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**Drugs with bite**

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By: James Mitchell Crow

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**New Sea Snake a Roughie**

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By: None
Venoms may not be the most obvious source of medicines but they are the hottest ticket in pharmaceuticals, says James Mitchell Crow.

A SNAKE with a pit viper’s style of fangs is an alarming experience. They are venomous, can grow to several metres long and will be on you long before you know they are there, sensing your body heat with a pair of highly sensitive infrared-detecting organs that sit just below their eyes. Burrowing into one of these creatures in their native forests in South America would not be good for anyone. Slightly ironic then it is from venom-harvesting a drug used to treat high blood pressure.

In fact, the toxic mixtures of chemicals we call venoms have a long history as medicinal treatments. From poisonous plants to toxic tarantulas, venomous animals provide insights into these ancient medicines around the world. Unlikely as it sounds, venoms have many of the attributes a good drug needs. When a venomous animal poisons one of its prey, the chemicals it injects must be stable enough to travel around the victim’s body, able to evade its defences until they reach the site of action, where they must hit the target with exquisite selectivity and minimal side effects. Millennia of evolution have honed venoms to achieve exactly what a doctor hopes an injected drug will do.

Nevertheless, western medicine has had difficulty tapping into this natural asset. In 1983, crotalidae, a drug based on pit viper venom, became the first venom-derived drug to be approved by the US Food and Drug Administration. In the following three decades pharmaceutical companies produced a trickle of other such drugs. Now, however, this trickle looks set to turn into a steady stream as venom research enters the genomics age, turning the once-feared job of sifting through toxic cocktails for potential cues into a high-throughput process. As a result, venoms are one of the hottest commodities in pharmaceuticals. New Scientist surveys what’s to offer.
Radioactive scorpion venom might sound like the stuff comic-book villains would use. In fact it is an experimental anti-cancer drug in clinical trials. The venom in question comes from the deathstalker scorpion (*Leiurus quinquestriatus*), a bright yellow beast native to north Africa and the Middle East. As the name suggests, its sting can be fatal.

Within that sting lies a peptide called chlorotoxin, which has an unusual property – it sticks strongly to tumour cells while ignoring surrounding healthy tissue, by binding to a cancer-specific protein called matrix metalloproteinase-2. This tumour-targeting makes it a promising ally in the fight against cancer. Load up chlorotoxin with a radioisotope, for example, and it will deliver its radioactive payload straight to a tumour. This approach has been investigated by TransMolecular, a company based in Cambridge, Massachusetts, as a way to treat glioma, a form of brain cancer. Chlorotoxin passed a phase II clinical trial in 2009.

More recently, the peptide has become the key ingredient in an experimental surgical tool called Tumor Paint. When chlorotoxin is tagged with a fluorescent dye, it will illuminate a tumour a trick that makes the surgeon’s job easier by helping to pinpoint cancerous growth and ensure that all the cancerous cells are removed and healthy tissue spared.

Chlorotoxin’s performance through the early stages of clinical trials has not gone unnoticed. In April 2011, TransMolecular’s tumour-targeter was snapped up by biopharmaceutical company Morphotek, a US-based subsidiary of Japanese drug giant Eisai. Though the company will not go into the details of its plans for chlorotoxin, spokesman Terry Cushmore says they intend to refine it before taking it into further clinical studies. “We are reconfiguring the peptide to enhance its utility for diagnosis and treatment of a wide range of cancer types based on the clinical findings of the earlier studies,” he says.
Divers beware - not all pretty seashells are harmless. Pick up one containing a live cone snail and it will defend itself with its sting. The result can be fatal.

Nevertheless, venom researcher Richard Lewis and his team at the University of Queensland in Brisbane, Australia, seek out these creatures along the Great Barrier Reef. “They’re a challenge to get,” he says. “During the day they hide, and you can turn hundreds of pieces of dead coral over before you find a cone snail.”

