

# Studying stonefish venom may help combat transplant rejection

December 2 2015

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The stonefish is one of the world's ugliest and deadliest fish. You'll know if you step on one; the fish protects itself using 13 razor sharp venom filled spines capable of slicing through reef shoes. The resulting pain is crippling, can last for days and may result in amputation of a limb or death.

Monash University researchers have solved the X-ray crystal structure of the lethal factor present in stonefish venom. The discovery has provided unexpected insight into a crucial human immune response that is

responsible for the failure of up to 30 per cent of [bone marrow transplant](#) therapies for treating leukaemia. The structural insights obtained from stonefish venom are now being used to develop immunosuppressants to improve the success rate of transplant therapies.

The work, published today in *Proceedings of the National Academy of Sciences (PNAS)*, reveals that the lethal component of stonefish venom, a protein called Stonustoxin, is an ancient relative of the human immune protein perforin.

In humans, perforin is an essential weapon unleashed to destroy virally infected and cancerous cells. Perforin proteins attach themselves to a diseased cell and assemble to form giant ring shaped holes, or pores, on the cell surface. Each pore contains around 20 perforin proteins that stick together in a symmetrical fashion. The pores are big enough to allow toxins to enter the cell, killing it from within. How these pores form is a mystery but the work on stonustoxin has revealed a key part of the pore assembly mechanism.

To make their discovery, the team used powerful synchrotron radiation to visualise the atomic structure of stonustoxin. Crucially, they found that the toxin contains two perforin-like proteins stuck together. By seeing how two of the proteins first interact, the researchers can build on this to understand how the full assembly of 20 perforin molecules forms a complete pore.

Unravelling the structure of the stonefish's lethal toxin was carried out at Monash University and the ARC Centre of Excellence in Advanced Molecular Imaging. The leading authors of the study were Dr Andrew Ellisdon, Dr Sheena McGowan and Professor James Whisstock.

"The lethal factor in stonefish venom is like a loaded gun - ready to fire as soon as it is injected into the foot of an unsuspecting victim," co-lead

author Dr Sheena McGowan said.

In humans, unwanted or excessive perforin activity is responsible for a range of medical problems including pancreatic cell destruction in type I diabetes and the rejection of bone marrow transplants in the treatment of leukaemia.

An international group of researchers, led by the Peter MacCallum Cancer Institute and including Monash based Professor Whisstock and his team, are working to develop perforin inhibitors.

"Already the structure of stonustoxin is starting to inform our drug development program, and we now understand the very first stages of perforin pore formation. This type of mechanistic information is extremely useful in developing new strategies to inhibit perforin itself," co-lead author Professor Whisstock said.

"People who step on a stonefish suffer agonising pain because the lethal stonustoxin protein attacks nerves. The treatment for envenomation includes an anti-venom together with soaking the wound in non-scalding hot water – the latter treatment unravels the [venom](#) and stops it punching holes," he said.

**More information:** Stonefish toxin defines an ancient branch of the perforin-like superfamily, *PNAS*,  
[www.pnas.org/cgi/doi/10.1073/pnas.1507622112](http://www.pnas.org/cgi/doi/10.1073/pnas.1507622112)

Provided by Monash University

Citation: Studying stonefish venom may help combat transplant rejection (2015, December 2)  
retrieved 1 May 2024 from

<https://phys.org/news/2015-12-stonefish-venom-combat-transplant.html>

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