SCN1A upregulation via antisense oligonucleotides targeting SCN1A-NAT as a novel therapeutic strategy for Dravet syndrome

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1. Haploinsufficiency of SCN1A leads to Dravet Syndrome

SCN1A Mutations Leading to Dravet Syndrome

Loss of SCN1A leads to reduced sodium currents and hypoxcitability of GABAergic inhibitory neurons, which results in hyperexcitability of neuronal network and seizures

Therapeutic Hypothesis

Upregulation of wild type SCN1A will ameliorate the manifestation of Dravet Syndrome

2. CAMP4 identifies RNA actuators: antisense oligonucleotides (ASOs) that specifically bind regulatory RNAs and increase the transcription of target genes

3. SCN1A NAT is present in human and mouse brain

Targeting Human SCN1A NAT

Targeting Mouse Scn1ANAT

4. ASO treatment upregulates SCN1A expression and restores neuronal function in vitro

Targeting Human NAT

Targeting Mouse NAT

SCN1A upregulation in patient fibroblasts

5. ASOs targeting SCN1A NAT decrease seizures in Dravet mice

6. ASO treatment upregulates SCN1A expression in non-human primates

7. Summary

- Mutations in SCN1A lead to Dravet Syndrome
- SCN1A-NAT regulates SCN1A expression
- ASOs targeting SCN1A – NAT upregulates SCN1A expression in vivo and in vitro in a mouse model of Dravet Syndrome
- ASOs targeting SCN1A – NAT restore neuronal function in vitro and reduce seizure frequency in a mouse model of Dravet Syndrome
- ASO CO-3527 targeting human SCN1A – NAT upregulates SCN1A mRNA and protein in non-human primates
- We are advancing CO-3527 into clinical trials for treating Dravet Syndrome

References

Sun et al (2010), Journal of Human Genetics (55), (421–427)