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

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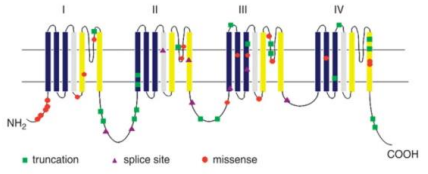
1. Haploinsufficiency of SCN1A leads to Dravet Syndrome

SCN1A Mutations Leading to Dravet Syndrome



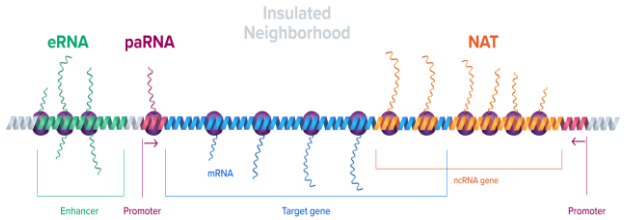
Sun et al, JHG, 2010

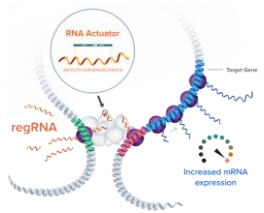
Loss of SCN1A leads to reduced sodium currents and hypoexcitability of GABAergic inhibitory neurons, which results in hyperexcitability of neuronal network and seizures

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



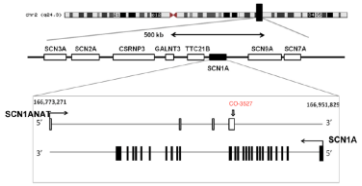


- SCN1A gene is associated with SCN1A-NAT
- CAMP4 is developing an antisense oligo targeting SCN1A-NAT* to upregulate SCN1A mRNA

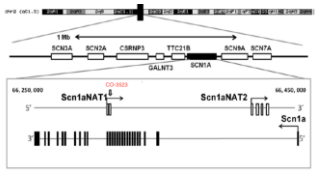
Natural Antisense Transcripts

3. SCN1A NAT is present in human and mouse brain

Targeting Human SCN1A NAT

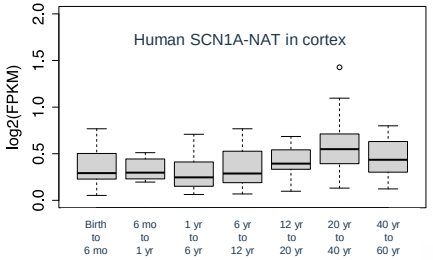


Targeting Mouse Scn1ANAT



Hsiao et al, eBiomedicine, 2016

CAMP4 ASO target SCN1A-NAT is steadily expressed throughout life

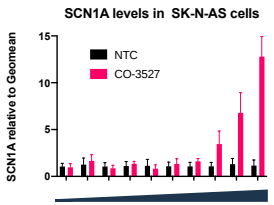


(source: Brainspan Atlas of the Developing Human Brain [brainspan.org])

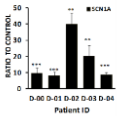
4. ASO treatment upregulates SCN1A expression and restores neuronal function *in vitro*

Targeting Human NAT

SCN1A levels in SK-N-AS cells

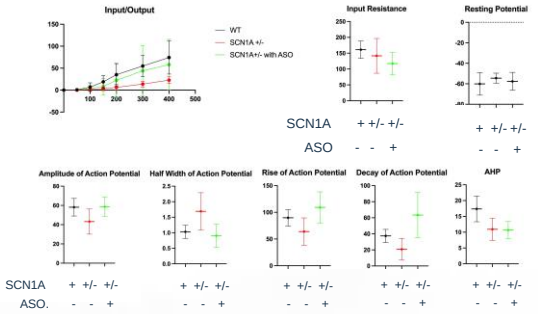


SCN1A upregulation in patient fibroblasts



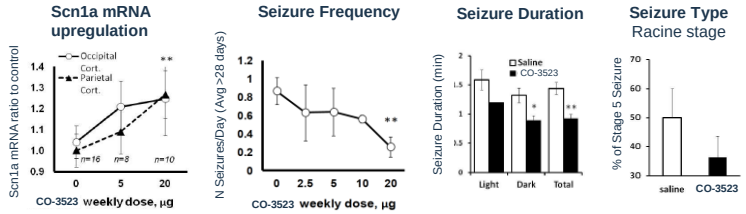
Targeting Mouse NAT

Hippocampal Neurons



Hsiao et al, eBiomedicine, 2016

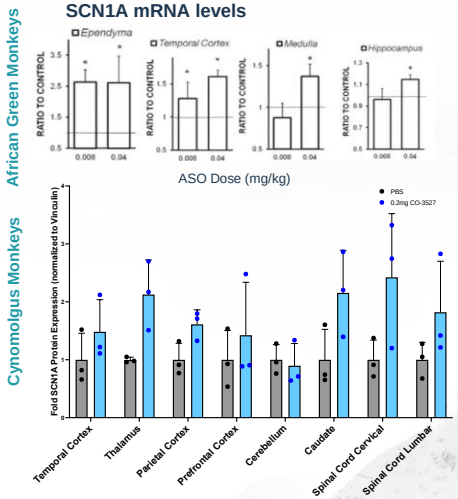
5. ASOs targeting SCN1A NAT decrease seizures in Dravet mice



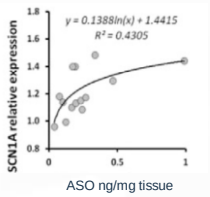
Similar effects seen in other measured parameters like seizure amplitude

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

SCN1A mRNA levels



Dose-dependent upregulation of SCN1A



Hsiao et al, eBiomedicine, 2016

7. Summary

- Mutations in SCN1A lead to Dravet Syndrome
- SCN1A-NAT regulates SCN1A expression
- ASOs targeting SCN1A – NAT upregulate SCN1A expression in vitro and in vivo 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)
Hsiao et al (2016), EBioMedicine (9), 257–277