It is worth the hunt. Cone snails are one of the youngsters of the venom world, developing their poisonous sting just a few tens of millions of years ago. As a result, their venoms are still an evolutionary work in progress. Members of the same species can deploy very different mixtures of chemicals. “Even individuals collected from the same place may only have a 25 per cent overlap in the venoms they produce,” says Lewis. That means they produce a vast array of potential medicines.

Cone snail venom is providing a complementary hunting ground to the more traditional snake venom research. Whereas snake venoms tend to target the cardiovascular system, cone snails prefer to shut down the nervous system of their prey. This means they have great potential as pain medications.

One cone snail venom compound discovered by Lewis and his team is about to go into phase II clinical trials. Code-named Xen2174, it works by boosting the signal along the body’s natural painkilling nerves that run along the spine. “In our initial safety study, we tested the drug in over 30 people with severe cancer pain, and the compound was able to produce a really quite profound reversal of pain in many of these patients, an effect that could last for many days with a single injection into the spine,” says Lewis. Buoyed by their success, the researchers are also starting to develop a painkilling venom-based compound to be given orally.

The deathstalker scorpion is helping in the fight against cancer.
Snake venom has a place in several ancient medical traditions. As early as the 1930s western pharmacists began testing cobra venom as a treatment for conditions ranging from asthma to multiple sclerosis (Expert Opinion on Biological Therapy, vol ii, p1469). But in recent years, modern techniques from mass spectrometry to high-throughput lab-on-a-chip bioassays have made life easier. Chemists can pick out and identify the specific venom components with beneficial effects, eliminating some unpleasant side effects and making the whole process safer.

One such component is now showing promise for treating multiple sclerosis. Quite what triggers MS remains unknown. What is clear, though, is that the body’s immune system begins to attack the insulating sheath that protects nerve cells, causing damage that can progressively impair sensory and cognitive function and movement. Bringing the immune system back into balance has proved very difficult, but a venom peptide called cobratoxin might hold the answer.

Last year, Florida-based firm ReceptoPharm had a patent approved for a version of cobratoxin chemically modified to remove its toxicity (US patent 8,034,777). The company claims that its modified peptide halted the development of MS in 90 per cent of laboratory rats with the rodent equivalent of MS. The peptide seems to stimulate the release of a messenger molecule called interleukin-27, which puts the brakes on an overactive immune response, bringing immune activity back down toward normal levels. ReceptoPharm is planning clinical trials to assess the compound’s efficacy in humans.

Meanwhile, a related venomous molecule called cobrotoxin has shown promise in treating HIV. A modified version of the toxin seems to impede the spread of the virus by blocking receptors on the surface of the body’s immune cells – the same receptors that the virus would otherwise latch on to before infecting the body’s immune cells.
In the warm, shallow waters of the Caribbean Sea, especially in the coral reefs around Cuba, lives a species of sea anemone called *Stichodactyla helianthus*. In the early 1990s a group of Cuban researchers on a diving expedition collected some specimens to analyse their toxins. The compound they discovered has spawned an experimental drug, ShK, which is about to go into clinical trials for treating multiple sclerosis (Toxicon, 001: 10.1016/j.toxicon.2011.07.016). It also has potential to treat a broad range of autoimmune diseases, including type 1 diabetes and rheumatoid arthritis.

Autoimmune diseases arise when the immune system mistakenly decides that one of the body’s own tissues is foreign and begins to attack it. In many cases the damage is caused by a particular group of immune cells called effector memory T-cells. These possess a unique ion channel called a Kv1.3 potassium channel without which they cannot function, and it is this channel that ShK targets. “ShK puts the cork in the bottle,” says Ray Norton at Monash University in Melbourne, Australia, who has been involved in the project since 1996. “In the presence of our compound, the cells become immobilised and wither and die.” Studies in animal models of MS have been a success, and the latest version of the compound is due to start clinical trials in humans by mid-2012. “In MS, there’s a lot of nerve damage – we can certainly stop further damage,” says Norton. “Time will tell whether we can reverse damage that has already happened – whether the innate repair mechanisms start to win out once the effector memory T-cells are taken out. We are hopeful.”

