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Antivenom slithers back to life

Snakebite treatment still relies on antivenom, a 130-year old technology, but biotech is on the job.

A venomous snakebite can cause paralysis, irreversible kidney failure, bleeding disorders leading to hemorrhage, or tissue damage that results in permanent disability. Every year, an estimated 4.5 million snake bites worldwide cause close to 100,000 deaths[1]. Most who are bitten survive, but not without lasting consequences — 2.7 million people are left with serious injuries. Low- and middle-income countries in Africa, Asia and Latin America bear the brunt, and in 2017 snakebite envenoming was formally listed by the World Health Organization (WHO) as a highest priority neglected tropical disease.

Antivenoms are one of biotech's early successes. They are antibody therapies that, injected into the patient after a bite, block and disable the toxins of a specific venom. The first antivenom was developed against cobra venom in 1895 by French scientist Albert Calmette. Calmette inoculated donkeys, and then horses, with small amounts of venom from *Naja naja*, or the spectacled cobra. The inoculated animals respond by producing antibodies that are then purified from their plasma and injected into patients with snakebite to counter the venom's toxic effect. Over a century later, the basic method for antivenom production has not changed, although some producers now use sheep.

Although the process is simple, it is not efficient. A snakebite can require large amounts of antivenom, and the number of antibodies retrieved from each plasma sample can be low. This has led to many antivenom shortages in recent years. Among other disadvantages, antivenoms need to be given within a short time window of the bite, and need to be administered intravenously. Also, the injection of large amounts of antivenom can cause 'serum sickness', in which the body's immune system reacts to the foreign horse (or sheep) serum component of the antivenom. Cutting corners in purification, often to reduce costs, can increase the risk of side effects.

One major limitation is that the antivenom must be tailored to a specific species of snake: the toxins in snake venom differ markedly from one species to another. Venom comprises 50–200 components, present in multiple protein isoforms, and these can differ even within a species depending on age, location and season. For a treatment to be effective, it is necessary to know the species of snake behind the bite. Furthermore, someone must have gone through the process of creating an antivenom for that species. For example, India has more than 60 venomous species of snake, and there is no specific antivenom against most of them. If you are bitten by a snake that is not one of the 'big four' (spectacled cobra, common krait, saw-scaled viper and Russell's viper), the antivenom will be largely ineffective[2]. And countries that suffer the most snakebites often lack the capacity to produce and distribute snake antivenoms at scale for their most common species of snake.

Now it seems antivenoms may finally be getting an upgrade. In February, researchers developed a synthetic antibody that neutralizes one of the most potent neurotoxins — a long-chain α-neurotoxin that causes paralysis, found in venom from mambas, cobras and Australian copperheads[3]. Scientists can produce such a universal antibody in cells, rather than animals. Further, these synthetic therapies would be less likely to elicit serum sickness than those produced in horses or sheep.

Several attempts have been made in past years to find safer and more effective antivenoms. Camelid antibodies, unlike those from sheep or horses, can be stored at room temperature. Not requiring a cold chain, these antibodies would be easier to get to remote locations. Additionally, because antibodies from camelids are smaller, they diffuse quickly throughout the body and could potentially be delivered through the skin.

Small-molecule drugs also have the advantage of working quickly, and a few have been repurposed to counteract venom toxins. For instance, 2,3-dimercapto-1-propanesulfonic acid (DMPS)[4] was originally developed to remove metals from the blood during metal poisonings. DMPS antagonizes the activity of snake venom metalloproteinases, and while it cannot act as a standalone treatment, it can hold off tissue damage and bleeding until another antivenom can be given. The company Ophirex has been working for a decade on varespladib, a small synthetic molecule, originally developed to treat sepsis, that inhibits secreted phospholipase A2 (sPLA2) toxins[5]. Varespladib is making its way through clinical trials, with phase 2 results to be reported at the end of 2024. Other small-molecule drugs have been repurposed against specific bites, but none has been shown to have broad efficacy[6,7] and nothing is yet in the clinic.

Monoclonal antibodies, as opposed to the polyclonal antibodies isolated from immunized animals, offer an alternative approach. These have been developed using a variety of cost-competitive platforms, such as phage display technology, which can screen for antibodies or antibody fragments with high affinity and cross-reactivity. Monoclonals can be produced at large scale in days, rather than the months it takes in horses. In mice, human immunoglobulin G antibody cocktails can protect against black mamba dendrotoxins[8], and they are more compatible with the human immune system. However, a recent study also showed that a promising monoclonal antibody caused enhanced toxicity in a mouse model mimicking snakebite, highlighting the need for better preclinical models in this area[9].

Advances in proteomics and genomics are helping. For snakes such as the coral snake, it is hard to get enough venom out of the gland to immunize a horse. By looking at the protein sequence of the venom's most significant toxins, researchers were able to map the epitopes to which an antibody could bind and then used pieces of DNA to immunize mice[10]. A similar approach was also shown to neutralize effects of the pit viper bite[11]. Reference genomes and transcriptomes for venomous snakes can identify toxin genes that show venom-gland-specific expression[12] and probably encode venom effector proteins.

Still, challenges remain in the hunt for a universal antivenom. A primary issue is funding. As with other neglected tropical diseases, there is limited funding for antivenom development and even less for clinical trials. Of the dozens of antivenoms supplied to sub-Saharan Africa, only a couple have been evaluated

in clinical trials. Part of the problem is that these drugs are not profitable, even if they are cheap to make. There are some organizations taking note: the WHO's antivenom initiative, and a $100 million Wellcome Trust program announced in 2019.

It's unlikely that a universal antivenom will come to fruition, but there is hope that more broadly acting cocktails of antivenoms for a given region will become available. Given a large dataset of genomics and proteomics data, this is something that could be tackled by AI protein design in the future. The other main issue is distributing antivenoms to those who most need them and producing them at scale regionally. Lab-synthesized versions will be crucial, and advances will need to be made to make these drugs shelf-stable, like varespladib.

The WHO has set a goal to reduce the global burden of snakebites by one-half by 2030, and it is looking as though biotech will help them get there.

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References

1. Longbottom, J. et al. *Lancet* https://doi.org/10.1016/S0140-6736(18)31224-8 (2018).
2. Laxme, R. R. S. et al. *PLoS Negl. Trop. Dis.* https://doi.org/10.1371/journal.pntd.0007899 (2019).
3. Khalek, I. S. et al. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.adk1867 (2024).
4. Albulescu, L. O. *Sci. Transl. Med.* https://doi.org/10.1126/scitranslmed.aay8314 (2020).
5. Lewin, M. R. *Toxins* https://doi.org/10.3390/toxins14110783 (2022).
6. Albulescu, L. O. et al. *Nat. Commun.* https://doi.org/10.1038/s41467-020-19981-6 (2020).
7. Hall, S. R. et al. *Nat. Commun.* https://doi.org/10.1038/s41467-023-43510-w (2023).
8. Laustsen, A. H. et al. *Nat. Commun.* https://doi.org/10.1038/s41467-018-06086-4 (2018).
9. Sørensen, C. V. et al. *Nat. Commun.* https://doi.org/10.1038/s41467-023-42624-5 (2024).
10. Ramos, H. R. et al. *PLoS Negl. Trop. Dis.* https://doi.org/10.1371/journal.pntd.0004484 (2016).
11. Prado, N. D. R. et al. *PLoS One* https://doi.org/10.1371/journal.pone.0151363 (2016).
12. Suryamohan, K. et al. *Nat. Genet.* https://doi.org/10.1038/s41588-019-0559-8 (2020).