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Poster P26

AAV9 MFN1 gene therapy as proof of principle for the treatment of CMT2A

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Mitofusin-2 (MFN2) is a mitochondrial outer-membrane protein involved in mitochondrial dynamics in most tissues; its mutations are directly responsible for Charcot-Marie-Tooth disease type 2A (CMT2A), a disabling and currently incurable motor and sensory neuropathy. Although MFN2 is ubiquitous in cells, its alterations disproportionately impact the nervous system, potentially due to unique energy demands and diminished levels of MFN1, an MFN2 isoform. This makes neurons more susceptible to disruption caused by mutant MFN2. Interestingly, overexpressing MFN1 can compensate for MFN2 loss, as shown in vitro and in vivo when expressed as a transgene, surpassing MFN2-focused strategies.

For the first time in this study, we evaluate the therapeutic efficiency of MFN1 modulation by systemic or local administration in presymptomatic and symptomatic CMT2A mice (Thy1.2-MFN2R94Q mice). Considering that AAV9 displays CNS tropism and crosses the blood–brain barrier (BBB) after systemic and intrathecal administration, and that AAV9–mediated gene therapies have been developed for neurological diseases, we selected AAV9 as in vivo shuttle for delivering the MFN1 gene.

The western blot analysis showed significant increase of human MFN1 protein levels in the brain and spinal cord of the AAV9::MFN1 treated animals compared to AAV9-null treated ones, confirming the molecular efficacy of our strategy. Phenotypic and neuropathological analyses of treated CMT2A mice are now on going. While additional studies are needed, these results offer a promising starting point for future clinical applications, paving the way toward the development of an effective treatment for CMT2A patients.