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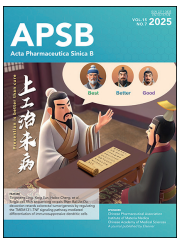

HIGHLIGHT

Reshaping antivenom therapy: A triple-synergy strategy featuring broadly neutralizing antibodies and a small-molecule PLA_2 inhibitor

KEY WORDS

Antivenom;
Neutralizing antibody;
PLA_2 inhibitor;
Triple-synergy strategy

Snakebite envenoming has been designated by the World Health Organization (WHO) as a neglected tropical disease, responsible for over 100,000 deaths and more than 300,000 cases of permanent disability annually. The burden is especially pronounced in Southeast Asia, sub-Saharan Africa, India, and Latin America[1]. Despite this, current clinical management still relies on polyclonal antivenoms derived from hyperimmunized animals—a century-old technology first introduced in the 1890s. These sera suffer from major limitations, including species specificity, high immunogenicity, protein impurity, short half-life, and cold-chain dependence, all of which hinder their global accessibility and therapeutic efficacy[2,3].

In a recent *Cell* publication, Glanville et al.[4] proposed a structure-guided, mechanism-based strategy for broad-spectrum snakebite therapy. By combining two recombinant human monoclonal antibodies with a small-molecule PLA_2 inhibitor. This combinatorial therapy conferred unprecedented protection against venoms from 19 medically important elapid species in preclinical models, including cobras, kraits, mambas, and taipans[4]. Fig. 1 summarizes the global challenge of elapid envenoming, the molecular targets and therapeutic mechanism, and the envisioned strategy for modular, globally deployable antivenoms. This work lays a solid foundation for developing a universal, recombinant, and modular antivenom platform.

1. Venom complexity and the case for conserved epitope targeting

Snake venoms are complex biological mixtures composed of proteins and small molecules with diverse toxic activities. These include neurotoxins (*e.g.*, 3FTX), cytotoxins, phospholipases A_2 (PLA_2), and metalloproteinases (SVMPs), which collectively disrupt synaptic transmission, damage cellular membranes, and interfere with coagulation pathways[5]. Among them, long-chain (LNX) and short-chain (SNX) 3FTX neurotoxins act by competitively binding to nicotinic acetylcholine receptors (nAChRs), rapidly inducing neuromuscular paralysis.

Traditional antivenoms are largely ineffective across species due to high venom variability. Instead of targeting this diversity, Glanville's strategy focused on exploiting evolutionary conservation. By identifying functionally essential, conserved epitopes shared across diverse 3FTX isoforms, the authors designed broadly neutralizing antibodies (bnAbs) capable of cross-species neutralization.

2. Antibody discovery from a hyperimmune individual

The authors screened memory B cells from a unique human donor who had undergone over 850 self-immunizations with diverse snake venoms. A combinatorial panning approach using venoms from black mamba, taipan, cobra, and krait led to the identification of two potent bnAbs:

- **LNX-D09**, targeting long-chain 3FTX (LNX), and
- **SNX-B03**, targeting short-chain 3FTX (SNX).

X-ray crystallography revealed that LNX-D09's CDR-H3 loop mimics the "loop C" of nAChR, allowing it to directly block the

