XENON

XEN901: A Novel, Highly Selective $Na_V1.6$ Inhibitor for the Treatment of Epilepsy

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Eilat XIV Meeting | May 15, 2018 | Madrid, Spain

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XEN901: A Highly Selective $Na_V1.6$ Inhibitor

- Potent and highly selective $Na_V1.6$ inhibitor
  - Avoid inhibition of $Na_V1.1$ and $Na_V1.5$ 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

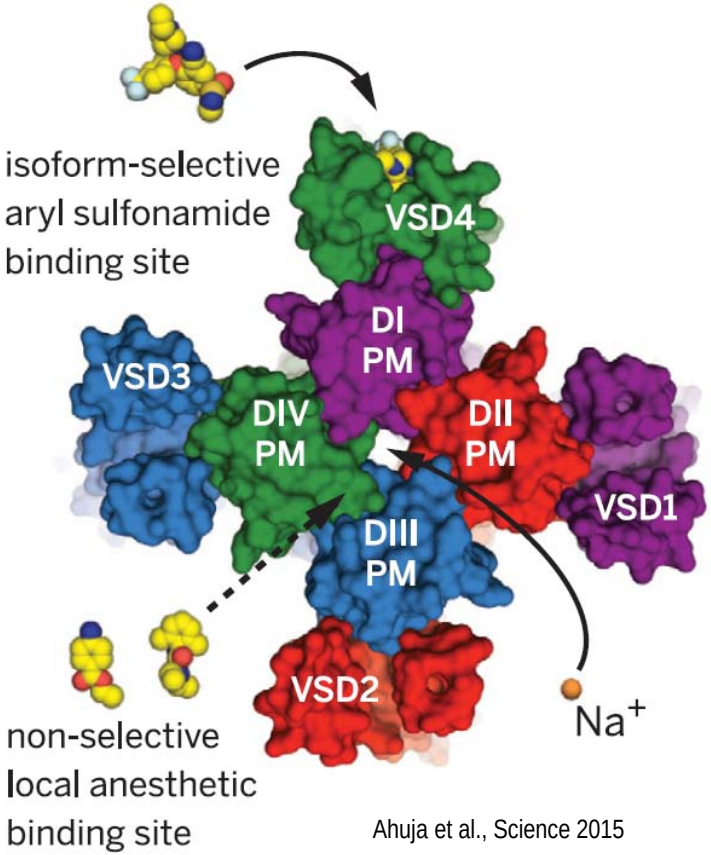
Potential Best in Class Sodium Channel Inhibitor

Rationale for Selective $Na_V1.6$ Inhibitors

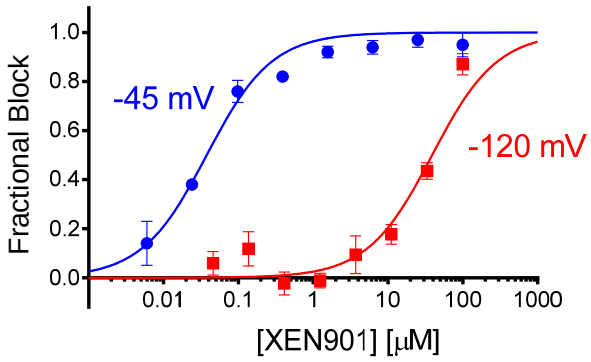
- Low TI of currently used Na_V inhibitors is generally dose limiting
  - Non-selective among Na_V's in CNS (1.1, 1.2 and 1.6) and CV (1.5)
    - Block of $Na_V1.1$ proconvulsant: highly expressed in GABAergic interneurons
      - Dravet Syndrome usually loss of function mutation in $Na_V1.1$
    - No benefit to block of $Na_V1.5$ 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 $Na_V1.6$ 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



