Dissecting Neuronal Specificity in Hereditary Neuropathy.

https://www.neurodegenerationresearch.eu/survey/dissecting-neuronal-specificity-in-hereditary-neuropathy/

Name of Fellow

Dr James Sleigh

Institution
Funder

Wellcome Trust

Contact information of fellow
Country

United Kingdom

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Dissecting Neuronal Specificity in Hereditary Neuropathy.

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The project/programme is most relevant to:

Neurodegenerative disease in general

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Research Abstract

Using fruit fly and cellular models, we have already established non-cell autonomous toxic effects from muscle as the process by which GARS mutations cause neuronal-specific

pathology, and provided a potential mechanism by which this might be mediated. This led to my working hypothesis that disruption of axonal guidance through direct disturbance of axonal transport may be the defective downstream process leading to neuropathology. In order to test my hypothesis, I now propose to extend my work into mammals by developing mouse and human neuronal models of CMT2D and to combine these with live-imaging studies. I will characterise both cell autonomous and non-cell autonomous defects of primary neuronal cultures from Gars mice and induced pluripotent stem cell-derived motor neurons from CMT2D patients. I will also monitor the dynamics of axonal transport and somatic sorting of signaling endosomes and other organelles (e.g. mitochondria) in my cultures, and subsequently confirm and expand t hese results in vivo by monitoring axonal transport by intravital microscopy in Gars mice. I believe that this combined approach will provide a powerful platform to deduce the disease mechanism linking toxic mutations in a housekeeping gene to the selective neuropathy observed in CMT2D patients.

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