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Discovery and optimization of peptide-based anti-cobratoxins

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Fully synthetic antivenoms - 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].

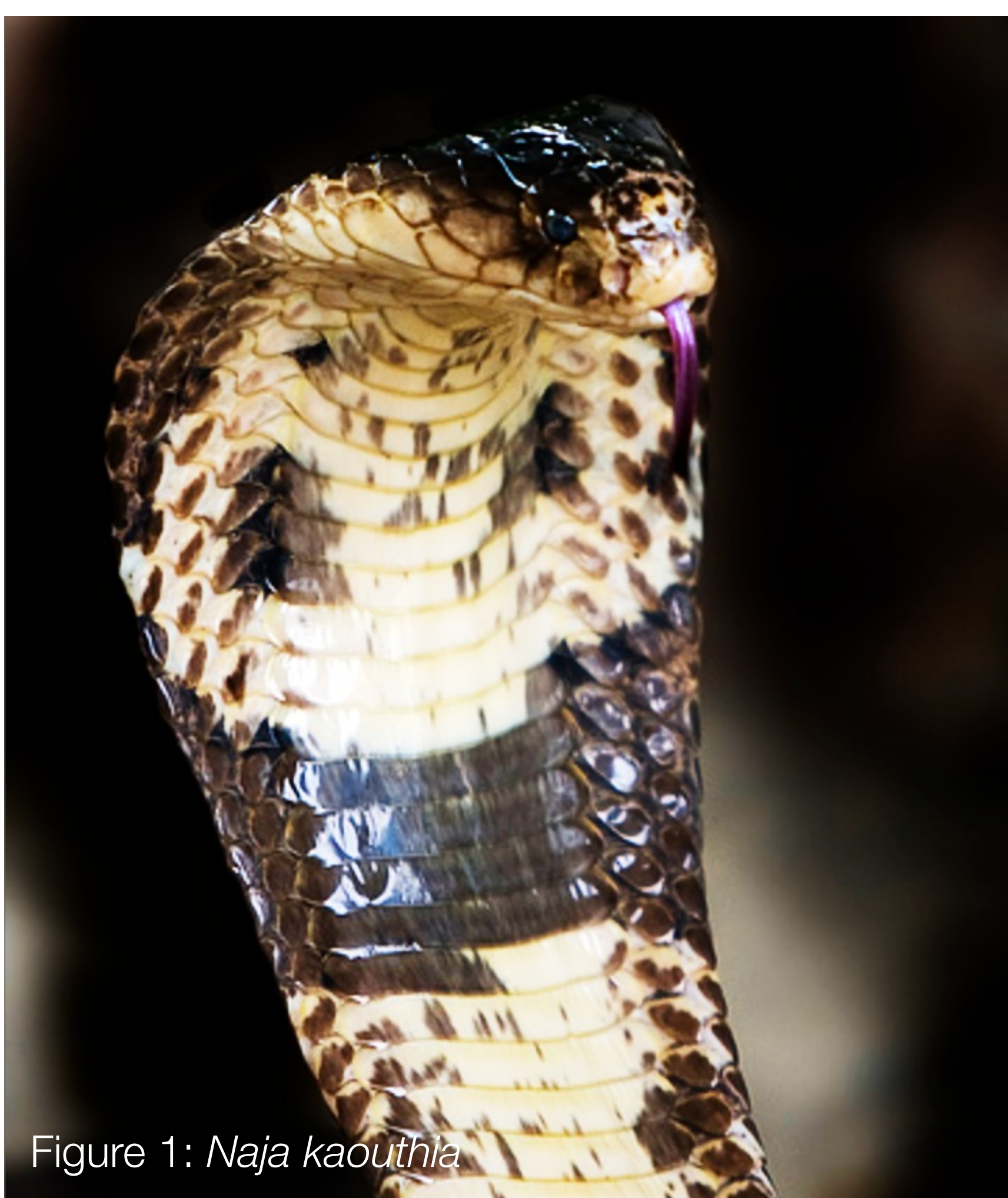


Figure 1: *Naja kaouthia*

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.

