Targeting Voltage-Gated Sodium Channels for the Treatment of Epilepsy

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Common antiepileptic drugs that target voltage gated sodium channels (VGSCs) are effective against partial and generalized convulsive seizures but also can exacerbate non-convulsive absence epilepsy and impair cognition in rodents and humans. Likewise, mice carrying loss-of-function mutations in the VGSC gene *Scn8a* ($Na_v1.6$ protein) exhibit reduced susceptibility to convulsive seizures, which points to this gene as a potential therapeutic target for epilepsy. However, these mutations also can lead to cognitive deficits and absence epilepsy which may limit the utility of these channels as a therapeutic target to achieve seizure control.

In order to understand the opposing consequences of VGSC hypofunction 1) partial and generalized convulsive seizure protection and 2) absence seizure generation, we evaluated convulsive seizure versus absence seizure susceptibility and performed a detailed electrophysiological examination of cortical and thalamic circuitry in conditional and global *Scn8a* mutant mice.

We found that conditional inactivation of *Scn8a* in cortical excitatory cells leads to increased seizure thresholds and is protective in an *Scn1a*-epilepsy model, while inactivation of *Scn8a* in interneurons was not protective. Interestingly, we observed reduced cortical field potential responses in global *Scn8a* mutant mice only under seizure promoting conditions. In contrast, reducing *Scn8a* activity in the thalamic interneurons, but not in cortical interneurons was sufficient to cause absence seizures.

We then used this information to develop a region specific targeting strategy to control seizures in a model of mesial temporal lobe epilepsy. We show that reducing *Scn8a* in the hippocampus by RNAi effectively reduces seizures and normalizes behavior in this model without causing absence seizures.

Together these studies point to *Scn8a* as a promising target for the treatment of epilepsy and demonstrate the utility of leveraging detailed models of seizure genesis to inform circuit-specific therapeutic strategies.