



**Principal Investigator(s): Louise Klem and Anders Nykjaer**

**Project Title:** Examining the neuroprotective and anti-inflammatory effects of sortilin inhibition and PGRN elevation in rodent models of Parkinson's Disease

**Study Rationale:** The sortilin receptor regulates progranulin levels and forms a complex that induces cell death. Sortilin receptor activity and progranulin deficiency are implicated in Parkinson's disease. Vesper Bio has developed small molecule sortilin inhibitors for oral administration, which increase brain progranulin levels. The aim of the project is to assess the efficacy of Vesper compounds in rodent models that present with key features of Parkinson's disease – neuroinflammation, neurodegeneration, alpha-synuclein accumulation, and motor deficits.

**Hypothesis:** Given the anti-inflammatory and neuroprotective effects reported for sortilin inhibition and progranulin elevation, we propose that Vesper compounds attenuate deficits in rodent models of Parkinson's disease: neuroinflammation, nigrostriatal neurodegeneration, and motor deficits.

**Study Design:** The efficacy of Vesper compounds will be evaluated in two mouse models: the MPTP model and a model overexpressing alpha-synuclein (AAV-A53T). MPTP will be administered through systemic injections over five days, while AAV-A53T will be delivered through precise surgery. Vesper compounds will be administered orally before and after these interventions. Motor performance will be evaluated using the cylinder test, open field test, rotarod test, and kinematic gait analysis. Further outcomes include markers of inflammation, gliosis, and nigrostriatal neurodegeneration.

**Impact on Diagnosis/Treatment of Parkinson's disease:** Sortilin inhibition and progranulin elevation could provide a novel and non-invasive treatment approach in Parkinson's Disease.

**Next Steps for Development:** Successful outcomes will pave the way for developing a candidate for clinical testing.