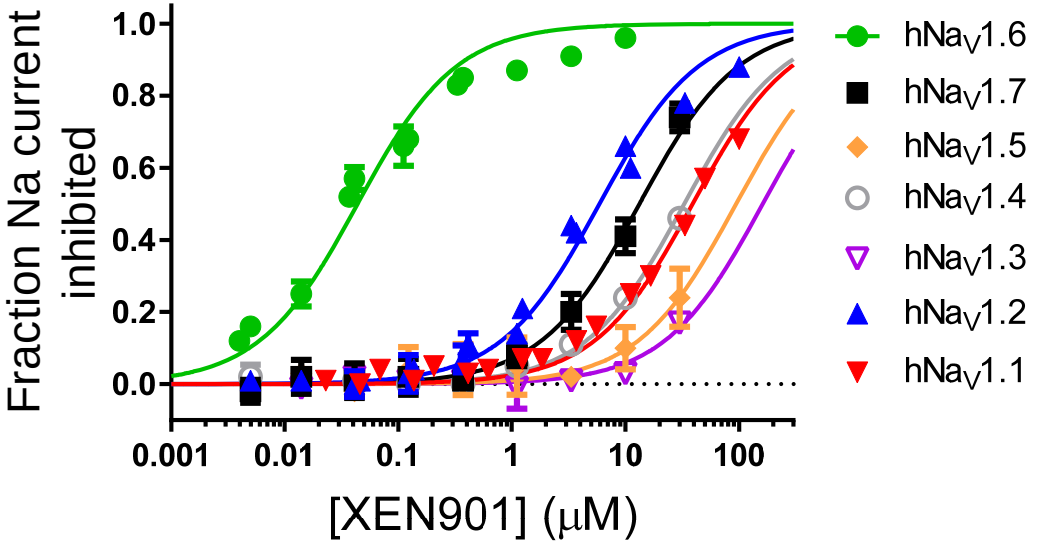
Ahuja et al., Science 2015

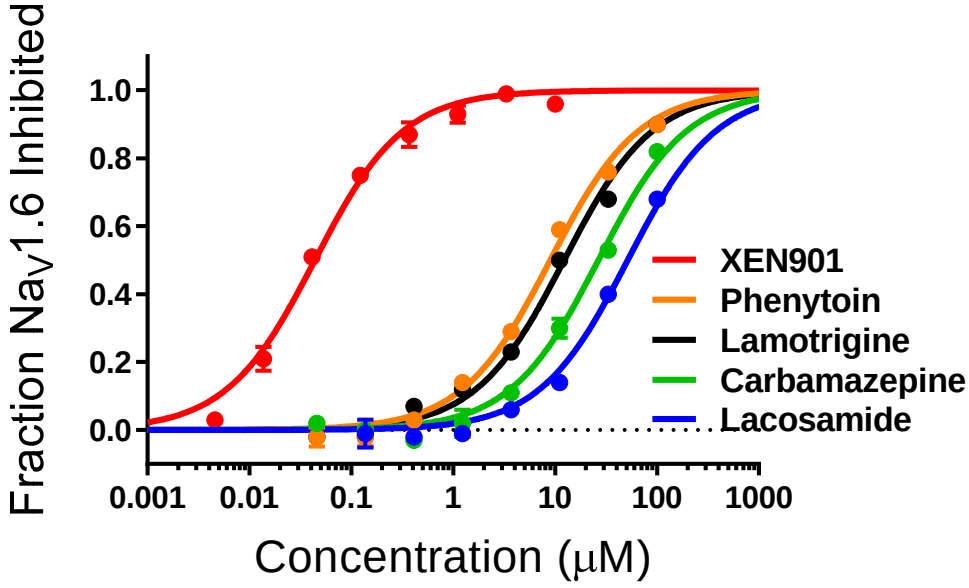


- State dependent block

Xenon's Approach: Target VSD4 in $Na_V1.6$ to Achieve High Selectivity

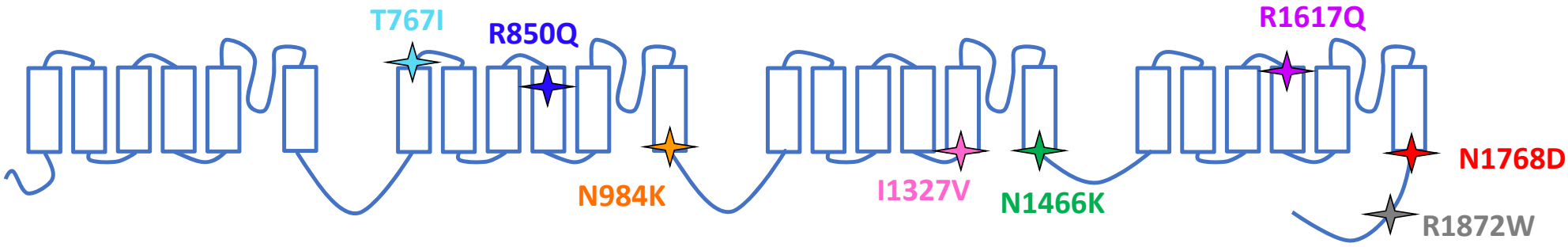
XEN901 is a Potent and Selective Inhibitor of $Na_V1.6$



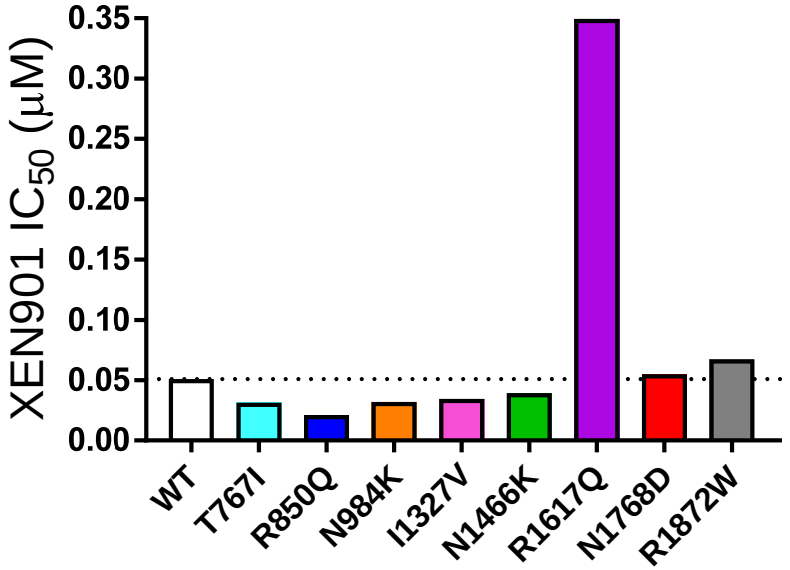


- >100-fold selective vs. other Na_V's
  - Inhibition of $Na_V1.1$ is pro-convulsant
  - Inhibition of $Na_V1.5$ poses CV risk
- >100-fold more potent than non-selective AEDs

