

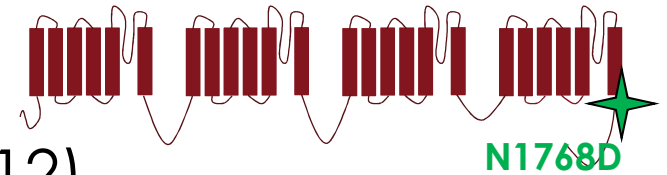
XENON

from families to genes, from genes to drugs.

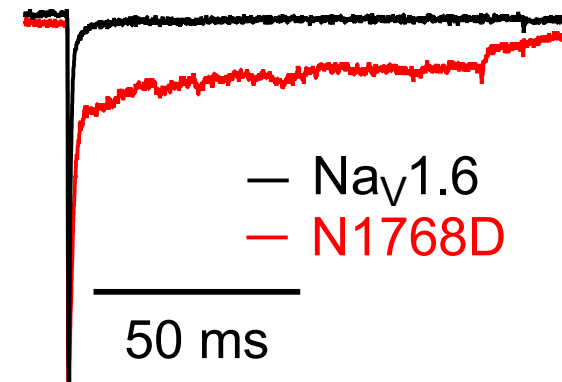
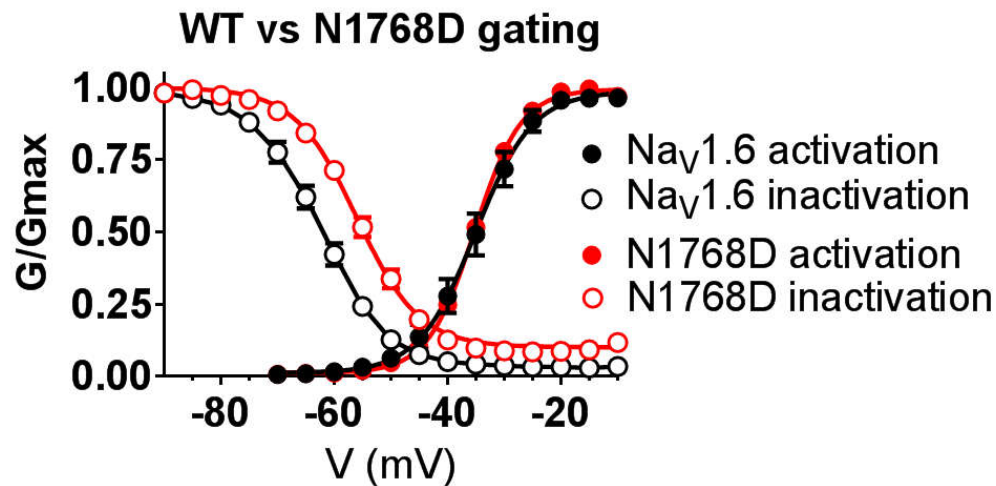
Selective Inhibitors of $Na_v1.6$
Inhibit Electrically Induced
Seizures in a Model of EIEE13

J.P. Johnson Jr.

Mouse model of EIEE13 (Na_v1.6 GOF)



