Parkinson's disease (PD) is a debilitating, neurodegenerative disease manifesting in the slowness of movement, tremors, rigidity, and many other symptoms that highly impact the quality of life. Currently available treatments help to manage symptoms for a period of time but we are incapable of either curing this disease or preventing it. Thus the search for a causal treatment is a priority yet still returns no results. In the brains of the patients evident is a progressive loss of so-called dopaminergic neurons, that is neurons that secrete dopamine in the brain region known as Substantia Nigra. A characteristic feature of surviving neurons is an accumulation of the protein - phosphorylated α-synuclein. Finding the reason for this accumulation and its exact mechanism could lead to developing causal treatment. During the course of our research, we found that the deletion of a specific gene, NFE2L1, in the nervous system of mice caused progressive degeneration of neurons and the whole nervous system and most importantly accumulation of phosphorylated α-synuclein.

NFE2L1 is a gene important for multiple cellular processes including antioxidant defense, metabolism, and, of particular note for the proposed study, proteasome regulation. The proteasome is a protein complex responsible for removing damaged or misfolded proteins. It also removes proteins that have fulfilled their role and are no longer necessary – making proteasome a way for cells to regulate proteins amounts. A system involving proteasome, called ubiquitin-proteasome system (UPS), is often disturbed in neurodegenerative diseases, including PD. NFE2L1 is able to stimulate the expression of genes encoding proteasome components and in turn control proteasome appearance. A great effort is extended in finding a way to handle UPS in order to develop a preventive or curative treatment. However, we still lack a reliable way to manipulate UPS in neuronal cells. Targeting NFE2L1 may be a way to accomplish this.

When the post-mortem brains of PD patients were examined, the amount of NFE2L1 in Substantia Nigra was lower as compared to controls, which makes its significance more apparent. Nonetheless, we still do not understand the exact role NFE2L1 plays in neurons and specifically dopaminergic neurons, nor do we know how to stimulate it in neuronal cells.

A number of studies focused on the potential neuroprotective role of NFE2L2, NFE2L1 family member, with which it shares many functions. Yet the differences between the outcomes of deleting these genes are striking and make it seems that they play complementary roles.

Fully uncovering those roles in regards to dopaminergic neurons may present a better understanding of UPS functioning, stress response and the way neurodegeneration develops. Stimulating NFE2L1 and/or its family members may be a way to create preventive or curative PD treatment, something that we are in great need of. In the presented project we propose uncovering the function of NFE2L1 in dopaminergic neurons by deleting this gene in mice embryos, deriving embryonic stem cells from them, and performing dopaminergic neuron differentiation on them. We will repeat the process on other established neuronal cell lines. We will analyze the effect of the deletion and compare it to the effect of the deletion of the two other NFE2L family members: NFE2L2 and NFE2L3. In the second part of the project, we will look for substances with a potential ability to activate NFE2L1 in order to propose a possible drug to use in treating or preventing PD. Afterward, we will test those substances with the fly model in collaboration with the Kyoto Institute of Technology. All of this will help uncover the importance of NFE2L1-3 function in dopaminergic neurons and the mechanisms governing the development of PD and help in developing causal treatment.