XEN901 is Potent Across EIEE13 Mutations

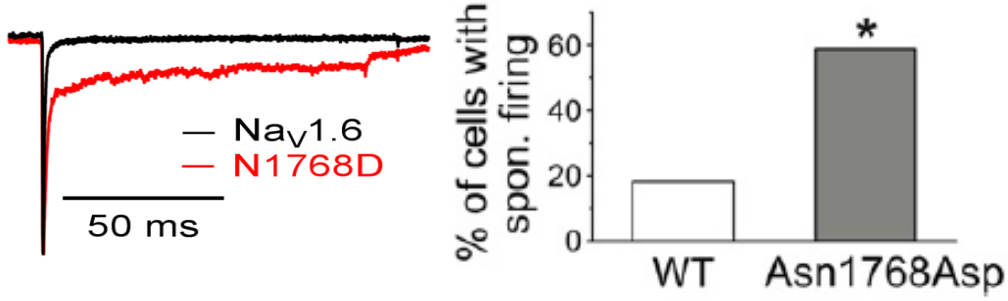


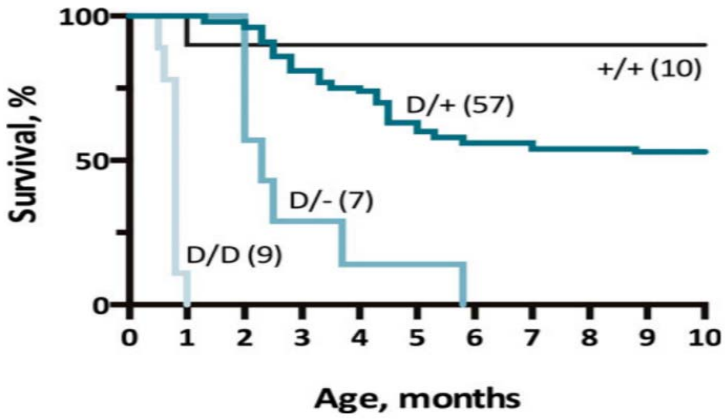
- Mutations known to cause EIEE13 were incorporated into $Na_V1.6$ and potency of block by XEN901 was evaluated
- 7 of 8 mutants are blocked with similar potency as WT channel
  - R1617Q in the binding site; although block is weaker, still more potent than currently available Na_V inhibitors