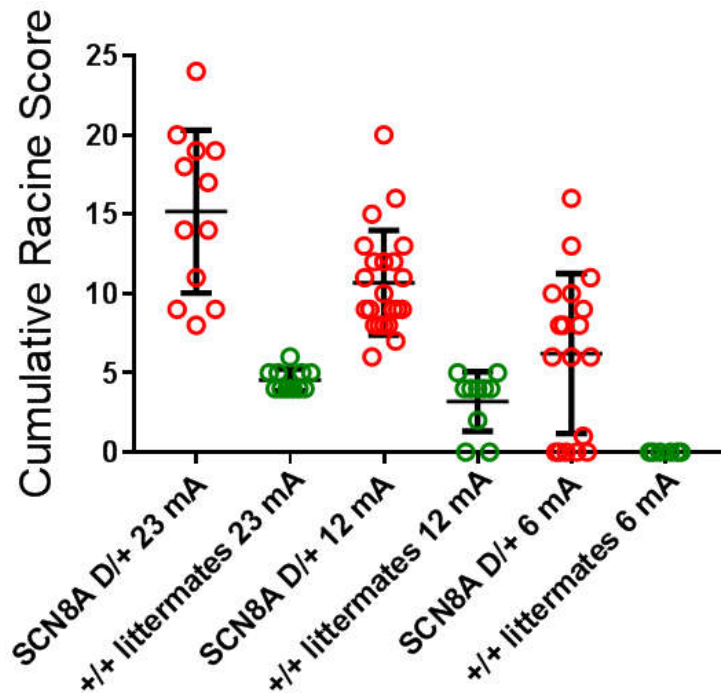
- N1768D mutation in Na_v1.6
 - identified by Veeramah et al. (2012)
 - mouse created by Wagnon et al. (2015)



- Seizures begin in ~60% of mice at p70-90. Number timing and frequency of seizures is unpredictable.
- For purposes of compound testing we needed a more rapid and consistent assay

6-Hz psychomotor seizure induction assay:

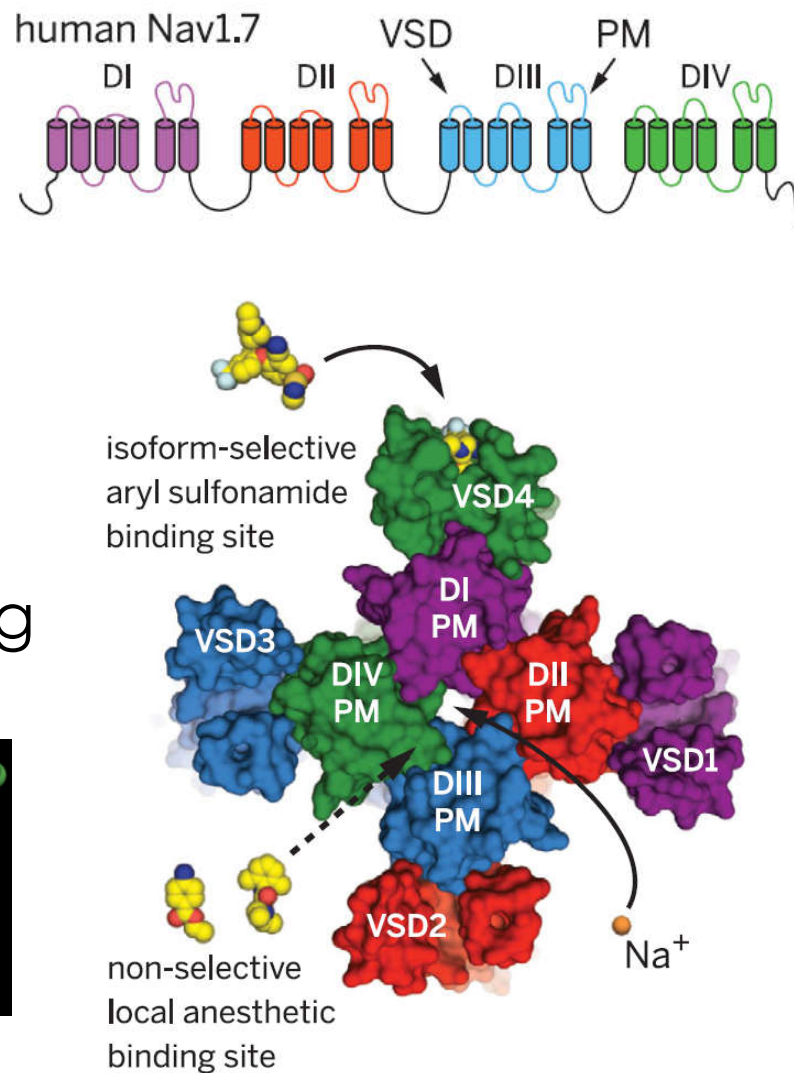
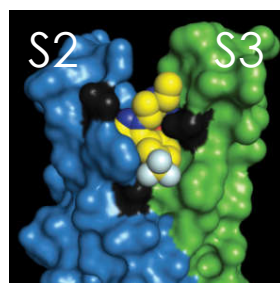
- A 2s 6Hz stimulus, is applied to the cornea of the mice to elicit a seizure
- WT mice are relatively resistant to stimulus
- N1768D^{+/-} mice are much more sensitive



