Huntington's disease (HD) is a rare, hereditary neurodegenerative disorder that causes cognitive, psychiatric, and motor impairments. The cause of disease is a genetic mutation characterized by an increased number of nucleotide repeats in the huntingtin gene. This mutation leads to the production of a protein with an elongated polyglutamine tract that forms insoluble aggregates. These toxic forms of huntingtin are observed mainly in the brain but also in peripheral tissues, even in the early stages of the disease. Clinical studies of Huntington's disease patients and preclinical models have shown that, in addition to neurodegeneration, this disease is associated with dysfunctions in skeletal muscle and the cardiovascular system. Evidence suggests that one of the mechanisms driving these changes involves disruptions in cellular energy metabolism.

Our previous research demonstrated that the level of NAD^+ - a key molecule in energy metabolism—is reduced in the skeletal muscle of a mouse model of HD and cellular models of the disease. Interestingly, similar changes were observed in cardiomyocytes lacking the huntingtin gene, suggesting that energy dysfunction may result not only from the aggregation of toxic huntingtin forms but also from the loss of its normal functions. The reasons for these effects remain unclear, largely due to the lack of data on the efficiency of NAD^+ production and consumption pathways in HD-affected tissues.

Therefore, this project aims to understand the role of NAD^+ metabolism in the pathophysiology of Huntington's disease and to evaluate the effectiveness of therapies that restore NAD^+ levels, with a focus on the mechanisms underlying these disruptions and potential therapeutic strategies.

The project will be conducted using cultured cells, *in vivo* HD models as well as clinical samples from HD patients. The cultured cell studies will use e.g. neuronal, cardiac, and myocyte cell lines overexpressing mHTT and lacking HTT, and corresponding controls. *In vivo* studies will include HD mouse model at different disease stages and their wild-type littermates to determine whether the deterioration in NAD^+ metabolism is a cause or a consequence of HD. All mice age groups will also be treated with NAD^+ precursor to investigate the efficacy of NAD^+-enhancing treatment at different stages of HD. Clinical studies will include analysis of metabolites and proteins related to NAD^+ metabolism in samples from HD patients. The results will be correlated with the clinical features of HD.

This will allow us to investigate NAD^+ dysfunction in different cell types affected by HD and to elucidate its mechanisms. Treatment with NAD^+ precursor will provide information about potential benefits for patients with HD, how exactly this has to be used and what is the mechanism of action. The knowledge provided by this project will contribute to the development of diagnostic tools and effective therapies for Huntington's disease.