Selective Potentiation of $Na_V1.1$ Channels by Small-Molecule XPC-837 in Dravet Mice Suppresses Spontaneous Seizures, Prevents SUDEP, Increases Long-Term Potentiation, and Normalizes Gene Expression

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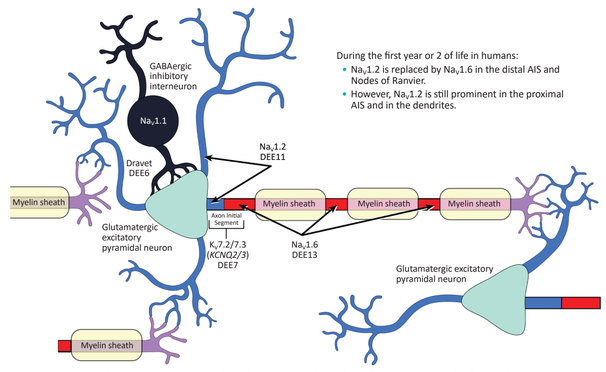
INTRODUCTION

- Loss-of-function variants of *SCN1A* cause Dravet syndrome by decreasing $Na_V1.1$ expression or conductance in inhibitory interneurons. The resulting hypoexcitability of interneurons reduces inhibitory input on excitatory neurons and leads to epilepsy and developmental delays[1,2]
- A precision medicine therapy for Dravet syndrome should restore $Na_V1.1$ activity specifically without impacting other neuronal proteins, especially ion channels
- We are developing orally available small-molecule $Na_V1.1$ potentiators that can directly target the underlying etiology of Dravet syndrome and thus provide a potentially disease-modifying therapy for Dravet syndrome



AIS, axon initial segment; DEE, developmental and epileptic encephalopathy; GABA, gamma-aminobutyric acid; KCNQ, potassium voltage-gated channel subfamily KQT member; K_V, voltage-gated potassium channel; Na_V, voltage-gated sodium channel.

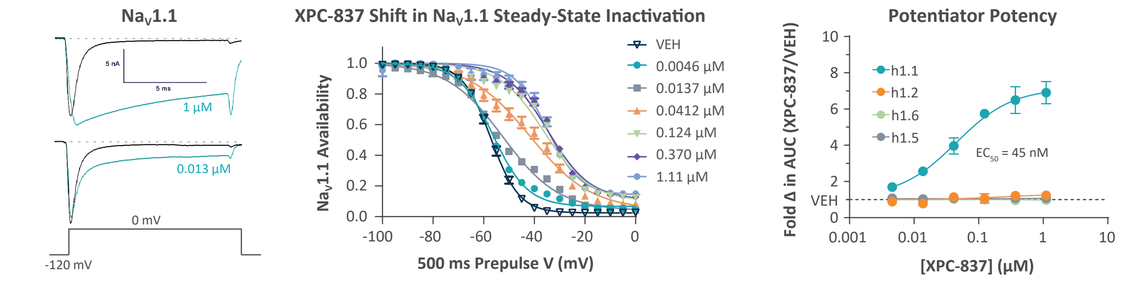
METHODS

- **Potency and selectivity:** Voltage clamp automated electrophysiology was used to assess potency and selectivity of XPC-837 in human embryonic kidney (HEK) cell lines stably expressing voltage-gated sodium (Na_V) channels. Error bars are ± standard error of the mean (SEM)
- **Electrophysiological recordings in brain slices:** Whole-cell current-clamp recordings were made in cortical layer 5. Fast-spiking interneurons expressing viral reporter were targeted for patching
- ***Scn1a*$^{+/-}$ mouse line:** Described in Miller et al[3]
- ***Scn1a*$^{+/-}$ rotarod:** *Scn1a*$^{+/-}$ male mice were tested at P21-22 and P24-P28, respectively
- ***Scn1a*$^{+/-}$ spontaneous seizure assay/sudden unexpected death in epilepsy (SUDEP):** *Scn1a*$^{+/-}$ mice were fed with medicated chow from P21 to P36
- **Long-term potentiation (LTP):** Hippocampal local field potentials were recorded from sagittal brain slices from female *Scn1a*$^{+/-}$ mice administered XPC-837 via medicated chow for 14 days. Stimulation of the cornu ammonis 3 (CA3) Schaffer collaterals with a theta burst high-frequency stimulation induced a long-term potentiation in cornu ammonis 1 (CA1) hippocampal neurons and compared between groups (1-way analysis of variance [ANOVA])
- **RNA-sequencing (RNA-seq):** Saphenous vein blood or hippocampal tissue was taken from wild-type, *Scn1a*$^{+/-}$, and *Scn1a*$^{+/-}$ + XPC-837 mice at P25-P27 and P35, respectively. Mice and samples were individually identified in a spontaneous seizure study for downstream analysis. Significant differential gene expression patterns were identified; all differentially expressed genes (DEGs) shown have $P<0.05$ for a change between analyzed groups, when corrected for multiple testing using the Benjamini-Hochberg (BH) false discovery rate

