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## From identification to multi-scale pharmacological evaluation of venom peptides against pain

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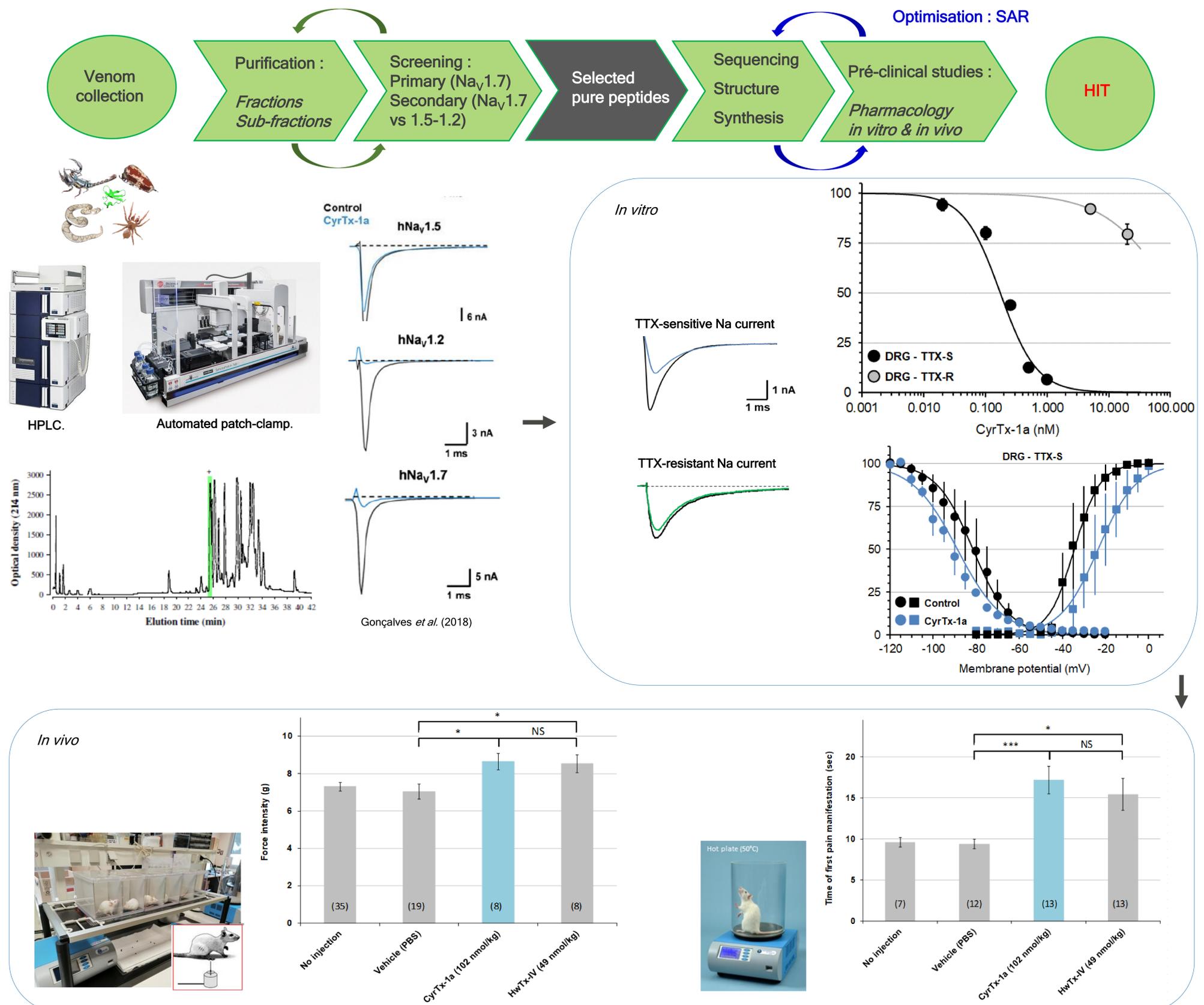
## Abstract

Pain care is a global public health priority and current pain relievers, although effective in many cases, are too often associated with side effects. A promising approach to manage pain and avoid central side effects is to target the dorsal root ganglia (DRG) neurons, located in the periphery. These neurons are wellknown to express various proteins involved in pain transmission, including the 1.7 subtype of voltage-gated sodium channels (Na<sub>v</sub>1.7), a major and genetically validated target for chronic pain treatment. Thanks to their high affinity and selectivity, venom peptides of animal origin have been identified as an original source of antinociceptive molecules.

The objective of my PhD is to identify and characterize, by multi-scale studies, a large number of novel antinociceptive venom peptides possessing high selectivity and potency for Na<sub>v</sub>1.7. For this purpose, an electrophysiological screening on cells overexpressing the human Na<sub>v</sub>1.7 allowed to identify novel hits from a unique and large venom collection of Smartox Biotechnology. The different studies, currently undertaken on some selected peptides, aim :

- (1) to chemically synthesize these peptides
- (2) to characterize their selectivity profile and safety issue, notably on cell lines overexpressing Na<sub>v</sub> subtypes (from 1.1 to 1.8) and on native systems such as the mouse cardiomyocytes and neuromuscular system,
- (3) to specify their efficiency and mechanism of action on mouse DRG neurons,
- (4) to evaluate *in vivo* their analgesic properties in vigilant mice
- (5) to determine their pharmacophore and optimize their functional properties, and
- (6) to provide evidence for the clinical potential of the best candidates in correcting *de novo* identified Na<sub>v</sub> channelopathies.

## Methodology and results



## Conclusion

Based on a collection of numerous and various venoms, this research strategy makes possible to identify and characterize different toxins of therapeutic interest in the context of their development as antinociceptive agents.

The evaluation of functional properties of cyriotoxin-1a reveals that the peptide exhibits marked antinociceptive properties, as evidenced in DRG neurons by its effects on TTX-sensitive Na<sub>v</sub> channels (Na<sub>v</sub> 1,7) and on tactile and heat sensitivity of mice *in vivo*. This allows us to consider a clinical development of the studied toxin.