



XENON

XEN901: A Novel, Highly Selective Na_v1.6 Inhibitor for the Treatment of Epilepsy

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XEN901: A Highly Selective $\text{Na}_v1.6$ Inhibitor

- Potent and highly selective $\text{Na}_v1.6$ inhibitor
 - Avoid inhibition of $\text{Na}_v1.1$ and $\text{Na}_v1.5$ to improve safety profile
 - Novel sodium channel binding site and mechanism of action
- Precision medicine to selectively address the etiology of Early Infantile Epileptic Encephalopathy type 13 (EIEE13)
 - Gain-of-function mutation in SCN8A causes EIEE13
 - Excellent efficacy in transgenic mouse model for EIEE13
- Treatment for focal seizures that achieves higher levels of ***seizure freedom*** with an improved side effect profile
 - Excellent efficacy in Maximal Electroshock Seizure (MES) models with high therapeutic index
- Favorable PK and safety profile in ongoing Phase 1
 - Expect regulatory filing for Phase 2 by year-end

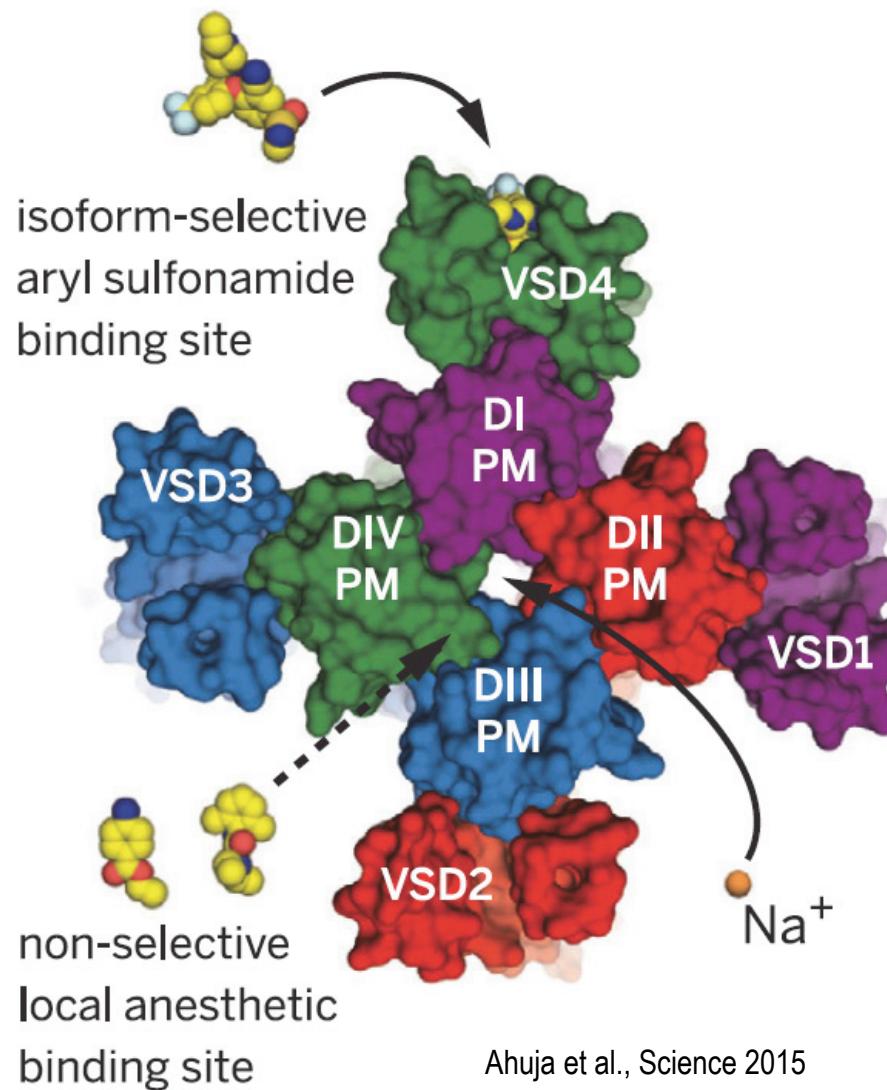
Potential Best in Class Sodium Channel Inhibitor

Rationale for Selective $\text{Na}_v1.6$ Inhibitors

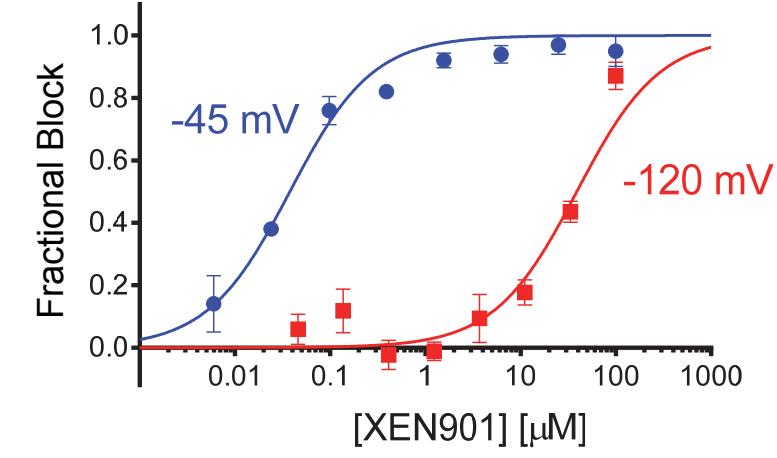
- Low TI of currently used Na_v inhibitors is generally dose limiting
 - Non-selective among Na_v 's in CNS (1.1, 1.2 and 1.6) and CV (1.5)
 - Block of $\text{Na}_v1.1$ proconvulsant: highly expressed in GABAergic interneurons
 - Dravet Syndrome usually loss of function mutation in $\text{Na}_v1.1$
 - No benefit to block of $\text{Na}_v1.5$ and introduces risk of CV adverse effect
 - Low potency – requires high dose/exposure
 - Adverse effects preclude achieving seizure freedom
- Precision medicine for treating etiology of EIEE13 (SCN8A epilepsy)
- Modest suppression of $\text{Na}_v1.6$ activity needed for seizure control

Highly Selective Inhibitors Targeting Voltage Sensor Domain IV

- Therapeutically used Na_v inhibitors bind in pore domain
 - Promiscuous, low affinity binding site
- High affinity and selectivity achieved by binding VSD4 in an extracellular site



