murdoch children's research institute

KAND Research Update 2024
KIF1A.ORG

Thank you

We extend our heartfelt gratitude to KIF1A.ORG for your generous support in advancing high-throughput targeted screening of repurposed FDA-approved drugs to address KIF1A defects. Your contribution is invaluable in our quest to find effective solutions and improve countless lives.

Your gift of $126,097.61US provided the following.

- Validation of the high-throughput technique
- Salary of CIA - Dr Simran Kaur
- Reagents and consumables

It is our great pleasure to share the following highlights and recent accomplishments of our study, made possible by your support.

What is KIF1A and KAND?

The KIF1A gene provides instructions for producing a protein crucial for transporting materials within cells, particularly in neurons. This protein helps move neurotransmitters and other crucial substances along neurons, ensuring proper brain function.

Disease causing changes (variants) in the KIF1A gene can cause KIF1A-Associated Neurological Disorder (KAND), a rare genetic condition. KAND is characterised by developmental delays, severe intellectual disabilities, treatment resistant seizures, blindness, wheelchair dependency, and other neurological impairments, all resulting from the disrupted function of the KIF1A protein and impaired communication between neurons in the brain.

Currently there is no cure for KAND, and existing treatments are nonspecific and incomplete, resulting in a huge burden on affected families.

Murdoch Children's Research Institute (MCRI) is at the forefront of research aimed at accelerating the diagnosis and treatment of KAND. We are leveraging advanced genetic technologies to identify KIF1A variants more rapidly and accurately. By doing so, we aim to provide earlier and more precise diagnoses for affected individuals, enabling timely interventions and better management of the disorder.

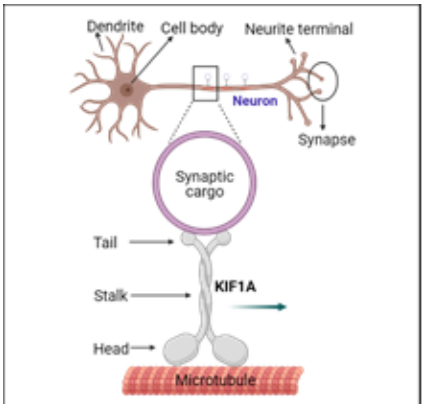


Fig 3: Schematic showing KIF1A transporting cargo along microtubules in neurons. Created with Biorender.com.

Exploring small molecule-based therapies

Although the structure and function of KIF1A are well-understood, there are currently no specific therapeutic agents available, with only symptomatic management as an option. Additionally, there were no active drug screening initiatives for KIF1A defects prior to our study.

Traditional drug discovery and development are slow and costly processes. To overcome these challenges, we adopted a "drug repurposing" strategy, focusing on testing existing FDA-approved drug libraries using advanced high-speed tests on disease-mimicking COS-7 cells developed in our lab.

Thanks to your generous support, we have been able to implement a high-throughput drug screening program that provides a cost- and time-efficient method for identifying targeted treatments. We hypothesise that this approach will uncover small molecules capable of improving the function of the defective KIF1A molecular motor in our model of KIF1A disorder.

The outcome of this research has the potential to have a critical impact on the affected children and their families. Notably, pathogenic KIF1A variants cause a range of progressive neurological diseases, making it highly likely that the therapeutic candidates identified through our high-throughput screening platform could have broader clinical applications.

Key investigators

- Dr Simran Kaur
- Dr Alejandro Hidalgo-Gonzalez
- A/Prof Wendy Gold
- Kelley Gao
- Prof John Christodoulou
- Dr. Henry Beetham
- Tim Sikora

Dr. Simran Kaur, an early career researcher at MCRI, is leading Australia's first KAND research program in collaboration with national and international collaborators including KIF1A.ORG to accelerate research into KAND. The team hopes to be able to develop effective treatments by better understanding disease pathophysiology, identifying disease biomarkers and therapeutic targets, developing novel therapeutics and KAND modelling using induced pluripotent stem cell models. These advances will improve long-term health outcomes for this vulnerable group of children and may potentially offer unprecedented and life-changing opportunities for individuals and families affected by KAND.

Objectives and Progress

Complete a high-throughput FDA-approved drug library screen using our COS-7 based cell model to identify hit compounds and validate key molecules in SH-SY5Y cell models.

