Human in vitro modeling of HSP

We are interested in deciphering pathologic mechanisms in hereditary spastic paraplegia (HSP) using human neurons. These neurons are derived from patients' fibroblasts that are reprogrammed into human induced pluripotent stem cells (hiPSC) and then differentiated into long-projecting cortical neurons to model HSP. We have recently used hiPSC to model the most frequent autosomal dominant form of HSP termed SPG4. Here, we were able to show a gene-dosage dependent rescue of impairments of the microtubule structure in patients' neurons with SPG4 mutations encoding spastin (Havlicek et al., 2014).

The other protein of interest, spatacsin, when mutated, causes a spectrum of neurologic phenotypes, ranging from young-adult onset amyotrophic lateral sclerosis (termed ALS5) to early onset complicated hereditary spastic paraplegias (termed SPG11). SPG11 is a multisystem degeneration, including the CNS and PNS and is associated with cognitive and motor impairment. We have generated iPSC from SPG11-linked HSP patients and respective controls. Intestestingly, we were able to model the neurodegenerative phenotype and demonstrate an axonal pathology due to the lack of Spatacsin (Perez-Branguli et al., HMG 2014) in cortical neurons from SPG11 patients generated from hiPSC.