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PATH TO TREATMENT

Two-Year Plan to First Clinical Trial

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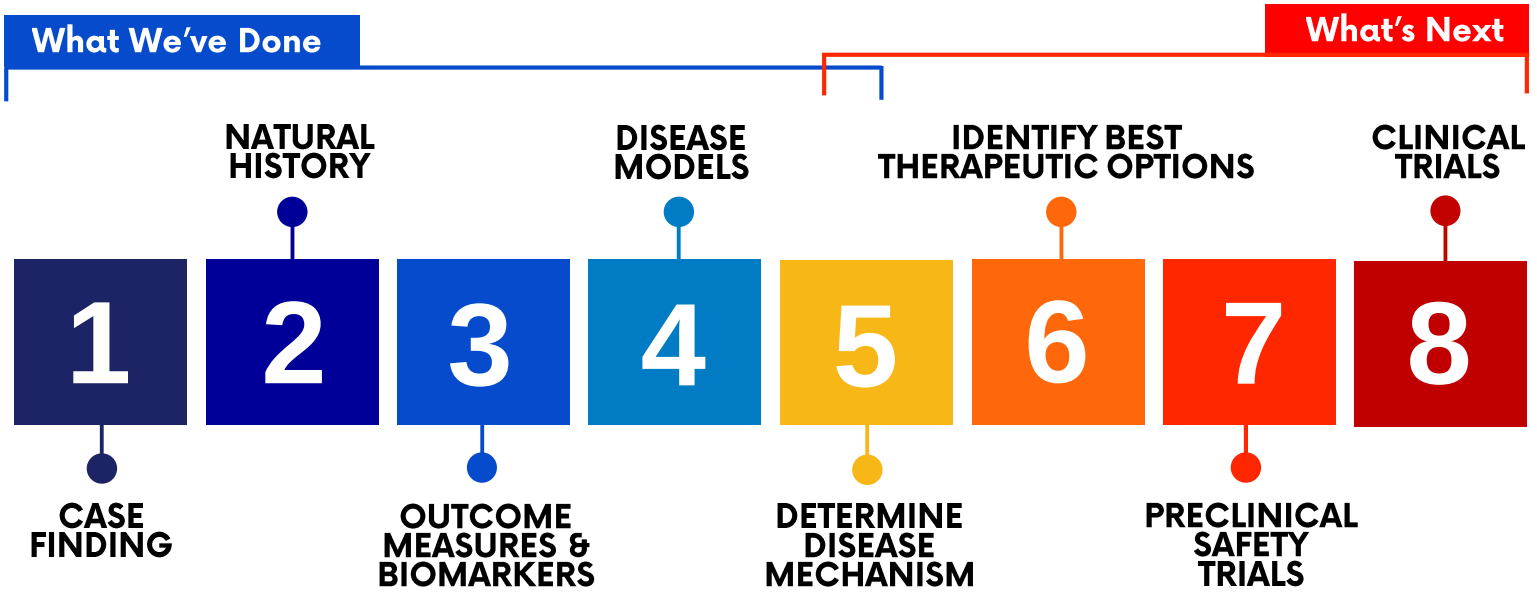
PATH TO TREATMENT

KIF1A.ORG is a parent-led organization established in 2017 to launch the world's first translational research program dedicated to discovering treatment for people affected by KIF1A Associated Neurological Disorder (KAND). There is no cure or treatment for this neurodegenerative disorder. Yet.

Our organization supports researchers who engage in collaborative and translational work to rapidly discover treatment for *this generation* of KAND patients. We have made tangible progress over the last three years, but time is running out. 2020 is a transformational year for KIF1A with a clear path to clinical trials.

This **Path to Treatment** outlines our immediate therapeutic strategy with defined objectives and resources needed to bring treatment options to families affected by KAND.



Last updated January 27, 2020

1 CASE FINDING

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The first step toward treatment: identify the disorder and find patients.

2011
First KIF1A patient identified

2016
Dr. Wendy Chung of Chung Lab (Columbia University, NYC) sees her first KIF1A patient, Susannah

Susannah's family starts building KIF1A.ORG

2017
Chung Lab launches world's first pre-clinical research program for KIF1A Associated Neurological Disorder (KAND) & becomes a center of excellence

Present
200–300 known KAND patients today

Tens of thousands likely misdiagnosed or undiagnosed

2 NATURAL HISTORY

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In order to develop KAND treatment, we must understand the disorder and create a longitudinal clinical picture of the disease. Our natural history study (NHS) gathers patient information to track how the disorder develops over time without treatment.

Chung Lab manages the world's only KIF1A NHS. In this comprehensive, **longitudinal** study, patient data is continuously collected from enrolled families to track how KIF1A mutations affect patients' development & health over time.

