TWS Symposium Berlin (21.03.2014)

Abstract of the presentation from Beate Winner/ Steven Havlicek:

The hereditary spastic paraplegias (HSPs) are a heterogeneous group of motorneuron diseases characterized by progressive spasticity and paresis of the lower limbs. Mutations in Spastic Gait 4 (SPG4), encoding spastin, are the most frequent cause of HSP. To understand how mutations in SPG4 affect human neurons, we generated human induced pluripotent stem cells (hiPSCs) from fibroblasts of two patients carrying a c.1684C>T nonsense mutation and from two controls. These SPG4 and control hiPSCs were able to differentiate into neurons and glia at comparable efficiencies. All known spastin isoforms were reduced in SPG4 neuronal cells. The complexity of SPG4 neurites was decreased, which was paralleled by an imbalance of axonal transport with less retrograde movement. Prominent neurite swellings with disrupted microtubules were present in SPG4 neurons at an ultrastructural level. Overexpression of the M1 or M87 spastin isoforms restored neurite length, branching, numbers of primary neurites and reduced the amount of neurite swellings in SPG4 neurons. We conclude that neurite complexity and maintenance in HSP patient-derived neurons are critically sensitive to spastin gene dosage. Our data show that elevation of a single spastin isoform level is sufficient to restore neurite complexity and reduce the number of neurite swellings in patient cells. In future, our human model offers an ideal system to investigate the proteomic and transcriptomic alterations underlying SPG4 related HSP. Moreover, the hiPSC-derived model system offers a platform for pharmacological screenings with the goal to restore physiological spastin levels in SPG4 patients.