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

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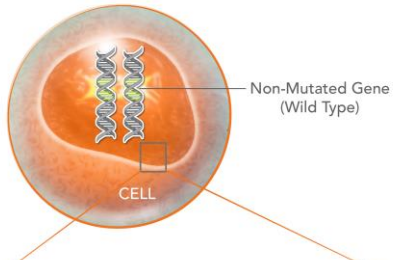
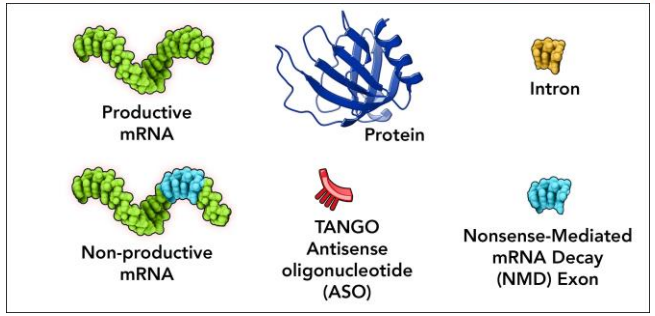
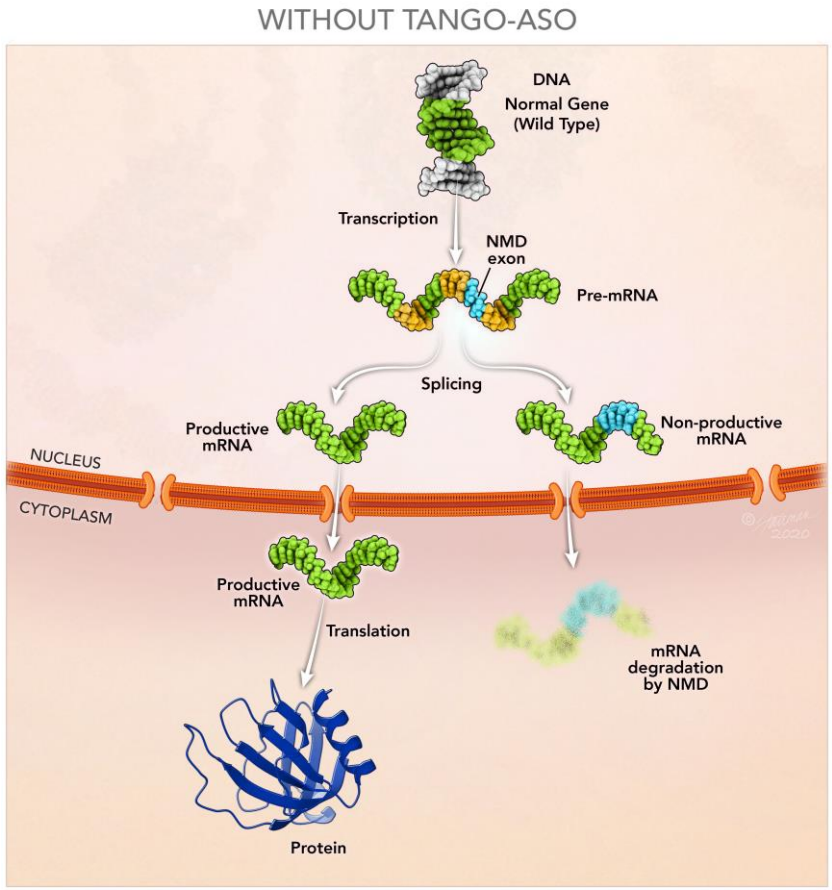
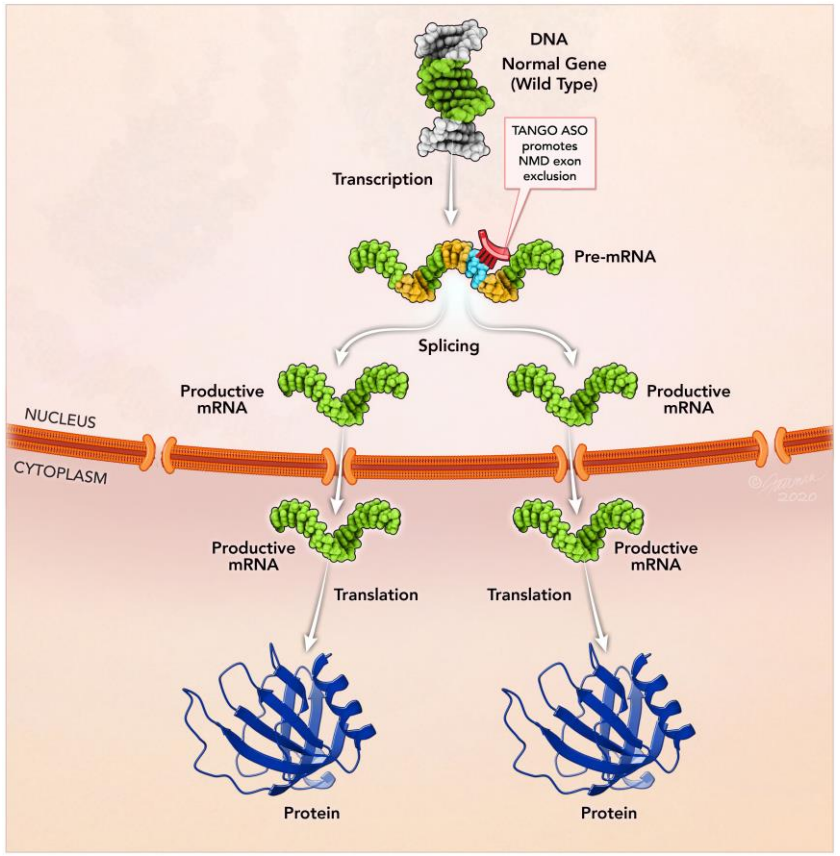
TANGO (Targeted Augmentation of Nuclear Gene Output) May Be Used to Treat Dravet Syndrome









