Servier Neuropsychiatry Grant in Medicinal Chemistry

"Modulation of degradation pathways underlying α-synuclein clearance in neurons"

Abstract: Neurodegeneration in Parkinson's disease (PD) is closely associated with the formation of proteinaceous intracellular inclusions called Lewy bodies. Misfolded α-synuclein which is the primary structural components of Lewy bodies progressively aggregates and accumulates as the disease progresses. In this regard, abnormal level of α-synuclein is believed to be critical in the neuronal loss and the development of PD. The intracellular α-synuclein homeostasis is critically controlled by two major mechanisms responsible for the degradation of proteins: the ubiquitin-proteasomal system and the autophagy-lysosomal pathway. The involvement of these processes under pathological conditions is not yet totally established, however a defective clearance of misfolded α-synuclein is thought as a key mechanism to the pathogenesis of PD. *In one hand*, the ubiquitin-dependent degradative process tightly controls levels of wild-type and misfolded α-synuclein and supports the significance of ubiquitin homeostasis in the development of α-synucleopathy. In line with this hypothesis, pattern of α-synuclein ubiquitination is modified in Lewy bodies, and changes in expression of ubiquitin-specific protease (e.g. Usp8, Usp9X) have been reported in PD. *In the other hand*, the autophagy-lysosomal pathway was linked to the degradation of accumulated and aggregated α–synuclein in neurons, leading to mitochondrial dysfunction and toxicity in primary cortical neurons. For instance, the clearance of α–synuclein is facilitated by activation of the chaperone-mediated autophagy and macroautophagy, *in vitro* and *in vivo*, respectively. Stimulating these degradation pathways may therefore represent promising therapeutic approach for treating PD and other neurodegenerative disorders.

The overall objective of this research proposal is to validate a molecular drug target that, by selectively modulating a protein degradation process, enhances the clearance of α-synuclein and reduces its toxicity in neurons. Aims of the study are as follows. *First*, identify and validate a drug target that regulates α-synuclein homeostasis and the pathway the target engages *in vitro*. Provide proof-of-concept evidence for the role of this drug target in α-synuclein toxicity in cultured neurons. *Second*, use and develop different chemical entities to modulate the target and setup a suitable assay on the target.