From bites to insights: Utilization of arachnid venoms in ion channel studies and their potential in therapeutic development

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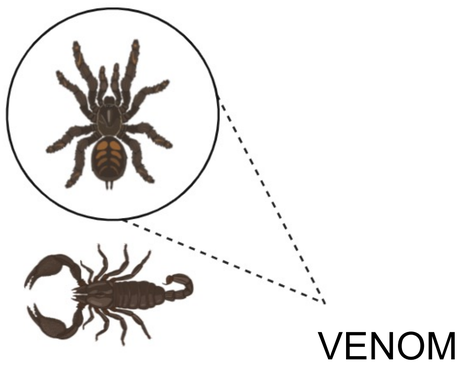
Inspired by nature to create heart therapeutics

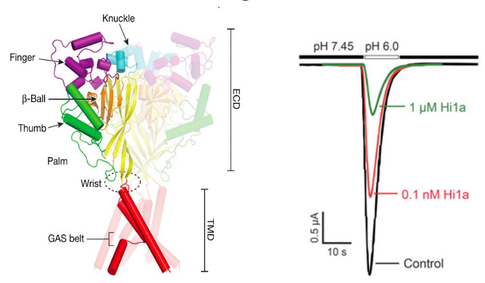


VENOM

Disulfide-bridged peptides
Other peptides
Enzymes
Mucus
Neurotransmitters

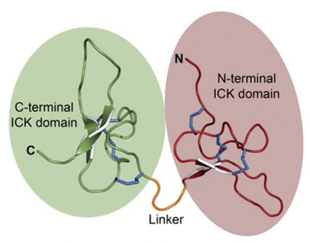
Australian funnel-web spider
H. infensa.

Hi1a targets ASIC1a channel

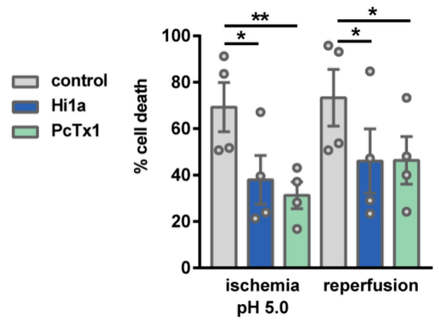


IC_{50}=0.5 nM[1]

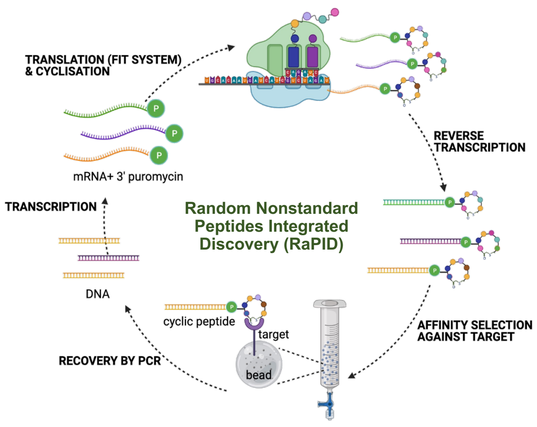
Hi1a peptide from the venom [1]

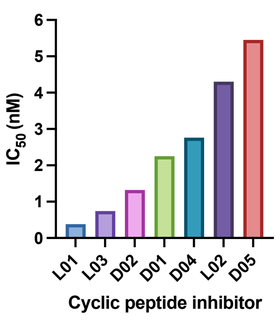


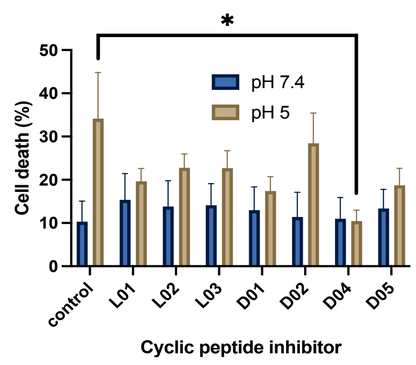
In vitro effect of Hi1a in the heart [2]