nature COMMUNICATIONS

Source: Lim, K.H., Han, Z., Jeon, H.Y. *et al.* Antisense oligonucleotide modulation of non-productive alternative splicing upregulates gene expression. *Nat Commun* **11,** 3501 (2020).

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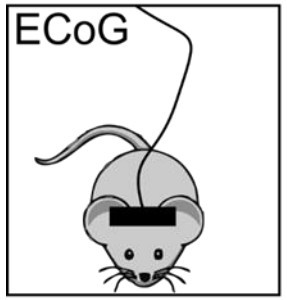
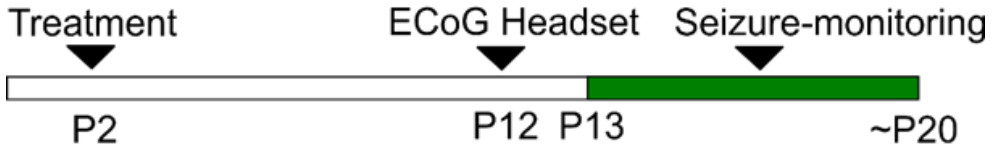
Approach to Evaluate the Impact of a Single Dose of STK-001 ASO Treatment

- Seizure Monitoring

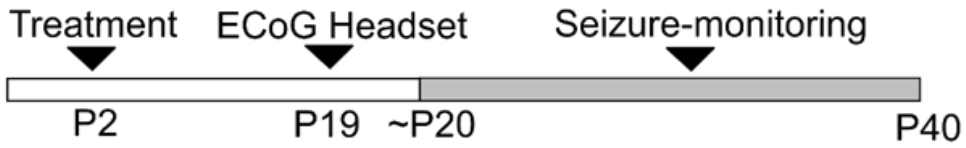


spontaneous seizures

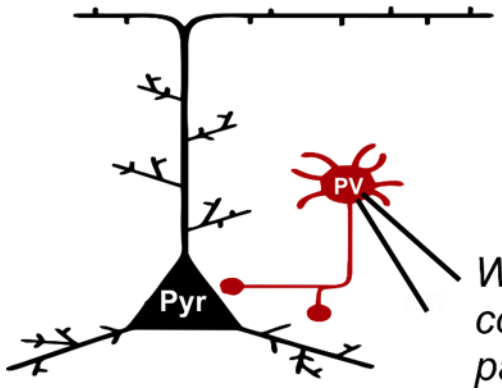
Group 1: Pre-weaning seizure-monitoring (8 hrs/day)

