DISCOVER — ENGAGE — IMPACT

TAKING THE STING OUT OF PAIN

A UQ team is using an unlikely approach to develop medicines for chronic pain, epilepsy and stroke – venom.

One in five Australian adults suffers from chronic pain.

This persistent affliction is not only costly to the healthcare system, but also takes a financial and emotional toll on the individuals who live with it, as well as their families.

And sadly, only one third of those patients experiences even 50 per cent pain relief when using current drugs.

Professor Glenn King, biochemist and structural biologist from the Institute for Molecular Bioscience (IMB) at The University of Queensland (UQ), is collaborating with pharmaceutical industry partners to prove that an unlikely source of medication may hold the key to overcoming these odds – venom.

One of evolution's most complex biological weapons, venom may hold the answer to solving a host of neurological threats. Venoms have evolved over time to have very specific effects on the nervous system of prey – some components cause pain, while others block it.

Venom components are valuable for drug discovery as they help us understand pain pathways, and the components that block pain have the potential to be effective painkillers.

Australia is home to many of the planet's most venomous creatures. With an expertise in translating venom-derived peptides into human drugs, the King Lab at UQ maintains the most extensive venom library in the world, which includes venoms from more than 600 species.

Professor King is primarily focused on treating three pervasive nervous system disorders – chronic pain, epilepsy, and stroke. His lab is working closely with several pharmaceutical companies to develop drugs for clinical use.

"We're interested in nervous system disorders, where the underlying cause of the disorder is either a defective ion channel or where the ion channel is in some way deeply involved in the cause of the disease," Professor King says.

"The sort of things we're talking about are stroke, epilepsy, chronic pain, and potentially other disorders such as Alzheimer's disease."

The neurotoxic class of venoms that Professor King studies are found in small invertebrates like spiders, scorpions, centipedes, assassin bugs and cone snails.

"These venoms are extremely complicated mixtures of ion-channel modulators, so we use them to try and find molecules that hit our target ion channel," he says.

Once a target molecule for a particular disease has been identified, the team at the King Lab begin screening their venom library against that target.

As Professor King explains, each of the 600 venoms in their library can contain between 100 and 1000 compounds, allowing them to screen tens of thousands of molecules in a single test.

"If we are targeting an ion channel, there will always be something in those 600 venoms that will hit it because that's what venom has evolved to do over many hundreds of millions of years"

"It's just a matter of finding the molecule that hits our target ion channel with a high level of potency and selectivity," he says.

Extracting a solution

Stroke is the third-highest cause of death in Australia and the leading cause of long-term disability. In 2018, almost 56,000 new and recurrent strokes will occur – one every nine minutes.

Professor King is using the venom of the deadly funnel-web spider to create medications that could protect the brains of people who experience a stroke.

The drug, named Hi1a after the Fraser Island funnel-web spider Hadronyche infensa that it originates from, could provide a treatment option to prevent brain death after stroke. Hi1a is the most potent inhibitor of an ion channel that's involved in the neuronal death caused by stroke.

"Two million neurons die every minute after the stroke starts. The sooner you can get a drug into the brain, the more neurons you will save and the better the outcome will be for the patient," Professor King says.

"Hi1a protects the brain really well, even when you administer it up to eight hours after the stroke."

At present, the only drug available to treat stroke is a clot-busting agent called tissue Plasminogen Activator, or tPA. In most cases, tPA is given to less than five per cent of patients because it can also induce brain haemorrhaging.

"The advantage of the drug we've developed is that while it effectively treats the brain damage caused by ischemic stroke, it should be okay to administer to haemorrhagic stroke patients.

"Therefore, stroke patients wouldn't need to undergo brain scans at the hospital to determine the type of stroke prior to receiving treatment. The first responder could administer drugs to protect the brain straight away," Professor King says.

"This would have a huge, positive impact on patient outcomes, particularly for those in rural locations. We're very excited about trying to take the Hi1a drug forward."

A cure for chronic pain

Professor King is the first to admit that developing painkilling drugs is a long and difficult process, but he and his team are determined to find better solutions for patients living with chronic pain.

