## A100 The Role of Long-Chain Fatty Acid Elongases in α-Synuclein Associated Neuropathology

Adwitia Dey, Souvarish Sarkar, Yagmur Micoogullari, John W. Hanna, and Mel B. Feany
*Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Brigham and Women's Hospital, Roxbury Crossing, MA*

**Introduction:** α-synucleinopathies are a group of incurable neurodegenerative disorders, where there is an urgent need to better understand targets and mechanisms controlling α-synuclein induced neuropathology. Targeting lipid metabolism represents a potential therapeutic strategy, as numerous studies have documented lipid abnormalities in human α-synucleinopathies. Our recently completed screen to identify neuronal modifiers of α-synuclein neurotoxicity recovered two Drosophila homologs of elongation-of-very-long-chain-fatty acid proteins (ELOVL)6 and ELOVL1/7. Here, we explored the role of a class of lipid enzyme(elongases) that are lesser-known to evaluate therapeutic targets that may attenuate α-synucleinopathy associated neurotoxicity. **Methods:** We addressed the role of these fatty acid elongases in a Drosophila model of α-synucleinopathy, in which human wild type α-synuclein is expressed in a pan-neuronal pattern using the Syb(synaptobrevin)-QF2 driver. We integrated (Elovl6 and 1/7) RNAi lines to knockdown neuronal elongase in α-synuclein flies. In a separate cohort, we dietarily supplemented α-synuclein transgenic flies with an established Elovl6 agonist stearate. Motor-deficit was measured with a validated negative geotaxis assay. Neuropathology was assessed by pan-neuronal and dopaminergic neuronal density in the anterior medulla. Cytoskeletal dynamics and downstream mitochondrial function was evaluated in whole-brain organ culture. **Results:** We discovered that the loss of neuron-specific ELOVL1/7 or supplementation with stearate could significantly rescue α-synuclein induced: 1. locomotor deficits, 2. neuropathology, 3. mitochondrial dysfunction and 4. actin-cytoskeletal abnormalities. that otherwise characterize toxicity in this model. These observations were followed up with experimentally targeted lipidomics in the Drosophila brain that preliminarily suggests upstream alterations in fatty acid species in the brain proper may lead to downstream dysregulation of cytoskeletal homeostasis and metabolism in this model. **Conclusion:** Ongoing investigations focus on identifying specific lipid species involved in the signaling mechanisms underlying the rescue phenotype. The translational advantage is the practicability of supplements as a therapeutic strategy. Ultimately, we aim to connect the relevance of our findings to patients by examining metabolic abnormalities and pathology in neurons derived from patients with Parkinson's disease.