- 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”
 - tonic-clonic seizure (5)
 - forelimb clonus (2)
 - loss of balance (3).
 - 5+2+3 = 10

Inhibitors Target Voltage Sensor Domain (VSD)

- Domain IV voltage sensor site
 - Wedges DIVS4 in inact state
 - Provides extreme state dependence
- Allows for robust selectivity
 - Patented chemistry targeting
 - $\text{Na}_v1.1/1.3$
 - $\text{Na}_v1.7$



Ahuja et al., Science. 2015 Dec 18;350(6267)

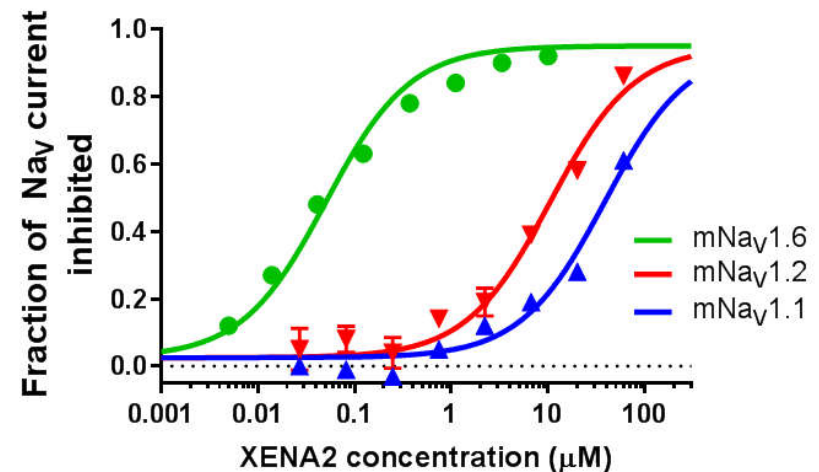
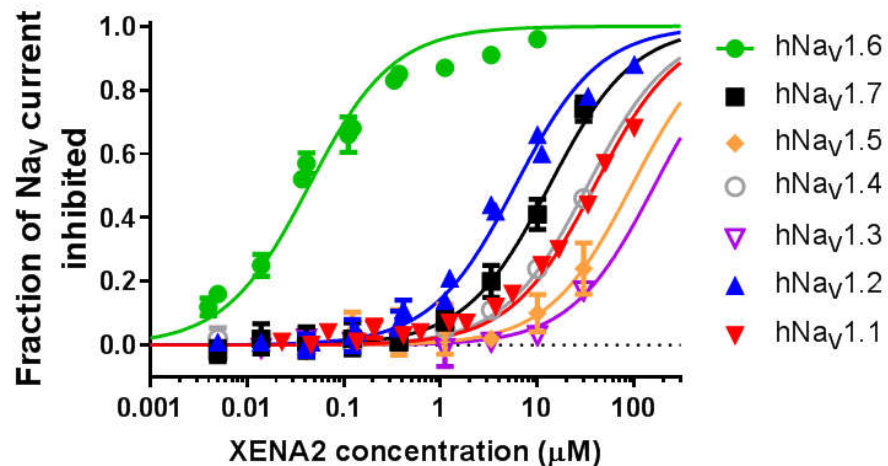
Genentech
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from families to genes, from genes to drugs.