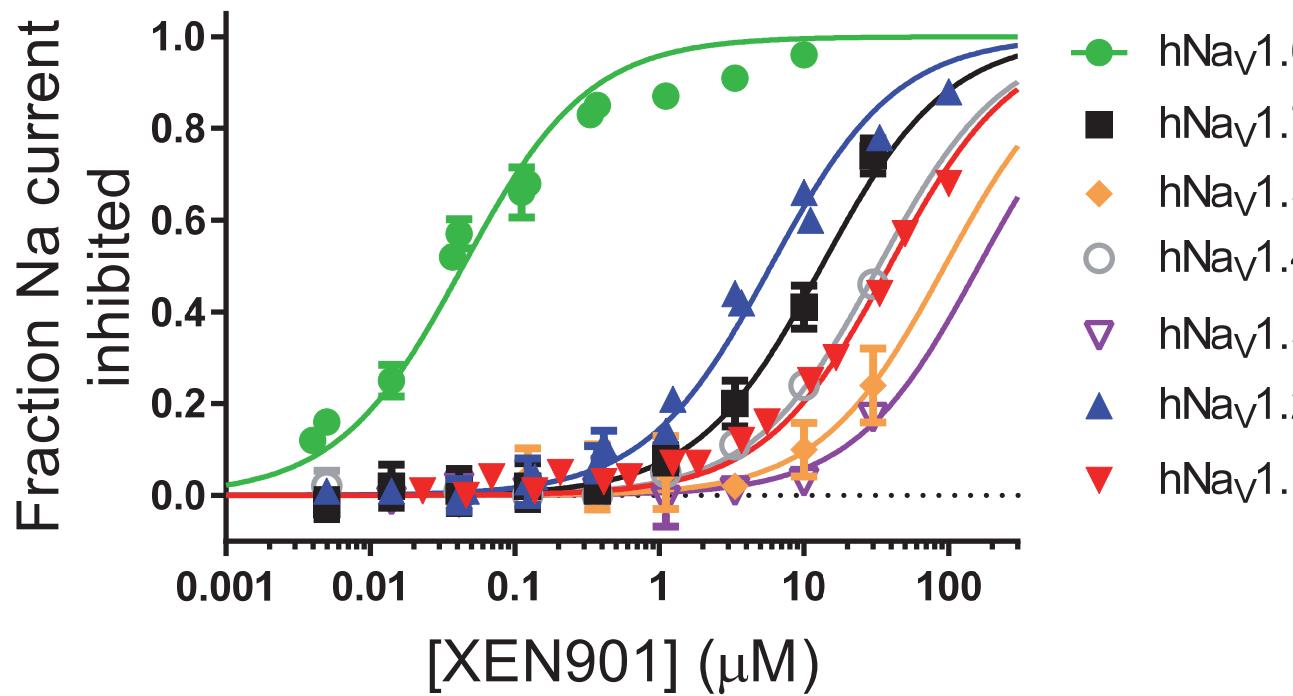
Ahuja et al., Science 2015



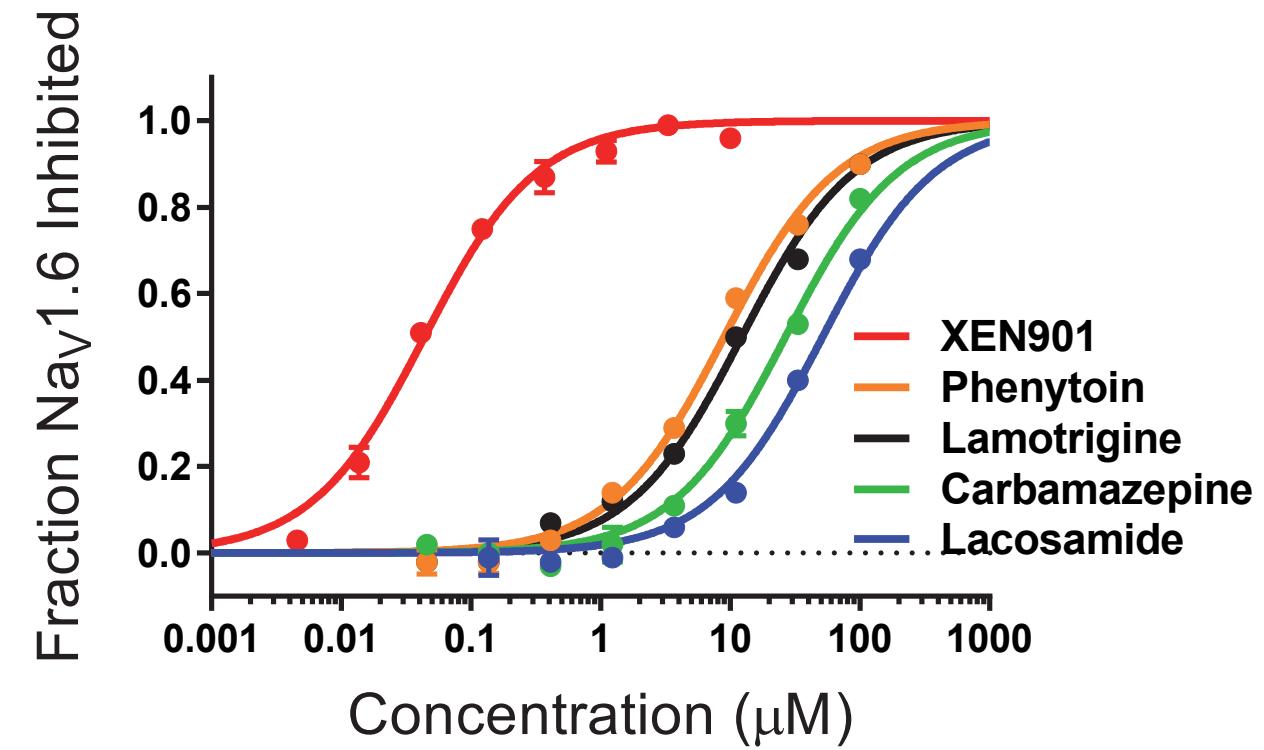
- State dependent block

Xenon's Approach: Target VSD4 in $\text{Na}_v 1.6$ to Achieve High Selectivity

XEN901 is a Potent and Selective Inhibitor of $\text{Na}_v1.6$

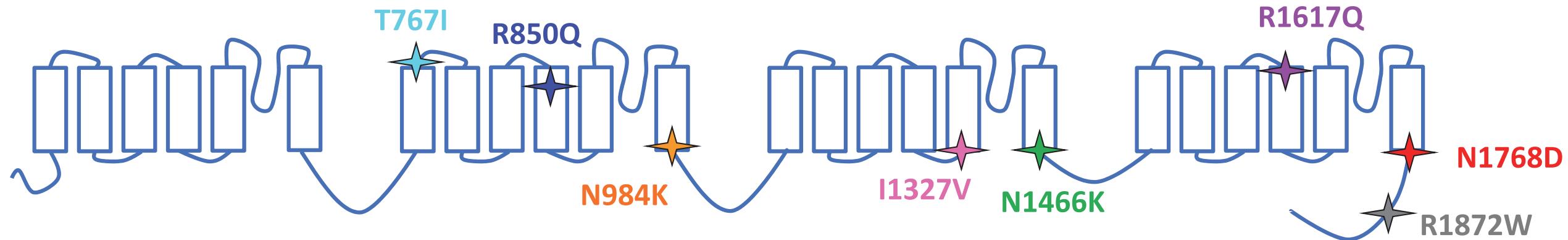


- >100-fold selective vs. other Na_v's
 - Inhibition of Na_v1.1 is pro-convulsant
 - Inhibition of Na_v1.5 poses CV risk

