

# 15

BMS

Judging Dept.

**Todd Miller**

Student

BMS

4

Anne Messer

Dept or Program Years in program

Mentor

## **Functional characterization of a huntingtin-specific single-chain Fv intrabody in a striatal model of Huntington's Disease**

Author (s)

**Todd Miller, Thomas L. Shirley & Anne Messer**

Huntington's disease (HD) is a member of a family of neurodegenerative disorders caused by expanded CAG repeats encoding polyglutamine. The extended polyglutamine causes the huntingtin protein to form insoluble aggregates and engage in aberrant protein-protein interactions. Therapeutic intervention to prevent aggregation, reduce abnormal interactions, and allow proper proteolytic processing may reduce HD pathogenesis. Intrabodies (single-chain Fv antibody fragments) can bind with high specificity and affinity to intracellular targets, potentially altering their folding and interactions. Intrabodies are potential curative agents and tools for drug discovery in an array of neurological disorders associated with altered protein structures. We have previously demonstrated that an intrabody targeting the N-terminus of huntingtin (upstream of the polyglutamine tract) dramatically reduces aggregate formation in non-neuronal cell lines and provides functional protection against expanded polyglutamine toxicity in organotypic brain slice cultures. Dual expression of both intrabody and HD exon 1-GFP fusion proteins from a single vector in a striatal cell model yields a more consistent expression ratio to characterize the in situ functional effects of the intrabody on the cellular and molecular levels. Preliminary findings suggest that the anti-huntingtin intrabody prevents the induction of a stress response by mutant HD exon 1-GFP in an immortalized striatal cell line. The intrabody also appears to enhance protein turnover as we found a decrease in the amount of soluble HD exon 1-GFP. No visible aggregation has been observed, suggesting that the stress response may be caused by soluble, expanded polyglutamine-containing protein.