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**Project title: Protein interaction networks in the pathogenicity of SBMA**

The molecular mechanisms of polyglutamine (polyQ) -induced neuronal cell death that underlies pathogenicity of Kennedy's disease are poorly understood. Several hypotheses have been put forward to explain the cytotoxic consequences of polyQ expansion in androgen receptor (AR) at the molecular level. These include aberrant protein-protein interactions, altered post-translational modifications, and perturbations to global protein folding homeostasis. The objective of this proposal is to determine the effect of polyQ expansion on the protein-interaction network of the AR. We will test the hypothesis that the protein-interaction network of the AR is significantly altered by the expansion of the polyQ element. Towards this end, we will employ quantitative proteomics tools (SILAC) to identify protein interaction partners of the AR that are differentially affected by polyQ expansion.

Using this approach, we will also examine protein –protein interactions broadly with polyQ expanded AR versus interactions that are specific to the soluble aggregated forms of the polyQ expanded AR. This may be significant since there is growing evidence that soluble, aggregated, misfolded polyQ-expanded proteins are likely mediators of neuronal dysfunction and cytotoxicity.

Altered AR interactome components discovered in this manner will not only shed light on the pathogenic mechanisms of Kennedy's disease but also yield attractive pathways and targets for development of therapeutic interventions.