RESULTS

XPC-837 Potently and Selectively Potentiates $Na_V1.1$

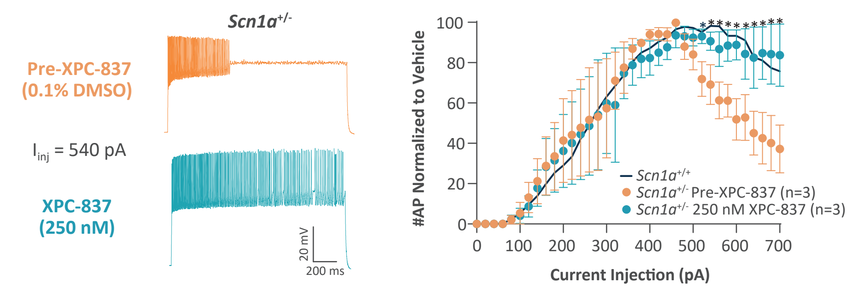
- XPC-837 stabilizes the open state of the $Na_V1.1$ channel selectively with a half-maximal effective concentration (EC_{50}) of 45 nM
- XPC-837 destabilizes steady-state inactivation and increases channel availability across a range of potentials close to neuronal resting membrane potentials



AUC, area under the curve; EC_{50}, half-maximal effective concentration; VEH, vehicle.

XPC-837 Normalizes Interneuron Function in *Scn1a*$^{+/-}$ Mice

- In brain slices from *Scn1a*$^{+/-}$ mice, parvalbumin-positive (PV+) interneuron firing frequency was significantly increased by XPC-837 at current injections where depolarization block occurred, indicating a higher firing frequency of fast-spiking inhibitory interneurons

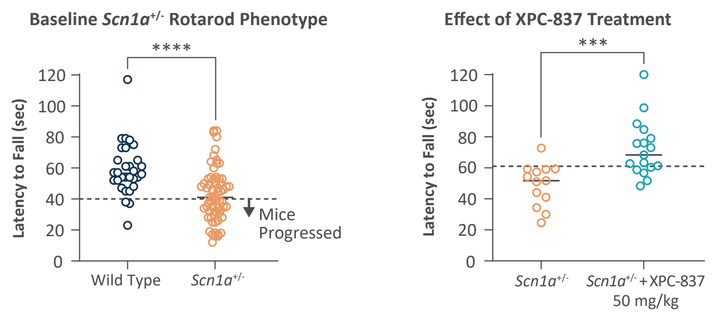


*$P<0.05$

AP, action potential; DMSO, dimethyl sulfoxide; I_{inj}, injection current.

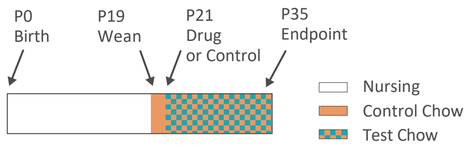
A Single Oral Dose of XPC-837 Improves Motor Performance in *Scn1a*$^{+/-}$ Mice

- XPC-837 rescues function in the rotarod assay of *Scn1a*$^{+/-}$ mice suggesting efficacy against non-seizure-related symptoms such as motor dysfunction

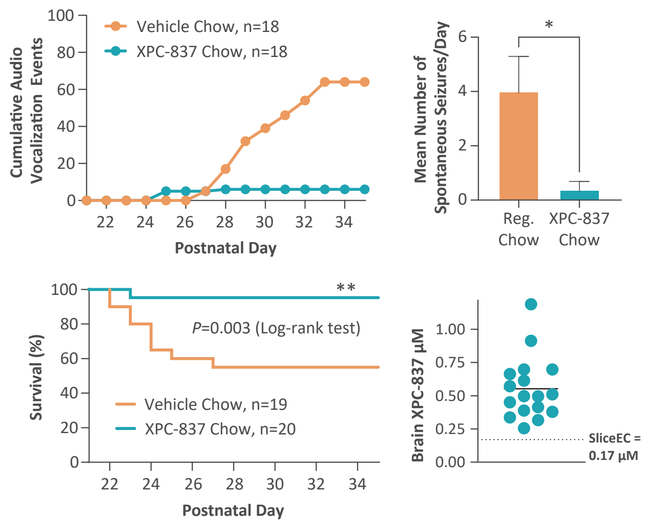


***$P<0.001$, ****$P<0.0001$.

Chronic Oral Dosing of XPC-837 Protects *Scn1a*$^{+/-}$ Mice From Spontaneous Seizures and SUDEP