Information collected includes genetic test results, developmental & medical history, symptomatic treatment, MRI, EEG, medical records, & patient/caregiver-reported data. **KIF1A families are highly engaged in the NHS.**

The KIF1A NHS has **150+** enrolled patients & continues to enroll newly diagnosed families. We have learned much about how KIF1A affects patients since starting the NHS in 2017. For the latest information, visit **kif1a.org/nhs.**

3 OUTCOME MEASURES & BIOMARKERS

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Our goal is to create treatment that is safe, effective, and meaningful to families.

OUTCOME MEASURES

What are meaningful therapeutic changes for KAND families?

- Seizure reduction?
- Improved cognition?
- Reduced spasticity?

BIOMARKERS

What can we measure in the body to evaluate change from baseline?

- Brain waves through EEGs?
- Cerebrospinal fluid?
- Neuron density/function?

What's Next

KAND families play a crucial role in research & development by providing valuable input on meaningful outcome measures. Our active community regularly provides samples needed to build a robust KIF1A biobank at Chung Lab. These samples are freely accessible to members of the scientific community, including biotech. Developing early biomarkers & outcome measures readies our community for clinical trials with appropriate endpoints.

4 DISEASE MODELS

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KAND disease models allow researchers to understand the mechanism of KIF1A, mirror human disease characteristics (phenotypes) and test potential therapeutics for safety & efficacy.

iPS Cells

Induced pluripotent stem cells have been generated from blood samples donated by KIF1A families, & are being differentiated into nerve cells.

Organoids

Researchers can also produce miniature 3D brains that closely resemble full-size brains of KIF1A patients.

Mouse Models

Mouse models with KIF1A mutations have been developed by The Jackson Laboratory & Chung Lab. These animal models are available to the scientific community.

What's Next

With a diverse & expanding resource of KIF1A models, researchers are understanding more about the disease. These tools allow researchers to test existing compounds (medicines) & new therapeutics in the lab before starting clinical trials in humans.

5 DETERMINE DISEASE MECHANISM

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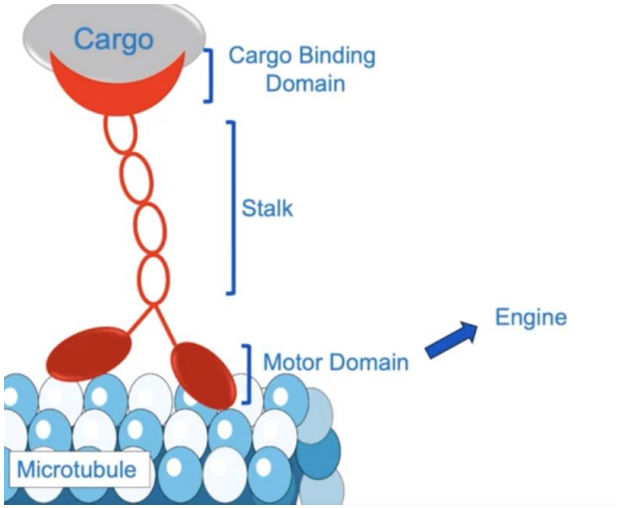
Identifying patients, expanding our Natural History, understanding meaningful outcome measures, and creating disease models allows researchers to determine the exact cause of disease. That "exact cause" is referred to as *Disease Mechanism*.



Source: Dominique Lessard, Berger Lab at University of Vermont, *What Is KIF1A? A Basic Science Explanation for KIF1A Families*

Scientists believe KAND is caused by dominant negative mutations in KIF1A. This rare mechanism of disease means mutations in KIF1A damage the protein encoded in the gene. This damaging effect prevents healthy function of the KIF1A protein, a protein that is vital for brain & nerve function.

For a basic science introduction to KIF1A, visit kif1a.org/what-is-kif1a.

6 IDENTIFY BEST THERAPEUTIC OPTIONS

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Three therapeutic approaches, or *modalities*, are the focus of our pipeline: small molecule, gene therapy, and antisense oligonucleotide therapy (ASO). Our strategy is to pursue multiple approaches in parallel, and rapidly bring treatments to the clinic in 2021.

Small Molecules include most drugs on the market today. In 2020, KIF1A researchers will conduct high-throughput drug screening, using technology to rapidly test thousands of compounds & identify possible drug candidates for KAND. This includes repurposing existing drugs with an established safety record that have already been developed to treat other diseases. This repurposing can save time & money in the therapeutic development process.