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

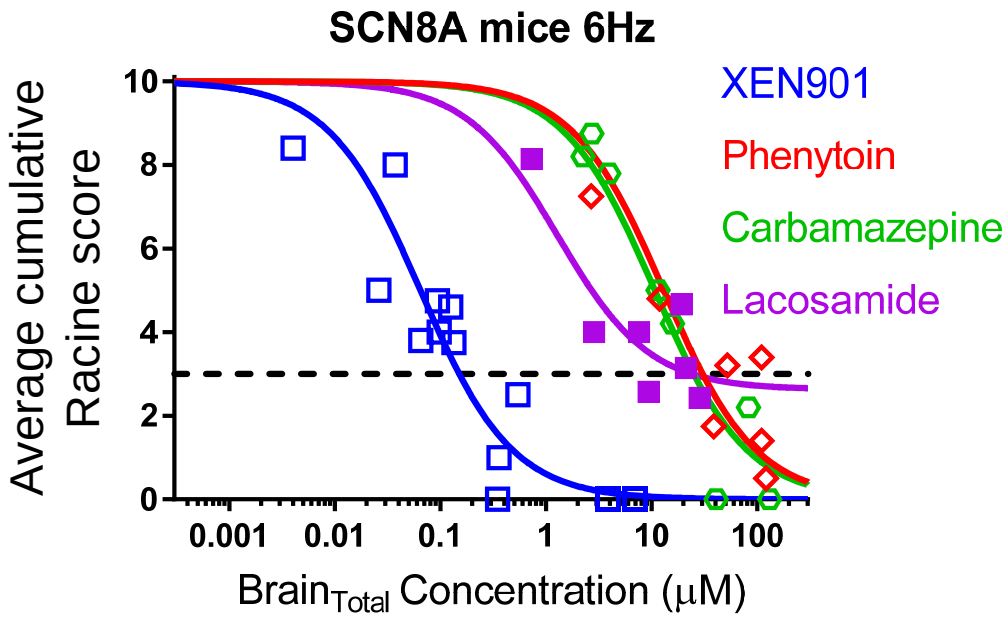




Veeramah et al., 2012

Seizure Control/Freedom in SCN8A Tg Mouse Model of EIEE13

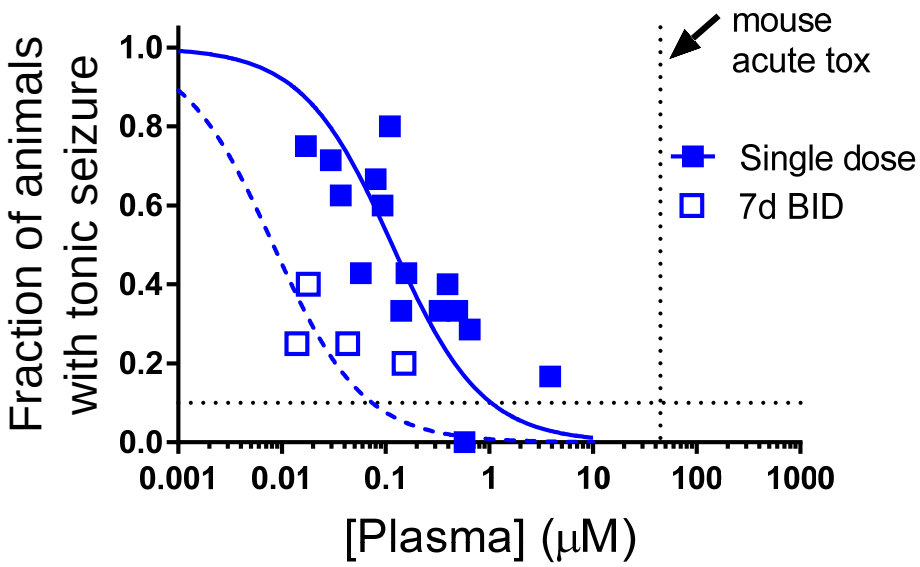
- XEN901 completely suppresses seizures in modified 6 Hz assay
  - Elicit tonic-clonic seizure in Tg mice, no seizures in wild type mice (dotted line)
  - Suppress to wild type at EC_{70}
- >100-fold greater potency compared to current treatments for EIEE13



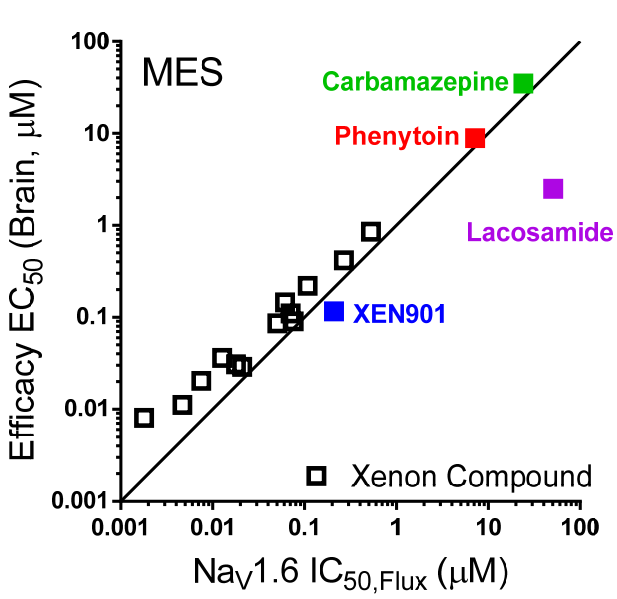
Modified Cumulative Racine Score
0 = no response
1 = Shaking/ Jerking / Facial Tremor, Freezing, Blinking
2 = Forelimb clonus or Straub tail
3 = Loss of balance, Rearing and falling
4 = Clonic Seizure
5 = Tonic-Clonic seizure with extension of hind limbs