In 2015, the King Lab discovered a series of seven molecules from tarantula venoms that block the molecular pathway responsible for sending pain signals from nerves to the brain.

The discovery, published in the British Journal of Pharmacology, could inspire a new class of potent painkillers with fewer side effects than current medications.

"Previous research shows people who lack Nav1.7 channels due to a naturally-occurring genetic mutation are unable to experience pain, so blocking this channel could potentially help us to switch off pain in people with normal pain pathways," Professor King says.

"We have nine sodium channels in our bodies and our challenge is to find peptides that can distinguish between these channels and target only Nav1.7 – something current pain relief drugs can't do, but spider venom peptides most likely can."

The King Lab are working in collaboration with a European pharmaceutical company to turn a venom peptide that blocks Nav1.7 into a clinical candidate within a year to commence preclinical studies for those with irritable bowel syndrome and severe gut pain.

Hope for seizure sufferers

Epilepsy is the most common neurological disorder in children – recurring seizures that can cause lasting damage to the brain, and are incredibly distressing for a young child's family. But epilepsy is not a single disease; rather, it is a diverse spectrum of disorders that comprise many types of seizures.

Dravet syndrome is a particularly severe paediatric epilepsy, the result of a gene mutation that reduces the level of one of the ion channels in the brain that is important for calming brain activity. Professor King and his team are developing a revolutionary drug to combat Dravet seizures.

"At around six months of age these children start to develop seizures that become more and more severe, and they often end up severely impaired," he says.

"The seizures are particularly difficult to control because they are unpredictable, and resistant to many frontline anti-epileptic drugs.

"You go from having a wonderful normal child to having a child that has very severe difficulties, so you can imagine how hard that is for the parents."

The King Lab found that the venom of the Togo starburst tarantula contains a molecule that activates the ion channel found at lower levels in Dravet syndrome. In mice with induced Dravet syndrome, the molecule successfully stopped seizures altogether.

But can this molecule translate the same effect to humans? "We don't know, but it's a promising start," Professor King says.

"We're at the stage where we have to do some final proof of principle experiments, but then we hope that the drug will be licensed and developed for human clinical trials.

Appreciating creepy-crawlies

Contrary to popular belief, Professor King considers Australia lucky to have such a large number of native venomous species.

"I think the thing that makes some people sceptical about the idea of turning venom molecules into drugs is that they think of venomous animals as dangerous to humans, but in fact, very few are," he says.

"There are 47,000 species of spiders, but only a handful that can hurt us – funnel webs, widow spiders, recluse spiders and Brazilian arm spiders.

"These few venomous creatures are so much more complex and wonderful than many would think – and there is always more we can learn from them."

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(Image credit: Lyndon Mechielsen)

Highlights to date:

2006: Professor Glenn King founds Vestaron Corporation to develop natural insecticides derived from spider venom.

2007: Professor King joins the Institute for Molecular Bioscience (IMB) at The University of Queensland, marking the beginning of his focus on translating venom-derived peptides into human drugs.

2015: The King Lab discover seven peptides in tarantula venom that block the molecular pathway responsible for sending pain signals from nerves to the brain. The findings were published in the *British Journal of Pharmacology*.

2016: An international research team, led by Professor King, identify an ion channel involved in transmitting mechanical pain, which is the type of pain experienced by patients with irritable bowel syndrome. The research, which was supported by the Australian National Health and Medical Research Council, is published in *Nature*.

2017: The King Lab at IMB discover the 'Hi1a' peptide that is shown in collaboration with researchers from Monash University to protect the brain from stroke-induced injury. This study, which was funded by the NHMRC, is published in *Proceedings of the National Academy of Sciences USA*.

2018: In collaboration with researchers at the Florey Institute, the King Lab describes a peptide that reduces mice with Dravet syndrome epilepsy from seizures and premature death. This study, which was funded by the NHMRC and Citizens United for Research into Epilepsy, is published in *Proceedings of the National Academy of Sciences USA*.

2018: Professor King is awarded an NHMRC Research Fellowship (2018–2022) for his research on translating venom peptides into human therapeutics.

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