Project Summary

we aim to study small molecule leads that may have therapeutic relevance in Parkinson’s disease (PD). Even as the second most common neurodegenerative disease afflicting the elderly across the globe, there is no cure for PD and it has come to represent a major socio-economic burden. PD is characterized by nigrostriatal degeneration of dopaminergic neurons while α-synuclein aggregation into Lewy bodies and Lewy neurites represents the pathophysiological hallmark of the disease. In simple terms, PD is a case of “protein-folding-gone-awry”. Current therapies aimed at replenishing depleted dopamine levels in the brain provide only symptomatic relief of motor defects.

The development of complementary approaches that can alleviate non-motor symptoms and/or confer neuroprotection remains a largely unmet clinical need. Towards this end, our approach seeks to provide a “disease-modifying” effect by conferring neuroprotection and promoting neuritogenesis. We will develop small molecule inhibitors against FKBP38, a non-canonical member of the FKBP co-chaperone family. Co-chaperones are an integral part of the cellular proteostasis network and mediate the functional diversity of cellular chaperones. Since FKBP38 has been shown to enhance α-synuclein aggregation in vitro, we hypothesize that its inhibition will reduce or abrogate the protein aggregation process and this, in turn, would reduce dopaminergic degeneration.
To test this hypothesis, we will conduct our studies using cell culture models of synucleinopathy as well as animal models of PD. By using a combination of gene expression analysis, pull down assays and immunofluorescence microscopy we will first evaluate the effects of FKBP38 inhibition in cell-based synucleinopathy model and then attempt to delineate the cellular signalling mechanism responsible for neuroprotection and neuroregeneration. Likewise, in animal PD models, electrophysiological, immunohistochemical and biochemical analysis will be combined with behavioural studies to understand how the different brain regions respond to FKBP38 inhibition. By comparing the data obtained from treated and control littermate animals, we will be able to identify physiological attributes of specific brain regions and this will shed light on new anatomical structures relevant to PD. Additionally, by the testing of inhibitors in clinically relevant animal models we aim to evaluate whether the compounds exhibit the therapeutic utility for halting PD progression. The proposed experiments will make use of well-established protocols and will be conducted in systems that are high retractable and can be easily obtained/generated. Since the proposal entails a multidisciplinary approach involving cell and molecular biology, biochemistry, neurophysiology and behavioural studies, the success of this project relies on highly collaborative effort between researchers from disparate areas of biology. In summary, this research proposal will not only identify potential leads but will also provide new information regarding the mechanism of the ligand-mediated neuroprotection and regeneration, which is likely to drive more rapid and robust therapies for this debilitating disease.
References