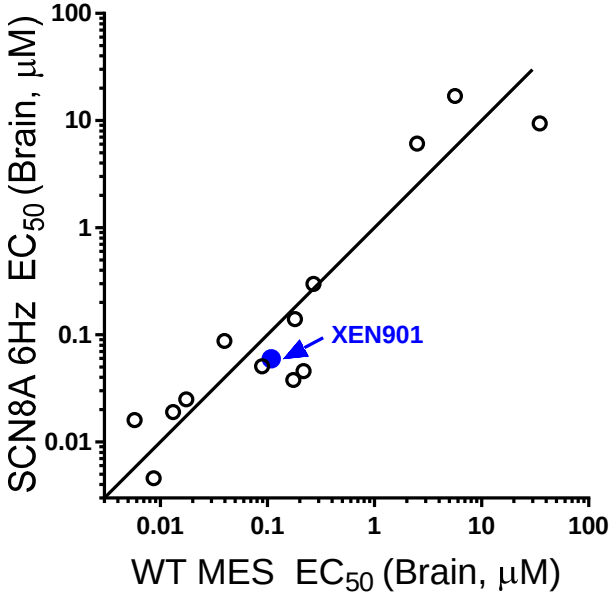
XEN901 is Potent and Efficacious in MES

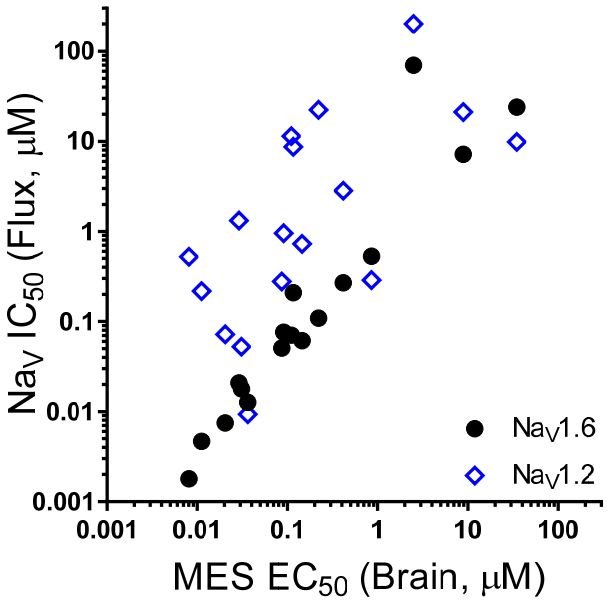
- Therapeutically used Na_V antagonists active in MES assay – good translational model
- Concentration-dependent increase in efficacy
- Doses of 3-200 mg/kg
- Chronic dosing leads to ~10x increase in potency
- High safety margin
- Similar observations in rat MES assay



Potency in the MES Model Driven by $Na_V1.6$



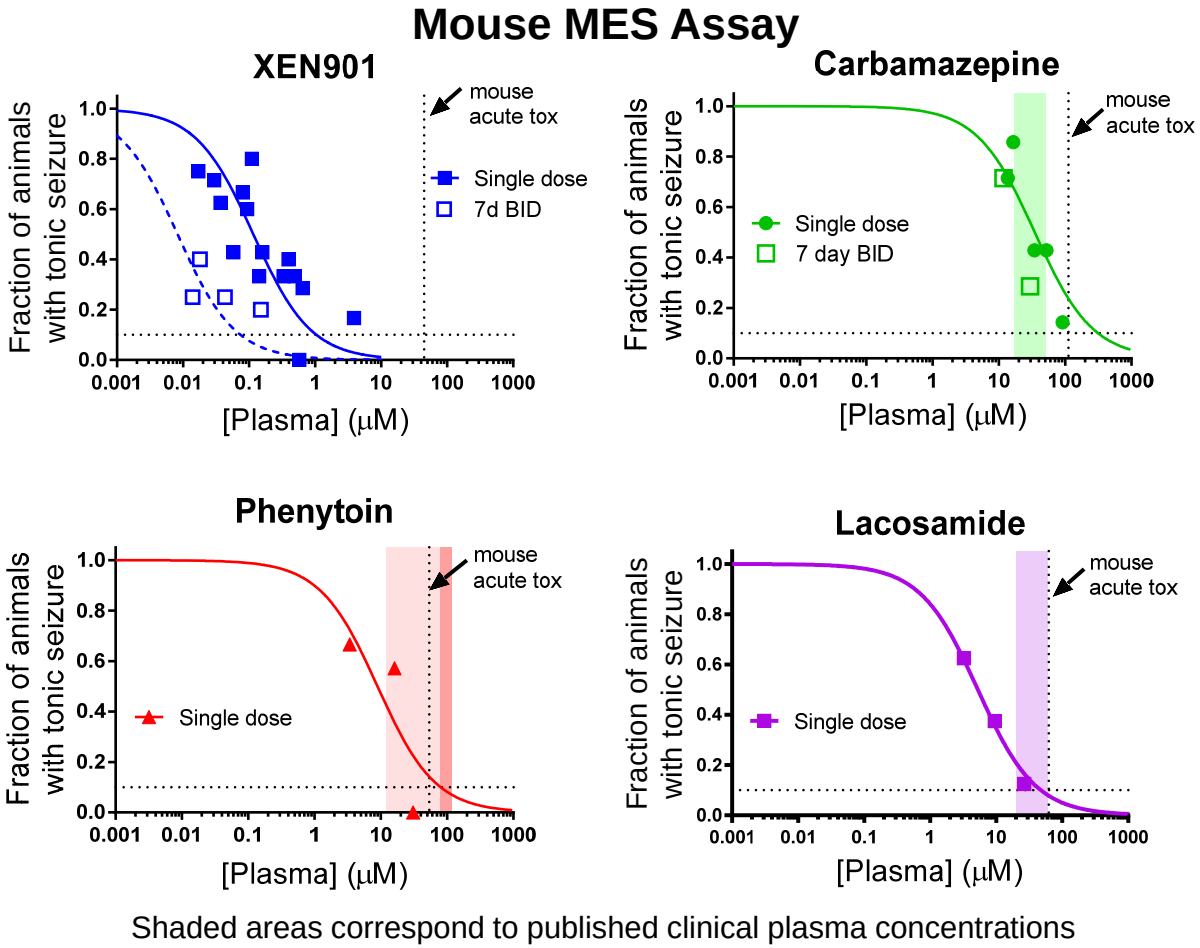




- Potency in both assays highly correlated with potency against $Na_V1.6$ and brain concentration
- Good correlation between SCN8A Tg mouse and MES assays
- Independent of potency at $Na_V1.2$ or other sodium channels