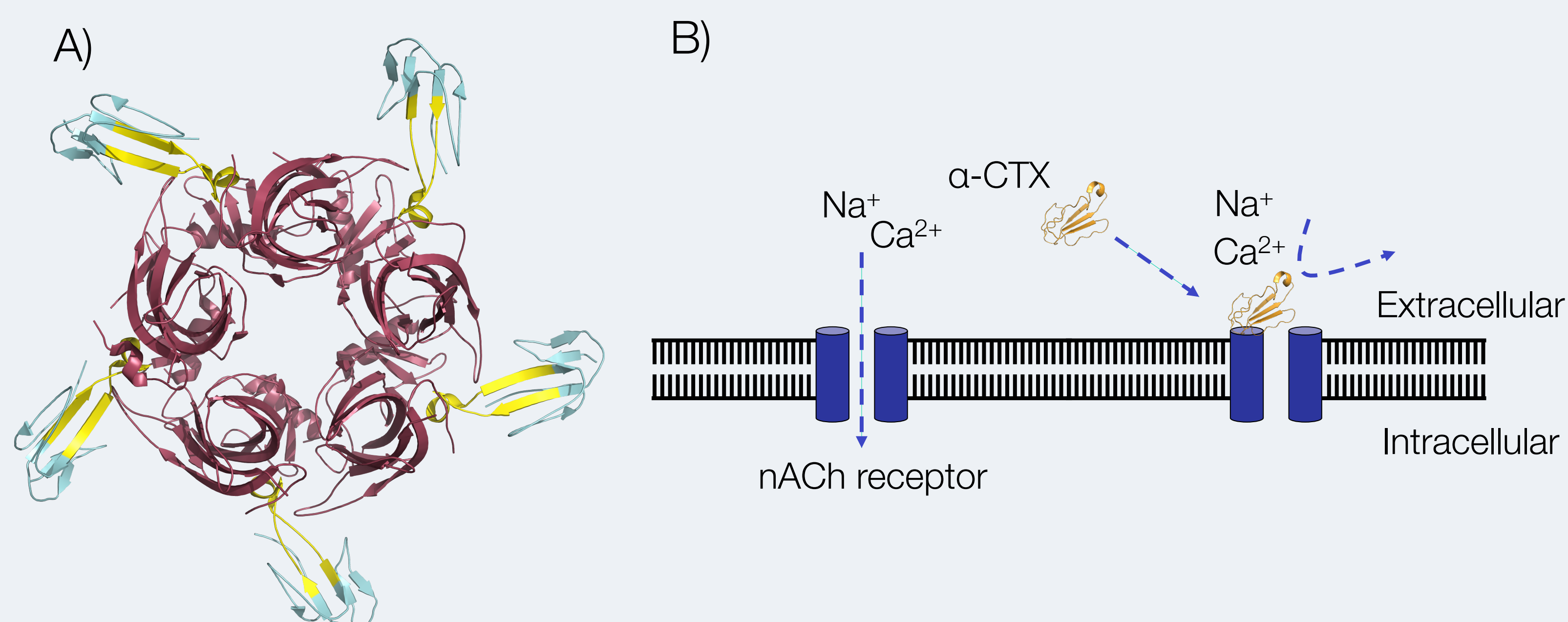


Figure 2. A) Crystallized structure of 5 α -CTX molecules (shown in blue, interaction regions in yellow) bound to the pentameric nAChR (in dark red) (PDB: 1YI5). B) Schematic overview of the physiological mechanism: α -CTX inhibits transmission of post-synaptic signals.

