Use of *Drosophila* to Study Molecular Mechanisms Underlying *GBA1*-associated Gaucher Disease and Parkinson Disease and Other Lysosomal Disorders

By Aparna Kuppuramalingam

Under the supervision of Prof. Mia Horowitz and Prof. Moshe Parnas

Biallelic mutations in the *GBA1* gene cause Gaucher disease (GD) by impairing lysosomal acid β-glucocerebrosidase (GCase) activity. Clinical phenotypes range from non-neuronopathic type 1 GD to neuronopathic types 2 and 3, with N370S and L444P being the most prevalent mutations in non-neuronopathic and neuronopathic GD, respectively. These mutations were introduced into the *Drosophila melanogaster* ortholog of *GBA1*. Unlike the outcomes of these mutations in GD patients, the N370S mutation led to the development of a severe GD-like phenotype in flies, whereas the L444P mutation resulted in a mild phenotype. These results underscore the differences between fly and human GCase enzymes.

Monoallelic mutations are a major cause of familial Parkinson disease (PD). Previous work in the lab showed that the transgenic expression of the human misfolded N370S and the L444P variants in flies led to the development of parkinsonian phenotypes. I aimed to investigate some enigmatic *GBA1* variants, considered either mild or polymorphic, by assessing their contribution to the development of parkinsonian signs in the flies. The tested milder variants triggered partial stress response and neuroinflammation without obvious signs of neurodegeneration. These findings imply that while mild *GBA1* mutations can trigger biochemical alterations, they are insufficient to induce parkinsonian phenotypes in the *Drosophila* model.

Monoallelic mutations in the *SMPD1* gene have been sporadically linked to PD. Biallelic mutations in this gene cause Niemann–Pick disease by impairing the lysosomal acid sphingomyelinase activity. Monoallelic expression of several human mutant misfolded *SMPD1* variants did not induce the Unfolded Protein Response (UPR) or parkinsonian features but rather activated the non-canonical ER Overload Response (EOR) and such variants cannot be evaluated in the fly model for parkinsonian outcomes.