In vivo effects, underlying signaling pathways and mechanism of action of ghrelin receptor agonist against pathological alpha-synuclein accumulation.

Parkinson's disease is second most common neurodegenerative disorder, affecting more than 10 millions of people worldwide. Causes of Parkinson's Disease are unknown, it's known however that most important risk factor is advanced age.

Most visible (although not sole) symptoms of Parkinson's Disease are motor dysfunctions, whose direct cause is death of dopaminergic neurons in the brain. So far no clinically proven ways to protect dopaminergic neurons from degeneration exists. Currently used treatments for Parkinson's disease only alleviate symptoms, while the disease is progressing at normal pace.

Major histopathological hallmark of Parkinson's disease is presence of Lewy bodies in the brains of deceased patients. Lewy bodies are abnormal intracellular aggregates of proteins – mainly one particular protein called alfa-synuclein – which instead of performing normal function stick together and accumulate in cell body. Lewy bodies seam to spread trough the brain as the disease progresses. This has prompted scientist to form hypothesis that alfa-synuclein – major component of Lewy bodies – might have prion-like qualities. Prions are proteins who can became infectious agents when they attain incorrect conformation. Such protein can spread between neurons and "spoil" other proteins, changing their conformation into infectious one, and the cycle can repeat indefinitely.

Initially controversial, now prion-like hypothesis for alpha-synuclein spreading gained lot of support, largely due to the development of novel model of Parkinson's disease based on induction of alpha-synuclein transformation into prion-like form trough administration of specially prepared alpha-synuclein fibrils.

I current project, by employing this novel fibril based model, I aim to investigate mechanism of how pharmacological activation of ghrelin receptor – which is present at dopaminergic neurons at high levels – might protect dopaminergic neurons from pathological forms of alpha-synuclein. To achieve this, I will employ advanced molecular and cell biology techniques such as CRISPR/Cas9 system, gene expression profiling and advanced microscopy techniques. The studies will be performed both on neuronal cultures and *in vivo*.