Na_v1.6 selective inhibitors

- Many iterations of optimization by the chemists (~2000 compounds) provided series with a new profile
 - Potent on Na_v1.6
 - Brain penetrant
 - Selective against other Na_v1 isoforms

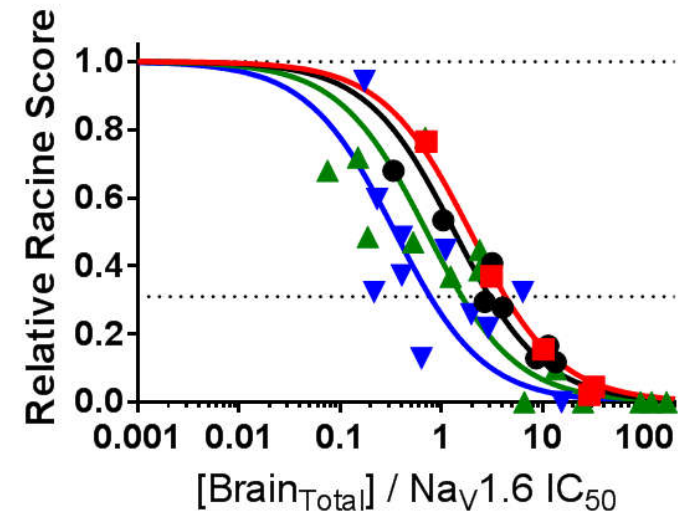
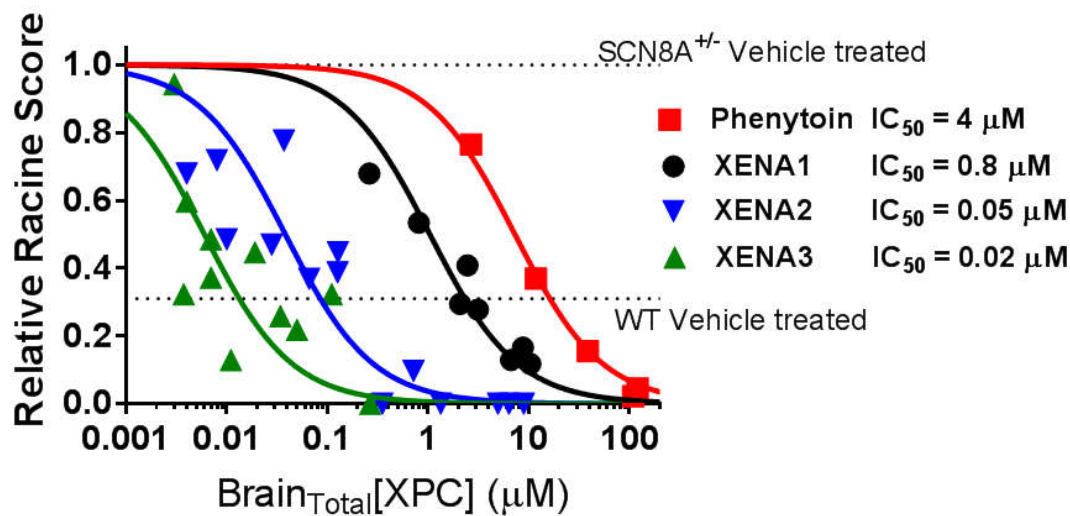


