In this project we will seek to understand a link between pathogenesis of myotonic dystrophy type 1 (DM1) and elevated levels of circular RNAs (circRNAs). CircRNAs are a particular class of RNA molecules of largely unknown functions and mechanism of biogenesis. CircRNAs are believed to be generated by head-to-tail splicing (back-splicing). This process may be facilitated by RNA-binding proteins (RBPs). It was proposed that muscleblind (MBNL)-family proteins support biogenesis of circRNAs. MBNLs are regulators of alternative splicing of pre-mRNAs and encode proteins critical for skeletal, cardiac, and nervous system function. These proteins are implicated in pathogenesis of DM1 which is the most common form of adult-onset muscular dystrophy. DM1 is caused by an expansion of CTG repeats in the 3'-*UTR* of the *DMPK* gene. The pathogenesis of DM1 is linked to the expression of *CUG mutation-containing transcript* (*rCUGexp*) and its nuclear accumulation in characteristic foci. The presence of the *rCUGexp* causes sequestration of MBNL proteins. One of the molecular consequences of the sequestration and functional inactivation of MBNL splicing factors is aberrant alternative splicing of many target genes found in DM1 patients. However, it remains an open question whether there are any other molecular consequences of the diminished levels of MBNLs in DM1. Our most recent study (Czubak K *et al*., 2019) that addressed this problem has shown that MBNLs are not the major factors involved in the biogenesis of circRNAs in DM1 since, surprisingly, we discovered a global upregulation of the molecules in skeletal muscles from DM1 patients. Also, in DM1 transgenic mice we found a subset of circRNAs that were elevated in comparison to control mice.

Thus, to determine the molecular causes and consequences of the elevated levels of circRNAs in DM1 we will address the following problems: **(i)** determination of whether circRNAs expression is regulated developmentally and depends on developmental changes in MBNL and CUGBP1 splicing factors; **(ii)** determination of a correlation between elevated levels of circRNAs and molecular and clinical features of DM1**; (iii)** determination of a link between the upregulation of circRNAs and expression of mutant *DMPK* mRNA; and **(iv)** determination of a sensitivity of circRNAs to the putative therapeutic small molecule kinase inhibitors which alleviate some of the molecular features of DM1. To address all these problems we will use human and mouse tissues and molecular biology tools. The outcome of the project will help in understanding circRNAs involvement in the development and progression of neurological disorders.