Huntington's disease (HD) is an incurable genetic neurodegenerative disease and its symptoms include movement disorders, cognitive impairments and personality changes of the patient, much like in Alzheimer's disease. The origin of the disease is a mutation resulting in an incorrect number of repeats of three nucleotides, CAG, in the DNA of the HTT gene. As a result of this mutation, a defective, toxic huntingtin protein is formed. The more CAG repeats is found in the gene, the more severe is the disease and the earlier it starts. Typically, the disease occurs in adulthood, but a very much increased number of CAG triplets evokes the juvenile form of Huntington's disease, which can manifest itself even in younger children. The existence of a juvenile form, as well as the results of studies in model mice, indicate that an important part of Huntington's disease are processes that disrupt the normal development of the human brain. Huntingtin is very important in brain development and its complete absence causes death of mouse embryos.

Therefore, the project will investigate the putative role of decreased level of huntingtin during brain development in HD. Not only absence but also lower huntingtin expression during development in mouse models leads to brain defects and neurological HD-like disease. When we analyze the expression of huntingtin in data from individual cells it becomes apparent that high levels of huntingtin are in almost all glutamatergic cells and low levels are in GABAergic cells, which is surprising as the GABAergic cells are affected at first in HD. Currently, there is no knowledge on huntingtin expression with single cell resolution during development of Huntington's disease embryonic brain. It is unknown how the expression load of huntingtin is connected to the dysfunction, differentiation, and interplay between key group of cells in developing and adult HD brain. Implication for therapy: HTT and its correct linkage to the degenerated groups of cells in HD would greatly influence the potential therapies. For instance, it would: enable selective therapies towards cells most affected and/or containing an appropriate load of mutant HTT expression; allow for avoiding the cells where HTT does not need to be eliminated (silenced) (e.g. overall low HTT expression) and/or where silencing of HTT is harmful to cell functions. Last but not least, it is unclear if silencing of mutant huntingtin as therapy in children is safe due to developmental role of HTT.

The objective of the project is to find out if low levels of HTT are a crucial factor in Huntington disease and juvenile Huntington disease. We will determine, if the decrease or alteration of total huntingtin during embryonic HD brain development contribute to differentiation, migration and other defects of group of cells and if this affects entire embryonic brain architecture. We will boost WT HTT levels and determine if we could restore or modify these defects of groups of cells or entire brain.

To achieve this goal, we will analyze individually each cell of the generated 3D brain organoids to identify deficiencies of cellular populations during early and advanced juvenile HD brain formation. In the past, such study was not possible due to the inaccessibility of human HD embryonic tissue. We will produce cellular aggregates, commonly called "mini-brains in the test tube". Such artificial tissue pieces resemble a very early stage of brain formation and may reflect diseases associated with the development of the brain.

We hope that thanks to this project we will identify the developmental processes altered in Huntington's disease and the mechanisms of these changes, which will allow us to better understand this disease and other diseases associated with the development of the brain such as autism.

Research on neurodegenerative diseases and their influence on the human brain structure is extremely important for understanding the general mechanisms of neurological diseases. Traditionally, these diseases are considered to be of advanced age. However, this belief may change soon. A suitable example illustrating such change in the view of the neurodegenerative diseases may be delivered by studies that show memory impairment in healthy three-year-olds from the genetic group of risk of Alzheimer's disease. These children had also smaller parts of their brain responsible for memory (hippocampus) than children who were not at risk. So, should it be applicable to start to treat a neurodegenerative disease right after birth or even before?