Summary

Splicing regulatory proteins like the serine and arginine rich protein family (SR proteins) are extremely important for regulation of our gene expression. SR proteins are involved in several key processes in the pathway from gene transcription to translation. These key steps include pre-mRNA splicing, transport, stability and regulation of the decay pathway nonsense mediated decay (NMD). The expression of SR proteins is tissue-specific, and the combination of splicing factors occurring in a tissue will determine the fate of a pre-mRNA transcript subject to alternative splicing. SRSF10 is a member of the SR protein family and is known to be highly expressed in the brain and spinal cord. Interestingly, SRSF10 is known to repress exon inclusion different from other members of the SR protein family, which are normally thought of as positive regulators of splicing. However, there is lack of knowledge regarding SRSF10 and especially the individual role of the two main isoforms of SRSF10.

Here we investigate the specific role of the two SRSF10 isoforms regarding the neurodegenerative disease Spinal muscular atrophy (SMA). The intronic silencer N1 is found to be important for proper splicing of the *SMN2* gene, and is also the target site of the newly released SMA treatment, Spinraza. We observed that SRSF10 binds to the N1 silencer and acts in a similar way as the well-known repressor hnRNP A1. Like hnRNP A1, the long isoform of SRSF10 increases the exon 7 skipping which leads to a truncated Survival of Motor Neurons (SMN) protein. On that basis, we hypothesize that the neuron specific splicing factor SRSF10 together with hnRNP A1 contributes to increased aberrant splicing of the *SMN* genes.

Furthermore, we performed genome-wide transcriptome analysis of the two individual isoforms of SRSF10. In detail, we performed expression and splicing analysis on RNA originating from SRSF10 depleted HeLa cells and HeLa cells that express either the short or the long isoform. We found that the long isoform of SRSF10 is the active form as it regulates far more gene targets compared to the short isoform.

Furthermore, *in vivo* studies of mice where the short SRSF10 was abrogated by intracerebroventricular (ICV) injections of the anti-short Splice shifting oligonucleotides (SSOs) show that there is a significant change in the regulation of important neuronal pathways like the axon guidance and myelination pathway. These data indicate a novel role for SRSF10 and provides new knowledge of SRSF10 as a neuronal splicing factor.