# Discovery and optimization of peptide-based anti-cobratoxins

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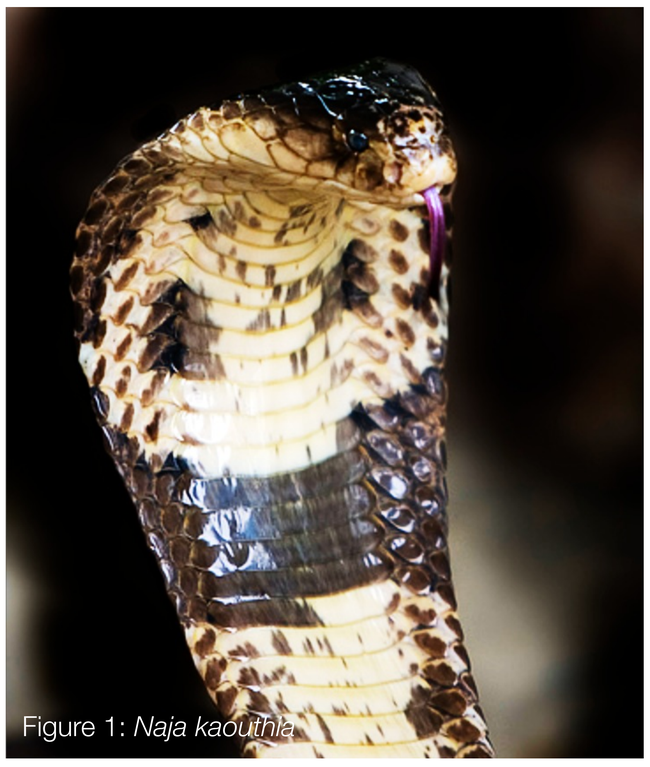
Figure 1: *Naja kaouthia*

# Discovery and optimization of peptide-based anti-cobratoxins

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## Fully synthetic antitoxins - The antivenoms of the future

More than 5.5 million people per year are victims of snake envenomation, resulting in 125,000 deaths and 400,000 amputations worldwide [1],[2]. Antivenoms are still produced by animal immunization procedures, and they are associated with a high risk of severe adverse reactions. Alternatively, synthetic peptides may open the possibility for new therapies with better efficacy and safety. Here, we report the discovery and optimization of a synthetic peptide directed against α-cobratoxin (α-CTX), the most toxic component of Monocled cobra (*Naja kaouthia)* [3].

## Discovery of Peptide 1 - Binder and inhibitor of α-cobratoxin

**1** Cobratoxins target and inhibit the nicotinic acetylcholine receptors (nAChRs), thus efficient anti-cobratoxins must block this interaction.

