Upregulation of SCN1A by regRNA-targeting antisense oligonucleotide CMP-SCN

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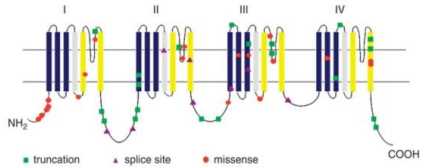
1. Haploinsufficiency of SCN1A leads to Dravet Syndrome

SCN1A Mutations Leading to Dravet Syndrome

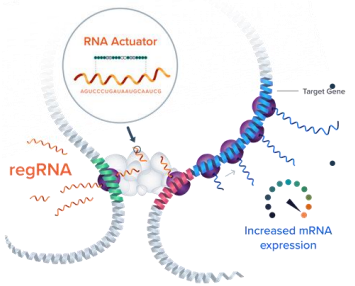


Sun et al, JHG, 2010

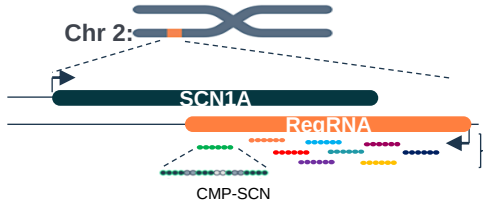
Loss of SCN1A leads to reduced sodium currents and hypoexcitability of GABAergic inhibitory neurons, which results in hyperexcitability of neuronal network and seizures

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

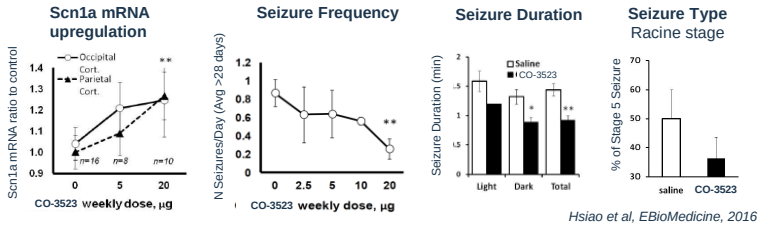


- SCN1A gene is associated with SCN1A-NAT*
- CAMP4 is developing an antisense oligo targeting SCN1A-NAT to upregulate SCN1A mRNA



*Natural Antisense Transcript

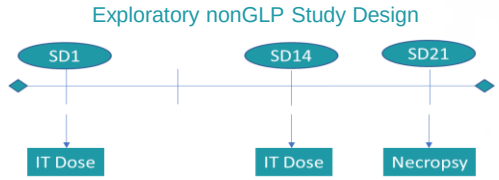
3. ASOs targeting SCN1A NAT decrease seizures in Dravet mice

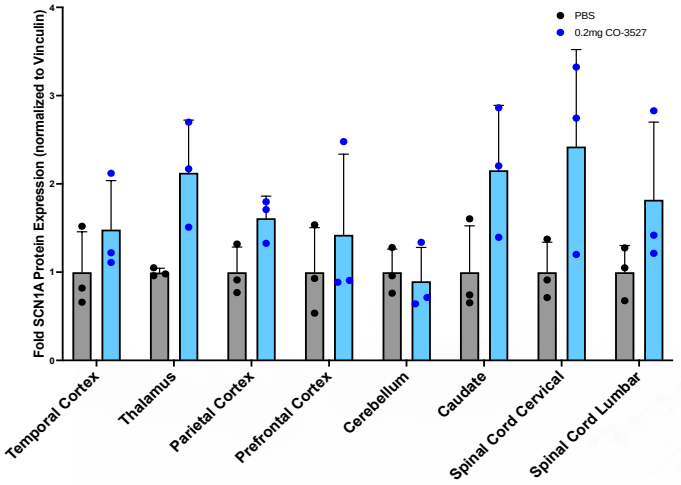


Hsiao et al, EBioMedicine, 2016

Similar effect observed in seizure amplitude and related parameters

4. CMP-SCN treatment upregulates SCN1A expression in cynomolgus monkeys





Protein levels were measured by western blot in different brain regions.

5. CMP-SCN well-tolerated in cynomolgus monkey

Antemortem Observations
- No clinical observations attributed to CMP-SCN up to 5 mg/dose
- No changes in body weight
- Clinical pathology was unremarkable and showed no treatment-related response

Postmortem Observations
- Microscopic review of CNS (brain, spinal cord, dorsal root ganglion) and selected systemic tissues (heart, liver, kidney, skeletal muscle) shows acceptable tolerability profile for CMP-SCN following Q2W intrathecal injection
  - Slight/rare immune cell infiltrates observed at all dose levels without evidence of dose response - attributed to injection procedure and clearance of ASO
  - No evidence of inflammation based on latent appearance of rare histiocytes and absence of local tissue effects
  - No observed treatment-related changes in heart, liver, kidney or skeletal muscle

Dose multiple of >25x compared to projected clinically efficacious dose in pediatric patients.

IND-enabling repeat dose toxicology studies underway

6. Summary

- Mutations in SCN1A lead to Dravet Syndrome
- ASOs targeting SCN1A-NAT upregulate SCN1A expression and ameliorate the seizure phenotype in a mouse model of Dravet Syndrome
- CMP-SCN targeting human SCN1A – NAT upregulates SCN1A protein in cynomolgus monkeys
- CMP-SCN readily distributes into cynomolgus monkey CNS tissues, without evidence of adverse histomorphologic effects at the studied dose levels and dosing frequency
- We are advancing CO-3527 towards 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