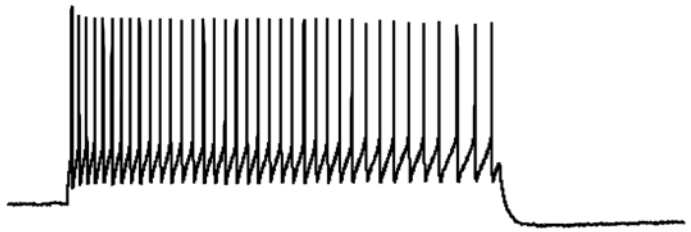


Group 2: Post-weaning continuous seizure-monitoring



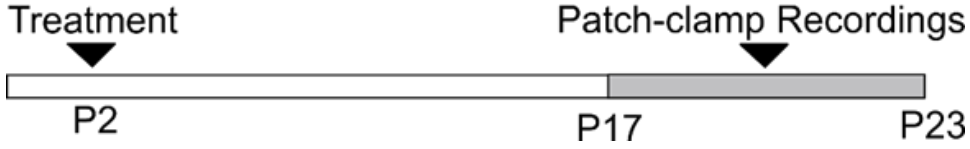
- Parvalbumin-positive Interneuron Excitability





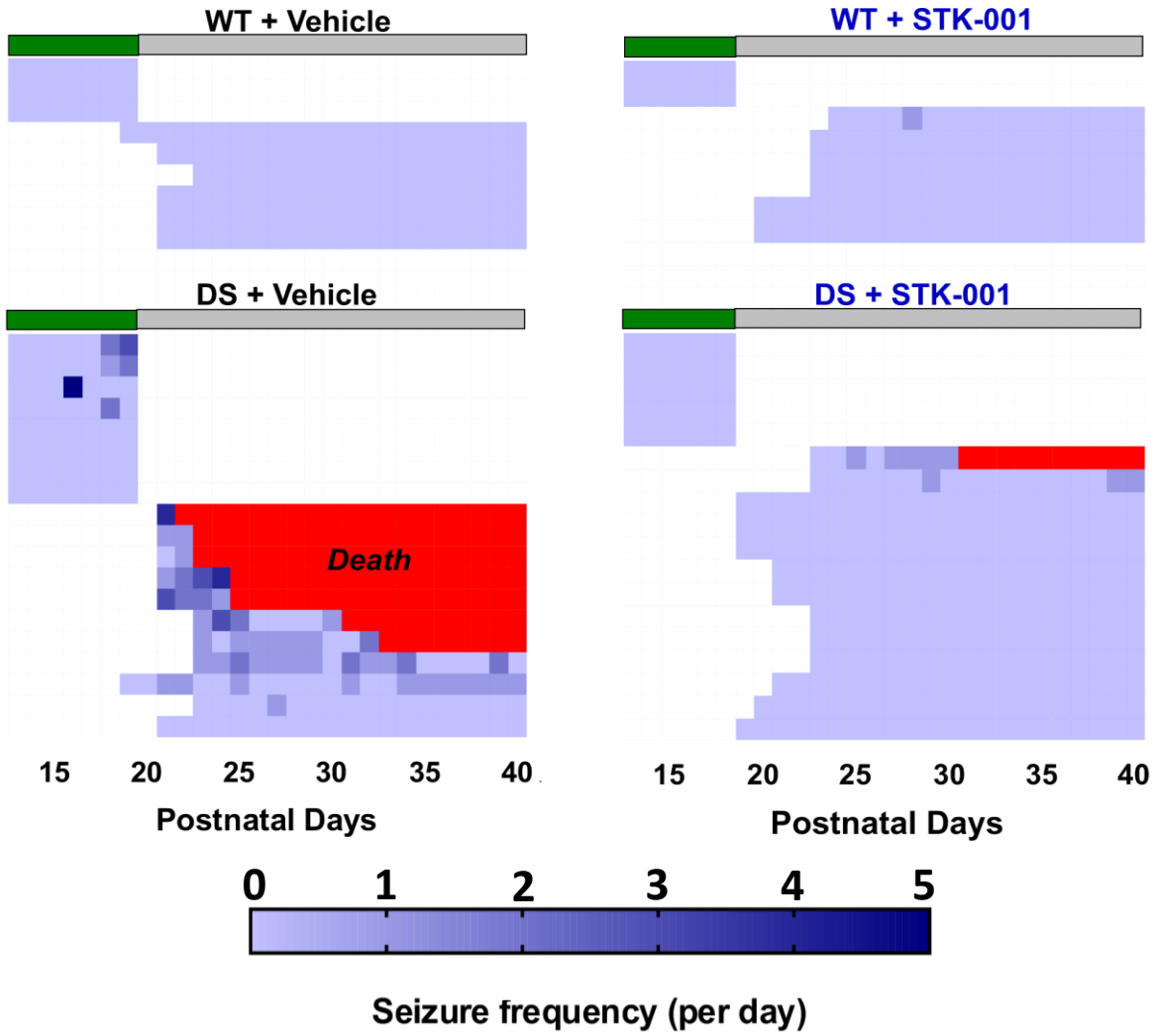
Whole-cell current-clamp recordings from cortical layer V tdTomato-positive parvalbumin-positive interneurons