Quite what such a compound is doing in the sea anemone in the first place is an open question. Possibly it acts to stun the fish that they eat. Ion channel function can vary significantly from species to species, and the ion channel’s role in fish could be very different from its role in our bodies.

A bite from a gila monster will really mess with your metabolism. Fortunately these lizards, found in the deserts of the south-west US, are large and lumbering and most humans can easily outpace them. Nevertheless, each year a handful of people do get close enough to discover that the gila monster’s bite delivers a painful cocktail of chemicals that causes nausea, fever and faintness – and can even induce a heart attack.

However, within the venom lies a very useful compound. Called exenatide 4, it triggers one of the body’s insulin-releasing pathways. This effect makes it ideal for treating type 2 diabetes, a condition in which insufficient insulin is produced to keep glucose levels in check. A synthetic version of exenatide, called exenatide, was approved as an anti-diabetes drug by the US Food and Drug Administration in 2005. Now the compound is being investigated for its anti-obesity properties as well, since it also slows stomach emptying, reinforcing feelings of fullness after eating.

Until around five years ago, the gila monster was thought to be one of just two venomous lizards – the other being the closely related beaded lizard found in nearby Mexico. We now know that lizards and snakes share a common venomous ancestor, and that many lizards – from iguanas to komodo dragons – which were never suspected of being venomous, come equipped with venom glands (Nature, vol 439, p 584).

Research into lizard venom has barely begun, so it may be a while before any other lizard-based medicine hits the pharmacy. But the wait could be worth it, says Bryan Fry at the University of Queensland in Brisbane, Australia, who has led the work on lizard toxin evolution. “If you want to find something useful, then the more novel the venomous animal, the more novel its venom.” And that gives the best drug leads, he says. “I think it is one of the strongest arguments we have for preserving biodiversity.”
“Cone snail venoms shut down the nervous system, making them potential painkillers.”

“Until recently the gila monster was thought to be one of just two venomous lizards.”

Its venom contains a compound that could help treat obesity.
New Sea Snake a Roughie

A new species of sea snake has been located in the Gulf of Carpenteria, and is distinguished by its uniquely rough scales.

“Some sea snakes have patches of rough scales,” says its discoverer, A/Prof Bryan Fry of the University of Queensland’s School of Biological Sciences. “However, this one has much rougher scales and they are all over its body.”

Publishing in *Zootaxa*, Fry named the snake *Hydrophis donaldii* after his boat captain David Donald, and admits that the rough scales make it less hydrodynamic. “Given the selection pressure to be as smooth and slippery as possible, the scales must have important ecological roles,” he says. “We think it is because they live in rocky environments and the scales protect them against sharp rocks that would cut other snakes to pieces.

“Weipa really is one of the last sea snake ‘Serengetis,’” Fry says. “We can see over 200 sea snakes in a single night’s hunting, whereas sea snake populations have really crashed elsewhere through overfishing removing their prey and also the snakes drowning in trawling nets.” Fry adds that while the snakes may be thin enough to slip through gaps in the nets, the volume of catch in the nets frequently prevents them from escaping.

Fry surveyed as many environments as possible around Weipa rather than simply searching areas known for their rich fish populations. He credits Donald for knowing where the rocky outcrops were located so that *H. donaldii* could be discovered and its habitat confirmed at similar locations.

Like other species in Australian waters, *H. donaldii* is a true sea snake and not a krait (AS, September 2004, p.5), but Fry says it looks nothing like its genetically closest relative. The venom has yet to be analysed but Fry is excited, reasoning: “All venomous animals are bioresources and have provided sources of many life-saving medications, such as treatments for high blood pressure and diabetes.”