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A multiscale functional approach to appraise the pharmacological interactions between spider venom peptides and Na_v1.7, a genetically validated analgesic target

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Abstract:

The current research focuses on multi-scale assessment of the pharmacological and functional properties of spider toxins previously selected by screening various venoms on Na_v1.7 subtype voltage-gated sodium channel, genetically validated painkiller target. After the synthesis of toxin hits, the studies involves electrophysiological approaches such as manual and automated patch-clamp for *in vitro* studies of mouse and human cells, intracellular micro-electrode recordings of *ex vivo* mouse neuromuscular junctions, and threshold-tracking techniques with the QTRAC software for *in vivo* studies of the mouse neuromuscular excitability, as well as structures / functions evaluation. These different approaches will allow:

- (1) To characterize the selectivity profile of toxins identified as active in the desired therapeutic targets (i) on cell lines expressing the functional subunit of these targets, but also of various other subtypes of channels and receptors, and (ii) on a more integrated scale in native systems such as cardiomyocytes, brain slices and the neuromuscular system of mammals (mice and /or rats).
- (2) To identify their mechanism of action and effectiveness (compared to some reference ligands reported in the literature) on validated targets in the area of pain, using native systems such as (i) cultured neurons of the dorsal root ganglion (DRG) isolated from adult mice, (ii) and human induced pluripotent stem (IPS) cells.
- (3) To determine the pharmacophore, i.e. the crucial amino acids in the toxin activity and effectiveness, in order to pave the way for engineering to optimize their functional properties.
- (4) To evaluate the potential antinociceptive effect of toxins by studying the perception of pain in vigils animals (mice and/or rats).