A phosphodiesterase inhibitor as a potential repurposing drug candidate for Machado-Joseph disease

P. Pereira Sena1, O. Riess1, T. Schmidt1

1 Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany

**ABSTRACT:**

Machado-Joseph disease (MJD), also known as Spinocerebellar Ataxia type 3, is a rare and incurable neurodegenerative disorder. With a prevalence of 1 to 5 cases per 100,000 people, MJD exhibits significant variability in the age of onset (ranging from 20 to 50 years), progression, and the resulting degree of disability in patients. MJD is caused by an aberrant polyglutamine expansion within the protein ataxin-3. This mutation leads to molecular hallmarks, including excessive activation of proteases such as calpains and caspases, leading to increased fragmentation of polyglutamine-expanded ataxin-3; accumulation of ataxin-3 in intracellular aggregates; and mitochondrial damage, among other cellular impairments. Drug repurposing for MJD and other rare polyglutamine ataxias holds the potential to provide faster and more affordable access to treatments for patients with unmet needs. We analyzed a phosphodiesterase inhibitor, already available on the market for other conditions, as a potential repurposing drug candidate for treating MJD. Using both transiently transfected and patient-derived MJD cell models, we provide evidence that this inhibitor reduces MJD hallmarks, thereby decreasing the cellular toxicity of mutant ataxin-3. More specifically, treatment with the phosphodiesterase inhibitor lowered the activation of proteases, reduced mutant ataxin-3 soluble levels and protein aggregates, and improved MJD cell viability, as assessed by the cleavage levels of the apoptotic marker PARP1, which we demonstrate that is increased in MJD. We believe that this candidate drug promotes beneficial effects in MJD through multiple intracellular mechanisms and are currently investigating the modulation of disease-related pathways that culminate in these observed effects. Considering that this phosphodiesterase inhibitor has been on the market for decades and is safely used by several million people annually, our data hold the promise of a faster implementation of an effective therapy for MJD, and perhaps also for other yet incurable polyglutamine SCAs, through the repurposing of a safe and readily available medication.