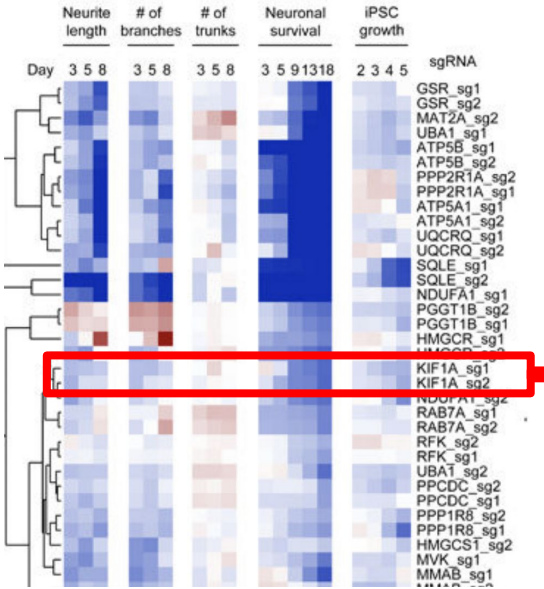


KIF1A deficient iPSC-neurons exhibit degenerative phenotype

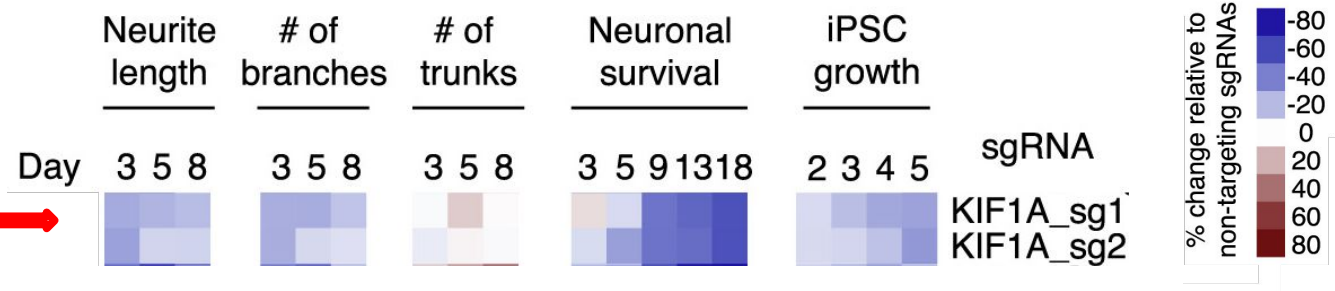
CRISPR Interference-Based Platform for Multimodal Genetic Screens in Human iPSC-Derived Neurons

Ruilin Tian,[1,2,3,7] Mariam A. Gachechiladze,[4,7] Connor H. Ludwig,[1,3,7] Matthew T. Laurie,[1] Jason Y. Hong,[1,3] Diane Nathaniel,[1,3] Anika V. Prabhu,[5] Michael S. Fernandopulle,[4] Rajan Patel,[4] Mehrnoosh Abshari,[6] Michael E. Ward,[4,*] and Martin Kampmann[1,3,8,*]

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).

Rarebase

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

Rarebase

KIF1A deficient iPSC neurons exhibit potential mitochondrial dysfunction

	KIF1A
MT-ND4	1.21290136
MT-CO3	1.06459374
MT-CO1	1.02520124
MT-CO2	1.00932
PERP	0.942737
FAU	0.86150456
GPATCH4	0.79668218
PSME2	0.79099896

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 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.

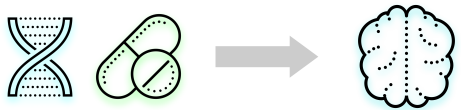
PEHO syndrome: KIF1A mutation and decreased activity of mitochondrial respiratory chain complex

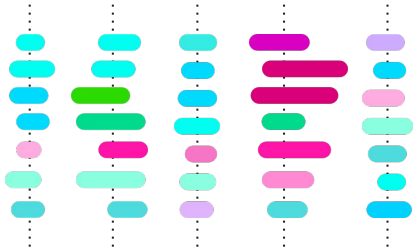
Debopam Samanta [a,*], Murat Gokden [b] (J. Clin Neurosci, 2018).

