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Development of a Recombinant Antibody-Based Treatment of Snakebites

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Improving Antivenom to Save Lives and Limbs

Antivenom for snakebites is produced by immunization of large mammals with snake venom using a traditional and expensive method developed in the 1880’s. Due to the animal origin, the products are highly immunogenic and come with a high risk of adverse side effects such as serum sickness and anaphylaxis, possibly leading to death [1].

This project aims at replacing existing snake antivenoms with a mixture of recombinant, humanized antibodies produced by modern cell-based fermentation technology [2]. It is anticipated that such an antivenom will reduce the current high risk of severe side effects, reduce cost, and thereby can be sold at 1/10 of the current price making the essential medicine available for > 700 M Africans [4].

Modern day technology allows development of monoclonal antibodies (mAbs) targeting snake toxins, however, identification, characterization of immunogenic features (B-cell epitopes), and availability of purified snake toxins or non-toxic analogs currently constitute major bottlenecks blocking the development of recombinant mAbs. We have set out to remove these bottlenecks starting by mapping antibody binding sites of existing horse-derived products and purified antibodies from snakebite victims using high-density peptide microarrays. Moreover, we are developing homology models of all relevant mamba toxins to map conserved sites and identify key residues for toxicity.

Modeling Short Neurotoxin 1 from Mamba Snakes

Figure 3 – Homology model of clinically relevant toxin from mamba (Dendroaspis) snakes. Surface and cartoon representations of short neurotoxin 1 (SN1) illustrating interspecies variation and the idea of finding one cross-reactive mAb. SN1 is a member of the large and diverse family of three-fingered toxins (3FTx). SN1 is known to antagonize the neuromuscular nicotinic acetylcholine receptor (nAChR) using finger 1 and 2 for binding [6]. Templates for homology model: 3ERA (crystal structure of mutant related Erabutoxin a from a sea snake with low affinity for nAChR) [7] and 2QC1 (nAChR bound distantly related α-bungarotoxin from the many-banded krait) [8].

Challenges in the near future

Figure 5 – Schematic overview of upcoming challenges related to protein research.

References

[6] Erabutoxin
[7] 3ERA
[8] 2QC1

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