Reg. No: 2015/18/E/NZ2/00678; Principal Investigator: dr Marta Olejniczak

There are nine known inherited neurodegenerative disorders caused by the expansion of CAG repeats within the coding region of associated genes. These include Huntington disease (HD) and number of spinocerebellar ataxias (SCAs).There is a positive correlation between the size of the expansion and the severity of symptoms, which usually appear at the 4-5th decade of life and lead to patient death. Despite many years of research on an effective method of treatment, these diseases are incurable and only their symptoms are controlled. The aim of the proposed project is to develop effective therapeutic tools for silencing the expression of mutated genes containing expanded CAG repeats associated with the presence of polyQ diseases. To increase the chances of success of the project we will apply two repeat-targeting strategies, involving targeting the mutant transcript or the mutant gene itself. The aim of the first part of the project is to use vector-based RNA interference technology reagents such as shRNA and sh-miR (artificial miRNA) in the experimental therapy of HD and SCA3 in mouse models of these diseases. In the second part of the project we will use CRISPR/Cas9 technology to shorten the expanded CAG repeats in the HTT and ATXN3 genes in cellular models of HD and SCA3. There is currently no publication describing successful using of CRISPR/Cas9 technology to edit polyQ encoding genes. Because CRISPR/Cas9 is one of the most promising genome-editing tools, we plan to further develop and study their efficacy, allele-selectivity and safety in experimental HD and SCA3 therapy using patient-derived cell lines.