2 Peptide P1 was identified by phage display selection.

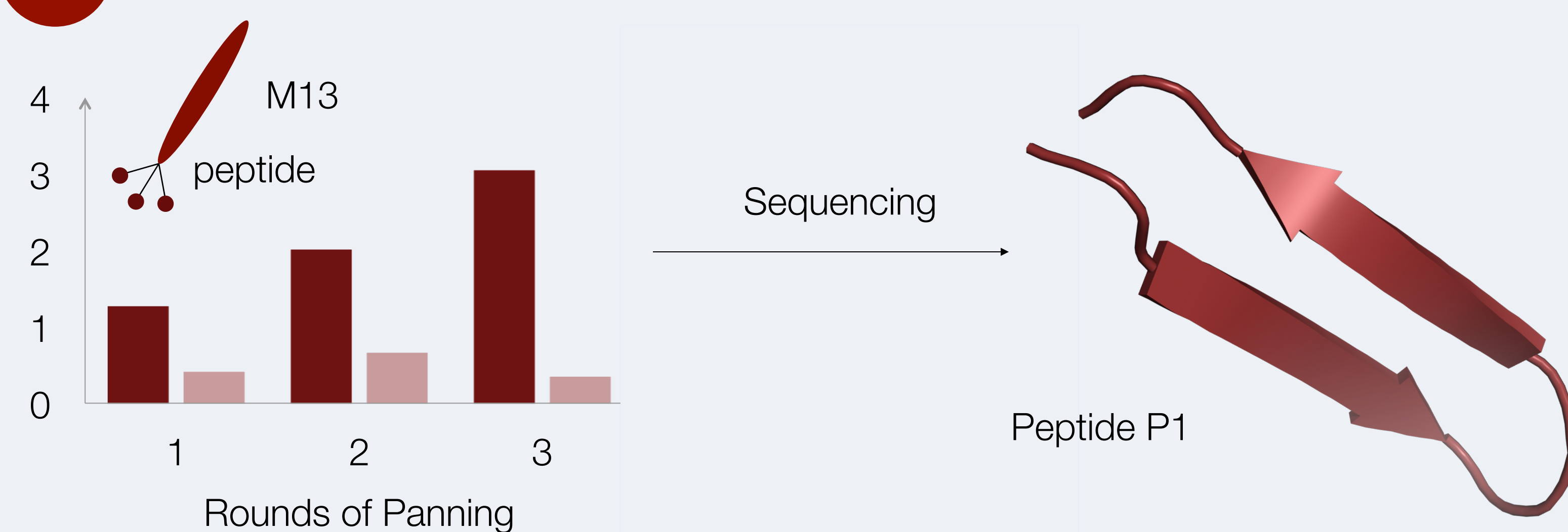


Figure 3. A) ELISA tests of panning rounds coupled to next generation sequencing lead to the discovery of Peptide 1. A 3D model of the peptide was obtained by the PEP-FOLD server [4].

