**Abstract**

Neurodegenerative diseases, including Alzheimer's disease and other dementias, Parkinson's disease and Huntington's disease, are incurable conditions that result in progressive degeneration and death of nerve cells. Neurodegenerative diseases are strongly linked with age and as world population growth is accompanied by increasing number of elderly people, the rise in frequency of this disabling disorders have a devastating impact on individuals, society and represents a significant economic burden for countries.

The primary goal of my research is to better understand causes and mechanisms of progression of these neurological disorders at the individual cell level in order to aid the design of targeted pharmacological interventions.

Pathological studies revelled that the brain of an affected individual contains abnormal nerve cells with aggregates of damaged proteins that are characteristic for each of these clinical disorders and which accumulation correlates with the disease progression. Thus, the ability to maintain a healthy cellular proteome through removal of toxic protein deposits proofs to be critical for cell health and survival, in particular for vulnerable long-lived neuronal cells. These toxic protein aggregates are observed not only in the cytosol of neuronal cells but also inside the nucleus. Moreover, recent studies report that the cellular communication between nuclear and cytosolic compartments is impaired at the early stages of the neurodegenerative diseases. However, the mechanism and impact of the observed phenotype on the development of these diseases is still not clear, mostly caused by our limited understanding of the basic mechanisms managing the nuclear protein quality control in mammalian cells. In cells the removal of erroneous proteins is mainly mediated by the ubiquitin-proteasome system (UPS) which is present in both the cytosolic and nuclear compartment of the cell. The function of this compartmentalization, how it is achieved and how substrate specificity is regulated is poorly understood. We have limited understanding which proteins are involved in the nuclear protein degradation system, how cells regulate its function or how it is interconnected with its cytosolic equivalent. Furthermore, it is not clear how the function of the nuclear protein degradation system and its crosstalk with the cytosolic protein quality control network is affected at the early stages of neurodegenerative diseases. Thus, a deeper understanding of mechanisms governing mammalian nuclear protein quality control and degradation systems is sorely needed to improve our understanding of the whole cellular protein homeostasis network, how this process is altered in a disease state and finally how we can potentially manipulate this process for a therapeutic benefit.

In this respect, in the proposed project I aim to identify and characterise the mechanisms governing the mammalian nuclear protein quality control and define the crosstalk between cytosolic and nuclear protein degradation systems in the context of neurodegenerative diseases. Moreover, in my research I will aim to understand how these processes are altered in neurodegeneration and what are the possible mechanisms. The proposed research will expand our basic knowledge not only of the nuclear protein quality control, but also improve our understanding of the entire cellular proteostasis network and how it is affected in neurodegeneration. My research has a potential to provide a new perspective on the mechanisms underlying the development of human neurodegenerative diseases and help to define novel future therapeutic strategies.