Elucidating neurodegenerative processes using direct profiling of selectively vulnerable neurons

As a consequence of extended life expectancy, neurodegenerative disorders are increasingly prevalent in modern societies. Neurodegenerative diseases, including well-known Parkinson and Alzhaimer disease, as well as little known spinocerebellar ataxias, produce a number of symptoms affecting cognitive and motor functions in patients. Neurodegenerative diseases are currently incurable. The most remarkable mystery of neurodegenerative disorders is selective neuronal vulnerability - a phenomenon in which dysfunction and death affect only specific subpopulations of neuronal cells. In spinocerebellar ataxia type 7 (SCA7), the most vulnerable neurons are big Purkinje cells (PCs) residing in the cerebellar cortex.

Scientists who explore molecular mechanisms of a disease frequently look at bulk neuronal tissue that contains not only affected neurons, but also all other cell populations present in the brain. Such an approach stems from the fact that the fraction of affected neurons is low and they cannot be easily separated from other cell populations. Consequently, the signal produced by vulnerable neurons is masked by other cells in the tissue.

The goal of this project is to find out which molecular mechanisms regulate selective neuronal vulnerability in PC neurons during the course of a neurodegenerative disease. As a representative model of neurodegeneration, I will use transgenic mice engineered to develop SCA7 with its key neurological aspects, including selective degeneration of PCs. Using recently developed advanced tagging techniques, I will label and isolate a pure fraction of PC nuclei from SCA7 and wild type mouse cerebella. Then, using deep sequencing techniques I will identify genes that show differential expression. I will also use an innovative single cell sequencing technique, which provides an opportunity to profile thousands of cells in a single experiment, to look for the genes showing abnormal expression and regulation in PCs and other cerebellar cell types. The subsequent bioinformatic analysis will allow me to identify new molecular networks and cellular processes selectively affected in Purkinje cells. Finally, I will take a look at the specific molecular perturbation that happens in SCA7. This perturbation, which we recently discovered in the cerebellum of SCA7 mice and patients, is related to increased DNA damage and faulty expression of genes regulating behavior of calcium ions. I will verify if these alterations are also relevant to PC-specific degeneration.

Successful completion of this project will help us understand why neurodegenerative diseases target only specific populations of neurons. Answering this question, for which there is currently no satisfactory explanation, may help develop targeted therapies that specifically protect affected neurons.