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Venomous animal peptides: An innovative approach to treat pain

(Ingénierie des Protéines et Cibles Thérapeutiques)

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Pain management is a world health priority, and current pain medications, while effective in many circumstances, are frequently associated with adverse side effects. Targeting dorsal root ganglion (DRG) neurons in the peripheral nervous system is a promising strategy for managing pain and limiting central side effects. These neurons are well-known to express various pain-related proteins, including the 1.7 subtype of voltage-gated sodium channels (NaV1.7), a genetically proven target for pain management. In this context, several small molecules have been described in the literature as NaV1.7 blockers but their limited selectivity and/or potency often prevented their therapeutic development. Concurrently, small reticulated peptides produced by venomous animals for predation or defense have been recognized as an original source of antinociceptive peptides.

My PhD project is to identify and then evaluate a large number of new antinociceptive venom peptides with high selectivity and efficacy for NaV1.7 using multi-scale experiments (from cell to whole organism). An electrophysiological screening on cells overexpressing human NaV1.7 was used to uncover novel hits from Smartox Biotechnology's unique and vast venom library. The current studies on some selected peptides aim (1) to chemically synthesize these peptides, (2) to characterize their selectivity profile and safety issue, particularly on cell lines overexpressing other NaV subtypes (from 1.1 to 1.8) and on native systems such as mouse cardiomyocytes and neuromuscular system, (3) to specify their efficiency and mechanism of action on mouse DRG neurons, and (4) to evaluate *in vivo* their analgesic properties in vigil mice. (5) to define their pharmacophore and optimize their functional characteristics, and (6) to provide evidence for the clinical application of the hit candidates.