Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A reduces seizures and rescues parvalbumin positive interneuron firing frequency in a mouse model of Dravet syndrome

Eric R. Wengert1,2, Pravin K. Wagley1, Anne Christiansen1, Samantha M. Strohm3, Numa Reza1, Zhou Han3, Sophina J2, Ian C. Wenker4, Ronald P. Gaykema5, Gene Liau1, and Manoj K. Patel1,2

1Department of Anesthesiology and 2Neuroscience Graduate Program, University of Virginia School of Medicine, Charlottesville, VA, United States; 3 Stoke Therapeutics, Inc., Bedford, MA, United States

Summary

- Dravet syndrome (DS) is severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, beginning in the first year of life. Cognitive regression, ataxia, speech impairment, sleep disturbances and an increased risk of sudden unexpected death in epilepsy are other aspects of the disease. Approximately 85% of DS cases are linked to a mutation in the SCN1A gene leading to haploinsufficiency of the voltage-gated sodium channel NaV1.1. We have developed a novel therapeutic approach to treat DS using STK-001, an antisense oligonucleotide designed to restore WT levels of NaV1.1 mRNA and NaV1.1 protein by inhibiting generation of a splice-switching non-sense mediated mRNA decay (NMD) (Zhou et al, 2020).

- The current studies test this approach using the Dravet syndrome (DS) mouse model that has been shown previously to recapitulate many phenotypes of DS (Miller et al, 2014). We evaluated the effects of STK-001 in this model by quantification of spontaneous seizure by electroencephalography (EEG) pre (P13-19) and post (P20-40) treatment. In addition, this model was crossed with mice harboring a parvalbumin (PV) reporter strain (F2:129S-Scn1atm1Kea/J) to allow visualization of PV-expressing interneurons. Electrophysiological recordings were taken from tdTomato-expressing cells in the somatosensory cortex between P17-23.

- These results provide evidence that TANGO technology can be used to rescue the seizure phenotypes in a mouse model of SCN1A-linked DS. Taken together, these data provide further evidence that STK-001 has the potential to provide a gene-specific, disease-modifying treatment to restore NaV,1.1 to physiological levels to provide therapeutic benefits for DS patients.

Conclusions

- TANGO ASO (STK-001) decreases seizure frequency and extends survival in a mouse model of SCN1A-linked DS.
- STK-001 restores high-frequency action potential firing in PV interneurons from DS mice.
- These effects of STK-001 in this model by quantification of spontaneous seizure by electroencephalography (EEG) pre (P13-19) and post (P20-40) treatment.

References


Approach

1. Seizure monitoring
2. Parvalbumin (PV) Interneuron Neuronal Excitability

All experimenters blinded to genotype and treatment throughout data collection and analysis

STK-001 administration reduces seizure frequency and improves survival in the DS mice

STK-001 administration restores the firing frequency of DS PV interneurons to control PV interneurons

Representative example traces of WT and DS PV interneuron excitability treated with vehicle or STK-001

Table: Comparison of membrane and action potential properties of WT and DS PV interneurons treated with vehicle or STK-001

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Membrane &amp; Action Potential Properties</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT STK-001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DS STK-001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicates significance p<0.05 compared to WT Vehicle
# indicates significance p<0.05 compared to Dravet Vehicle
* indicates significance p<0.05 compared to Dravet STK-001