Myotonic Dystrophies (DM) and Fragile X-associated tremor-Ataxia Syndrome (FXTAS) are dominant neuromuscular and neurodegenerative human disorders caused by RNA gain of function of expanded CUG and CCUG repeats (two forms DM1 and DM2; CUG^{exp} and $CCUG^{exp}$) and CGG repeats (FXTAS; CGG^{exp}). Repeat tracts are located within potentially untranslated regions of specific genes. RNA toxicity is caused by (i) sequestration of specific nuclear proteins on mutant RNA with CUG^{exp} or CGG^{exp} within nuclear foci and (ii) induction of biosynthesis of toxic oligopeptides containing mono-amino acid tracts, encoded by triplet repeats according to untypical translation mechanism known as Repeat-Associated Non-AUG (RAN) translation. Since the causative molecular targets are well defined, DM and FXTAS are highly amenable to the development of DNA, RNA or protein targeting therapy. We and others demonstrated that reduction of protein sequestration on toxic CUG^{exp} or CGG^{exp} and inhibition of RAN translation using various oligonucleotide-based approaches or small compounds led to promising results in cellular and animal models of DM and FXTAS. However, we noticed that development of new, more efficient therapeutic strategies needs deeper understanding of molecular mechanisms of pathogenic process in both so far incurable diseases.

One of the already described pathomechanisms of DM1 is sequestration on CUG^{exp} RNA splicing factors, which belong to the family of Muscleblind-like proteins (MBNLs), what results in misregulation of alternative splicing and polyadenylation of hundreds of genes. In this project, we will explore new possible functions and protein interactors of MBNLs, especially in context of regulation of RNA metabolism in cytoplasm, e.g. stability, translatability, and length of poly(A) tail of RNAs which interact with MBNLs. This will provide insight in cellular processes which can be misregulated because of MBNL sequestration in DM, provide new knowledge about functions of MBNL in physiological conditions, e.g. development. We will also investigate the mechanism and dynamics of nuclear CUG^{exp} foci formation, valuable not only in DM context, but also for other neurological diseases with ribonuclear foci occurrence.

In parallel, we will investigate the pathomechnisms in FXTAS: the origin of increased level of toxic *FMR1* mRNA containing CGG^{exp}; RAN translation mechanism to explain the efficiency of polyglycine and polyalanine synthesis, as well as dynamics, nature and genetic modifiers of polyglycine aggregates formation, which is the pathogenic hallmark of FXTAS.

Moreover, new therapeutic strategies of both diseases will be tested. We are going to analyze the effect of some compounds targeting CTG^{exp} or CGG^{exp} in RNA or DNA, which we previously identified (e.g., antisense oligonucleotides, small molecules), on efficiency of somatic expansion what potentially can slow down occurrence and severity of symptoms in cell and animal models of the diseases.

In summary, the outcome of our project will allow us to better understand the contribution of studied mechanisms in pathogenesis of DM and FXTAS. This is needed to find potential drug targets for neurodegenerative diseases. Importantly, our results will be exploitable beyond the scope of DM and FXTAS, as we expect to decipher new physiological functions of MBNL proteins and mechanisms of aggregation of homopolymeric amino acids.