Striving for Seizure Freedom with XEN901

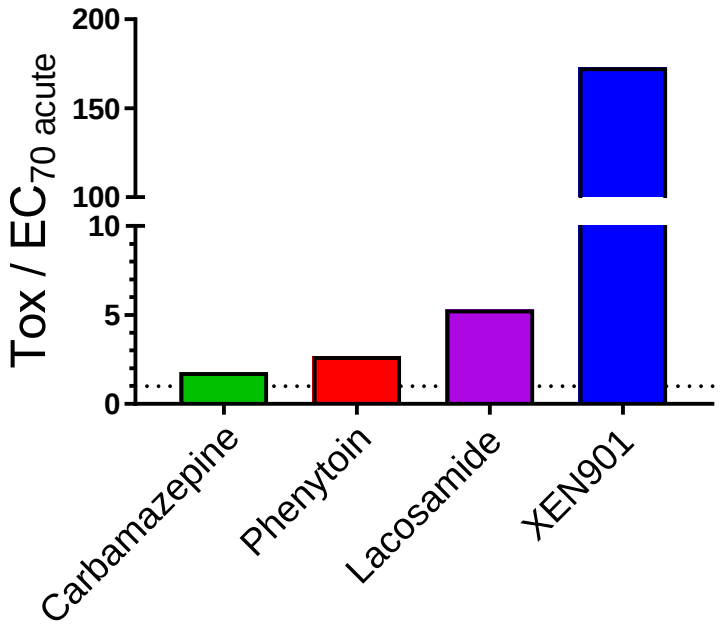
- Current Na_V channel AEDs require 1-5 times the mouse MES EC_{50} for clinical efficacy.
- Current agents lack therapeutic index needed to achieve seizure freedom for many patients
- High TI of XEN901 could enable high level of efficacy with minimal adverse events



Shaded areas correspond to published clinical plasma concentrations

Improved Therapeutic Index Over Other Na_V Inhibitors

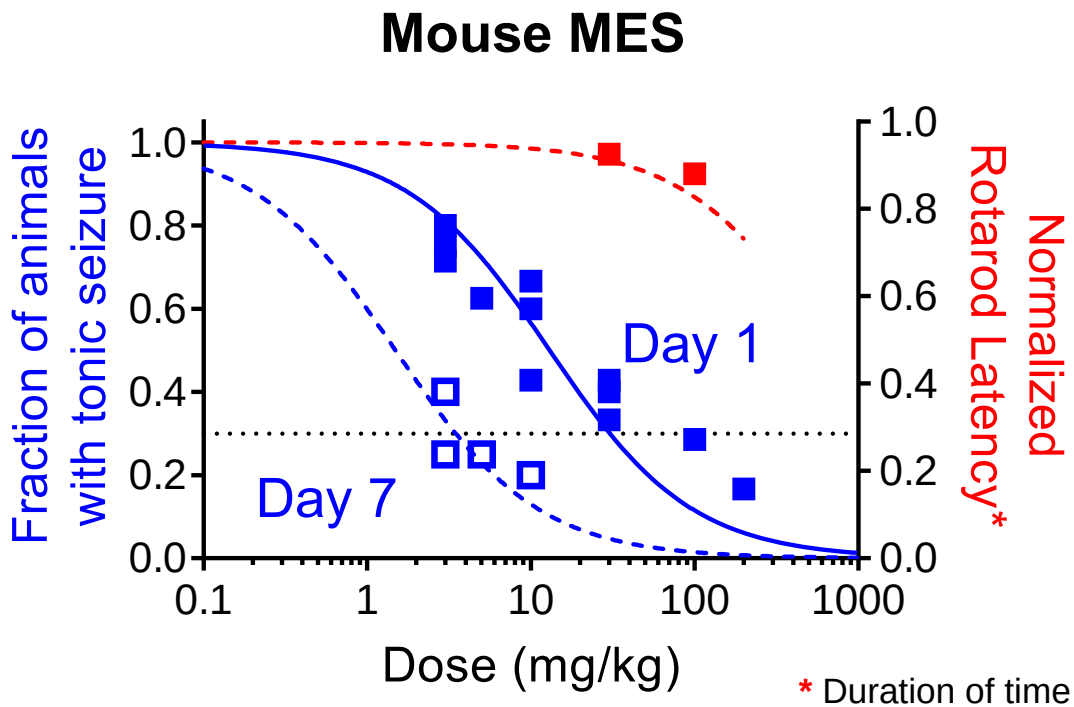
Compound	EC_{70} Plasma (μM)	Toxic Plasma Levels (μM)	Safety Margin
XEN901 (acute)	0.264	45	170
Phenytoin	20	54	1.7
Carbamazepine	60	233	3.8
Lacosamide	12	63	5.3