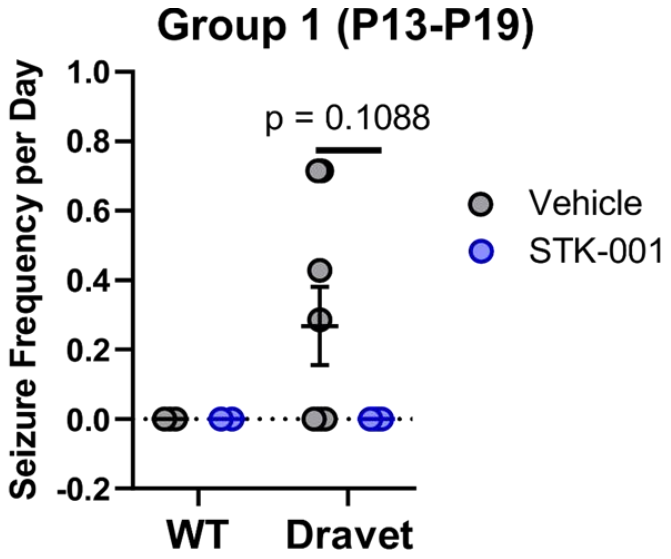
Electrophysiology Recordings of PV interneurons

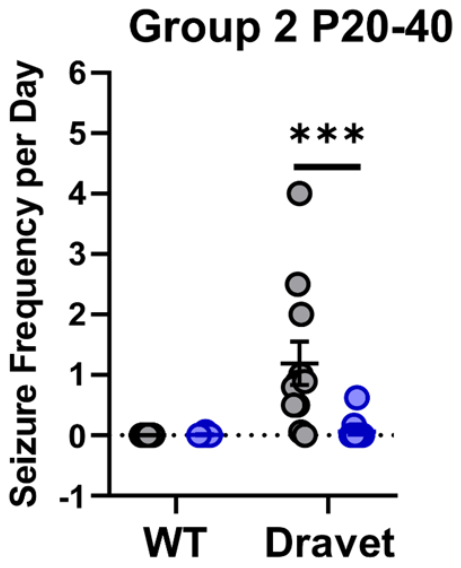


All experimenters blinded to genotype and treatment throughout data collection and analysis

