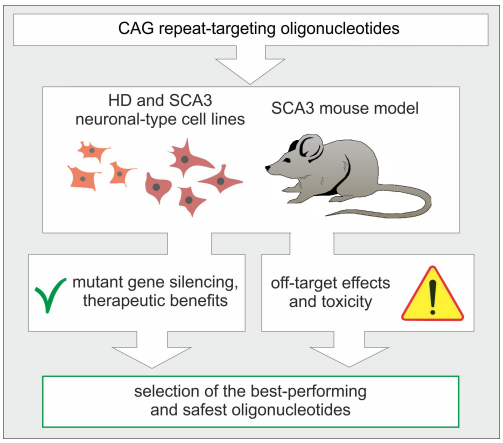
Comprehensive analysis of the therapeutic potential of oligonucleotides for the treatment of polyglutamine diseases

Polyglutamine (polyQ) diseases comprise a group of nine genetic diseases caused by the expansion of the CAG triplet repeat, which encodes glutamine, located in unrelated single genes. In the last 15 years synthetic oligonucleotides (ONs) have become a powerful tool to specifically silence the expression of a mutant gene. In case of polyQ diseases, both non-allele-selective and allele-selective strategies using ONs based on the targeting of regions containing SNP variants or expanded CAG repeat tracts have been considered. Despite the recent advances in the development of therapeutic strategies for polyQ diseases, many questions remain unanswered, e.g. the widespread effects of activity of the potentially therapeutic tools are unknown.



This project will involve investigating the silencing activity of various types of ONs using neuronal-like cell lines. In addition, initial testing will be conducted using mouse models. Mainly, the CAG repeat-targeting ONs will be mainly tested as they are a promising option due to direct targeting of the mutation site. Huntington's disease (HD) and spinocerebellar ataxia type 3 (SCA3), both caused by CAG repeat expansion, located in ORF of HTT and ATXN3 gene, respectively, will be used as models in this study. The therapeutic potential of various ONs will be assessed based on broad analyses of their activity. Moreover, the silencing efficiencies of different RNAi- and ASO-based ONs will be compared, including use in in vivo experiments.

The project objectives will be achieved through the following tasks:
1. Testing of the efficiency of the ONs in silencing the mutant gene in neuronal-type cell lines
2. Global analysis of transcriptome changes caused by the ONs
3. Detailed analysis of the molecular pathways affected by the ONs
4. Testing of selected ONs in the SCA3 mouse model

In addressing these tasks specific analyses will be performed in order to fully characterize the activity of the tested ONs as well as the molecular effects of this activity. These analyses will enable an important comparison of activity, safety and therapeutic potential of various types of ONs. Moreover, the research using the different polyQ disease models will provide insight into a possible universal therapeutic approach for the treatment of CAG repeat expansion disorders.
The goal of this project is to substantially advance the therapeutic potential of CAG repeat-targeting with synthetic ONs. The therapy-oriented research using cell and mouse models of polyQ diseases will provide new knowledge regarding the advantageous features and limitations of various mutant gene inhibitors. This new information will be useful to better design pre-clinical studies using mouse models of the diseases and clinical studies with human patients. Another important outcome of this project will be to provide more conclusive data to assess the importance of allele-selective silencing of mutant polyQ genes.