We have developed a customised model using CV-1 cells (a type of cell line) that either express the normal (wild type) or mutated (variant) version of the KIF1A protein. We used this model to study several harmful KIF1A variants found in KAND patients and found a significant issue with how materials are transported inside cells.

Our team has developed a high-throughput screening method using the state-of-the-art Stafford Fox Drug Discovery Facility at MCRI. This approach evaluates small molecules (potential drugs) for their ability to enhance KIF1A expression, which could help counteract harmful mutations. We conducted two initial rounds of screening with cell lines that consistently express KIF1A and tested a library of 4,222 FDA-approved drugs from Compound Australia (Griffith University).

The screening process identified 8 different chemical compounds that target the same biological process in cells and were effective in both of our tests. They increased the production of a specific protein, KIF1A, in the cells, with higher amounts of the compound leading to greater protein production. These drugs have potential as treatments for KAND.

1. **Test existing kinesin modulators to examine their potential effect on KIF1A motor domain using our COS-7 based cell model**

Kadakkuzha et al. (2014) published results from tests on several chemicals to determine their effects on a motor protein called KIF5B. Since KIF1A and KIF5B are similar, we tried the same chemicals on KIF1A. However, these chemicals did not have a noticeable effect on KIF1A.

2. **Validate the selected hit compounds in our KIF1A patient-specific iPSC-derived neuronal cell models.**

We further tested the promising compounds on CV-1 cells at MCRI to fine-tune their concentrations before moving on to a different KAND disease model. Recent advancements in stem cell technology have led to the creation of brain organoids, which help us study early brain development and specific brain issues in patients. These organoids, made from Induced Pluripotent Stem Cells (iPSCs), allow us to test how the compounds affect brain function. In collaboration with the Children's Medical Research Institute (CMRI), we are treating these brain organoids with the promising compounds for 48 hours to see how they impact their function.

3. **Additional key highlights**

The generous funding from KIF1A.ORG has enabled Dr. Simran Kaur to establish Australia's first KAND research program at MCRI in collaboration with several partners. At MCRI, Dr. Kaur leads a team of researchers investigating projects aiming for further understanding of KAND (2 Research Assistant, 2 Honours students and 1 PhD student).

Achievements and discoveries

As a team, we are committed to sharing the results of our research with the scientific community, participants, and the broader public. We aim to extend the impact of our work through published papers, with three publications currently in progress. Additionally, we were grateful to be invited to present our recent findings at several global conferences and symposiums, including:

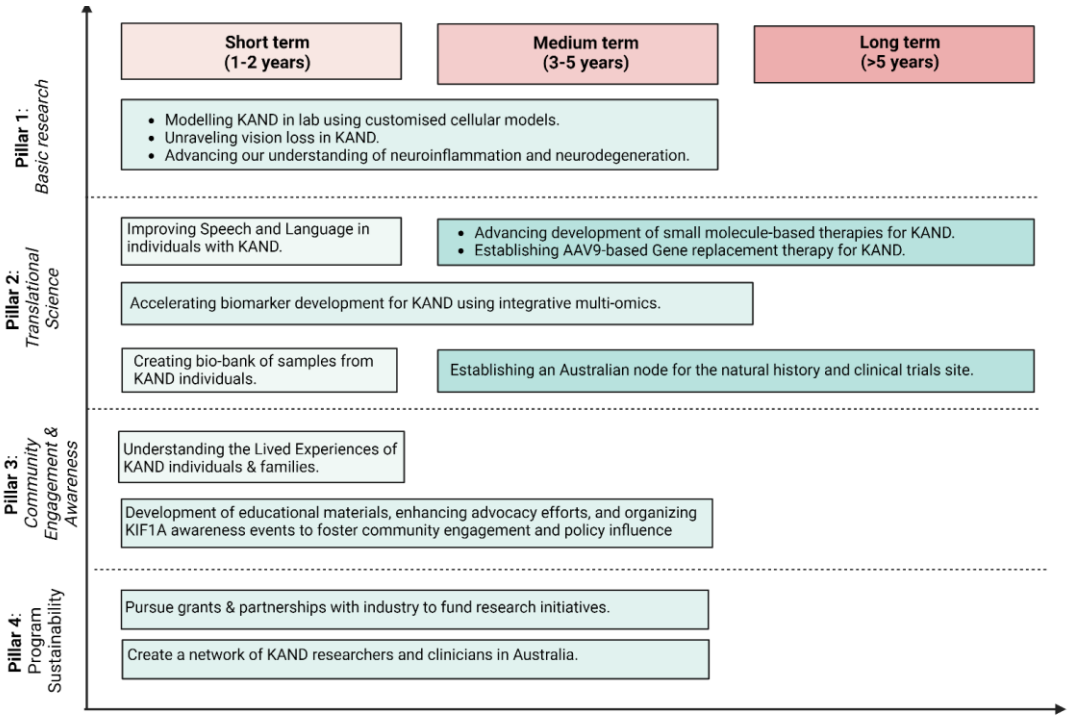
- 2023 KAND Family & Scientific Engagement Conference (Invited speaker).
- 2023 International Congress of Genetics and Genomics (Poster presentation).
- 2023 Australasian Society for Stem Cell Research (Poster presentation).
- 2023 MCRI Neurodevelopment Flagship seminar (Invited speaker).
- 2023 MCRI International Review Meeting (Invited speaker).
- 2022 MCRI Postdoc Symposium (Office of Research Award for best multidisciplinary research project)
- 2022 KAND Family & Scientific Engagement Conference.
- 2022 MCRI Inaugural Postdoc Symposium (Innovation Award for best presentation).
- 2020 Human Genetics Society of Australasia (HGSA).

