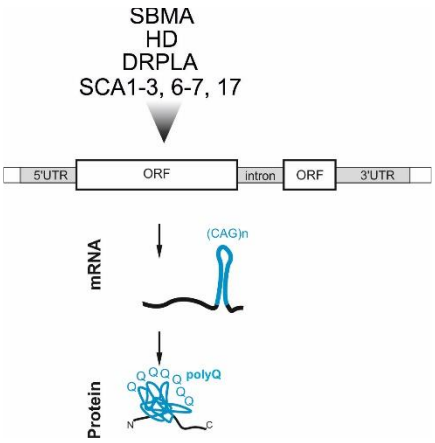
Identification of CAG repeat-binding proteins and imaging RNA-protein interactions in cells

A group of human polyglutamine (polyQ) diseases is caused by CAG repeat expansion in different single genes. These disorders include, among others, Huntington's disease and several spinocerebellar ataxias. Until now these diseases remain incurable. The mutation, which occurs in the coding part of the implicated gene, results in formation of mutant RNA with expanded CAG tract and protein with lengthened polyglutamine tract (see figure). Both gene products, RNA and protein, were shown to be toxic to cells, however, the RNA-triggered pathogenic pathways of these diseases are not well understood. In this project we aim to better recognize the role of RNA in the pathogenesis of polyQ diseases.

We will investigate what proteins bind to CAG repeats in transcripts with the use of high throughput analyses. Proteins that interact only with mutant transcript and their normal cellular functions are compromised by this binding will be further studied as proteins potentially involved in the pathogenesis.

We will also gain insight into dynamics of intracellular trafficking of mutant and normal transcripts and their interactions with CAG repeats binding proteins. We will look for differences between normal and mutant RNAs in the velocity of their cellular movement and localization. We will image the transcripts from their transcription site, through nuclear transport, formation of RNA foci, export through nuclear pores, cytoplasmic transport to their decay.

The results of this project will contribute to better understanding of the molecular and cellular basis of polyQ diseases by providing new information about mechanisms of RNA toxicity, which is poorly recognized at present.



CAG repeats expansion is located in ORF of distinct single genes in mutiple neurodegenerative diseases (SBMA, HD, DRPLA and numerous SCAs). Expression of mutant allele results in formation of toxic RNA with CAG tract and protein with expanded polyQ tract.