

## **Pattern of functional TTX-resistant sodium channels reveals developmental stage of human iPS- and ES cell-derived nociceptors**

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### Research question and background

Neuropathic pain is an often disabling and difficult to treat symptom that cannot be adequately mimicked in animal models. Recently, inherited neuropathic pain syndromes were linked to mutations in voltage-gated sodium channels (Navs). All Navs undergo expression changes during development, and pain syndromes linked to Nav mutations occur at certain periods in life. These striking variations in disease onset may be due to modulation of the mutation phenotypes by co-expression of different Nav subtypes, but experimental support for this hypothesis is still missing. Expression and function of Navs depend critically on the cellular background, sounding a strong note of caution when translating data from rodent to man. This holds particularly true for nociceptors whose excitability is controlled by a complex interplay between TTXs and TTXr Navs. Thus, there is urgent need for the availability of human nociceptors to investigate the (patho-) physiology and pharmacology of human nociception in an appropriate model.

### Methods and tissues used

Using human pluripotent stem cells (hPSC)-derived nociceptive sensory neurons, generated by applying an optimized, previously published protocol (Chambers et al., 2012), we explored the maturational stages of hPSC-derived human nociceptors and deciphered the electrophysiological characteristics of their Navs focusing on TTXr subtypes. We are currently in the process of comparing our data with gene expression analysis derived from human DRGs, provided from NBB.

### Results and conclusion

hPSC offer the opportunity to generate distinct neuronal phenotypes including nociceptors. Using a chemical based approach, we generated human nociceptive sensory neurons that expressed respective markers and showed electrophysiological properties indicative for the presence of tetrodotoxin sensitive (TTXs) and resistant (TTXr) voltage-gated sodium channels (Navs). In contrast to their counterparts derived from rodent dorsal root ganglia, TTXr currents of hPSC-derived nociceptors unexpectedly display a significant shift of the voltage dependence of activation and fast inactivation towards more hyperpolarized potentials. The reason for this apparent discrepancy is most likely a substantial expression of the developmentally important Nav1.5 channel. We are currently in the process of evaluating the human tissue provided by NBB.

In view of the obstacles to recapitulate neuropathic pain in animal models, our data advance human nociceptors as a much better suited model to study developmental and pathogenetic processes in human nociceptive neurons and to develop more specific small molecules to attenuate pain.