**Please nominate 1 category that best fits your submitted abstract:**

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| Paediatric and/or congenital diseases  Maternal and/or prenatal health  Cardiometabolic diseases  Chronic diseases  Healthy aging  Cancer  Neurodegenerative diseases  Public health  Other |

**Please nominate 2-5 subject areas relevant to your submitted abstract:**

|  |  |
| --- | --- |
| Aged care  Allied health  Animal models  Biochemistry  Bioinformatics  Biomarker research  Biotechnology  Cardiovascular research  Cancer  Cell biology  Clinical research  Commercialisation  Computational biology and/or statistics  Consumer advocacy  Dentistry  Developmental biology  Drug discovery  Drug target identification and validation  Education and training  Endocrinology  Environment  Epidemiology  Genetic counselling  Genetics, epigenetic or small RNAs  Healthcare | Health economics  Health policy  Health promotion  Imaging and computing  Immunology  Indigenous health  Industry  Invisible illnesses  Medicinal chemistry  Microbiology  Molecular biology  Neuroscience  Nutrition  Pain management  Pathology  Personalised Medicine  Rare diseases  Physiology  Psychology  Public health  Reproductive biology  Technology  Tele-health  Virology  Other (please specify): |

**Gene replacement therapy as a potential treatment strategy for *KIF1A*-associated neurological disorders** (250 characters max.)

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*6 Kids Neuroscience Centre, Kids Research, The Children’s Hospital at Westmead, NSW.*

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**Background and Aims:** Kinesin-3 family member 1A (KIF1A) is a transporting protein specifically expressed in neurons. Variants in *KIF1A* cause a group of rare progressive neurological disorders, known as *KIF1A*-Associated Neurological Disorder (KAND). Currently ~500 people have been genetically diagnosed with KAND, but no cure has been discovered. Gene replacement therapy (GRT) approach to restore KIF1A protein level and hence function via the delivery of a normal *KIF1A* gene copy offers hope to reverse KAND symptoms at one time. However, unlike existing GRT therapies, the full-length *KIF1A* gene is too large to be packaged into a standard AAV9 vector. To address this issue, we aim to develop a mini-gene therapy, where a smaller but functional version of the *KIF1A* gene will be designed.

**Methods:** Plasmid containing full-length KIF1A tagged by green fluorescence protein mCitrine is used (KIF1A(FL)-mCit). Multiple constructs will be generated through deleting sequences with no characterized function (miniKIF1A-mCit). SH-SY5Y (human neuroblastoma) cells and COS7 (African green monkey kidney fibroblast) cells will be transfected with KIF1A(FL)-mCit and miniKIF1A-mCit. Cargo localization will be investigated through co-transfecting with plasmid containing synaptophysin, a cargo of KIF1A, tagged by red fluorescence protein mCherry (synaptophysin-mCherry).

**Results:** Our anticipated outcomes involve successful transfection of neuronal cells with designed mini-gene construct, enabling it to efficiently transport cargoes to neurite terminals. In this scenario, both synaptophysin and miniKIF1A would be localized at cell's periphery. Conversely, when introduced into non-neuronal environments devoid of positive regulators and specific cargoes, the miniKIF1A should exhibit autoinhibition and confining signals to cell body.

**Conclusions and Significance/Impact:** By strategically removing coding sequences from the uncharacterised domain in KIF1A, we can create a miniKIF1A that satisfies the AAV9 capacity. Our work lays the foundation for potential GRT development for KAND and the successful construct can be subjected to *in vivo* validation and clinical trials.

(300 words max.)

**Lay Title:** MiniKIF1A gene therapy as an ‘one-for-all’ solution for patients with *KIF1A*-associated neurological disorders (100 characters max.)

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**Lay Summary:** Kinesin-3 family member 1A (KIF1A) protein transport cargoes via the microtubule ‘highway’ in brain cells. Variation in this gene leads to a multisystem disorder termed *KIF1A*-associated neurological disorders (KAND), resulting in early death. There is no cure for KAND yet and existing treatments are non-specific, resulting huge burden on families. This study aims to address this unmet therapeutic need by developing gene replacement therapy (RT) to deliver a healthy version of *KIF1A* gene and restore KIF1A protein level and function. Currently no companies are developing gene therapies for KAND, thereby providing a competitive edge in KAND therapeutics market worldwide.

(100 words max.)