Development of AAV-mediated gene therapy for hereditary spastic paraplegia

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Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders characterised by selective axonopathy of corticospinal tract axons. HSPs affect >800,000 individuals worldwide and there is currently no curative treatment. The pathogenic mechanisms leading to neurodegeneration remain unclear, although different HSP genetic subtypes share common dysregulated pathways. Therefore, I aim to carry out a screen to identify disease-relevant phenotypes in human neurons. This will be performed in iPSC-derived human cortical neurons (i^3Ns) using a CRISPR-inhibition (CRISPRi) approach, an innovative set of technologies that I have established in our laboratory. I will then use the results of this screen to select robust, quantitative phenotypes for proof-of-concept experiments to show that AAV-mediated gene therapy can effectively restore a normal phenotype in human neurons. In addition to expanding our understanding of the molecular pathways underlying HSP this project will identify novel therapeutic strategies as candidates for further development.