Targeting axonal transport defects in Charcot-Marie-Tooth disease type 2J

Claessens A (1,4), De Blasis R (1), Ferri C (1), Gentile F (1), Sicardi S (2), Del Carro U (2), Villarroel-Campos D (3), Sleigh J (3), Schiavo GP (3), D'Antonio M (1), Timmerman V (4)

1) Biology of Myelin Unit, Division of Genetics and Cell Biology, IRCCS Ospedale San Raffaele, Milan, Italy.
2) Movement Disorders Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy.
3) Department of Neuromuscular Diseases and UCL Queen Square Motor Neuron Disease Centre, UCL Queen Square Institute of Neurology, London, United Kingdom.
4) Peripheral Neuropathy Research Group, Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.

Affecting approximately 1 in 2500 individuals worldwide, Charcot-Marie-Tooth disease (CMT) is the most prevalent inherited peripheral neuropathy. Patients present with a range of symptoms from progressive muscle weakness to sensory loss and pain. This clinical variability is reflected in its genetic heterogeneity, with mutations in over 100 genes identified to date. The lack of effective treatments for CMT underscores the importance of identifying common disease mechanisms across subtypes to guide therapeutic development.

One potential unifying mechanism in CMT is the involvement of axonal transport defects. Axonal transport is the process whereby motor proteins traverse microtubule networks within axons to bi-directionally deliver essential cargoes (e.g., organelles, RNAs and proteins) between the neuronal cell body and distal axon terminals. Defective axonal transport has been implicated in many neurodegenerative diseases, including CMT.

We recently generated and characterized a mouse model for CMT2J, a late-onset subtype marked by axonal degeneration, and found indications of impaired axonal transport through in vivo imaging of endosomal trafficking in peripheral nerves. We repeated this experiment, now including CMT2J mice lacking histone deacetylase 6 (HDAC6) – an emerging therapeutic target for CMT subtypes marked by axonal transport dysfunction. Interestingly, these mice's endosome dynamics resembled those of wild-type mice, indicating that HDAC6 could be a promising target to rescue axonal transport defects and degeneration in CMT2J.

To extend these findings, we are developing 3D in vitro models to replicate the peripheral nervous system (PNS). Briefly, induced pluripotent stem cells from CMT2J patients are differentiated to motor neuron spheres and fused with muscle spheres. This mimics the directional growth and interactions of the PNS and would allow the investigation of defective pathways and test potential therapeutics for CMT2J, like HDAC6 inhibitors.