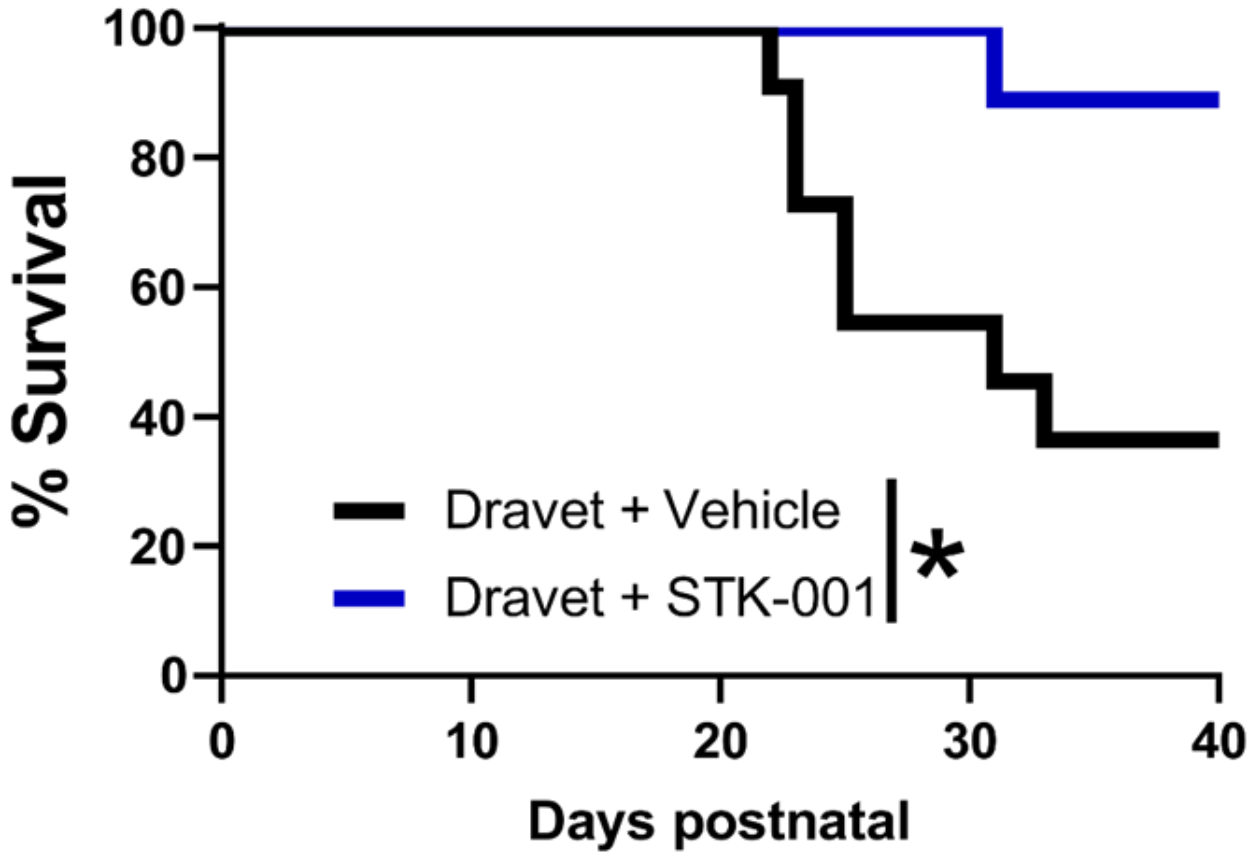
STK-001 Administration Reduces Seizure Frequency in DS Mice