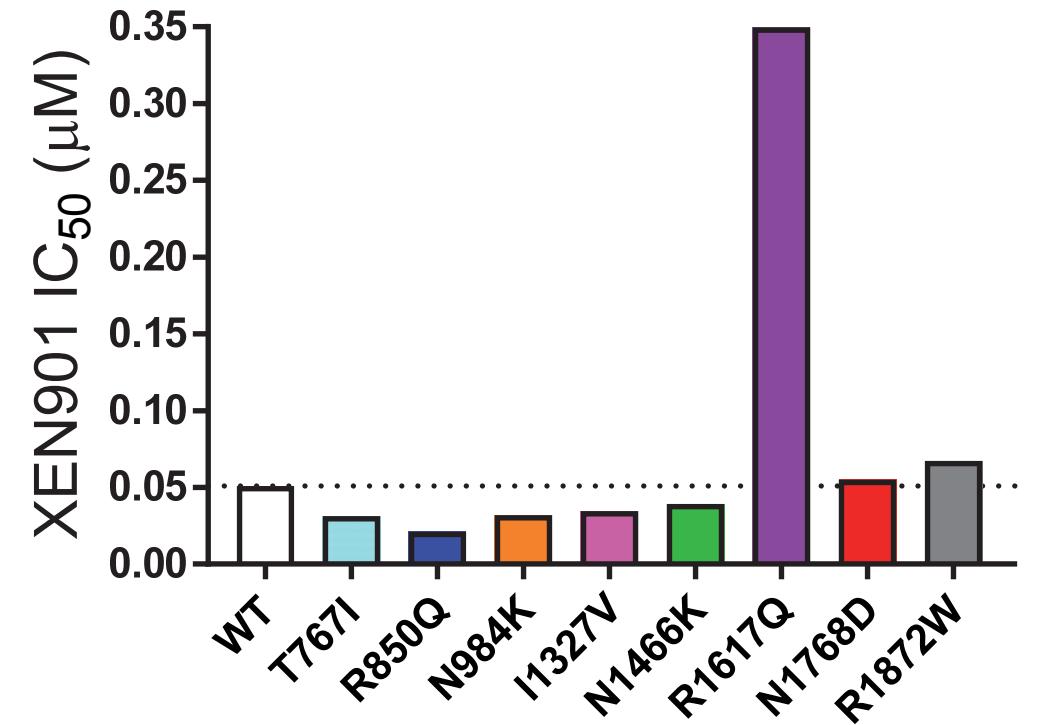


- >100-fold more potent than non-selective AEDs

XEN901 is Potent Across EIEE13 Mutations

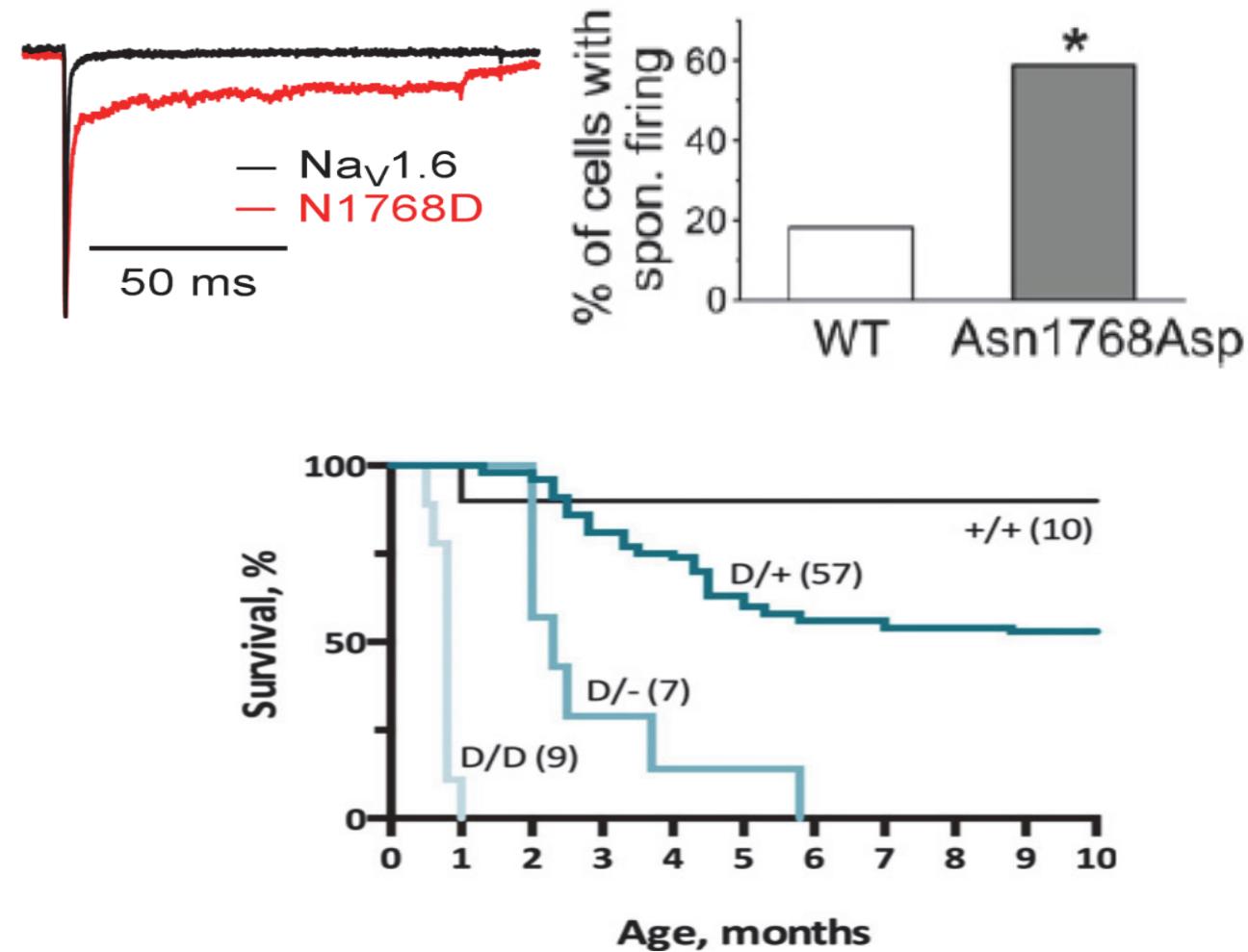


- Mutations known to cause EIEE13 were incorporated into $\text{Na}_v 1.6$ and potency of block by XEN901 was evaluated
- 7 of 8 mutants are blocked with similar potency as WT channel
 - R1617Q in the binding site; although block is weaker, still more potent than currently available Na_v inhibitors



Early Infantile Epileptic Encephalopathy Type 13

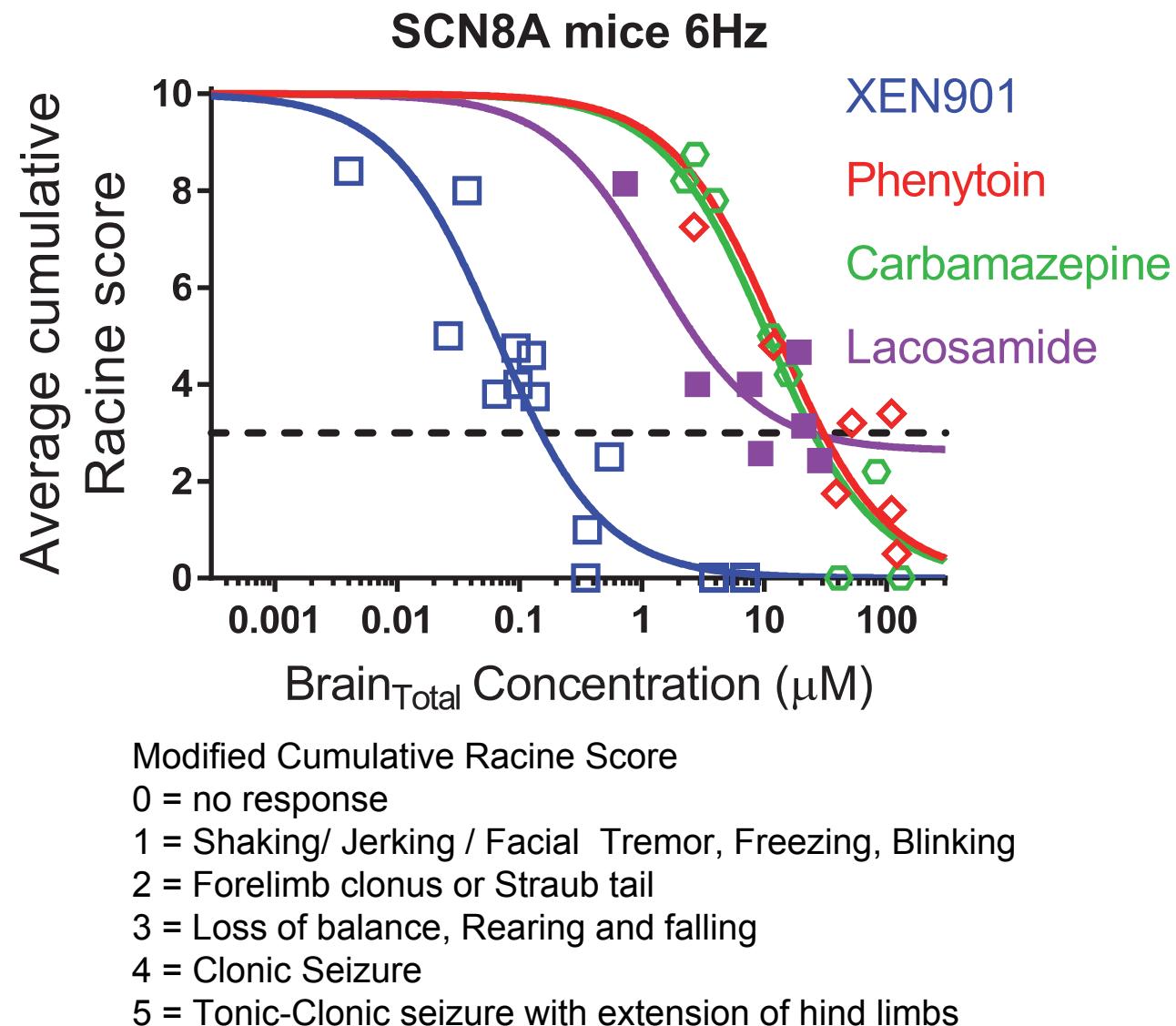
- Precision medicine to treat the etiology of a severe childhood epilepsy
 - Caused by SCN8A GOF mutations
 - Early genetic testing support estimates of ~15-20% of Dravet patient numbers
 - ≈50 births/year in U.S.
- SCN8A mouse model of EIEE13
 - Use for target engagement and screening assay
 - Phenotype similar in mice and humans



