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

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Dravet Syndrome

• Severe developmental and epileptic encephalopathy

• CAUSED primarily by physiologically loss-of-function SCN1A mutations resulting in hypofunction of inhibitory interneurons

• Patients suffer refractory seizures, cognitive and motor impairments, and have a substantial risk for SUDEP

• Demand for therapeutic strategies that directly address genetic cause of disease
TANGO (Targeted Augmentation of Nuclear Gene Output) May Be Used to Treat Dravet Syndrome

Approach to Evaluate the Impact of a Single Dose of STK-001 ASO Treatment

- Seizure Monitoring

- Parvalbumin-positive Interneuron Excitability

**Group 1: Pre-weaning seizure-monitoring (8 hrs/day)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECoG Headset</th>
<th>Seizure-monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>P12</td>
<td>P13</td>
</tr>
<tr>
<td></td>
<td>~P20</td>
<td></td>
</tr>
</tbody>
</table>

**Group 2: Post-weaning continuous seizure-monitoring**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECoG Headset</th>
<th>Seizure-monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>P19</td>
<td>~P20</td>
</tr>
<tr>
<td></td>
<td>~P20</td>
<td>P40</td>
</tr>
</tbody>
</table>

**Electrophysiology Recordings of PV interneurons**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patch-clamp Recordings</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>P17</td>
</tr>
<tr>
<td></td>
<td>P23</td>
</tr>
</tbody>
</table>

All experimenters blinded to genotype and treatment throughout data collection and analysis.
STK-001 Administration Reduces Seizure Frequency in DS Mice

**Graphs:**
- **Group 1 (P13-P19):**
  - WT + Vehicle vs. WT + STK-001
  - DS + Vehicle vs. DS + STK-001
  - Seizure frequency (per day)
  - Death marker
- **Group 2 (P20-40):**
  - WT vs. Dravet
  - Seizure frequency (per day)

*Statistical analysis:* p = 0.1088
STK-001 Administration Improves Survival in DS Mice
STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (1)

DS PV interneurons are hypoexcitable
STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (2)

- DS PV interneurons are hypoexcitable
- STK-001 treatment rescues the firing frequency to WT levels
STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (3)

- DS PV interneurons are hypoexcitable
- STK-001 treatment rescues the firing frequency to WT levels
- Interestingly, treating WT with STK-001 slightly altered PV interneuron firing frequencies at high current injections
Conclusions and Future Directions

• STK-001 reduced seizure frequency and extended survival in DS mice with no significant deleterious effects observed in WT mice

• Treatment with STK-001 rescues neuronal excitability of parvalbumin-positive inhibitory interneurons in DS mice, which supports the hypothesis that restoration of excitability to inhibitory interneurons is a viable approach toward rescuing DS mice from seizures and death

• Potential future evaluations:
  - Collect electrophysiology recordings of voltage-gated sodium channel activity
  - Explore effects on other inhibitory interneuron populations (SST, VIP, etc.)
  - Examine impact on network excitability (synaptic inhibition, etc.)

• STK-001 is currently being evaluated in patients with Dravet Syndrome
Acknowledgements

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### Membrane and Action Potential Properties

<table>
<thead>
<tr>
<th></th>
<th>Resting Membrane Potential (mV)</th>
<th>Input resistance (MΩ)</th>
<th>Action Potential Threshold (mV)</th>
<th>Rheobase (pA)</th>
<th>Action Potential Amplitude (mV)</th>
<th>Upstroke Velocity (mV/ms)</th>
<th>Downstroke Velocity (mV/ms)</th>
<th>APD50 (ms)</th>
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</thead>
<tbody>
<tr>
<td>WT PBS</td>
<td>-68.9 ±1.4</td>
<td>110±6</td>
<td>-34±1</td>
<td>239±24</td>
<td>56±2</td>
<td>355±14</td>
<td>-225±13</td>
<td>0.37±0.03</td>
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<tr>
<td>WT STK-001</td>
<td>-68.3±1.0</td>
<td>139±13&lt;&amp;^</td>
<td>-36±1</td>
<td>168±19&amp;</td>
<td>62±2&amp;</td>
<td>290±13*</td>
<td>-158±10&lt;&amp;^</td>
<td>0.55±0.02&lt;^</td>
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<td>DS PBS</td>
<td>-69.9±1.0</td>
<td>102±7#</td>
<td>-35±1</td>
<td>290±22&lt;&amp;^</td>
<td>55±2#</td>
<td>299±11*</td>
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<tr>
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</table>

* indicates significance p≤0.05 compared to WT PBS
# indicates significance p≤0.05 compared to WT STK-001
& indicates significance p≤0.05 compared to Dravet PBS
^ indicates significance p≤0.05 compared to Dravet STK-001