NEWS FROM THE PIT

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New Universal Antivenom! But does it work on the venom proteome at your home?

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Whenever new innovations for the treatment of venomous snake bite are announced, there is typically a fair amount of initial enthusiasm and interest. The recent publication promising yet another “universal antivenom” is no exception [1]. However, as with most important issues, what matters most about the utility of an antivenom is “location, location, location”. Where you practice and treat venomous snake bites and how your local vipers kill their prey are the critical facts to know before evaluating any new antivenom panacea. The present newsletter exams the promise of this new antivenom [1] with a practical eye towards what it actually treats and compares it to how a snake bite is treated in North and Central America.

NEWSLETTER HIGHLIGHTS

Discussion of a new antivenom and how it treats and compares to how a snake bite is treated in North and Central America.

Image 1: Sidewinder (*Crotalus cerastes*)

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In brief, the investigators harvested and identified broadly neutralizing antibodies from the blood of an individual that had injected himself 856 times with at least 19 different venoms over 18 years [1], and then the antibodies by themselves or in combination with the phospholipase A_2 (PLA_2) inhibitor varespladib were administered to mice envenomed with Elapidae venoms (e.g., black mamba, taipan). The envenomed mice either had death delayed or prevented for up to a day. On page 14, the first passage of the Discussion states: "We demonstrate the successful combination of a minimal cocktail of broadly neutralizing antibodies and a small-molecule inhibitor as a proof of principle for a universal antivenom" (underlining by the present author). The tacit assumption was that demonstration of protection from death for mice caused by neurotoxicity from venoms with a predominance of three finger toxins (3FT), or long-chain neurotoxins (LNX), and/or PLA_2 in the venom proteome somehow bestows the title of "universal" to their antivenom. Nothing could be further from the truth.

While elapid venom proteomes are neurotoxic, the vast majority of snake bites in the United States involve rattlesnakes, cottonmouths, and copperheads that have venoms with a predominance of enzymes/proteins that cause tissue damage. Ironically, the source of the antibodies had injected himself with Western diamondback and Mojave rattlesnake venom, and yet antibodies developed from exposure to these toxins were never reported as tested [1]. These Viperidae venoms have tissue destroying serine proteases (SP), metalloproteinases (MP), and PLA_2. While varespladib can inactivate PLA_2 activity and potentially diminish the tissue injury/edema or neurotoxicity of Viperidae envenomation, the highly toxic and indeed lethal effects of SP and MP on mice – and humans – would be expected to not be affected by varespladib or any of the antibodies showcased in the new "universal antivenom" presented [1]. A comparison of the venom proteomes of medically important Viperidae and Elapidae species are presented in figure 1 to demonstrate the marked differences in these two snake families as referenced [2,3]. As presented, the combination of antibodies from one hyperimmune individual combined with varespladib would not be effective as a therapy for North/Central America, especially compared to therapy with CroFab® and ANAVIP®.

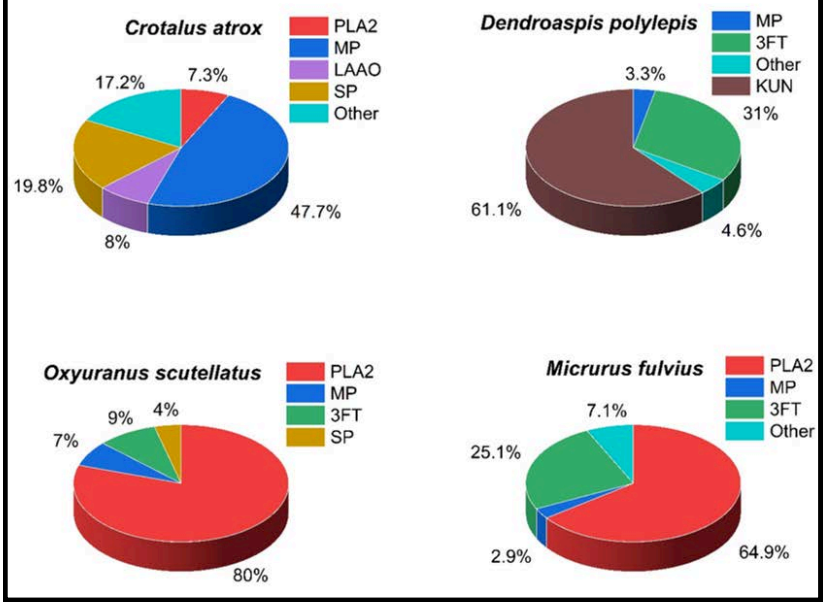

Figure 1: Enzymatic abundance of venom proteomes of the Western diamondback rattlesnake (*Crotalus atrox*), the black mamba (*Dendroaspis polylepis*), the costal taipan (*Oxyuranus scutellatus*), and the Eastern coral snake (*Micrurus fulvius*). As can be easily seen, not only are Viperidae venom proteomes different from Elapidae venom proteomes, but there is significant variation among Elapidae venoms.

PLA_2 = phospholipase A_2 (neurotoxins, tissue damage); KUN = Kunitz-type inhibitors (neurotoxins, inhibit voltage-dependent potassium channels); LAAO = L-amino acid oxidases (tissue damage); 3FT = three-finger toxins (neurotoxins); MP = metalloproteinases (tissue damage); SP = serine proteases (tissue damage); other = other proteins.

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The “Dr. Jekyll & Mr. Hyde” approach to antivenom development (a.k.a. injecting yourself with any venom you can get your hands on) is simply not practical. No one person, or even a supermarket full of people, could ever inject themselves with all the Elapidae and Viperidae snake venoms in the world and produce all the broadly neutralizing antibodies needed – there are just too many species! Oh, and there is an ethical problem, as it is likely that a significant number of people injected with venom may experience significant injury or death despite all precautions taken. Further, human beings have accidents, develop diseases, grow old, and die – taking their broadly neutralizing antibodies with them. These are just a few reasons why the manufacturers of antivenoms used in North and Central America use large animals instead of people to produce CroFab® (made with healthy sheep) and ANAVIP® (made with healthy horses). The same approach with large animals as a source of antibodies should be (and has been) used to generate antivenoms for decades.

The search for universal, or generally very useful, antivenom solutions and routes of administration is underway and likely will be a topic of interest for decades to come. Recombinant versions of endogenous inhibitors of venom proteins; inorganic ruthenium-containing compounds that inhibit PLA_2, MP and SP; and, “nanosponges” that act as molecular sponges that adsorb venom are among the latest innovations. These new antivenoms may be administered intravenously or into the bite site. As the new releases continue to appear there will be excitement; however, whatever the headline, keep in mind your own, home venom proteome.

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References

1. Cell. 2025;188:1-18.
2. Toxins. 2017;9:290.
3. J Proteome Res 2009;8:3055–3067.

Conflict of Interest: The author is the inventor of the use of CORM-2 as a remedy for venom induced coagulopathy, with USPTO patents (#10,314,860 and #10,828,326) owned by the University of Arizona Board of Regents. The author also is the owner of a company, Trinity Antivenoms, LLC, that is inactive and that possesses no assets.