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Taking the bite out of snake venom

More effective treatments for snakebites that afflict millions of people worldwide every year are emerging from EU research.

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In November 2023, police in the southern Dutch city of Tilburg issued an alert about an “extremely venomous” snake that was two metres long and had escaped from its confines.

The green mamba was eventually found behind a plaster wall in the owner’s house, easing public concern and ending what had been a national news item.

Millions of bites

The incident gave city dwellers in Europe rare exposure to a threat that many millions of people elsewhere face on a regular basis.

Every year around 5.4 million people globally – often in the world’s poorest communities – are bitten by venomous snakes, with countries such as Bangladesh, Burkina Faso, India and Nigeria estimated to have large numbers of cases.

Globally, these bites cause between 81 000 and 138 000 deaths and around 400 000 permanent injuries including amputations resulting from severe tissue damage. Snakebite envenoming is deemed a neglected tropical disease by the World Health Organization and is more deadly than all other WHO-recognised neglected tropical diseases.

Professor Nicholas Casewell is seeking to reduce these numbers as part of a research project that received EU funding to improve snakebite treatments, which have barely changed in the past 100 years.

‘If you get the right antivenom quickly enough, then they can be effective – they are life-saving treatments,’ said Casewell, an expert in snakebites at the Liverpool School of Tropical Medicine in the UK. ‘But they have so many deficiencies associated with them.’

Antivenoms are currently produced by injecting horses or sheep with low doses of venom so that the animals develop antibodies against it. Blood serum containing these antibodies is then collected from the host animals to be used as antivenom – a process first demonstrated by a French physician named Albert Calmette in the 1890s.

Antivenoms are expensive, prove often to be ineffective and need to be kept refrigerated. They can also cause severe adverse reactions such as rashes, joint pain, fever and lymph-node swelling.

Furthermore, large pharmaceutical companies have stopped producing antivenoms because they aren't considered to be financially viable. That increases the need for new treatments.

New nanoparticle

The project in which Casewell is involved brings together research institutes and universities from Belgium, France, Portugal and the UK. Called ADDovenom, it runs for four and a half years until March 2025.

The researchers have turned to a new synthetic nanoparticle to develop more effective snakebite treatments. Virus-like, it is known as an ADDomer.

ADDomers are self-assembling because they are made up of many copies of the same protein. These proteins can be modified in a way that enables them to grab and neutralise specific targets.

In the case of ADDovenom, those targets are the toxins in snake venom.

Vipers and mambas

The project focuses on the saw-scaled vipers and mambas of Africa. They cause a substantial medical burden among snakes in the sub-Saharan region.

Saw-scaled vipers signal when they feel threatened and may bite by coiling into a pretzel shape and rubbing their scales together – an action that creates a sizzling sound.

Mambas, which are closely related to cobras, seek to scare off aggressors by rearing up and hissing.

The venom from these two types of snakes has very different effects. In saw-scaled vipers it causes internal bleeding, while in mambas it triggers paralysis.

Under ADDovenom, proteomics experts at the University of Liege in Belgium have been analysing the venom of these snakes harvested at the herpetarium at the Liverpool School of Tropical Medicine, which houses the largest collection of venomous snakes in the UK and is one of the most diverse in Europe.

Venoms are a mix of different components. The project's goal is to identify and neutralise the most dangerous toxins in saw-scaled vipers and mambas.

'We now know the composition of these venoms and we can extract the most abundant and most pathogenic toxins,' said Professor Christiane Berger-Schaffitzel, a biochemist at the UK-based University of Bristol who runs the project. 'These are our targets.'

More effective, affordable

Current antivenoms work in anything but a targeted fashion.

At most only around a third of antivenom antibodies target snake venom. The rest are antibodies that the animals from which the antivenom was created had circulating in their bodies to fight off other pathogens.

This, combined with the fact that the antibodies are animal-derived, is why antivenoms can make people sick. Patients develop a condition known as serum sickness, which is an allergic reaction to these additional and unnecessary components in the animal serum.

Extracting venom from a saw-scaled viper. © Simon Townsley

‘Here we are trying to do things in a much more rational, informed way,’ Casewell said.

The researchers hope that, as well as being more effective, their planned treatments will be safer.

And because ADDomers remain stable at high temperatures, the treatments wouldn’t need to be refrigerated, making them more accessible to remote rural communities in the tropics.

While the project will wrap up in less than a year, the research won’t.

As well as further developing ADDomer nanoparticles for different toxins, the scientists will examine how these products could be manufactured to scale to keep them affordable.

‘The cost is really important because we are talking about developing countries and rural areas,’ Berger-Schaffitzel said. ‘People definitely have problems affording treatment.’

Just when ADDomer-based treatments will become available depends on matters such as the protection they confer in mice against the toxins and the viper venom. For a life-saving treatment, the goal is a broad reactivity across venoms from different vipers.

Lab-made antibodies

ADDomers aren’t the only hope for developing new ways to tackle snakebites.

Other EU-funded researchers are trying to do so with human monoclonal antibodies. These are laboratory-produced clones of the human body’s countless antibodies.

‘We have antibodies in our blood, but it is a mix of millions of different antibodies,’ said Andreas Hougaard Laustsen-Kiel, a professor in antibody technologies at the Technical University of Denmark. ‘A monoclonal one is just one of these many, many antibodies.’

Engineered monoclonal antibodies are already used in several areas of medicine, mainly as targeted therapies for cancer and as treatments for autoimmune diseases including rheumatoid arthritis.

Laustsen-Kiel and colleagues are engineering antibodies that neutralise multiple related toxins in snake venoms.

‘It is relatively straightforward to find a monoclonal antibody that just binds one target,’ he said. ‘The more difficult thing is to find a monoclonal antibody that binds several different targets.’

Their project, MABSTER, is due to wrap up in December 2024 after five years.

As with ADDovenom, the researchers have been focusing on snake toxins that cause a significant medical burden.

MABSTER has developed and tested on mice a mixture of antibodies that can neutralise coral snake venoms, a family of brightly coloured, highly venomous snakes that live in the Americas.

The team is also close to completing a mix for treating bites from African cobras and mambas, according to Laustsen-Kiel.

Fewer side effects

In addition to engineering the antibodies to target specific toxins, the team is trying to ensure the antibodies survive longer in the body to fight new toxins again.

Normally, after an antibody has bound to its target, known as an antigen – in this case a venom toxin – it neutralises the antigen and signals it for destruction. In this process, the antibody remains occupied by the antigen until both are destroyed.

By engineering the monoclonal antibodies to be sensitive to their microenvironment, it’s possible to programme them so that they release the antigen during cellular recycling of the antibody-antigen complex, according to Laustsen-Kiel.

This leaves the antibody intact and free to go and bind more toxins.

Recycling antibodies in this way could allow lower doses of treatment to be used, increasing efficacy and potentially reducing side effects.

Laustsen-Kiel echoed Berger-Schaffitzel by stressing the importance of affordability when it comes to such treatments.

‘The next big research question is how to manufacture these things cheaply,’ he said.

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