RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine
September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Investigating the neuroprotective potential of RBM3-inducing antisense-oligonucleotides in preclinical models of neurodegenerative disorders

Tom Haltenhof[1], Alberto Pauletti[2], Elisabeth Stauffenberg, Nadja von Wiegen[1], Lukas Maas[1], Marco Preussner[1], Sonja Bröer[2] & Florian Heyd[1]

[1]Department of Biology, Chemistry, Pharmacy, Institute of Chemistry and Biochemistry, RNA Biochemistry, **Free University Berlin**, Berlin, Germany; [2]Faculty of Veterinary Medicine, Institute of Pharmacology and Toxicology, Berlin, Germany

Neurodegenerative diseases are increasingly prevalent in the aging population, yet currently no disease-modifying treatments are available. Increasing the expression of the cold-shock protein, RNA binding motif protein 3 (RBM3), through therapeutic hypothermia (TH) is remarkably neuroprotective. TH is a medical therapy where the body temperature of patients is intentionally lowered (typically to around 32-34°C) to protect the brain from neuronal loss. Despite good results of TH, its use is strongly limited due to severe side effects and countermeasures of the human body that require induced coma and strong concurrent medication. As RBM3 has been shown to mediate the beneficial effects of TH, inducing RBM3 expression in an temperature-independent fashion holds immense therapeutic potential. We recently discovered an alternative, temperature-dependent poison exon (E3a) within RBM3 intron 3 (Preussner et al. 2023) to be solely responsible for cold-induction of RBM3. We further identified two evolutionarily conserved exonic splicing enhancers (ESE) within E3a regulating its temperature-dependent inclusion. Using antisense-oligonucleotides (ASOs) against one ESE results in quantitative exclusion of E3a and strongly increased RBM3 expression independent of cooling. Notably, a single administration of ASO to exclude the poison exon, using FDA-approved chemistry, results in long-lasting increase of RBM3 expression in mouse brains. In prion-diseased mice, this treatment leads to remarkable neuroprotection, with prevention of neuronal loss and spongiosis.

Although underlying pathomechanisms of diverse neurodegenerative diseases strongly differ, a common consequence is the loss of certain types of neurons in the human brain. As cooling of these patients is impractical, because of the chronic nature of these diseases, our ASO-based approach to induce RBM3 opens a therapeutic intervention strategy. We will present data from preclinical cell culture and in vivo models of neurodegenerative diseases.