

Department of Molecular and Cellular Biology  
**Graduate Seminar MCB\*6500**

Friday, March 19, 2021 @12:45 p.m.

*presented by:*

**Natalie Porte-Trachsel**

*(Advisor: Dr. Scott Ryan)*

**“Investigating the role of LC3B in the aggregation and seeding of alpha-synuclein in Parkinson’s Disease model systems”**

Parkinson’s disease (PD) is the second most prevalent neurodegenerative disorder, characterized by the loss of dopaminergic neurons and the buildup of Lewy bodies, primarily consisting of the protein alpha-synuclein. The aggregation of alpha-synuclein is a hallmark feature of PD, and the role of this protein in PD pathogenesis is supported by the observation that mutations in the gene encoding alpha-synuclein, SNCA, are causal in familial disease cases. Alpha-synuclein has the ability to transmit cell-to-cell, although exact mechanisms behind how this transmission occurs remain elusive. The accumulation and toxicity of alpha-synuclein is often associated with impairment of chaperone mediated autophagy and macro-autophagy. LC3B is a key protein in the autophagosomal pathway, and our lab sought to investigate the relationship between alpha-synuclein and LC3B in PD models. It was discovered that neurons with mutations in the SNCA gene, used as a PD model system, showed increased colocalization of phosphorylated alpha-synuclein and LC3B. These mutant systems also revealed that alpha-synuclein binds LC3B and forms insoluble microaggregates, phosphorylated alpha-synuclein localizes to the surface of endosomes, and alpha-synuclein mutant neurons seed alpha-synuclein pathology to wildtype neurons. With these results, I aim to determine the impact of alpha-synuclein seeding from mutant to healthy neurons on the aggregation of LC3B *in vitro*, using an hiPSC co-culture system, and *in vivo*, using a Nod Scid Gamma mouse model. As well, I aim to determine the impact of inhibiting exosome biogenesis on the movement of alpha-synuclein from diseased to healthy neurons *in vitro*, using an hiPSC co-culture system.