Na_v1.6 potency predicts efficacy

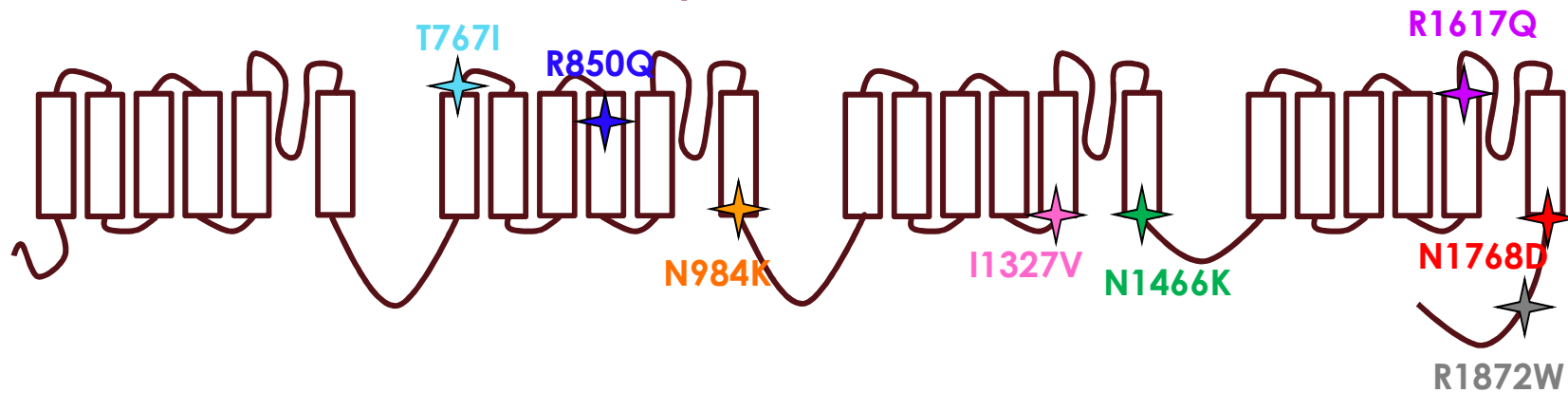
- *in vitro* Na_v1.6 potency + brain concentration predicts *in vivo* efficacy
- EC₇₀ *in vivo* = 1-5X *in vitro* IC₅₀
- Selectivity should allow better coverage of Na_v1.6 and improved safety profile

Fold selectivity

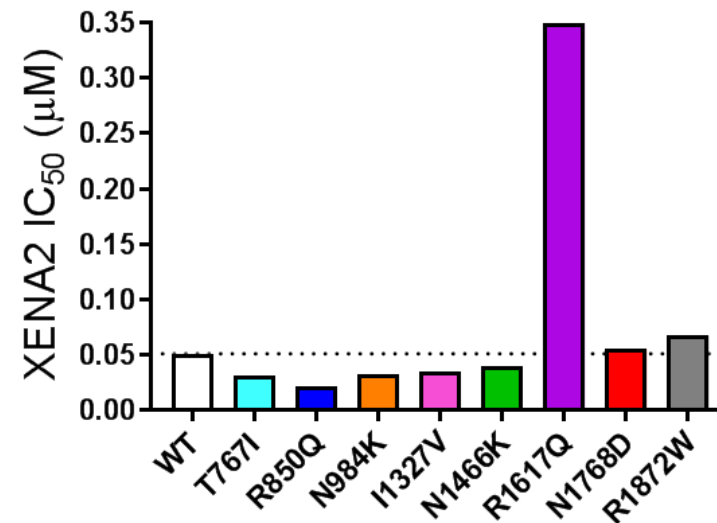
	hNa _v 1.6 IC ₅₀ (μM)	Na _v 1.1 /1.6	Na _v 1.2 /1.6	Na _v 1.5 /1.6
Phenytoin	4	2	3	1.5
XENA1	0.8	10	8	13
XENA2	0.05	500	120	>500
XENA3	0.02	2400	15	>500



SCN8A mutations found in patients and tested for block by XENA2



- R1617Q is in the XEN binding site: 7X less potently blocked
- Other mutants are blocked with similar potency as WT channel



Future

- $\text{Na}_v1.6$ selective inhibitors show encouraging efficacy in SCN8A GOF mice
- Efficacy in this model seems largely driven by potency on $\text{Na}_v1.6$ and brain concentration
- Xenon is committed to moving the best of it's $\text{Na}_v1.6$ inhibitors into clinical trials for epilepsy



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