Grants and Awards (in AUD)

- KIF1A.org Philanthropic Funding: 1 year (2021: 175,234.79)
- 2021 National Health and Medical Research Council (NHMRC) Ideas grant: 3 years (2022-2025; $776,019.50).
- MCRI Innovation Fund: 1 year (2023; $25,000)
- MCRI Career Interruption Award: 3.5 months (2022; $15,000)
- Early Career Academic Conference Support Scheme, University of Melbourne (2023; $3,998)
- KIF1A.ORG Travel Award (2023; USD1600)
- Human Genetics Society of Australasia Travel Award (2021; $1,535)
- Faculty of Medicine, Dentistry and Health Sciences Award for Excellence in Engagement-Partnerships (with KIF1A.org), University of Melbourne (2022; $5,000).
- MCRI Staff Awards for Inspiring Others (2023)

Next steps

Dr. Kaur is dedicated to expanding the KAND research program at MCRI, driven by four foundational pillars: basic science, translational science, community engagement and awareness and program sustainability. Her vision is to co-design and advance this program in close partnership with KAND families, ensuring their voices are at the heart of every initiative.



Pillar 1: Basic Science

Project 1: Modelling epilepsy in KAND using customised cellular models.

Project 2: Unravelling vision loss in KAND: Insights from mouse models and brain-retinal organoids for identifying therapeutic pathways.

Project 3: Advancing our understanding of neuroinflammation and neurodegeneration in KAND using human tissue and iPSC derived cellular models.

Pillar 2: Translational Science

Project 1: Advancing development of small molecule-based therapies for KAND.

Project 2: Establishing AAV9-based Gene replacement therapy for KAND.

Project 3: Accelerating biomarker development for KAND using a novel integrative multi-omics approach.

Project 4: Improving Speech and Language in individuals with KAND.

Project 5: Establishing an Australian node for the natural history of KAND and clinical trials site for KAND therapeutics.

Pillar 3: Community Engagement and Awareness

Project 1: Understanding the Lived Experiences of Individuals and Families Affected by KIF1A-Associated Neurological Disorders: A Qualitative Approach.

Project 2: Accelerating the development of educational materials, enhancing advocacy efforts, and organising KIF1A awareness events to foster community engagement and policy influence.

Pillar 4: Program Sustainability

A key focus will be ensuring the sustainability of the research program. To continue with this ambitious agenda, securing funding is essential. Dr. Kaur's current salary is covered by an NHMRC grant that expires in May 2025, making it a top priority to secure ongoing funding for her role. Additional funding will also be needed for additional projects. To maintain long-term viability, the team will actively pursue grant opportunities and seek philanthropic support to advance research into KAND.

Your support has been instrumental in advancing this groundbreaking research. We are deeply grateful for your contribution, which has brought us closer to finding effective treatments for those affected by KIF1A defects.

Please do not hesitate to contact us should you require any further information or have any questions.

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