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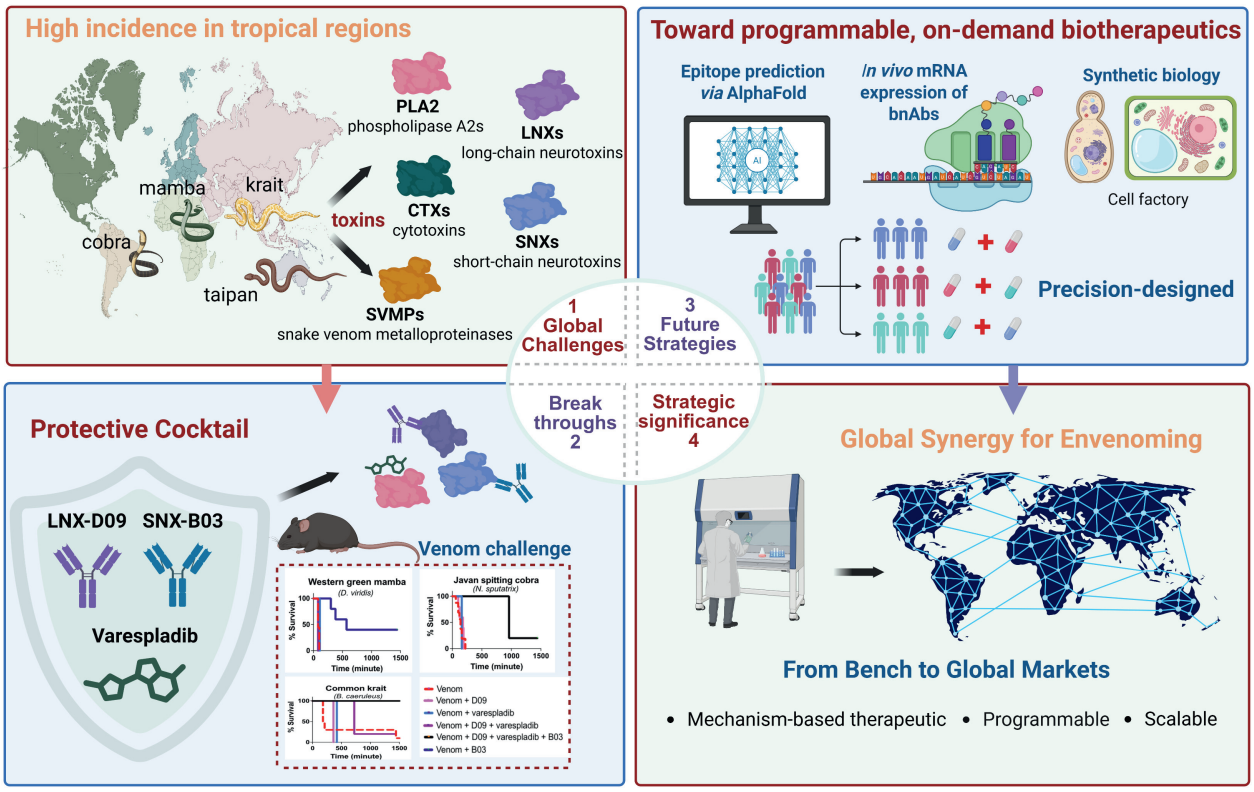

Figure 1 Schematic illustrating a strategy for developing broad-spectrum antivenoms. The approach combines two recombinant human monoclonal antibodies—LNX-D09, targeting long-chain neurotoxins (LNXs), and SNX-B03, targeting short-chain neurotoxins (SNXs)—with the phospholipase A_2 (PLA_2) inhibitor varespladib to achieve robust protection against medically important elapid venoms. This mechanism-based, serum-free strategy exemplifies the future of programmable, scalable, and globally deployable antivenoms. Reproduced with permission from Ref. 4. Copyright © 2025 Elsevier.

toxic interface. SNX-B03 employs a similar receptor-mimicking mechanism[4]. Notably, LNX-D09 shares high structural similarity with 95Mat5, a previously described antibody identified *via* yeast display[4,6]. While 95Mat5 was derived from an *in vitro* synthetic antibody platform, LNX-D09 was isolated from a hyperimmune human donor with documented elapid exposures, highlighting two distinct yet convergent discovery paths toward targeting structurally conserved toxin epitopes. The use of hyperimmune donors enables access to affinity-matured, *in vivo*-selected antibodies with proven immunogenicity in humans—potentially enhancing developability and clinical translation. These findings suggest convergent evolution toward structurally conserved toxin hotspots and validate the feasibility of targeting "toxicity cores" that are critical for venom function and resistant to evolutionary drift.