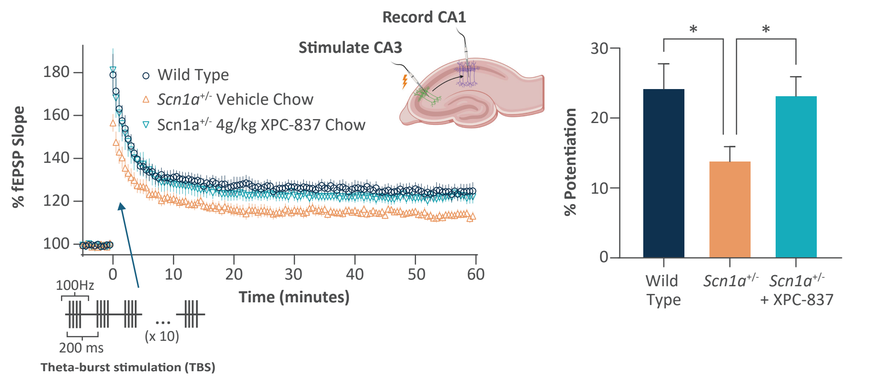
- *Scn1a*$^{+/-}$ mice were fed with chow containing 4 g/kg of XPC-837 or regular chow from P21 until P35
- Audio detection of vocalizations associated with behavioral seizure was used to identify spontaneous seizures in male mice; seizures were confirmed by manual video review
- Chronic dosing led to significant suppression of seizures with brain exposures at the end of the experiment on P36 of 0.55 µM. The chronic brain exposure is comparable to the ex vivo concentration found to be efficacious in correcting firing deficits in PV+ interneurons in brain slices
- Female *Scn1a*$^{+/-}$ mice were significantly protected from SUDEP



*$P<0.05$, **$P<0.01$.
SliceEC, effective concentration in brain slices.

Chronic Oral Dosing of XPC-837 in *Scn1a*$^{+/-}$ Mice Increases LTP – A Potential Cellular Correlate of Learning and Memory

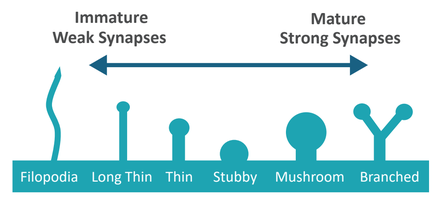
- Female *Scn1a*$^{+/-}$ mice were fed chow containing 4 g/kg of XPC-837 or regular chow from P21 until P34 before LTP recordings were made



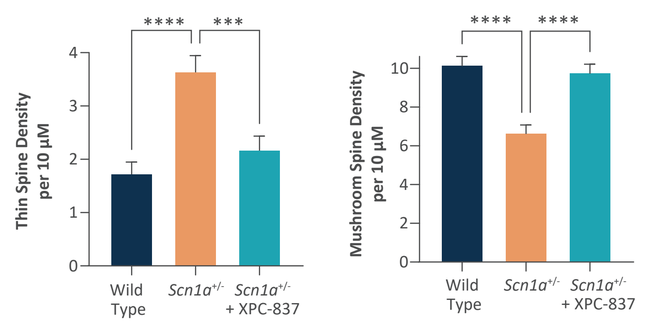
*$P<0.05$.
CA, cornu ammonis; fEPSP, field excitatory postsynaptic potential; LTP, long-term potentiation.

XPC-837 Produces a More Mature Spine Morphology in *Scn1a*$^{+/-}$ Mice

- The deficit in female *Scn1a*$^{+/-}$ mouse dendritic spine maturation[4] was corrected by XPC-837
- XPC-837 decreased thin spines and increased mushroom spines



Adapted from Risher et al with permission under Creative Commons Attribution 4.0 International (CC-BY 4.0) license.[5]

