

**P009** SUMO modification of Httex1p in HD pathogenesis  
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Huntington's disease is a late-onset autosomal dominant neurodegenerative disease caused by an abnormal expansion of polyglutamine in the Huntingtin protein (Htt). The precise molecular mechanisms that underlie pathogenesis are complex. Since post-translational modifications modulate the activity of proteins and may alter their biological function, we are investigating whether modification of mutant Huntingtin (Htt) protein can influence its pathogenicity. We previously found that Htt can be SUMO modified and that SUMO modification itself is relevant to HD pathogenesis *in vivo*. SUMOylation involves a cascade of enzymes, similar to the ubiquitin pathway, with an E1 activating enzyme, an E2 conjugating enzyme, multiple E3 ligases, which may provide substrate specificity, and isopeptidases that both cleave the SUMO moiety from target proteins and are involved in processing of SUMO itself. Identifying specific E3 ligases that SUMOylate Htt, or isopeptidases that cleave SUMO from Htt offer attractive targets for therapeutic development.

We have confirmed that Htt can be SUMO modified using *in vitro* reconstitution assays followed by mass spectroscopy. Preliminary data suggests that multiple PIAS proteins may serve as Htt E3 SUMO ligases. We also have strong evidence suggesting that the SUMO isopeptidase SUSP1 (SENP6) is a key candidate for Htt deSUMOylation. The major objectives of this research is to both understand the underlying biochemistry involved in Htt SUMOylation and to define novel therapeutic opportunities for HD.