Veeramah et al., 2012

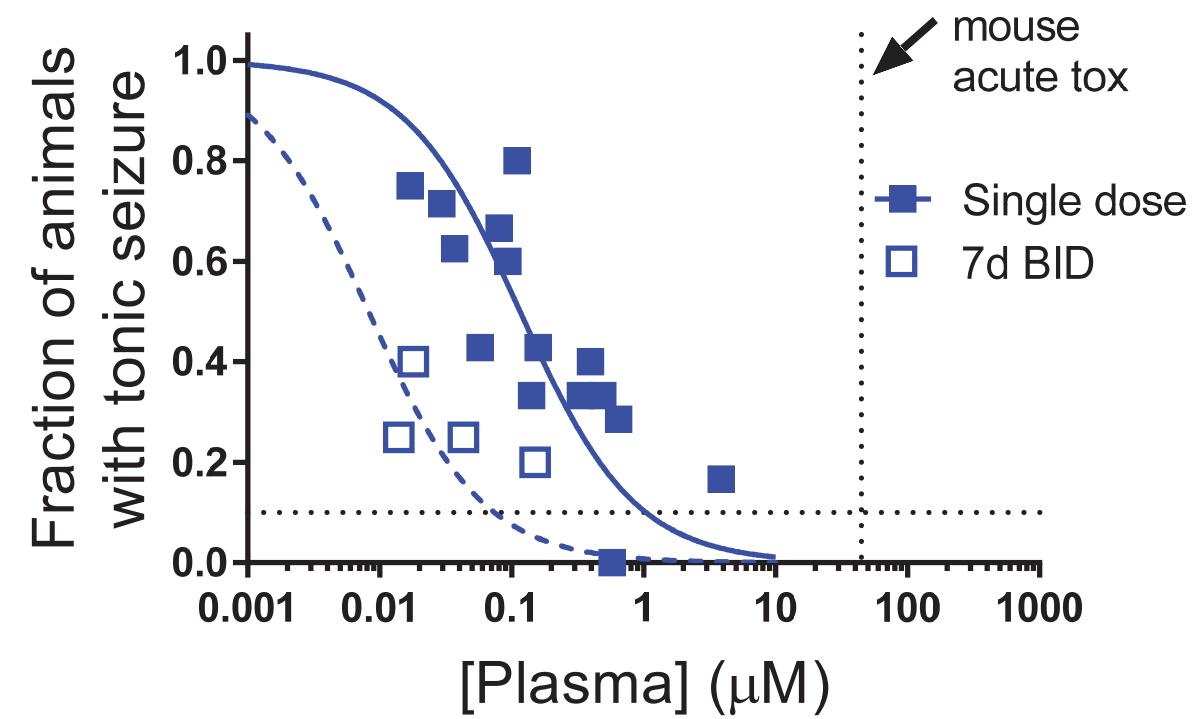
Seizure Control/Freedom in SCN8A Tg Mouse Model of EIEE13

- XEN901 completely suppresses seizures in modified 6 Hz assay
 - Elicit tonic-clonic seizure in Tg mice, no seizures in wild type mice (dotted line)
 - Suppress to wild type at EC₇₀
- >100-fold greater potency compared to current treatments for EIEE13