Gene therapy is the process of replacing defective genes with healthy ones, adding new genes to help the body fight or treat disease, or deactivating problem genes. Learn more from the FDA. There are several gene therapy approaches to consider for KAND, like replacing defective KIF1A genes with healthy copies, or recruiting a different gene or pathway to compensate for the dysfunctional KIF1A protein caused by mutations in the gene.

ASOs or antisense oligonucleotides are synthetic strands of nucleic acids that can bind to messenger RNA (instructions for protein production) to alter a gene's expression. For example, if a KAND patient has a healthy copy of KIF1A & a mutated copy of KIF1A (heterozygous), an ASO could reduce, or "knock down," disease-causing proteins without interfering with the body's healthy copy of KIF1A.

7 PRECLINICAL SAFETY TRIALS

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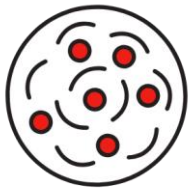
Before we start clinical trials in humans, we'll test our best therapeutic options in the lab to evaluate safety. Preclinical research takes place *in vitro* and *in vivo*.



In Vitro

Latin for "in glass"—think of experiments taking place in petri dishes or test tubes using organism components like iPS cells.

In Vivo

Latin for "within the living"—think of experiments with animals like mice living with KIF1A mutations.

Preclinical trails allow us to make informed decisions before designing clinical trials for humans. How might the drug affect the body? Does the drug have any toxic effects? Does the drug provide therapeutic benefit? What is a safe dosing strategy? Regulatory agencies (FDA) will not allow clinical trials in humans without strong preclinical data.

8 CLINICAL TRIAL

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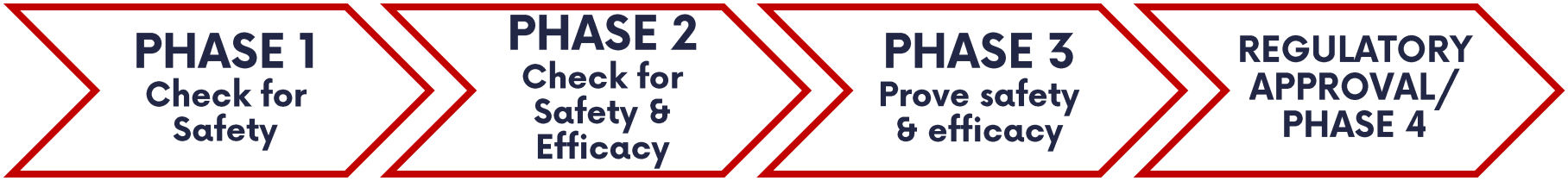
Once we have a therapeutic target with strong safety and efficacy data from preclinical trials, we'll work closely with relevant regulatory agencies to move forward with human clinical trials. Clinical trials are generally broken into the following stages:



KAND families have a significant unmet therapeutic need.

Our objective is to create global clinical trials and bring treatment to this generation of KAND patients. With increased resources, KIF1A researchers & clinicians will have the capacity to pursue, research & develop treatments for KAND before we lose any more children to this degenerative disease.

WE HAVE A BOLD AND ACHIEVABLE PLAN TO MAKE TREATMENT A REALITY IN 2021.

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Together with our research partners and clinicians, KIF1A.ORG is positioned to translate our robust preclinical work into real treatment. Visit our Tools for Development page at KIF1A.ORG for details. Every day we go without KAND treatment our children lose skills and abilities they work so hard to gain. Some children never develop skills so many us take for granted. Together, we can #StopTheClock on KAND.

KAND CLINICAL FUNDS NEEDED TODAY

Year One

Required staff

2 Research nurses:	$260,000
2 Research assistants:	$170,000
2 PhD research fellows:	$160,000
MD research fellow:	$150,000
Bioinformatics PhD fellow:	$80,000
Administrative assistant:	$80,000
Research administrator:	$55,000

Research infrastructure

Computer server space:	$80,000
Patient assistance:	$50,000
Travel costs:	$50,000
Biorepository:	$30,000
Clinical/disease database:	$25,000
Total	**$1,190,000**

Year Two

Required staff & infrastructure

Continue Year One resources	$1,190,000
Assistant professor:	$200,000
Wet space (300 Sq Ft):	$40,000
Dry space (500 Sq Ft):	$40,000

KIF1A mutation cell line & screening

High throughput drug screen:	$1,000,000
2 Research scientists:	$300,000
Gene editing postdoc fellow:	$90,000
Maintain mouse colony:	$50,000
Mouse model (3 generations):	$45,000
Cell-based disease models (3 mutations):	$27,000
Reagents/Labware:	$20,000
Total	**$3,002,000**

LEARN MORE AND JOIN OUR MISSION AT KIF1A.ORG

Contact: impact@kif1a.org