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Poster P25

Gene replacement therapy efficiently restores normal phenotype in hiPSC-derived in vitro models of VRK1-related motor neuropathies

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The distal hereditary motor neuropathies (dHMN) comprise a heterogeneous group of diseases characterized by length-dependent predominantly motor neuropathy. We have described VRK1 as the gene responsible for dHMN, associated to upper motor neuron signs[1]. We have demonstrated that dHMN due to VRK1 mutations lead to reduced levels of VRK1 in the nucleus, and that this depletion alters the dynamics of coilin, a phosphorylation target of VRK1. Patients' hiPSC-derived Motor Neurons (hiPSC-MN) display Cajal Bodies (CBs) disassembly, defects in neurite outgrowth and branching, altered Action Potential (AP) waveform and decreased Axonal Initial Segment (AIS). length[2].

Here, we want to demonstrate, in vitro, that we can rescue the effect of the loss-of-function mutations in VRK1 using AAV-based transfer of the therapeutic gene inpatiens' hiPSC-MNs.

We treated hiSPC-MNs from two patients from different families and different mutations, with AAV6 vectors expression a GFP tagged VRK1 protein under the control of a CMV promoter (AAV6-CMV.Vrk1.GFP). The patients are the one published in [1] and a patient compound heterozygous for the following variants: NP_003375: p.Arg389Hisfs*7;Lys357Valfs*11.

Using a dose of 5,5*10^3 viral genome/MN, at Day 23 of differentiation for 24 hours, we were able to efficient transduce more than 50% of the total hiPSC-MN. In treated motor neurons at final Day 30 of differentiation, we observed restored levels of VRK1, restoration of the CB size to values similar to the control, restoration of a normal AIS length, correlated to a restoration of normal AP amplitude and amelioration of the global electrical parameters in treated versus non treated patient's hiSPC-MNs (n=3 independent experiments).

In conclusion, we made the proof of concept that re-expression of the wild-type VRK1 protein in motor neurons from patients with dHMN-VRK1 rescues the disease phenotype in vitro.

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