We produced smaller and less complex peptides, with a high potency for ASIC1a and easier to produce

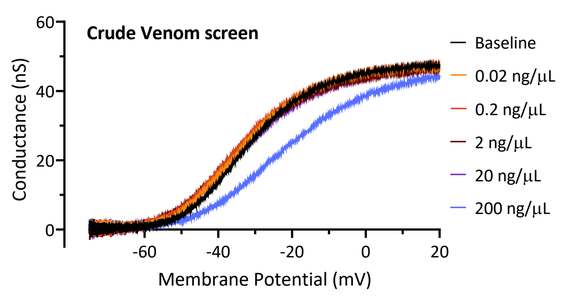


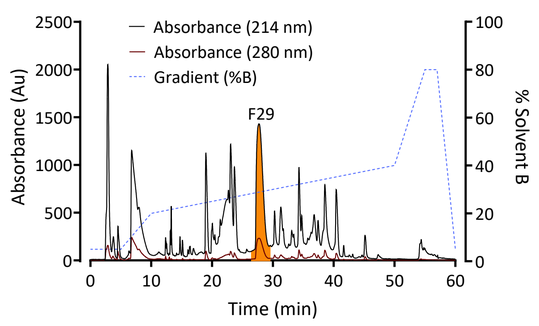


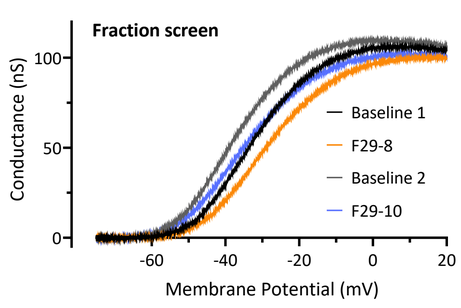


Novel peptide modulators of K_v7.2-7.3

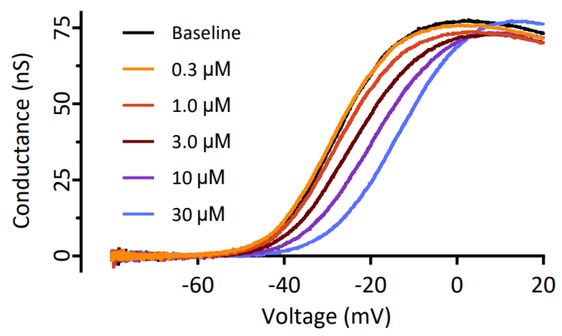
Mutations in the voltage-gated potassium channel K_v7.2-7.3 are associated with a wide spectrum of early-onset epileptic disorders. Patients with a **gain of function** mutation in the encoding KCNQ2 genes show severe developmental delay with prominent language impairment and autistic features, often accompanied by infantile- to childhood-onset epilepsy.[3] To treat this phenotype, selective negative modulators of the ion channel that shift the activation potential back towards normal activity are needed. Spider venoms provide a rich source of peptides that target ion channel activity.[1]







Effect of the venom peptide modulator obtained from the fraction



IC_{50}	6.37 μM
$V_{1/2}$	9.58 mV

Several challenges:

- Screening venoms using manual patch clamp.
- Hundreds of venoms to screen
- Folding of peptides
- Off-target problems

Outlook for finding modulators of K_v7.2-7.3

High-throughput screening of venoms

Synthesis of potential peptide modulators

Electrophysiology on K_v7.2-7.3 and off target ion channels

Brain organoids to test toxin activity on neuronal systems

Animal models with K_v 7.2-7.3 mutations

References
[1] Chassagnon *et el.* PNAS. 2017. 114 (14) 3750-3755
[2] Redd, *et al.* Circulation. 2021. ;144:947–960
[3] Miceli, *et al. J. Neurosci*. 2015, *35*, 3782–3793.

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