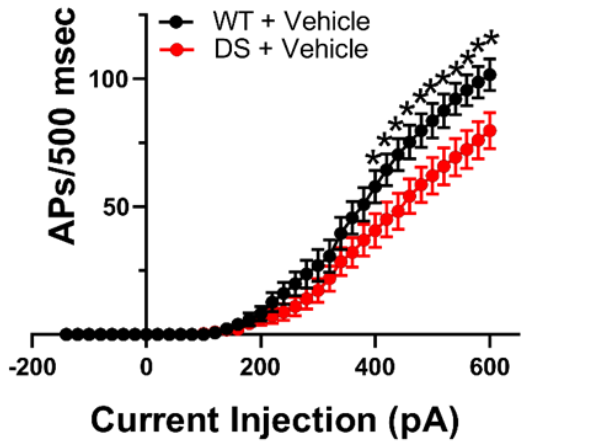


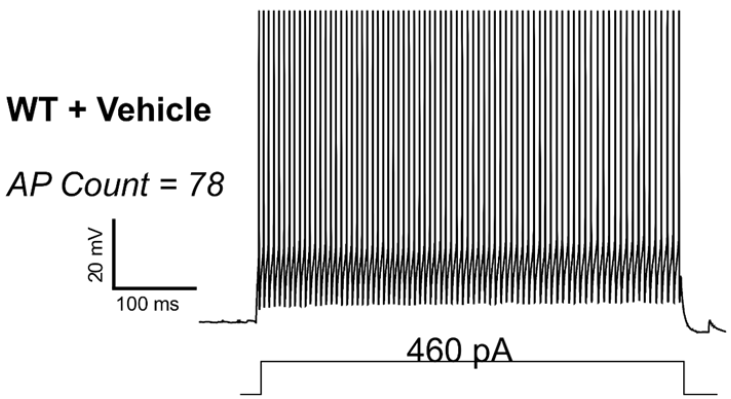


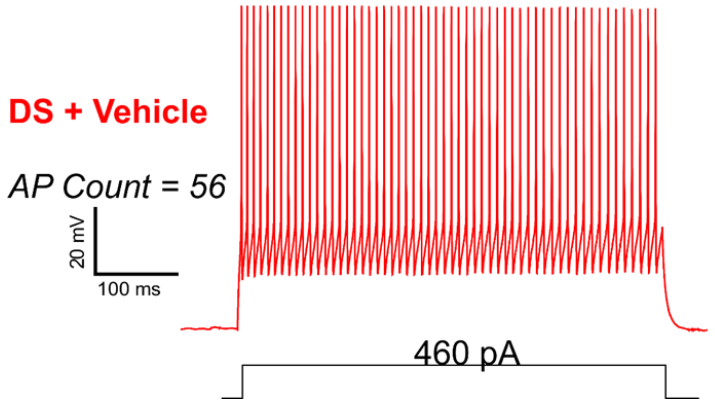
STK-001 Administration Improves Survival in DS Mice



STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (1)

