Neurodegeneration means a progressive loss of structure or function of cells building up the nervous system, which are called neurons. Huntington's disease (HD) is a neurodegenerative, heritable disorder, that is caused by the aggregation of a mutated protein called huntingtin (mHTT). The main symptoms of HD are uncoordinated and disturbed body movements. They may begin even at the age of 30 years. There is no effective treatment for HD, so finding new indicators (markers) of HD and targets for pharmacological treatment is needed. Neurodegeneration process in HD is first observed in the type of neurons called "medium spiny neurons" (MSNs) in the region of the forebrain, that is responsible for motor functions, called "striatum". Researchers are looking for causes of HD. One hypothesis is that, like other neurodegenerative disorders, it is induced by disturbances in calcium ions (Ca^{2+}) signaling in brain neurons. In MSNs from the striatum of HD models, a dysregulation of Ca^{2+} equilibrium (scientifically named homeostasis) was indeed observed by us and other researchers. This phenomenon can be caused by the accumulation of mHTT in striatal neurons and obstruction of the functions of various proteins involved in gene expression, calcium homeostasis, and molecular signaling. One of these molecular pathways is called "store-operated calcium entry" (SOCE). A release of Ca^{2+} from cell compartment "endoplasmic reticulum" (ER) is regulated through activation of particular receptors. Receptors are proteins responsible for receiving signals from the environment. STIM proteins detect Ca^{2+} content in the ER, and when it decreases, they interact with molecular channels in the cellular membrane, called ORAI, and cause their opening. A mechanism of this calcium influx, aforementioned SOCE, helps to restore the original level of Ca^{2+} in the ER.

In the striatum of a mouse model of HD (named YAC128), we observed previously increased amounts of huntingtin-associated protein 1 (HAP1), which binds to mHTT, mentioned above. In MSNs from YAC128 mice, we showed previously that IP3R1 receptors and SOCE activity are strongly elevated by HAP1 form A (HAP1A). Our preliminary results so far indicate that HAP1A could also cause the so-called "unfolded protein response" (UPR). It is a cellular response protecting cells against accumulation of various unfolded proteins in the ER area (named "ER stress"). Increased UPR level has been implicated in several other neurodegenerative disorders other than HD, including Alzheimer's and Parkinson's disease. It is hypothesized that its inhibition might hold a key to unlocking doors for new treatments. The goal of this project is to examine this mechanisms in HD.

More specifically, we aim to check, if switching on the UPR by dysregulated Ca^{2+} signals is important to neuronal cell death in HD. Our experiments will be performed in cell cultures of MSNs neurons from the striata of YAC128 mice, as well as in neurons delivered by reprogramming of fibroblasts from Huntington's patients at different stages of HD development. At the beginning, we will inhibit increased Ca^{2+} signals in the HD mouse model and examine the effects on the activation of UPR. Next, we will investigate, if inhibition of UPR prevents neuronal death. To validate observations from mice HD model, we will use human MSNs from HD patients. In this project, we will be able to deliver first proofs that there is a link between increased Ca^{2+} signaling, UPR, and pathology in communication between neurons. Studies will use a number of innovative techniques including biochemical, molecular and cell biology methods.

To summarize, the proposed research will provide new knowledge on the molecular mechanisms that could be responsible for neurodegeneration in HD. Abnormal Ca^{2+} signaling may cause activation in UPR and thereby induction of neuronal cell death. Results from experiments in the mouse and human model of HD may help to understand reasons for neurodegenerative mechanisms in patients suffering from this disease. Finally, the realization of this project could help to identify novel therapeutic targets and thus the development of potential new drugs for HD.