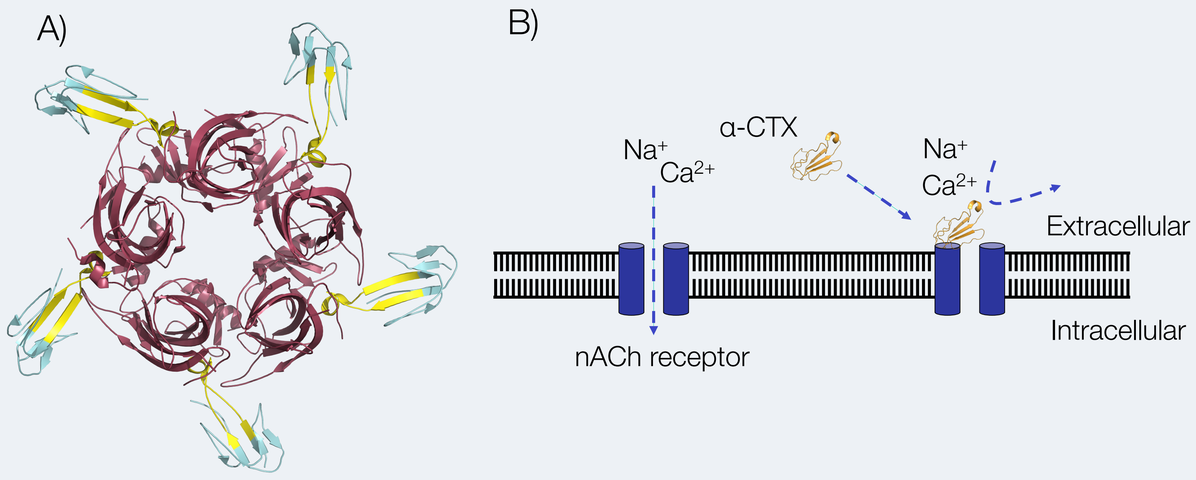


*Figure 2. A) Crystallized structure of 5 α-CTX molecules (shown in blue, interaction regions in yellow) bound to the pentameric nAChR (in dark red) (PDB: 1YI5). B) Schematic overview of the physiological mechanism: α-CTX inhibits transmission of post-synaptic signals.*

**2** Peptide P1 was identified by phage display selection.

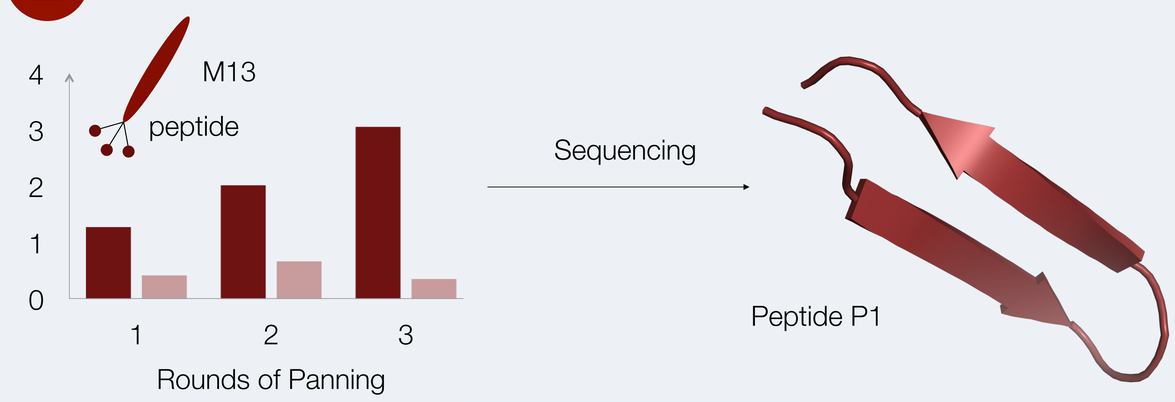


*Figure 3. A) ELISA tests of panning rounds coupled to next generation sequencing lead to the discovery of Peptide 1. A tridimensional model of the peptide was obtained by the PEP-FOLD server [4].*

