Drug discovery for MJD - Low molecular weight drugs

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Machado-Joseph disease or spinocerebellar ataxia type 3 is a late-onset neurodegenerative disorder caused by expansion of a polyglutamine tract within the protein ataxin-3, for which there is no effective treatment. We have developed transgenic animal models expressing the mutant human ataxin-3 cDNA for the study of this disorder, in the mouse (CMVMJD135) and in the nematode *Caenorhabditis elegans*. These models show marked neuronal dysfunction, with loss of motor coordination, and the typical pathological feature of ataxin-3 aggregation, and can be used both to study the mechanisms of disease and to test therapeutic strategies *in vivo*.

In this presentation I shall discuss our drug discovery efforts and most recent findings using hypothesis-based as well as unbiased hypothesis-free approaches (drug repurposing screenings), in these transgenic models. We have identified hsp90 inhibitors and serotonin signaling modulators as promising candidates for pharmacotherapy in MJD, but also discovered the beneficial impact of neuroprotective compounds such as tauroursodeoxycholic acid (TUDCA) and creatine in delaying disease onset and progression. The results of such preclinical studies inform us on the therapeutic efficacy of specific compounds but also provide important clues to the key aspects of pathogenesis that are amenable to therapy. Translation of the most promising findings to the clinic is challenging but also warranted.