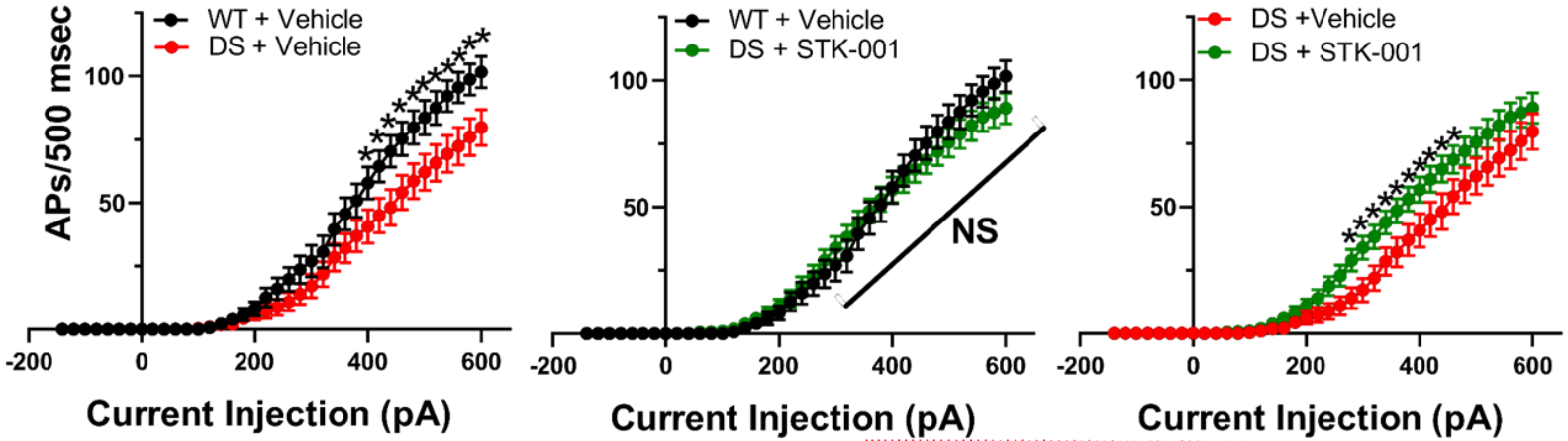


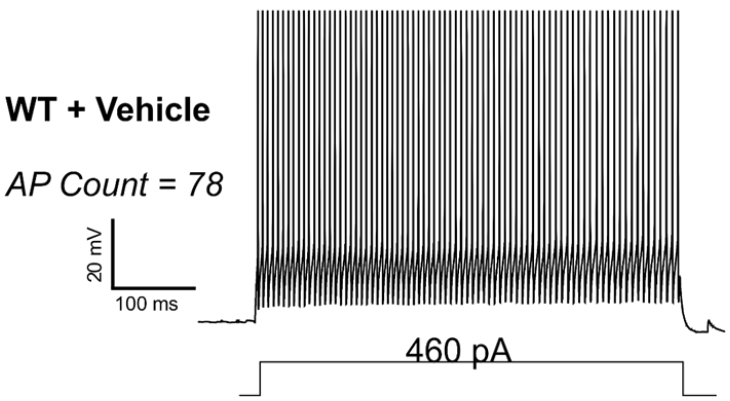


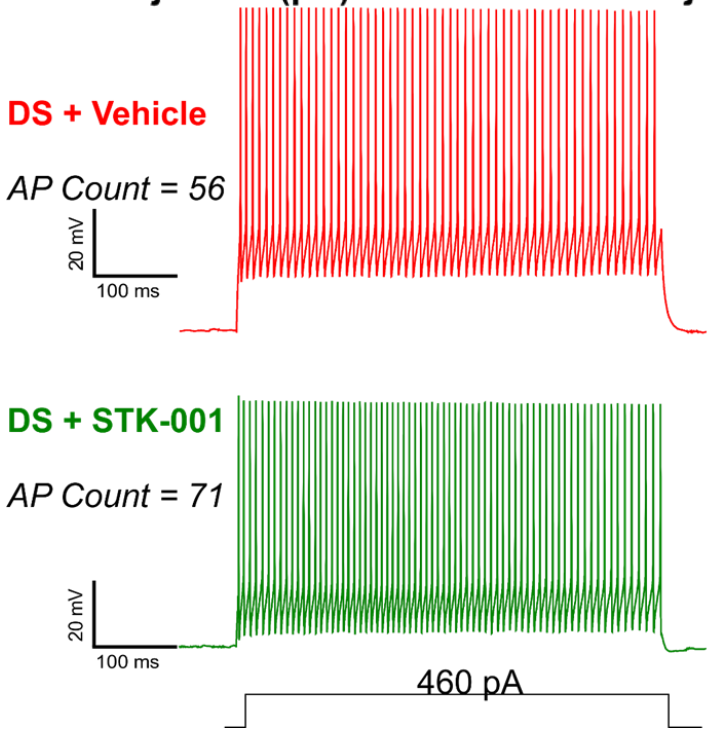


DS PV interneurons are hypoexcitable

STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (2)