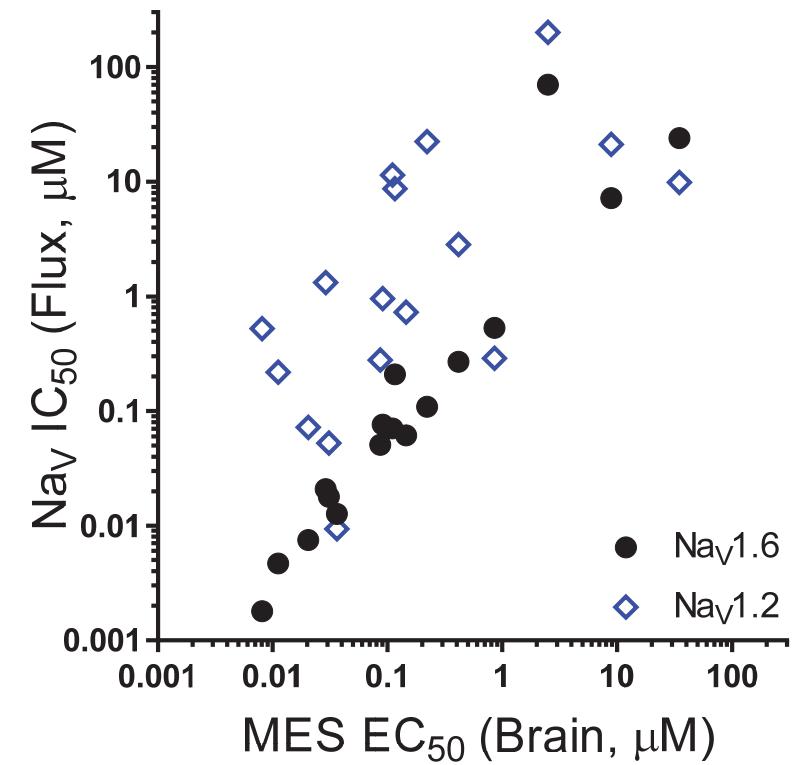
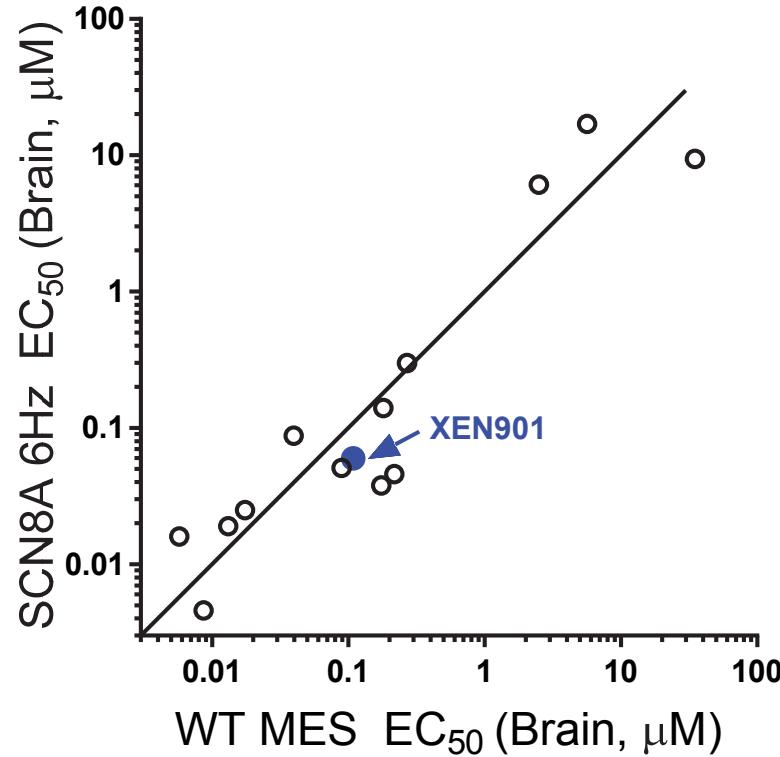
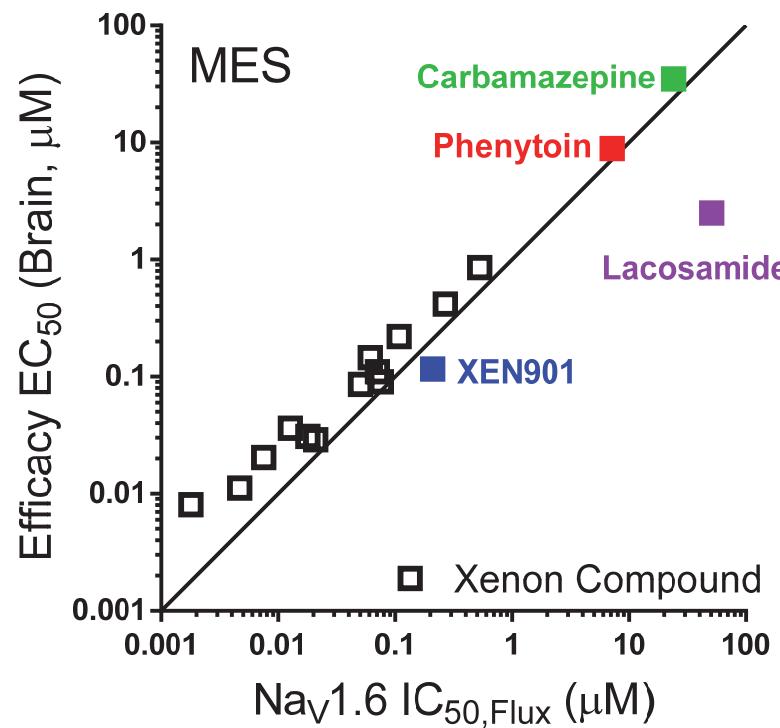


XEN901 is Potent and Efficacious in MES

- Therapeutically used Na_v antagonists active in MES assay – good translational model
- Concentration-dependent increase in efficacy
- Doses of 3-200 mg/kg
- Chronic dosing leads to $\sim 10x$ increase in potency
- High safety margin
- Similar observations in rat MES assay



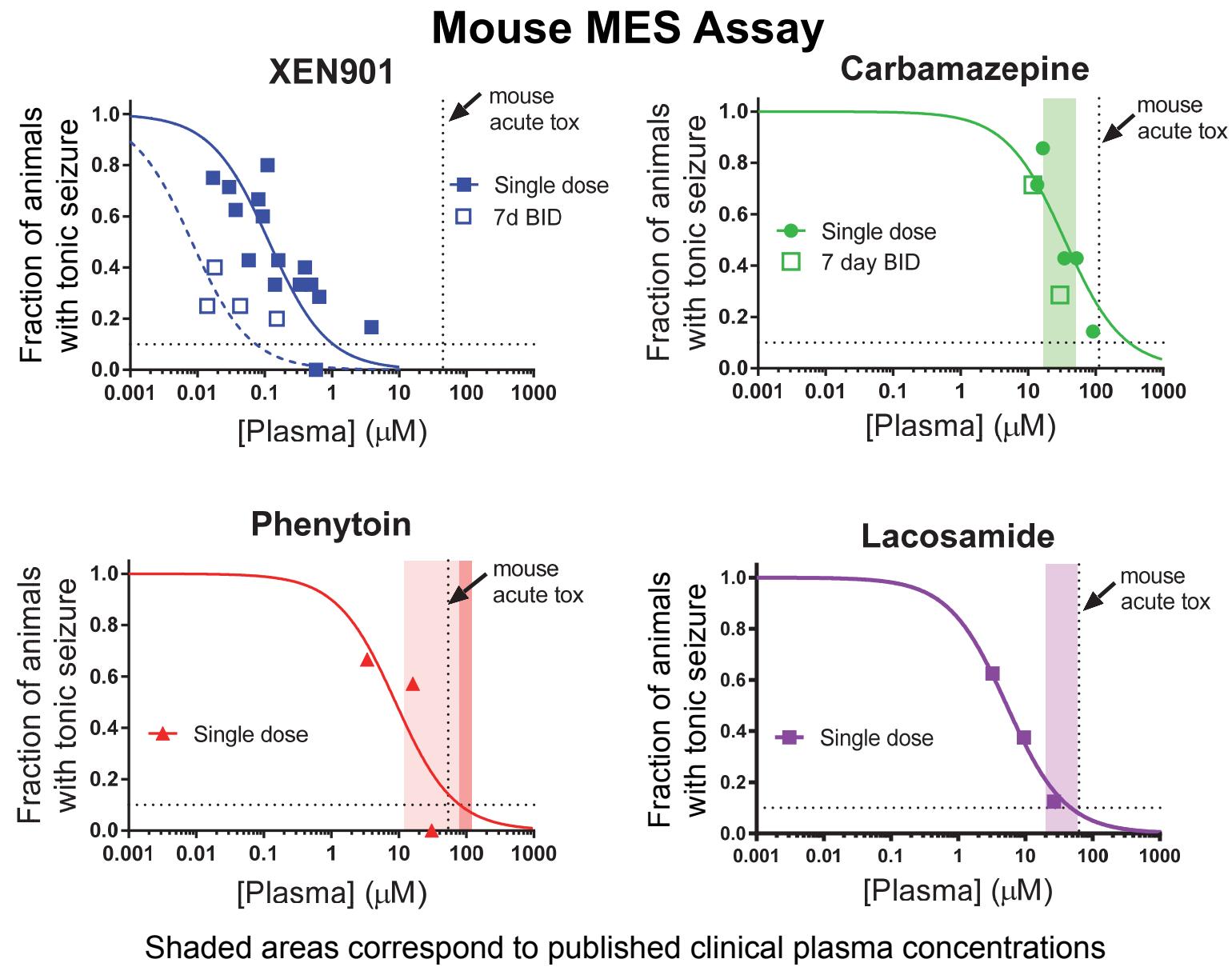
Potency in the MES Model Driven by $\text{Na}_v1.6$