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

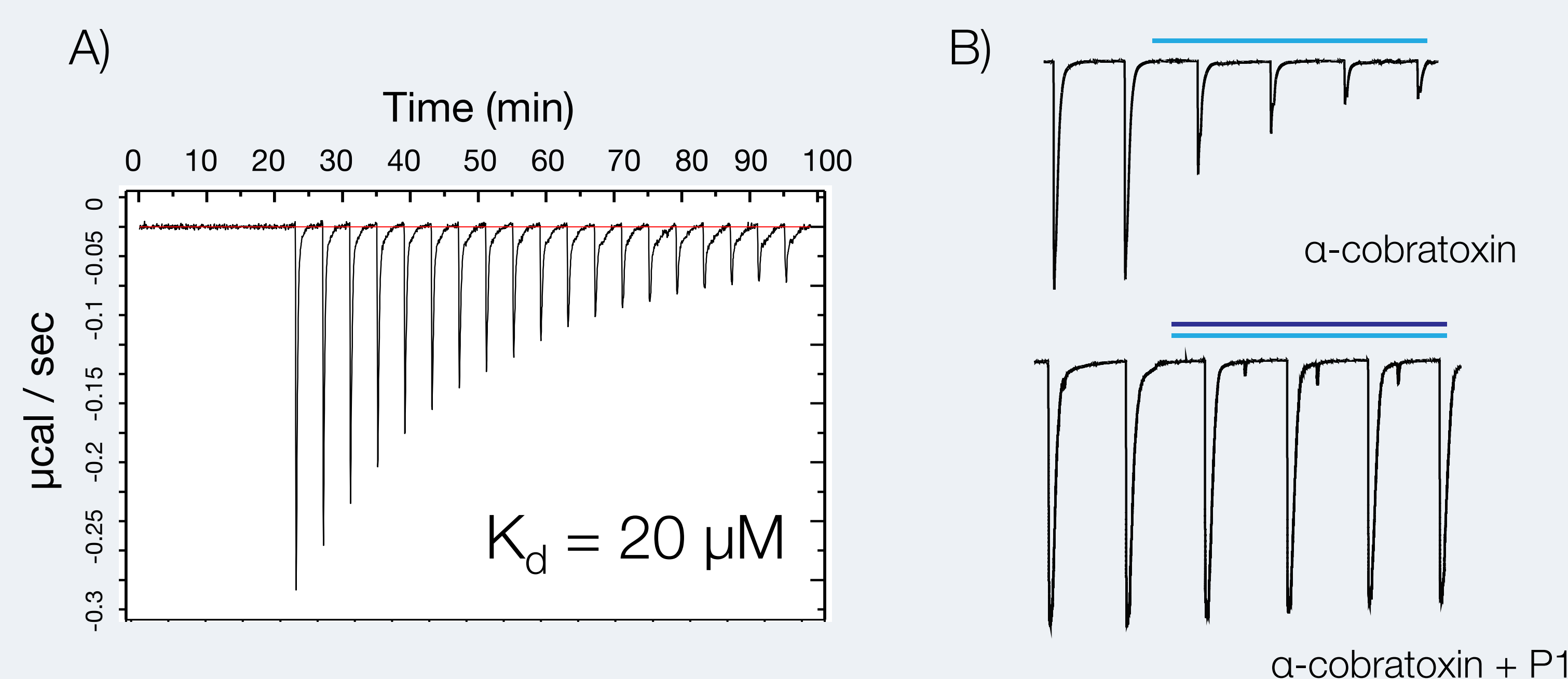


Figure 4. A) The K_d between Peptide 1 and α -CTX was determined by Isothermal Titration Calorimetry (ITC). B) Neutralization capacity was confirmed by two electrode voltage clamp (TEVC) assays: measured ion currents through the nAChR in *Xenopus laevis* oocytes show that Peptide P1 prevents α -CTX from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