- 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

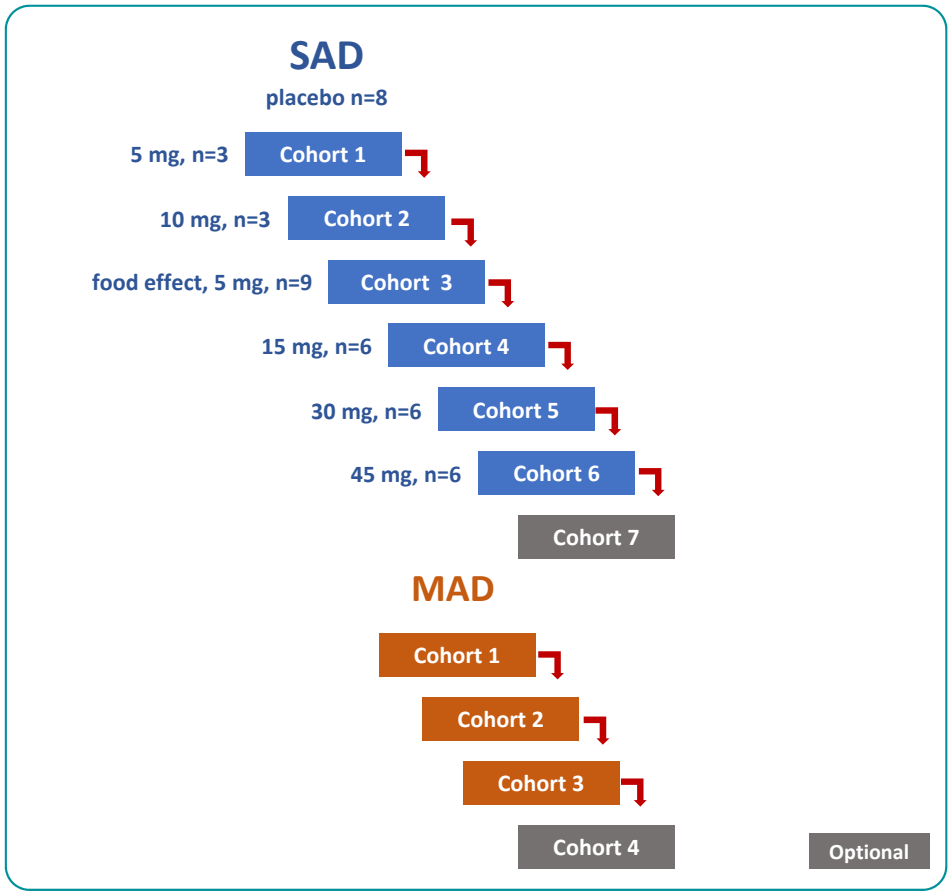
- Rotarod assay to assess possible motor impairment
- Data expressed as function of dose (for comparison with literature values)
  - Safety margin based on dose in mouse MES for XEN901 : >25
  - Other literature comparisons:
    Carbamazepine(po): 7.7
    Phenytoin (po): 10.3
    Lacosamide (ip): 6.0