- Potency in both assays highly correlated with potency against $\text{Na}_v1.6$ and brain concentration
- Good correlation between SCN8A Tg mouse and MES assays
- Independent of potency at $\text{Na}_v1.2$ or other sodium channels

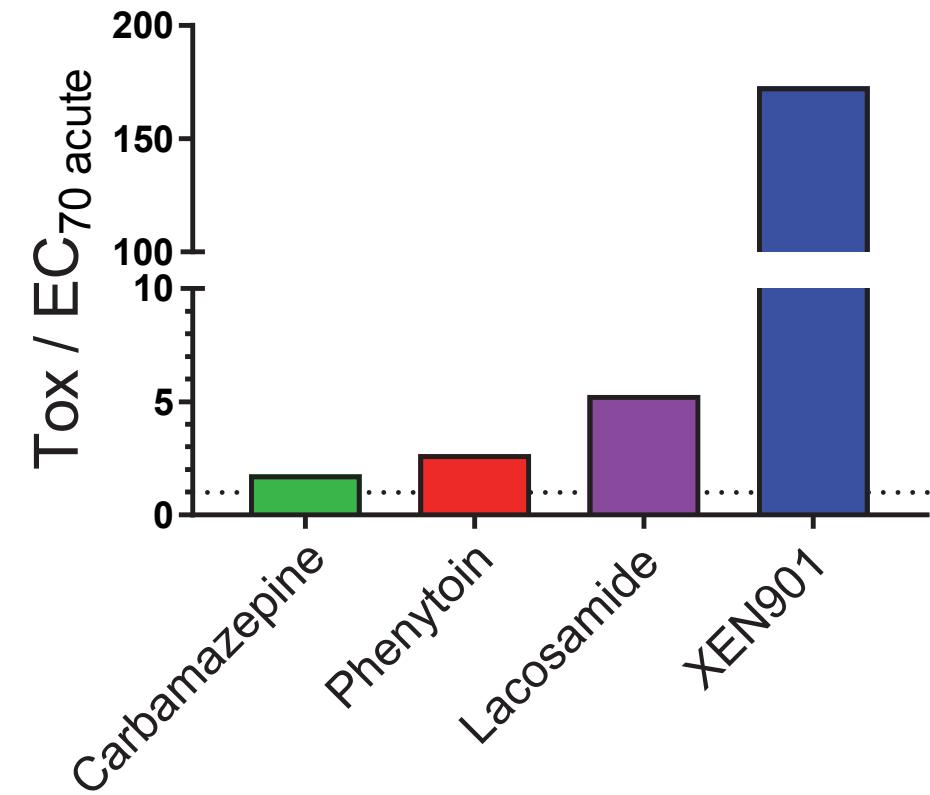
Striving for Seizure Freedom with XEN901

- Current Na_v channel AEDs require 1-5 times the mouse MES EC_{50} for clinical efficacy.
- Current agents lack therapeutic index needed to achieve seizure freedom for many patients
- High TI of XEN901 could enable high level of efficacy with minimal adverse events



Improved Therapeutic Index Over Other Na_v Inhibitors

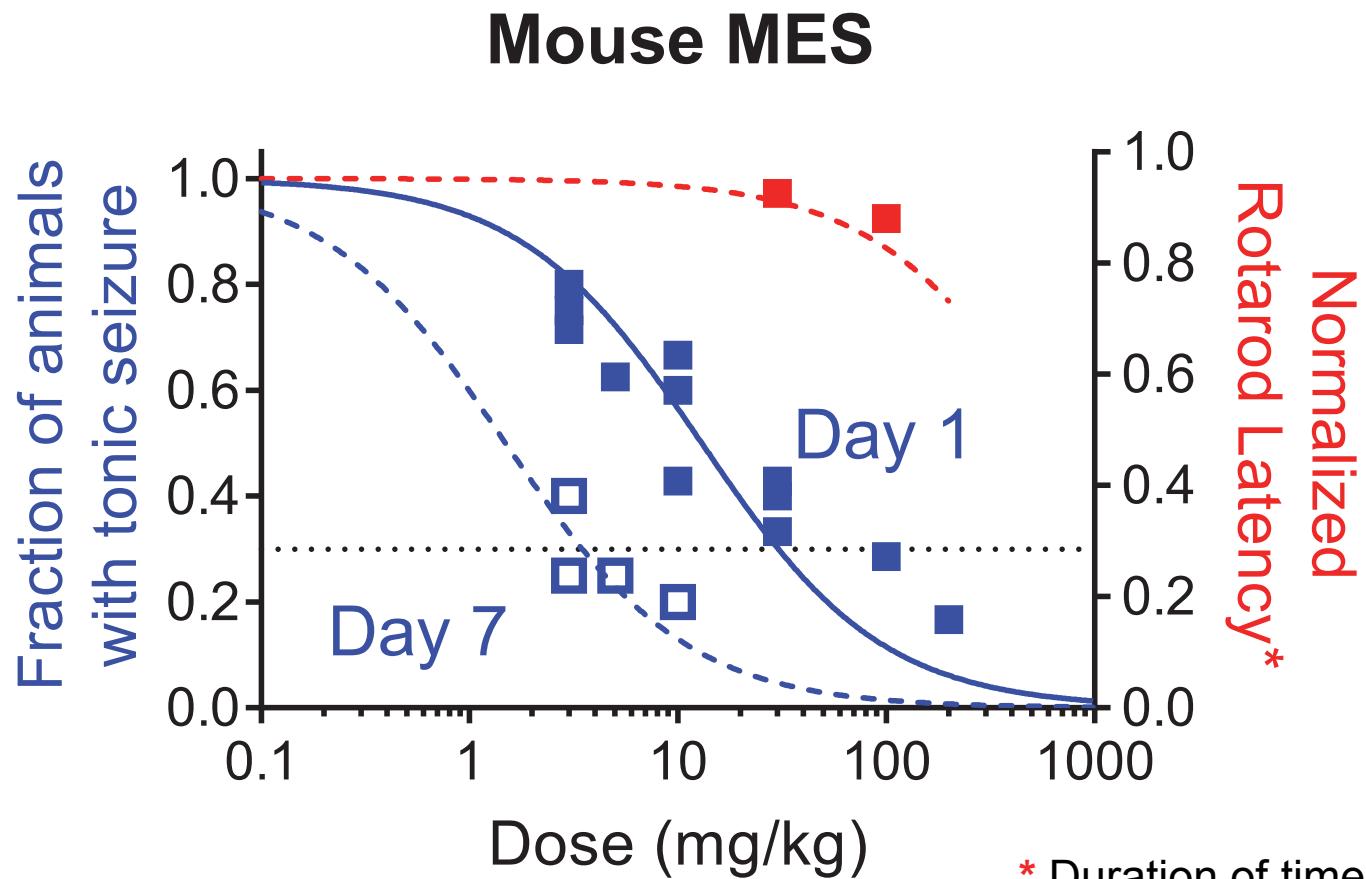
Compound	EC_{70} Plasma (μM)	Toxic Plasma Levels (μM)	Safety Margin
XEN901 (acute)	0.264	45	170
Phenytoin	20	54	1.7
Carbamazepine	60	233	3.8
Lacosamide	12	63	5.3



- EC_{70} = plasma concentration where 70% of mice are protected from tonic seizure induction in MES assay
- Toxic = minimum plasma concentration where severe adverse behavioral effects were observed