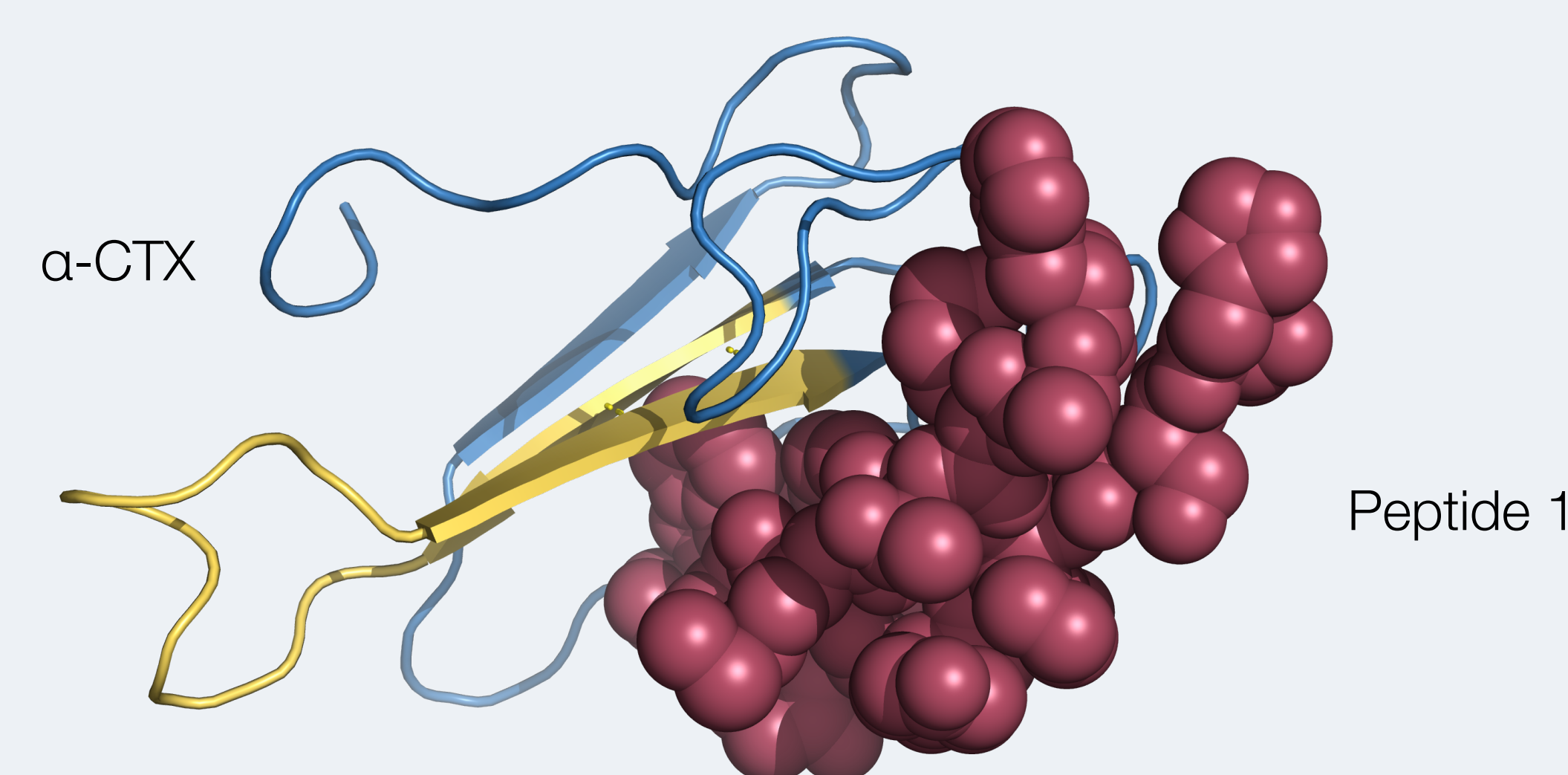


Figure 5. A) A 3D model of the interaction between Peptide 1 and α -CTX was obtained using the CABS-dock web server [5]. Peptide 1 binds to the II loop of α -CTX (shown in yellow), which is also involved in the interaction with nAChRs residues.

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.

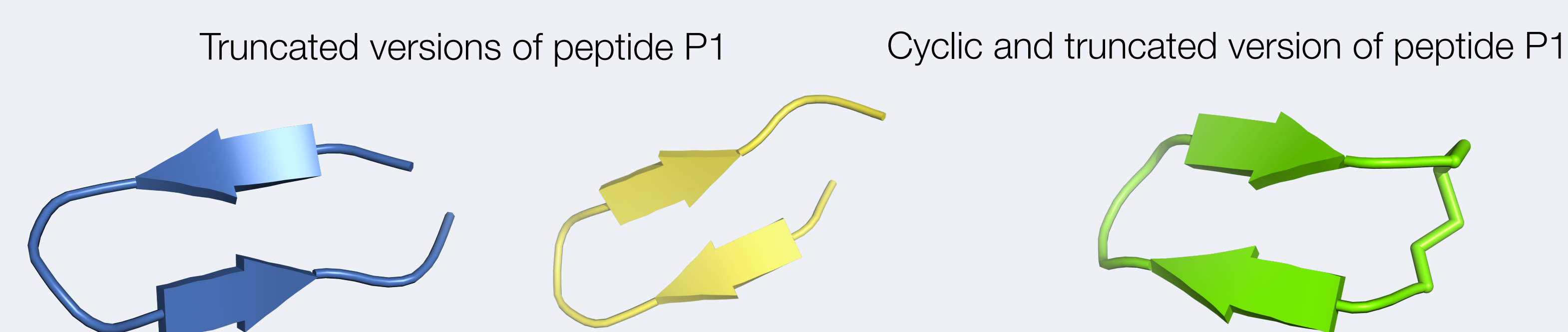


Figure 6. Models of two truncated versions and a truncated and cyclic version of Peptide 1, obtained through the PEP-FOLD server.

References

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