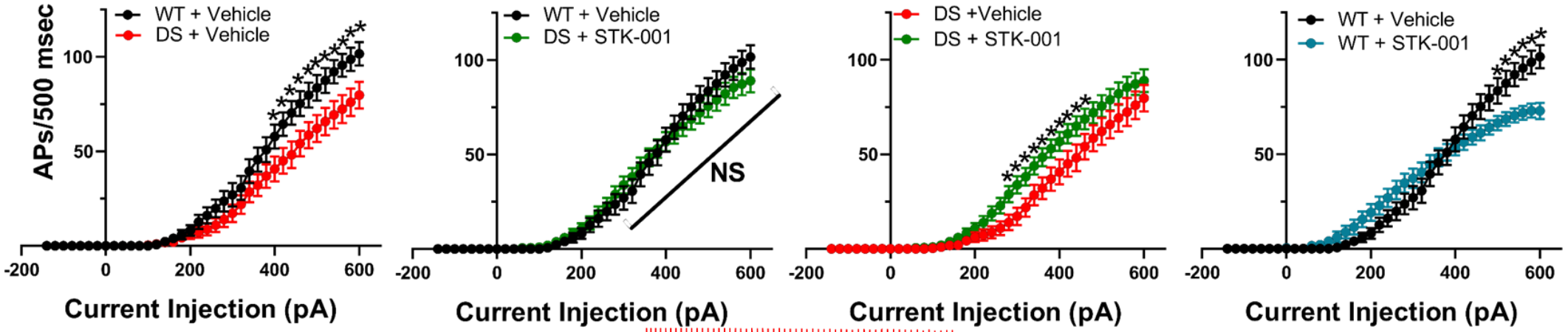


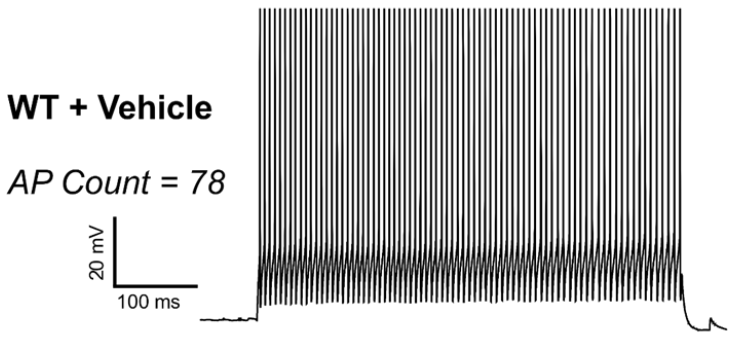


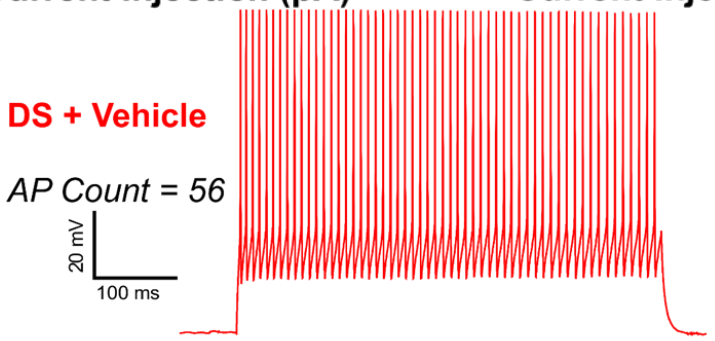


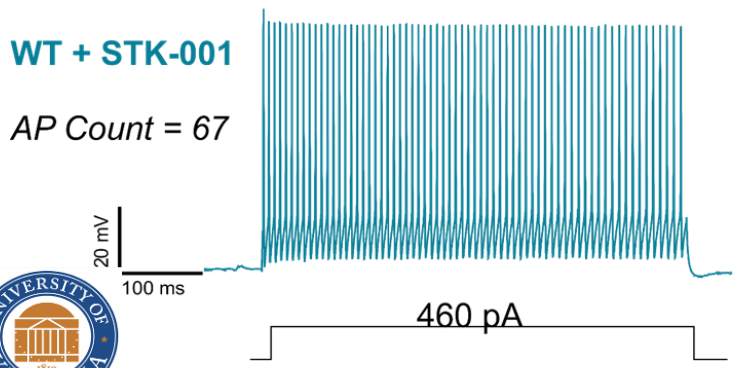
- DS PV interneurons are hypoexcitable
- STK-001 treatment rescues the firing frequency to WT levels

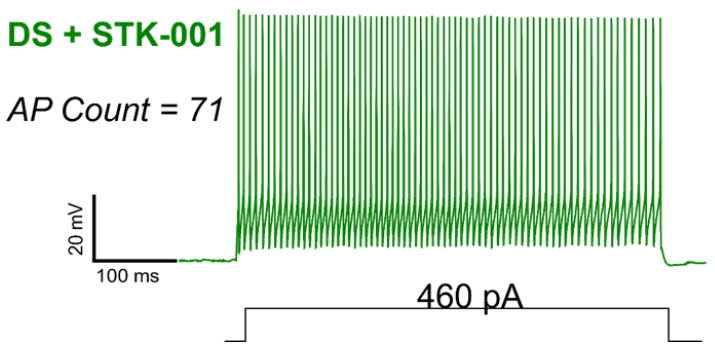
STK-001 Treatment Rescues Parvalbumin-positive Interneuron Excitability in DS Mice (3)











- 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

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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

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Acknowledgements

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Membrane and Action Potential Properties

	Resting Membrane Potential (mV)	Input resistance (MΩ)	Action Potential Threshold (mV)	Rheobase (pA)	Action Potential Amplitude (mV)	Upstroke Velocity (mV/ms)	Downstroke Velocity (mV/ms)	APD50 (ms)
WT PBS	-68.9 ±1.4	110±6	-34±1	239±24	56±2	355±14#&^	-225±13#	0.37±0.03#
WT STK-001	-68.3±1.0	139±13&^	-36±1	168±19&	62±2&	290±13*	-158±10*^	0.55±0.02*^
DS PBS	-69.9±1.0	102±7#	-35±1	290±22#^	55±2#	299±11*	-197±10	0.46±0.05
DS STK-001	-67.2±0.9	103±5#	-37±1	214±21&	57±2	301±11*	-197±9#	0.41±0.02#

* 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