Poster 3.030

Selective Inhibitors Suggest $Na_V1.6$ Activity Is the Primary Driver of Efficacy for Voltage-Gated Sodium Channel Targeted AED's

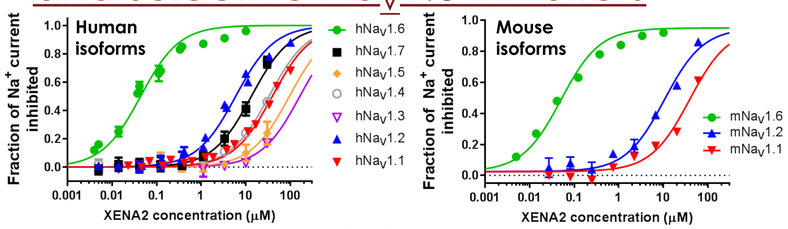
Parisa Karimi Tari, Celine Dube, Karen Nelkenbrecher, Matthew Waldbrook, Kuldip Khakh, Elaine Chang, Noah Shuart, Samuel Goodchild, Clint Young, Sophia Lin, Clark Xie, Richard Dean, Janette Mezeyova, Angela Hussainkhel, Girish Bankar, Andrea Lindgren, Luis Sojo, Thilo Focken, Christoph Dehnhardt, James Empfield, Ray Winquist, Charles J. Cohen, **J.P. Johnson Jr.**

Xenon Pharmaceuticals, 200-3650 Gilmore Way, Burnaby, BC V5G 4W8

Introduction

Na_V inhibitors are useful anti-epileptics, but available drugs don't distinguish between Na_V isoforms and can inhibit other channels like Ca_V's and K_V's. Inhibition of $Na_V1.1$ is expected to compromise efficacy and safety due to it's role in inhibitory interneurons. Inhibition of $Na_V1.5$ introduces cardiac risk. We set out to create new drugs that selectively block $Na_V1.6$.

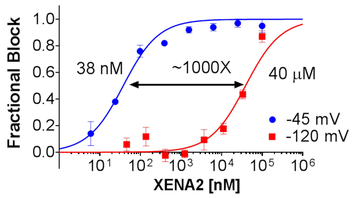
Novel chemistry provides potent and selective $Na_V1.6$ inhibitors



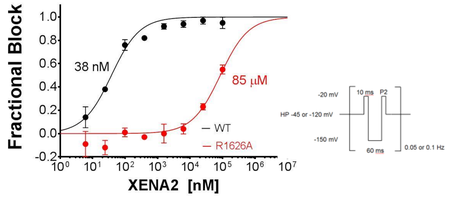
>1000X selectivity vs $Na_V1.1$ (inhibitory interneurons)

>1000X selectivity vs $Na_V1.5$ (cardiac isoform)

Inhibition via the domain IV voltage sensor is highly state dependent



Forcing channels to the resting state reduces potency 1000X



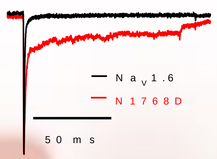
Neutralizing the 4th Arginine of DIV S4 reduces potency 1000X

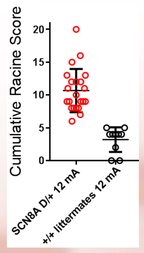
Mouse model of EIEE13 ($Na_V1.6$ N1768D+/- gain of function)

Mutation: Veeramah et al. (2012). Mouse model: Wagnon et al. (2015)

Altered channel gating causes seizures in 60% of mice beginning ~ p70.

