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## **Venoms in drug discovery: a case study on voltage-gated channels**

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Among all chemical modalities available in ion channel drug discovery, venoms are very attractive for identifying potent and selective compounds for almost all subunits of this therapeutic target family. Here, we describe a high-throughput approach for the identification and characterization of voltage-gated modulators from a large venom collection. Using this strategy, we were able to describe different mechanism of actions of subfractions and in particular antagonists of the Nav1.7 channel subunit. These results are illustrated with the characterization of the first peptide isolated from the *Cyriopagopus schioedtei* spider. This peptide, named cyriotoxin-1a (CyrTx-1a), is composed of 33 amino acids, contains the ICK structural motif and inhibited hNav1.1-1.3 and 1.6-1.7 in the low nanomolar range, compared to the micromolar range for hNav1.4-1.5 and 1.8. In agreement, CyrTx-1a was 635 times more efficient at inhibiting tetrodotoxin (TTX)-sensitive than TTX-resistant sodium currents recorded from adult mouse dorsal root ganglia neurons. Within a narrow therapeutic window of concentration, CyrTx-1a exhibited an analgesic-like effect in mice by increasing reaction time in the hot plate assay and decreasing tactile sensitivity in automated plantar von Frey experiments. Finally, *in vivo* electrophysiological experiments showed that CyrTx-1a was approximately 170 times less efficient than huwentoxin-IV at altering mouse skeletal neuromuscular excitability properties. This pharmacological profile paves the way for further engineering studies aimed at optimizing the potential antinociceptive properties of CyrTx-1a. We will conclude by discussing these results in the context of an integrated drug discovery research platform.

**Keywords:** Cyriotoxin-1a, sodium channel, Nav1.7

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