Targeting Voltage-Gated Sodium Channels for the Treatment of Epilepsy

Christopher Makinson, PhD
Postdoctoral Fellow
Stanford University
Department of Neurology and Neurological Sciences
Huguenard Lab
Epilepsy Overview

- Excessive neuronal activity and hypersynchrony
- Affects ~3-4% of people in their lifetime
- Genetic vs. symptomatic epilepsy
- Co-morbidities are common in epilepsy
- ~30% of patients do not respond well current treatments
Background: Voltage-gated sodium channel (VGSC) epilepsies

**VGSC genes: Epilepsy risk genes**

- **SCN1A**
- **SCN2A**
- **SCN3A**
- **SCN4A**
- **SCN5A**
- **SCN10a**
- **SCN8A**
- **SCN9A**
- **SCN11A**

Red – Brain
Purple – Skeletal Muscle
Blue – Heart
Green – PNS
Black - Ubiquitous

**VGSC blockers: Antiepileptic drugs**

- Phenytoin
- Carbamazepine
- Lamotrigine
- Felbamate
- Topiramate
- Oxcarbazepine
- Zonisamide
- Rufinamide
- Lacosamide
- Eslicarbazepine acetate
Thalamocortical seizures by loss of Scn8a

Absence seizures detected in the cortex and thalamus

Makinson et al., Neuron 2017
Knockdown of *Scn8a* in RT causes thalamocortical seizures

Makinson et al., *Neuron* 2017
Targeting *Scn8a* in adult animals confers resistance to proconvulsants

Makinson et al., *Neurobiol Dis* 2014
Deletion of *Scn8a* confers resistance to *Scn1a* epilepsies

Makinson et al., *Neuron* 2017
Targeting *Scn8a* for the treatment of temporal lobe epilepsy

Makinson et al., *Neurobiol Dis* 2014
Targeting *Scn8a* reduces epileptiform hippocampal bursting *in vitro*.

Makinson et al., *Neurobiol Dis* 2014
Targeting *Scn8a* in the hippocampus reduces seizures *in vivo*

Makinson et al., *Neurobiol Dis* 2014
Targeting *Scn8a* in treatment-resistant temporal lobe epilepsy

Wong, Makinson et al., *Scientific Reports* 2018
Targeting *Scn8a* in treatment-resistant temporal lobe epilepsy

Wong, Makinson et al., *Scientific Reports* 2018
Targeting $Scn8a$ in treatment-resistant temporal lobe epilepsy

Wong, Makinson et al., *Scientific Reports* 2018
Conclusions

↓ *Scn8a* in cortical circuits leads to widespread reductions in neural excitability and ↓ convulsive seizures

↓ *Scn8a* in the thalamus leads to ↑ non-convulsive thalamocortical seizures

↓ *Scn8a* selectively in the hippocampus is an effective seizure control strategy in models of temporal lobe epilepsy

Some side effects can be avoided using a brain region and cell-type selective targeting strategy

Viral-mediated RNAi approaches may represent a viable alternative to pharmacology for difficult classes of therapeutic targets (e.g. VGSCs)
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