The main goal of the project "The influence of ALS-associated FUS mutations on U7 snRNP activity and the expression of core canonical histone genes in human cells" is to investigate the molecular mechanisms underlying altered RNA metabolism in Amyotrophic Lateral Sclerosis (ALS) due to mutations in Fused In Sarcoma (*FUS*) gene.

Dysfunctional RNA metabolism is implicated in a wide variety of neurodegenerative diseases. During the last years many mutations in proteins with important roles in RNA metabolism leading to neurodegeneration have been identified. For example, mutations in the gene *FUS*, which encodes a nuclear RNA-binding protein of the hnRNP family, were identified in patients with an inherited form of amyotrophic lateral sclerosis. ALS is a fatal neurodegenerative disease characterized by progressive loss of motor neurons of the primary motorcortex, brainstem and spinal cord. The average age at onset is 60 years, and annual incidence is 1 to 2 per 100 000 persons. Death due to respiratory paralysis occurs on average 3 years after symptom onset. Most reported FUS-linked ALS causing mutations are missense mutations clustered within nuclear localization signal (NLS). The mutations disrupt the interaction with nuclear importer and lead to almost abolished or significantly reduced nuclear import of FUS and to cytoplasmic accumulation of FUS aggregates in neurons and glial cells of ALS patients. Thus, nuclear import defects was suggested to be involved in the pathogenesis of FUS-associated disease. However, the downstream consequence(s) of this mislocalization on cellular pathways remains largely unknown.

My reported data and preliminary result demonstrate the implication of disturbed histone gene expression in altered glial cells and motor neurons homeostasis in FUS-linked ALS. I recently found that FUS is involved in regulation of histone gene expression during cell cycle by interaction in the nucleus with U7 snRNP and histone transcription factors. FUS was shown to activate histone gene expression in the phase of DNA replication and is supposed to inhibit histone gene expression in other phases of the cell cycle (Raczyńska et al., *Nucl. Acids Res*., 2015, 43:9711-28). Moreover, in preliminary experiment we observed that the ALS-associated FUS mutant traps U7 snRNA in the cytoplasm. Therefore, my research hypotheses assume that ALS-linked FUS mutations disrupt the nuclear function of U7 snRNP and de-regulate the histone gene expression. Replication-dependent histones are essential for cell survival and their expression must be tightly linked to DNA replication. However, their synthesis must be inhibited in other cell cycle phases as extra histones would be toxic to the cell. I suggested that FUS mutations lead to inhibition of transcription and disturbed 3'end processing of histone gene transcripts in proliferating glial cells that results in genome instability and cell cycle arrest. On the other hand, in terminally differentiated neurons FUS mutants can lead to destabilized transcription control mechanism that in turn might results in aberrant activation of histone synthesis. Nevertheless, disturbed regulation of histone gene expression might be the molecular mechanisms underlying altered glial cells and motor neurons homeostasis in ALS.

The FUS mutations chosen for examination in this project are known to be critical in the ALS-disease pathogenesis from toxic effect of the cytoplasmic aggregates in neurons and glial cells of ALS patients: P525L, R521G, R514G and R495X. Our work plan is focused on four main questions: a) whether ALS-linked mutations in FUS could affect cellular location of U7 snRNP; b) do ALS-linked FUS mutants affect the transcription and 3'end processing of replication-dependent histone transcripts in proliferating glial cells; c) whether ALS-linked FUS mutants affect the expression of histone genes in differentiated neurons; d) could ALS-linked FUS mutants interact with histone transcription factors, NPAT and hnRNP UL1?

I am convinced that further studies for elucidation of the pathological mechanism of this poorly understood disease related to the regulation of histone gene expression are necessary. The nowadays knowledge about pathomechanism of ALS is still not complete. It is difficult to predict the future outcome in ALS research, but the identification of novel molecular pathway caused by the aberrant gene might advance our research in this area. This is important question as with the increasing number of people reaching elderly age, the incidence of neurodegenerative disorders and proportionally the connected health costs constantly raise. I hope that I gain with my proposed research more mechanistic insights into FUS-linked neurodegenerative disorders to reveal potential therapeutic strategies.