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From Toxins to Therapeutics

Researchers are finding new drugs for chronic pain and autoimmune diseases by modifying animal venom-derived molecules that target the nervous and immune systems.

By Dan Cossins | March 19, 2013

Animal venoms are a veritable treasure trove of proteins and peptides fine-tuned by millions of years of evolution to kill or incapacitate both predator and prey. Usually delivered via injection through an assortment of fangs, barbs, spines, and stingers, venom toxins evade the body's defenses to seek out target cells, where they prevent blood cells from clotting, for example, or block ion channels on nerve cells to shut down or subvert their function.

A Caribbean sun anemone (*Stichodactyla helianthus*)

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Such high molecular specificity and potency has long made venom a promising source of drug candidates. More than 30 years ago, the US Food and Drug Administration approved the first venom-derived drug, a therapy for hypertension, called Capoten, copied from a pit viper venom peptide. A handful of venom-derived drugs have since been approved for cardiovascular disease, and in 2004, a venom-derived painkiller hit the market. Now, thanks to an increasing knowledge of the human nervous and immune systems, the pipeline from fang to pharmacy is expanding even further, with more pain medications and drugs that target to autoimmune diseases such as multiple sclerosis and rheumatoid arthritis.

"We're really at beginning of something exciting," said

Glenn King, a molecular biologist at the University of California, San Diego.

They later demonstrated in rodent models of multiple sclerosis (MS) that ShK-186 dramatically reverses paralysis. It was absolutely remarkable to watch," said Beeton. "We saw the disease almost completely go away." And importantly, the drug did not broadly suppress the immune system, as treated animals were still able to fight off both chlamydia and influenza.

In December last year, Seattle-based biotechnology company Kineta completed Phase 1a human trials, testing for the safety of ShK-186 in healthy volunteers. Although the results are yet to be

Cone snail (*Conus magus*)

WIKIMEDIA, JAN DELSING

published, Beeton said the team was "very happy with the results," and added that Phase 1b trials are due to begin this April. There is a long way to go before it hits the clinic, but ShK-186 currently holds great promise as a treatment for a range of autoimmune diseases, from MS to lupus and rheumatoid arthritis, said King. "ShK is one of the most exciting examples [of venom-derived drugs] at the moment. The implications are profound if it gets through."

Fighting pain with venom

The first—and as yet, the only—approved venom-derived drug that acts on the nervous system is the painkiller Prialt, a chemically identical version of a peptide isolated from the cone snail (*Conus magus*). Approved in 2004, Prialt works is injected into the fluid around the spine, where it blocks a calcium ion channel in neurons and inhibits the cells' ability to transmit pain signals to the brain.

But there are several promising leads for new venom-derived painkillers. Earlier this year, for example, researchers at the National Center of Scientific Research (CRNS) in Paris announced the discovery of two peptides isolated from black mamba venom that can block neuronal acid-sensing ion channels (ASICs), which play a key role in the pain pathway. In mice, these peptides—dubbed mambalgins—showed potent analgesic effects, as powerful as morphine, with no obvious toxicity. The peptides also induced less tolerance than morphine. The researchers are now developing mambalgins into a human pain therapeutic with the venom-focused pharmaceutical company Theralpha.

Another painkilling peptide, also under development by Theralpha, is derived from hannalgesin, a neurotoxin isolated from King Cobra (*Ophiophagus Hannah*) venom. Although the mechanism of action for this peptide—known as THA903—is not yet clear, pre-clinical studies have shown that it has a far stronger analgesic effect than morphine and, crucially, can be taken orally. "We drop a solution [of the peptide] under the tongue of the animal and within minutes you can find it in the blood," said Manjunatha Kini of the National University of Singapore, who developed the hannalgesin-based peptide.

Black mamba (*Dendroaspis polylepis*)

WIKIMEDIA, TIM VICKERS

Meanwhile, other researchers are continuing to derive potential therapeutics from cone snails. *Conus catus*, for example, a close relative of Prialt's source *C. magus*, yields a toxin that the Australia-based company Relevare Pharmaceuticals has developed into an intravenous treatment called Leconotide. The drug blocks the same channel as Prialt and is currently in Phase 1 trials. And in January this year, Kineta announced that it has obtained the rights from the University of Utah's Baldomero Olivera, who isolated the molecule that became Prialt, to advance a portfolio of drug candidates based on another snail venom-derived compound, Conotoxin Rg1a, for the treatment of chronic pain.

Moreover, these promising drug candidates are likely just the tip of the iceberg, researchers agree. It is estimated that less than 0.1 percent of the venom proteome of cone snails—thought to harbor around 100,000 peptides—has so far been tapped, and fewer than 0.01 percent of roughly 10 million active molecules found in spider venoms. But, Kini explained, "with the advent of technologies that enable proteomics and transcriptomics, it is becoming much easier to isolate and study toxins from venom found in minuscule quantities," such as those yielded by spiders, scorpions, and cone snails—and even the nanoliters produced ticks and mosquitoes.

"There are thousands of venoms that we haven't even looked at yet," said Beeton, "so we have millions of molecules that are all potential drugs still to be explored."

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