To create a model of on-target efficacy we optimized a 6Hz stimulus assay that provokes a tonic clonic seizure in all p60 heterozygous mice, but not in WT littermates



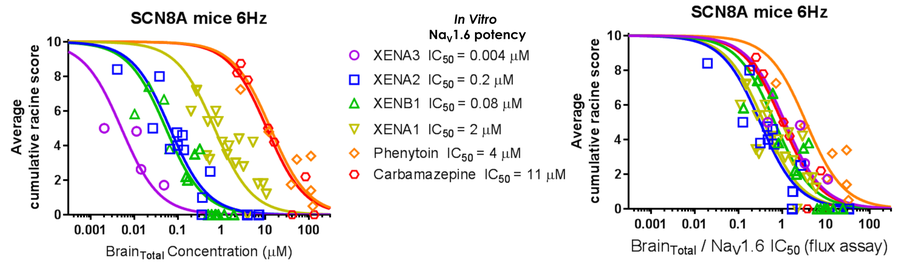


Modified Racine Score

- 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

- Each mouse receives a "cumulative Racine score"
  - Example: 5 (tonic-clonic seizure)
    + 2 (straub tail)
    + 3 (loss of balance)
    = 10 Cumulative Racine Score

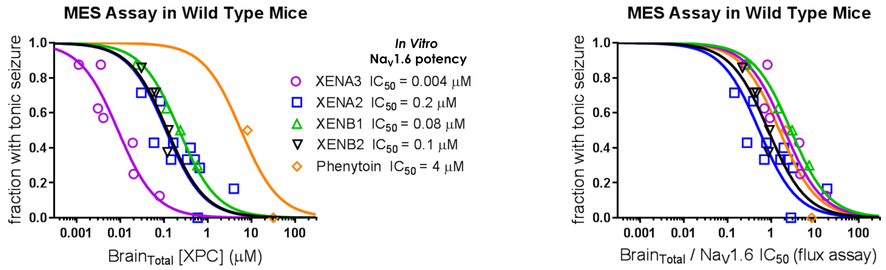
Efficacy in SCN8A N1768D+/- mice correlates with $Na_V1.6$ potency and brain exposure



Normalizing for potency shows robust *In vivo* efficacy is achieved when brain level exceeds 1-10X the $Na_V1.6$ IC_{50}

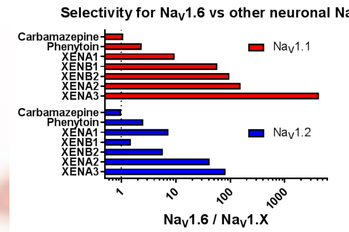
The Maximal Electroshock (MES) Assay predicts clinical efficacy for NaV AEDs.

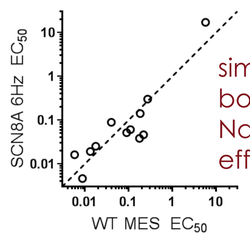
We find MES Efficacy in WT Mice correlates with $Na_V1.6$ potency and brain exposure



Robust *In vivo* efficacy when brain concentration exceeds 1-10X *In vitro* $Na_V1.6$ IC_{50}

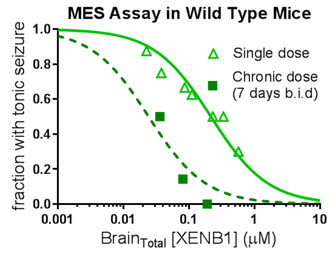
Compounds with dramatically different selectivity profiles have similar potency and efficacy in both SCN8A$^{N1768D+/-}$ and WT Mice





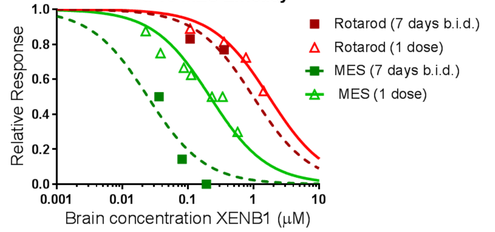
similar potencies in both assays suggests $Na_V1.6$ inhibition drives efficacy in both cases

Chronic Dosing Improves potency For Selective Compounds



Compounds do not accumulate after repeat dosing, but a given dose or brain exposure is more effective

Chronic dosing improves apparent safety margin



Robust window against motor impairment grows larger (>30X) after chronic dosing since tolerability is unchanged

Conclusions

1. **$Na_V1.6$ inhibition predicts efficacy of Na_V inhibitor AED's and novel $Na_V1.6$ selective compounds in EIEE13 model and WT mice.**
2. **We anticipate that selective $Na_V1.6$ inhibitors will provide robust clinical efficacy with an improved safety profile**

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