XEN901: Favorable Motor Impairment Safety Margin

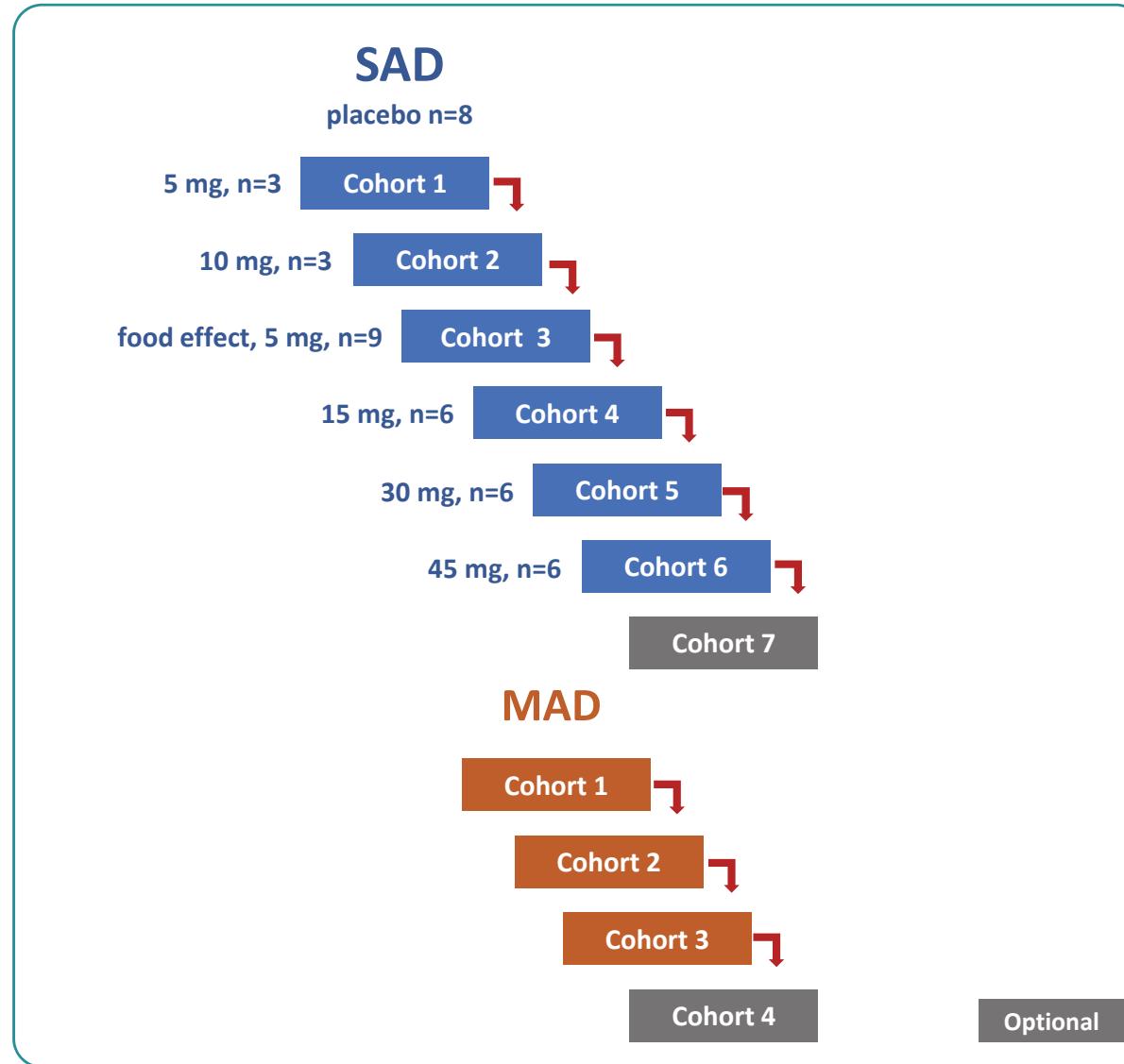
- Rotarod assay to assess possible motor impairment
- Data expressed as function of dose (for comparison with literature values)
 - Safety margin based on dose in mouse
MES for XEN901 : >25
 - Other literature comparisons:
Carbamazepine(po): 7.7
Phenytoin (po): 10.3
Lacosamide (ip): 6.0



* Duration of time on rotarod normalized by time with vehicle

Potential Best in Class Safety Margin for XEN901

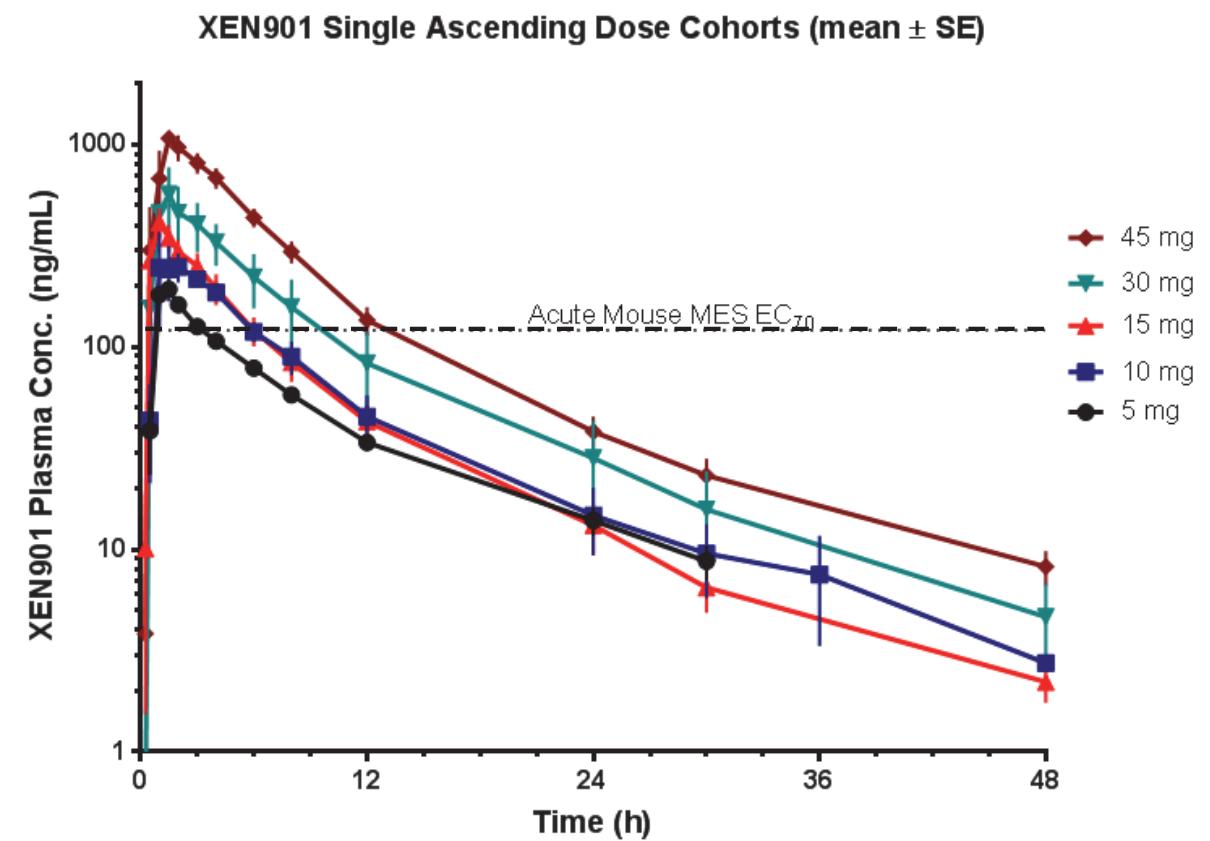
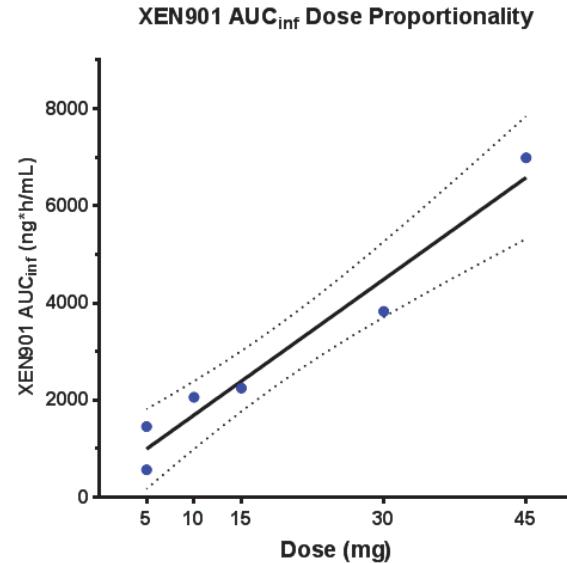
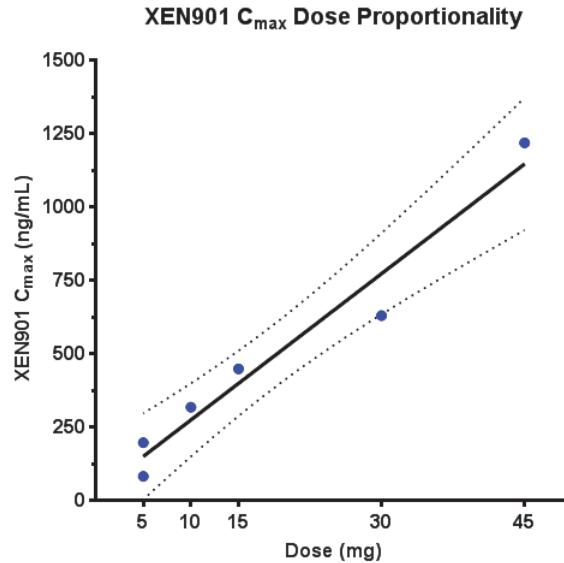
XEN901 Phase 1 Trial Design