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



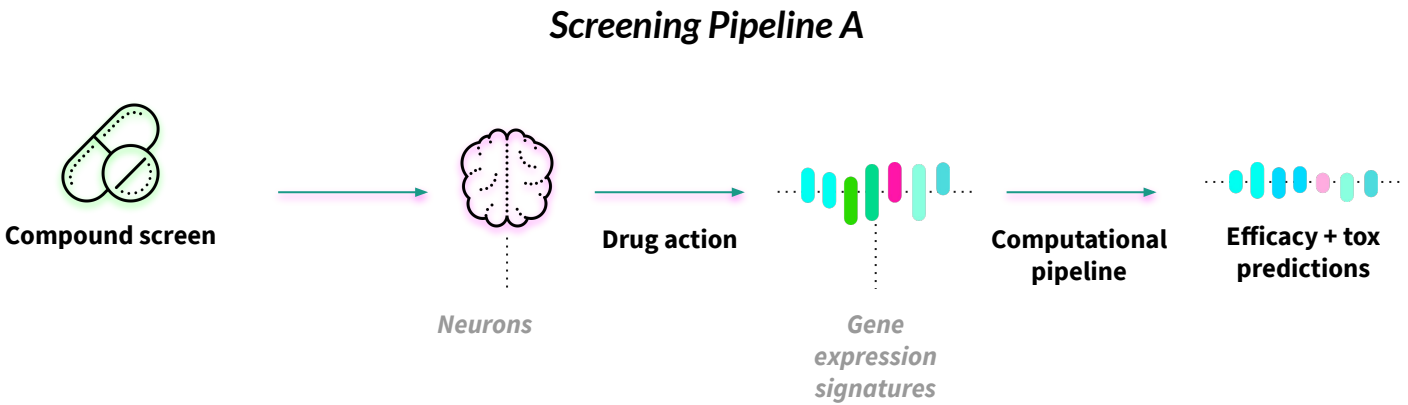


Prediction ***Validation*** ***Learning***

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.

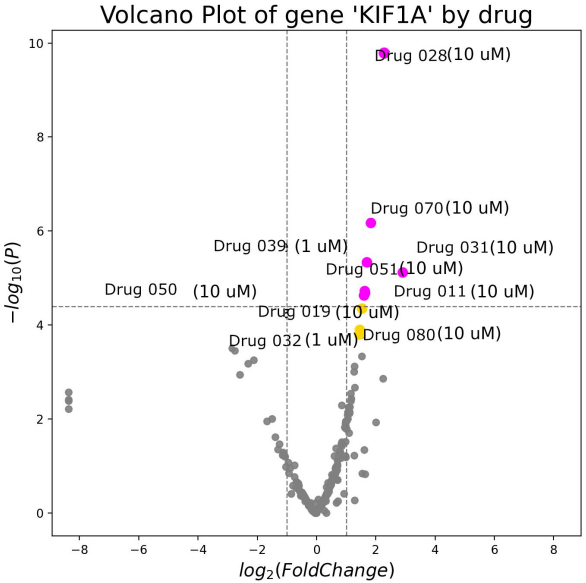
To learn more, contact us at: **function@rarebase.org**

Screening for drugs and targets that upregulate gene expression



Rarebase function

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**

Rarebase

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

View job

Senior Scientist (Neuroscience Drug Discovery)

Full-time US

View job

[July 2021]

Rarebase

Blue Yard

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

Onno Faber
Co-founder and CEO

AllStripes

Omid Karkouti
Co-founder and COO

perception BIOSYSTEMS

Notable

Baylor College of Medicine

UC San Diego

Hayley Brooks
Chief of Staff

Chan Zuckerberg Initiative

23andMe

BROAD INSTITUTE

Elizabeth Iorns, PhD
Scientific Advisor

Science EXCHANGE

UNIVERSITY OF MIAMI

ICR

Nicole Perfito, PhD
Director of Research Operations

Science EXCHANGE

UNIVERSITY of WASHINGTON

Berkeley UNIVERSITY OF CALIFORNIA

Lynsey Chediak
Head of Partnerships

WORLD ECONOMIC FORUM

HOUSE OF COMMONS