* Duration of time on rotarod normalized by time with vehicle

Potential Best in Class Safety Margin for XEN901

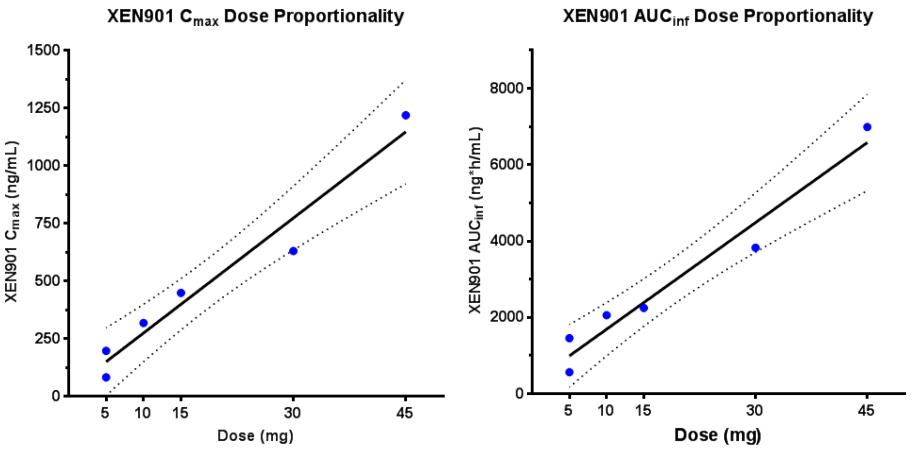
XEN901 Phase 1 Trial Design

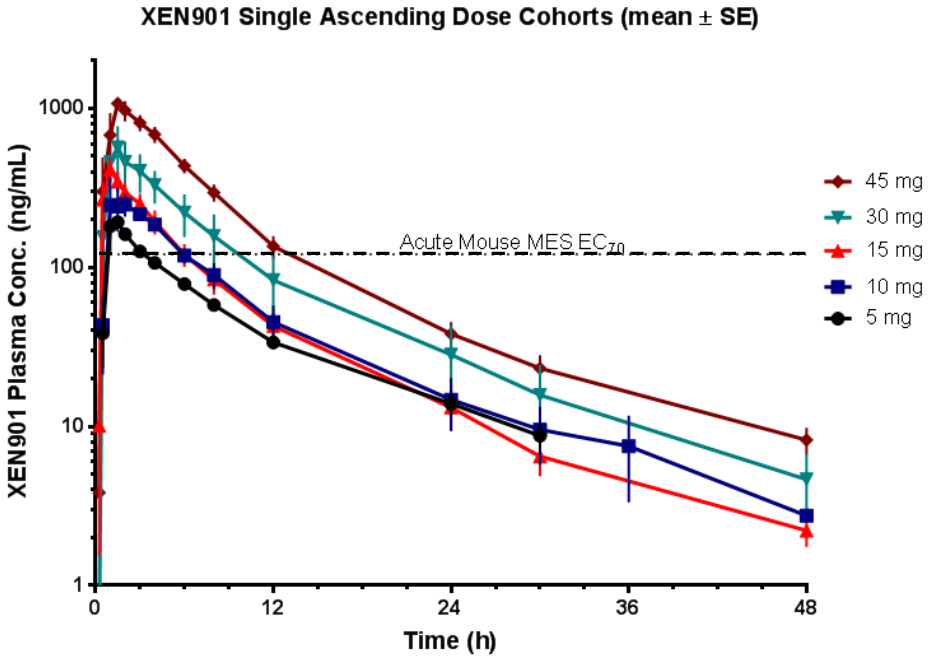


Anticipate Complete Phase 1 Results in H2, 2018

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 ($t_{½}$ = 8-11 hours)



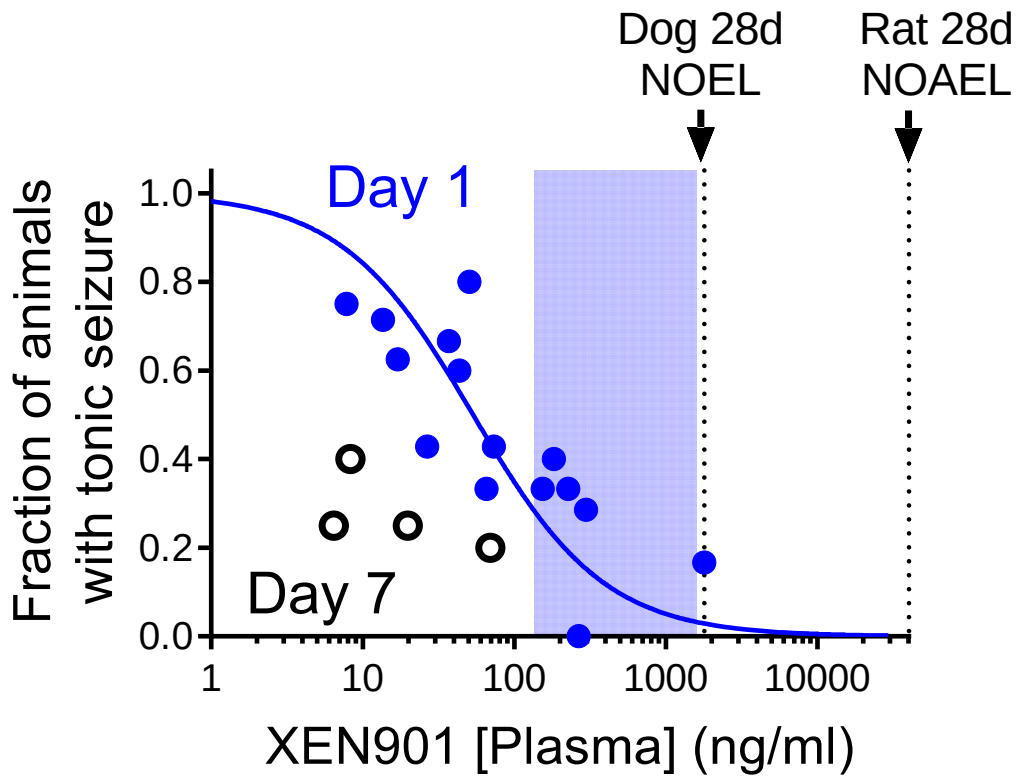


Interim Preliminary Safety Summary

- 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 EC_{90}



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 $Na_V1.6$ 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

Acknowledgements / Contributors

Chemistry
Kristen Burford
Sultan Chowdhury
Shannon Decker
Christoph Dehnhardt
Jim Empfield
Thilo Focken
Wei Gong
Mike Grimwood
Abid Hassan
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Y. Paul Goldberg
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Lena Legkaia
Rostam Namdari
Robin Sherrington

University of Michigan (mouse model)
Miriam Meisler
Jacy Wagnon