

## 2010 MSG Abstract

### Mechanism of Axonal Degeneration in a *Drosophila* Model of Distal SBMA

Thomas E. Lloyd<sup>1, 2</sup>, Katie O'Hara<sup>1</sup>, JiHan Kim<sup>2</sup>, Wendy Imlach<sup>3</sup>, Brooke Sahin<sup>2</sup>, Bryan McCabe<sup>3</sup>, and Alex Kolodkin<sup>1</sup>

<sup>1</sup>Department of Neuroscience and <sup>2</sup>Neurology, HHMI, Johns Hopkins University School of Medicine, Baltimore, MD, <sup>3</sup>Columbia University Medical Center, New York, NY

P150/*Glued* is the major subunit of dynactin, a complex that functions with dynein in minus-end directed microtubule transport. The CAP-Gly microtubule-binding domain of *Glued* is mutated in distal spinal and bulbar muscular atrophy; however, the function of this domain in neurons is unknown. We introduced disease-associated mutations in the CAP-Gly domain of *Drosophila Glued* using homologous recombination and by generating transgenic animals. *Gl<sup>G38S</sup>* flies exhibit severe and progressive loss of locomotor function, early lethality, and axonal swellings that contain numerous membrane-bound vesicles. Live imaging of mitochondrial transport in *Gl<sup>G38S</sup>* larval nerves suggests that processivity of retrograde axonal transport is disrupted, leading to an increase in the frequency of pauses and reversals and a decrease in "run" length and duration. Interestingly, the dynein retrograde motor (*dhc*) accumulates at terminal boutons of the larval neuromuscular junction (NMJ) and in sensory axonal termini in the CNS. Overexpression of G38S mutant *Glued* or presynaptic RNAi-mediated knockdown of *Glued* leads to accumulation of *dhc* on endosomal membranes at the terminal boutons of the NMJ, suggesting that *Glued* is critical for initiating dynein-mediated retrograde axonal transport. Together, these data suggest that the presynaptic retractions that occur early in motor neuron degenerative disease begin with an inability to initiate retrograde axonal transport of endosomes.

Sponsor: Packard Center for ALS Research, NINDS K08 award

There is no financial conflict of interest.