



Drug Development Gets Dangerous

It has been an unusually hot summer. Vast swathes of the globe have experienced prolonged heatwaves and jellyfish, bees, wasps, scorpions, snakes and spiders have thrived in the balmy temperatures. All of these creatures have varieties that are able to produce venom, deployed via a delivery mechanism (such as a sting, barb or fang) to catch prey and/or act as a defense mechanism. Although usually painful rather than fatal to humans, venomous species still account for more than 80,000 deaths annually. Indeed, a recent envenoming study reported by *The Lancet* on July 12, 2018, predicted that 90% of the global population live within range of areas inhabited by snakes, and 272.91 million individuals are exposed to venomous snakes where no effective therapy exists. Venoms typically comprise a complex mix of biochemicals that are evolutionarily adapted to interact with a variety of cellular components within the target organism. Some of these active compounds have exquisitely potent and selective modes of action that have the potential to be coopted for medicinal use. In fact the term pharmacology is derived from the ancient Greek pharmakon, meaning remedy and poison, and this dichotomy between the harmful and beneficial actions of venom has fascinated mankind for millennia.

Although the surge in bites and stings this summer has been largely unwelcome, researchers who dedicate their time to understanding venom have used it as an opportunity to gather more samples. Venomics describes the study of venom and its toxicological profiles via the integration of -omics technologies. As high-throughput techniques have improved, so too has the ability to separate and identify peptides and enzymes of interest within a heterogeneous venom often containing more than 1000 components. The purification of individual molecules, followed by their functional interrogation using relevant assays, has enabled the identification of numerous novel therapeutic leads. Sterile blister packs and tablet bottles often belie the exotic origin of their active ingredients. The first venom-derived drug that entered general medical use was captopril, which was granted US Food and Drug Administration (FDA) approval in 1981. Based on a peptide found in the venom of a species of lancehead viper, captopril was shown to be an extremely effective angiotensin-converting enzyme inhibitor. Thanks to its vasodilatory properties, captopril was marketed as a treatment for hypertension and congestive heart failure, and its huge commercial success fueled the quest to develop new venom-inspired drugs.

The current number of venom-inspired US FDA-approved drugs in common use is rather modest (~6), although the drug development pipeline is healthy as attested by the many spin-out companies trying to commercialize promising compounds. One such example is Blaze Bioscience, founded by Jim Olson, a neuro-oncologist at the Fred Hutchinson Cancer Research Center (Seattle, USA). While screening venom from the death stalker scorpion, one of the peptides, chlorotoxin, was found to bind with high affinity to cancerous cells whilst sparing non-malignant cells. This preferential binding was due to chlorotoxin's affinity to matrix metalloprotease MMP-2 subtypes that are upregulated on the surface of certain cancers. By conjugating chlorotoxin to a fluorescent dye (BLZ-100, tozuleristide), Olson devised a Tumor Paint that could be used by surgeons to aid resection of

tumor masses. This innovative approach has been successfully tested in Phase 1 trials in adults with breast or brain tumors, and in children with central nervous system (CNS) tumors. A Phase 2 trial extending its use in pediatric CNS tumors is due to start imminently.

Other successful early-phase clinical trials include the anti-tumor properties of SOR-C13 (Soricimed Biopharma) which is derived from soricidin – a venom secreted by the northern short-tailed shrew. SOR-C13 is a highly selective inhibitor of TRPV6 calcium ion channels that are overexpressed in some solid tumors and are thought to play a role in their growth. Based on encouraging early-phase trials, the US FDA has awarded orphan-drug status to SOR-C13 for the treatment of ovarian and pancreatic cancer. Dalazatide is another promising drug developed by Kv1.3 Therapeutics to treat systemic disease. Derived from a Caribbean sea anemone peptide, dalazatide is a potent and highly specific Kv1.3 potassium ion channel inhibitor that has demonstrated proof of concept in a Phase 1b trial in psoriasis. Kv1.3 is frequently found on T effector memory cells and this strategy is thought to have promise in other T-cell-mediated autoimmune disorders. A Phase 2 trial is in preparation to treat individuals with sporadic inclusion body myositis, a rare disease that currently lacks effective treatment options.

Venomics offers the opportunity to pick apart the underlying causes of a particular disease and ask whether new or complementary pharmacological intervention might be more effective than the current standard of care. For example, venomics has directly helped to improve the mechanistic understanding of voltage-gated sodium (Na_v) channels and their role in a variety of diseases. There are nine human Na_v channels ($\text{Na}_v1.1$ - 1.9), whose gene mutations are associated with a range of human channelopathies. By finding a drug that can modulate a specific Na_v it might be possible to offset the channel defect and correct the disease. For instance, the spider venom peptide Hm1a displays selective $\text{Na}_v1.1$ activation and can reduce seizures in a mouse model of Dravet syndrome, as recently reported in *PNAS*, June 29, 2018. In a separate study, another spider venom peptide, Pn3a, was shown to potently and selectively inhibit $\text{Na}_v1.7$. In humans, mutations in this channel can cause insensitivity to pain, therefore the hypothesis was that pharmacologically blocking this channel might result in analgesic effects. Pn3a did not display any analgesic effects in multiple mouse pain models, however, when co-administered with sub-therapeutic doses of opioids, profound analgesia was elicited. The mechanisms underlying this intriguing observation are not yet understood, but this result might provide an alternative pain-relief option and perhaps circumvent the highly addictive properties of opioids.

It is no coincidence that many healthcare organizations including the World Health Organization, British Medical Association and American Medical Association, have as their emblem the snake-entwined Rod of Asclepius, owned by the Greek god of Medicine. By harnessing nature's toolbox and applying cutting-edge methodologies to augment desired properties, venomics has and will continue to benefit medicine. *EBioMedicine* will keep a close eye on this voyage of translational discovery: stings and bites, new drugs in sight!

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