**Making novel pain drugs by selectively targeting Nav1.7**

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Sodium channel Nav1.7 is an attractive pain target based on human genetic evidence. The selective Nav1.7 channel blockers thus hold promise as potential painkillers with improved safety and reduced unwanted side effects compared to existing therapeutics. To understand how the loss of Nav1.7 results in CIP (congenital insensitivity to pain) and whether inhibition of Nav1.7 in the adult would lead to the same phenotype, we employed a tamoxifen inducible Nav1.7 cKO mouse line. We firstly found that Nav1.7 mediated the majority of TTXs sodium current on DRG nociceptive neurons, and the genetic deletion of Nav1.7 resulted in significant reduction of neuronal excitability. We next found that both chronically genetic deletion and acutely pharmacological inhibition of Nav1.7 in adult mice led to the abolishment of behavioral responses to the most, but surprisingly not all, modalities of noxious stimulus. Lastly, we demonstrated that Nav1.7 selective blockers bound to the surface of voltage-sensor domain IV (VSD4), therefore inhibiting channel activity through a voltage-sensor trapping mechanism. All these data expand the depth of knowledge surrounding Nav1.7 biology as it relates to pain, and provide preclinical proof of efficacy that lays a clear path towards translation for the therapeutic use of Nav1.7-selective inhibitors in humans.