**3** Peptide 1 binds to α-CTX and inhibits its interaction with nAChRs

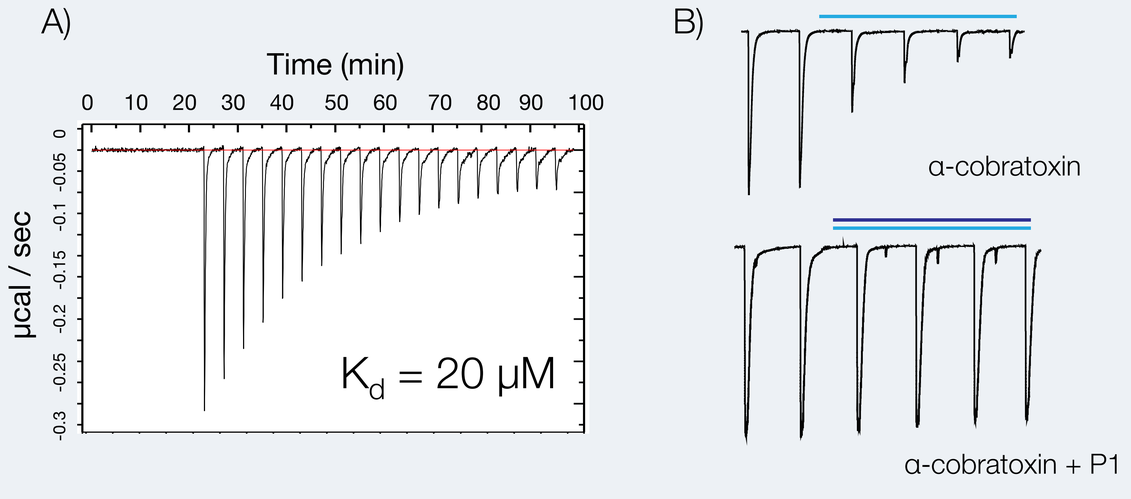


*Figure 4. A) The $K_d$ between Peptide 1 and α-CTX was determined by Isothermal Titration Calorimetry (ITC). B) Neutralization capacity was confirmed by two electrode voltage clamp (TEVC) assays: measured ion currents through the nAChR in Xenopus laevis oocytes show that Peptide P1 prevents α-CTX from inhibiting the ion current.*

**4** According to docking studies Peptide 1 binds to the same α-CTX residues that are involved in the interaction with nAChRs.

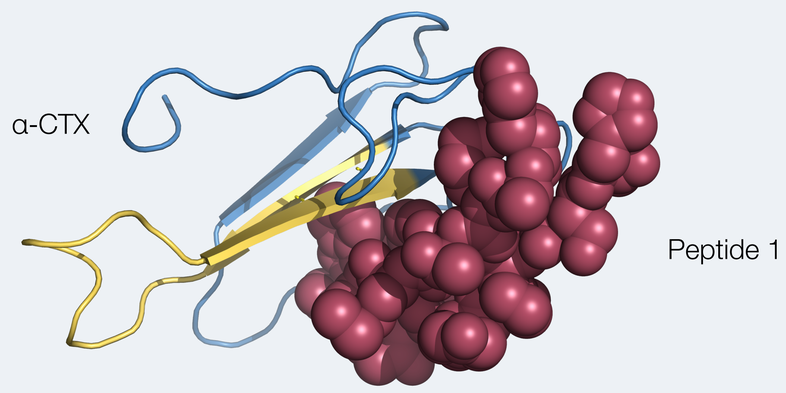


*Figure 5. A) A tridimensional model of the interaction between Peptide 1 and α-CTX was obtained using the CABS-dock web server [5]. Peptide 1 binds to the II loop of α-CTX (shown in yellow), which is also involved in the interaction with nAChRs residues.*

## Future perspectives – Optimizing Peptide 1

Truncated and cyclic versions of Peptide 1 are expected to **show increased affinity and neutralization capacity.**

Other elapid venoms are rich in α-neurotoxins structurally similar to α-CTX, thus Peptide 1 and its optimized versions may **provide protection against** the neurotoxic effects exerted by **α-neurotoxins present in a broad range of venoms.**

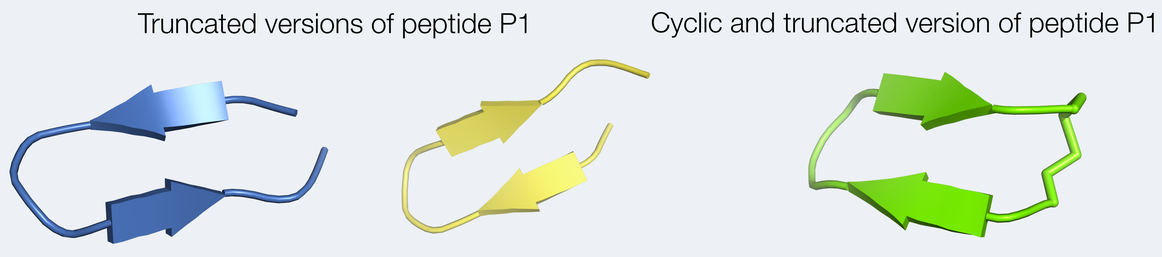


*Figure 6. Models of two truncated versions and a truncated and cyclic version of Peptide 1, obtained through the PEP-FOLD server.*

References

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