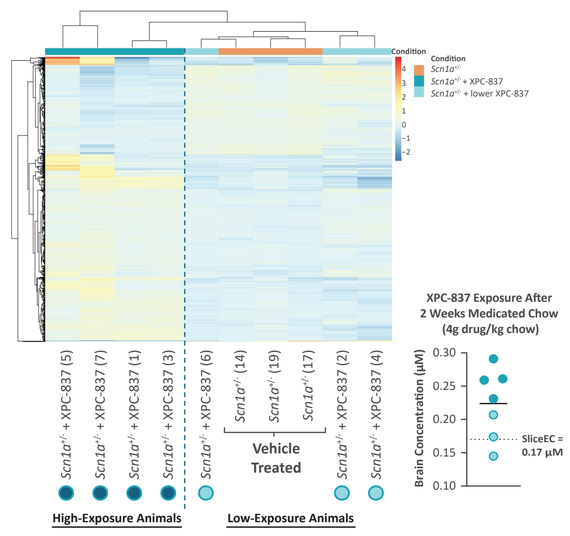


***$P<0.001$, ****$P<0.0001$.

XPC-837 Modulates Hippocampal Gene Expression in *Scn1a*$^{+/-}$ Mice

- XPC-837 brain exposure in female *Scn1a*$^{+/-}$ mice at P35 correlates with significant DEG profiles in the hippocampus when compared with untreated *Scn1a*$^{+/-}$ mice[6]
- Mice with lower XPC-837 brain exposure have DEG profiles similar to untreated *Scn1a*$^{+/-}$ mice
- *Scn1a*$^{+/-}$ mouse #19 is a surviving untreated animal with seizures, #14 & #17 clustered around this 'symptomatic' *Scn1a*$^{+/-}$ mouse

Significant DEGs Between *Scn1a*$^{+/-}$ + XPC-837 and *Scn1a*$^{+/-}$ Mice (Hippocampal Tissue)

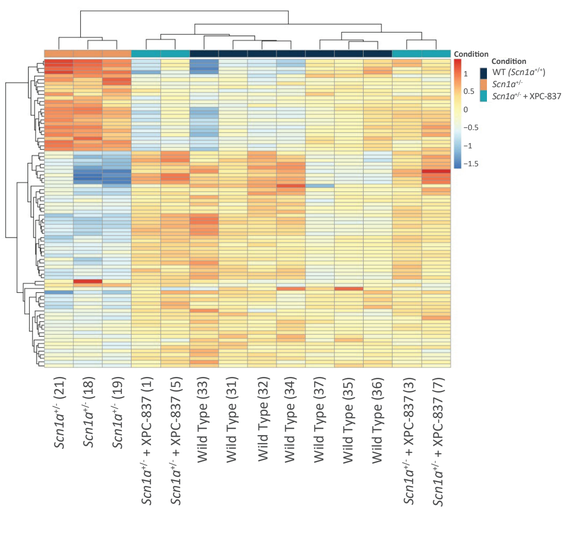


Numbers in parentheses indicate individual mouse represented by the column.
DEG, differentially expressed genes; SliceEC, effective concentration in brain slices.

XPC-837 Modulates Peripheral Gene Expression in *Scn1a*$^{+/-}$ Mice

- Significant difference in DEGs identified between *Scn1a*$^{+/-}$ and wild-type mice
- *Scn1a*$^{+/-}$ mice with high exposure of XPC-837 were aligned with wild-type expression of the DEGs
- Suggests that XPC-837 realigns *Scn1a*$^{+/-}$ 'disease-related' genes back toward wild-type levels
- Blood sampling of mice early (P25-27) avoids survivor bias that can be present in the brain tissue data analysis at P35

Significant DEGs Between *Scn1a*$^{+/-}$ vs Wild-Type and Similarities Between *Scn1a*$^{-}$ XPC-837 vs Wild-Type (Saphenous Blood)



Numbers in parentheses indicate individual mouse represented by the column.
DEG, differentially expressed genes; WT, wild type.

CONCLUSIONS

- XPC-837 is an orally available, central nervous system (CNS)-penetrant, highly $Na_V1.1$-selective small-molecule potentiator that stabilizes open states, and increases channel availability and Na^+ flux
- This mechanism of action increases interneuron excitability in *Scn1a*$^{+/-}$ mouse neurons
- Acute dosing of XPC-837 improves motor performance in the rotarod assay, supporting the potential for improvements in motor function in patients with Dravet syndrome
- Chronic dosing over 14 days with XPC-837 in chow suppresses spontaneous seizures, prevents SUDEP, increases LTP, and produces a more mature dendritic spine morphology
- RNA-seq data demonstrate patterns of gene expression differences in blood cells between wild-type and *Scn1a*$^{+/-}$ mice; these differences were normalized by administration of XPC-837 to *Scn1a*$^{+/-}$ mice
- Efficacious concentrations of XPC-837 in chronic dosing experiments in *Scn1a*$^{+/-}$ mice were similar across assays and consistent with brain slice data
- XPC-837 represents a novel, mechanistically differentiated, orally available compound with the potential to provide an improved therapeutic profile for the overarching treatment of Dravet syndrome

References: **1.** Claes L, et al. *Am J Hum Genet*. 2001;68(6):1327-1332. **2.** Tai C, et al. *Proc Natl Acad Sci USA*. 2014;111(30):E3139-E3148. **3.** Miller AR, et al. *Genes Brain Behav*. 2014;13(2):163-172. **4.** Pizzamiglio L, et al. *Neurobiol Dis*. 2025;207:106853. **5.** Risher WC, et al. *PLoS One*. 2014;9(9):e107591. **6.** Hawkins NA, et al. *Exp Neurol*. 2019;311:247-256.

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