Allele-selective therapy for polyglutamine diseases with the use of RNA interference technology

Polyglutamine (polyQ) diseases are a group of inherited neurological disorders caused by the expansion of unstable CAG repeats in the respective genes. The common pathogenic factor in this group of disorders is toxic protein with elongated glutamine domain that forms intracellular aggregates and causes neuronal degeneration. Currently no therapy is offered to patients and gene therapy approaches, including RNA interference (RNAi) technology, are very promising. In our laboratory we developed and patented therapeutic strategy for polyQ disorders which uses RNAi tools and expanded CAG tract as a target. We use **vector-based RNAi tools** which allow for stable and long-lasting action of a therapeutic molecule after single administration. One of the most important features of the proposed strategy, distinguishing it from the currently developed approaches, is the preferential silencing of the mutant proteins. There are, however, many questions regarding this approach: (i) what is the potency and selectivity of reagents depending on the CAG tract length? (ii) is it possible to achieve the allele-selectivity of silencing in all patients? (iii) is this strategy universal for all nine polyQ disorders? and (iv) is it safe?
Therefore the goal of this project is **to better characterize CAG repeat- targeting strategy**, its possibilities and limitations. With the use of new reporter constructs with different length of the CAG repeat tract we will characterize the **potency and allele-selectivity** of CAG-targeting genetic vectors. By using different cellular models of polyQ diseases (e.g., SCA1, SCA7, DRPLA) we will verify the hypothesis about **universal therapeutic strategy** targeting expanded CAG tracts in polyQ disorders. An important challenge for therapeutic molecules that target CAG repeats is the existence of other genes that contain similar repetitive regions. With the use of bioinformatics tools we will search for the most specific molecules and we will verify their **safety** experimentally in human neurons.

In recent years, groundbreaking research has been conducted on HD therapy. Among many clinical trials which have been started in last year only one uses selective approach towards mutant huntingtin. Gene therapy for other polyQ diseases is less advanced. Therefore, the development of universal and allele-selective CAG- targeting strategy for the treatment of polyQ diseases is very important not only for the pharma industry but also for patients suffering from these rare diseases.