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Rescue of CMT2A pathology by two therapeutic approaches aimed at restoring defective organelle contacts and associated pathways

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Charcot-Marie-Tooth disease type 2A (CMT2A) is the most common axonal form of CMT and results from mutations in the MFN2 gene, which encodes mitofusin-2 (MFN2), a critical regulator of mitochondrial fusion and ER-mitochondria contact sites. Our previous work first demonstrated that disruption of ER-mitochondria contacts in CMT2A leads to altered calcium signaling and ER stress, underlying the disease pathology. The large number of MFN2 mutations distributed across all domains of the protein presents a significant challenge for broad therapeutic approaches.

In this study, we directly addressed these pathomechanisms by developing and testing two novel therapeutic strategies. Our gene therapy approach involved neuron-specific overexpression of wild-type MFN2, as well as a modified MFN variant designed to compensate for mutated MFN2. In parallel, we tested a pharmacological approach using IFB-088, an enhancer of the integrated stress response, in collaboration with Inflectis Bioscience.

Utilizing iPSC-derived motor neurons from CMT2A patients, we showed that both gene therapy and IFB-088 effectively restore ER-mitochondria interactions and improve mitochondrial function, resulting in reduced axonal degeneration. Furthermore, in a preclinical mouse model expressing the MFN2Arg94Gln mutation, our intrathecal delivery of AAV9 carrying therapeutic MFN2 transgenes led to significant improvements in locomotor function and reduction of axonal pathology, which was associated with restored mitochondrial and ER-mitochondrial contacts in the spinal cord and nerves. Importantly, our recent data also reveal that IFB-088 alone can prevent locomotor deficits in these mice.

Overall, our work establishes proof of concept for both gene and pharmacological therapies that specifically target the organelles dysfunctions we previously identified in CMT2A. These promising results open avenues for future clinical development with the potential to benefit CMT patients.