3. Triple-synergy strategy: Combining antibodies and small molecules

While 3FTXs are major lethal components, they are not the sole contributors to venom toxicity. In species such as taipans and tiger snakes, PLA_2 enzymes constitute a significant proportion of venom activity. To address this, the authors incorporated varespladib, a potent small-molecule PLA_2 inhibitor with broad-spectrum efficacy[4]. Combining LNX-D09 with varespladib provided effective neutralization against most venoms tested. However, certain species with SNX-dominant toxicity (*e.g.*, green mamba, krait) required the addition of SNX-B03 for full protection. The resulting three-component cocktail—LNX-D09, SNX-B03 and varespladib—achieved either complete survival or significant survival extension in mice exposed to venoms from all 19 elapid species prioritized by WHO[4]. Taking the Common Krait Venom as an example, it caused 100% lethality after 3 h. The combination of LNX-D09 and varespladib improved treatment efficacy, resulting in 20% survival of mice. However, including SNX-B03 along with LNX-D09 and varespladib resulted in full protection (100% survival rate). Similarly, Eastern brown snake venom was 100% lethal after 2 h. Compared with LNX-D09 alone (extended survival of 40% mice to 6 h) and varespladib alone or with LNX-D09 (extended survival of 100% mice to 6 h), the three-component mixture, however, resulted in a 7.6-fold survival extension, with 40% mice surviving over 20 h.

4. Toward clinical translation: Modular antivenom redefined

While therapeutic monoclonal antibodies (mAbs) have revolutionized modern medicine, they often entail high development costs, complex purification processes, and temperature sensitivity, necessitating cold chain logistics and increasing overall deployment costs. Compared with animal-derived sera, recombinant human antibodies offer several advantages: reduced immunogenicity, longer half-life, reproducibility, and scalability. Fc-region engineering can further optimize pharmacokinetics and enhance effector functions. The all-recombinant nature of this triad strategy also eliminates batch variability and contamination risks associated with serum-based products.

The authors propose this combination as a modular antivenom platform. As venom composition varies across regions and species, additional antibodies targeting SVMPs or procoagulant enzymes can be incorporated to expand coverage—particularly toward viperid snakes. Such adaptability paves the way for globally deployable, precision-designed antivenoms[4].

5. Future perspectives: AI, synthetic biology, and mRNA technologies

The future of antivenom development is likely to be shaped by advances in AI-driven protein design, bioengineering, and new delivery platforms. Tools like AlphaFold and RosettaFold enable rapid identification of conserved toxin epitopes and in silico antibody optimization. Nanoparticle-based delivery systems may improve tissue targeting and pharmacokinetics.

mRNA-based antibody expression systems offer another transformative opportunity. Encoding bnAbs in mRNA may enable in vivo production of neutralizing antibodies, allowing for rapid, on-demand protection in snakebite-prone or resource-limited areas[7]. Together, these innovations are driving antivenom therapy toward a programmable, scalable, and mechanism-based therapeutic paradigm.

6. Conclusions

The study by Glanville et al.[4] represents a paradigm shift in snakebite therapy. By integrating structural immunology, cross-species antibody discovery, and small-molecule synergy, the authors challenge the century-old model of animal-derived, species-specific antivenoms. Their strategy exemplifies the principles of next-generation biotherapeutics: precision, modularity, scalability.

Beyond scientific innovation, this work holds tremendous public health value. In regions with high snakebite incidence and limited healthcare infrastructure, a recombinant, stable, and broad-spectrum antivenom could dramatically reduce mortality and disability. As synthetic biology and precision pharmacology continue to evolve, the vision of a universal antivenom is rapidly transitioning from possibility to reality.

Author contributions

Longlong Luo: Conceptualization, writing original draft. Xiang Gao: Conceptualization, supervision. Yangyihua Zhou: Drawing & editing. Ning Shi: Investigation. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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