Anticipate Complete Phase 1 Results in H2, 2018

PK in Phase 1 SAD Study with XEN901

- XEN901 shows dose proportional exposure with single doses of 5-45 mg
- PK displays low inter-individual variability
- PK profile suitable for at least BID dosing ($t_{1/2} = 8-11$ hours)

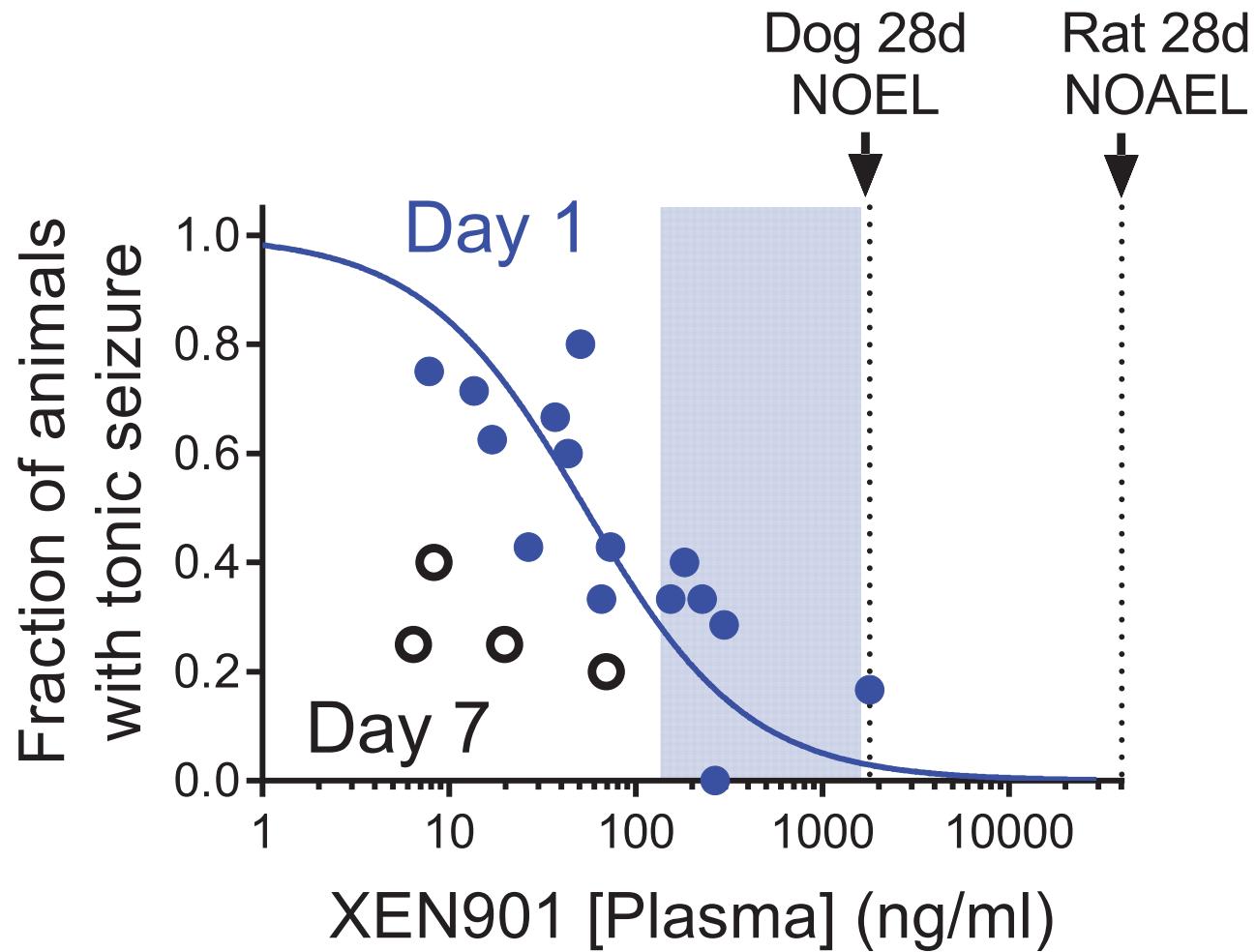


Interim Preliminary Safety Summary

- Ongoing placebo-controlled, randomized (3:1), double-blind study
 - Single doses completed at 5, 10, 15, 30, and 45 mg
- No SAEs or deaths
- No clinically significant ECG, or Laboratory findings
- All reported AEs to date are mild or moderate
 - Related AEs were mild and resolved spontaneously
 - Most common AE was headache
- Overall safe and well tolerated with C_{max} up to 1600 ng/mL in SAD

Interim Results Show Good Safety and Tolerability of XEN901

Safe Exposure in Phase 1 at or Above EC₉₀



Shaded area corresponds to range between
highest C_{max} and C_{12hrs} at 45 mg dose

XEN901 Proposed Phase 2 Clinical Planning

- Anticipate completing ongoing Phase 1 SAD and MAD in H2, 2018
- Expect regulatory filing for Phase 2 clinical trial in adult focal seizures by year-end
- Pediatric development options currently being evaluated
 - Focal seizure population
 - Explore precision medicine in SCN8A population

XEN901 Summary

- XEN901 inhibits $\text{Na}_v1.6$ with high potency and selectivity
 - Novel binding site and mechanism of inhibition
 - Isoform selectivity enables high therapeutic index
- Best in class safety margin
 - Demonstrated seizure freedom in rodent models
 - Excellent PK, safety, tolerability to date in Phase 1 at predicted therapeutic plasma concentration
- Promising for treatment of both focal seizures in adults and as a precision medicine for treating infants with EIEE13 or other childhood epilepsies

“Best-in-Class” Potential of XEN901

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