

Effect of brain region- and cell-specific expression of pathological TDP-43 on *Drosophila* neurodegenerative behavior phenotypes

Amelia Bunnell, Marina Rodriguez, May Khanna

Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville, Florida, USA

As our population ages, debilitating neurodegenerative diseases are becoming ever more prevalent. Transactive response DNA binding protein 43 kDa (TDP-43) pathology is seen in every case of amyotrophic lateral sclerosis (ALS) and in more than half of Alzheimer's disease cases. TDP-43 is an essential protein involved in multiple aspects of transcriptional regulation and post-transcriptional RNA processing. In diseased states, it is cleared from the nucleus and mislocalized to the cytoplasm, which causes a combination of loss-of-function and toxic gain-of-function effects. ALS brains present with TDP-43 phosphorylation, ubiquitination, and truncation into 20-25 kDa C-terminal fragments. There are mutations known to cause this pathology. This project uses *Drosophila* to test the hypothesis that the functional consequences of TDP-43 toxicity vary depending on the affected brain region or neuronal subtype. We will use a GAL4/UAS system to induce human TDP-43 (hTDP-43) expression and TBPH deletion in neurons critical for olfaction, memory, and motor behavior. We will select a panel of available region- and cell-specific GAL4 drivers and design new UAS responder lines carrying wildtype hTDP-43 or ALS-associated mutants. We will then assess behavioral phenotypes associated with motor function, olfaction, and memory to determine how hTDP-43 expression and dysfunction in different neuronal contexts contribute to distinct neurodegenerative outcomes. Currently, we are optimizing behavioral testing methods while developing the UAS flies. We have tested the Y-maze for olfaction using hTDP-43 flies (which express hTDP-43 everywhere) and are in the process of designing and building the apparatus for olfactory memory testing.

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Presenter name and contact information:

Amelia A. Bunnell, Graduate Assistant
Department of Pharmacology and Therapeutics
University of Florida College of Medicine
Gainesville, Florida, USA
Email: ameliaabunnell@ufl.edu