Huntington's disease (HD) is the neurodegenerative nervous system disease. It occurs with a frequency of 1 in 15 thousand people. The name of the disease comes from the American doctor George Huntington, who described this dissorder for the first time in 1872. Mainly, HD in adult people (aged 35 - 50 years). The median survival time from the diagnosis is around 15 - 20 years. The cause of Huntington's disease is a mutation in gene coding the protein named huntingtin. The disease is an autosomal dominant inherited dissorder, which means that statistically 50% of the offspring will inherit a mutated huntingtin gene. Accumulation of mutant huntingtin protein was observed ot only in brain, but also in skeletal muscle and heart. It is believed that dissorders caused by mutant huntingtin were associated with mitochondrial dysfunction, but the exact mechanisms of the HD pathogenesis remain unknown.

It is known that peripheral pathologies such as skeletal muscle atrophy might have a significant contribution to the HD presentation. It has been shown that HD patients had reduced muscle strength by 50% on average in comparison to healthy matched controls. HD subjects showed also a deficit in the mitochondrial oxidative metabolism and this may support a role for a mitochondrial dysfunction as a key factor involved in HD-related muscle pathogenesis. Due to the fact that mitochondrial dysfunction may play a crucial role in HD pathology, a biological function of PPAR γ coactivator 1α (PGC-1α) has been carefully assessed. PGC-1α is a transcription co-activator that interacts with a broad range of transcription factors that are involved in a wide variety of biological responses including mitochondrial biogenesis, glucose/fatty acid metabolism, fiber type switching in skeletal muscle. Reduced levels of PGC-1α and its target genes in skeletal muscle of HD transgenic mice and HD subjects have been found. These findings showed that impaired function of PGC-1α, might play a critical role in the skeletal muscle dysfunction in HD. Moreover, our recent studies underlined the deterioration of energy metabolism in murine HD hearts that was accompanied by a cardiac substrates preference shift from glucose to fatty acids. It is well known that a failing heart typically shifts metabolism from a carbohydrate oxidation towards fatty acids metabolism leading to a contractile dysfunction and intensify the progression of pump failure. A reduced lipid metabolism (a major cardiac metabolic substrate) may result in a reduced ATP production. Therefore, we conclude that elevated blood lipid concentration may have a positive implication for a cardiac metabolism and function. Moreover, it is known that APOE ε4 allele is involved in lipids metabolism and is a strong risk factor for another neurodegenerative disorder like late-onset Alzheimer disease.

This study, for the first time, aims to clarify the role of ehnaced lipids metabolism on exercise capacity, skeletal muscle, cardiac metabolism and function in HD mouse model. Moreover, we might be in position to define a role of lipids metabolism during HD neurodegeneration. To fulfill intended goals we will generate a new genetic mouse model such as: ApoEKO:R6/2. Furthermore, we will investigate a role of PPAR activators under hypercholesterolemia on the exercise capacity, skeletal muscle, cardiac metabolism and function and neurodegeneration in HD settings. Obtained results may lead to a better understanding of biochemical and molecular mechanisms of HD related myopathies and may have a significant input into development of therapies in HD. Moreover, further work is necessary in order to fully appreciate the complexity of the pathways that are affected during neurodegeneration in HD.