CAMILLA CARVALHO/INST. BUTANTAN

Milking snakes is a key part of producing conventional antivenom.

MEDICINE

# Synthetic biology tackles antivenom

*Artificial antibodies could ease global snakebite burden.*

BY CARRIE ARNOLD

When the medical charity Médecins Sans Frontières called the worldwide shortage of snake antivenom a public-health crisis last September, Brazilian biochemist Paulo Lee Ho wasn't surprised. He has spent his career at São Paulo's Butantan Institute searching for better ways to create antivenom to treat bites from coral snakes.

Conventional methods rely on natural coral-snake venom, which is hard to come by: the snakes produce only small amounts with each bite and are hard to raise in captivity. So Ho and others have turned to proteomics and synthetic biology in the hope of improving the quality and availability of antivenom. "We need a new way to meet the demand for antivenom from the Ministry of Health," he says.

These efforts are bearing fruit. Last month, Ho and his colleagues reported[1] that they had engineered short pieces of DNA that, when injected into mice, triggered antibodies against coral-snake venom. The scientists then boosted the animals' immune response by injecting them with small pieces of synthetic venom antibodies synthesized in *Escherichia coli* bacteria. In a separate study[2], another group of researchers in Brazil used synthetic antibody fragments to neutralize the effects of bites by the pit viper *Bothrops jararacussu*.

Such progress is encouraging, given the severe medical burden caused by snakebites in the developing world, says Robert Harrison, head of the Alistair Reid Venom Research Unit at the Liverpool School of Tropical Medicine, UK. Each year, around 90,000 people die after being bitten by venomous snakes[3].

Yet antivenoms are still made using a method that has not changed for more than a century. Large animals, typically horses, are injected with small amounts of purified proteins extracted from snake venom, which prompts the production of antibodies. Plasma containing these antibodies is then given to snakebite victims.

But this life-saving treatment is limited in important ways. Each antivenom is effective against only a single species or, at most, a small group. And the drugs must be refrigerated, difficult in tropical countries without reliable electricity. "When you think about it, it's amazing these antivenoms work at all," says Leslie Boyer, director of the Venom, Immunochemistry, Pharmacology and Emergency Response Institute at the University of Arizona in Tucson.

The number of pharmaceutical companies that make antivenoms is declining, because the drugs are not very profitable. In 2010, for instance, pharmaceutical giant Sanofi of Paris ended production of the antivenom Fav-Afrique, which is designed to treat the bites of ten of Africa's most poisonous snakes.

Ho hopes that his approach will help to fill this void. Rather than relying on venom from live coral snakes, he began with small pieces of coral-snake DNA that code for venom toxins. He and his colleagues injected these DNA pieces into mice to prime their immune systems; a month later, they gave the animals a booster shot containing synthetic venom antibodies.

Only 60% of mice injected with a lethal dose of coral-snake venom survived after receiving Ho's experimental treatment, compared to nearly 100% for existing antivenoms. But Ho is undaunted. "This result shows there are other ways to obtain neutralizing antibodies," he says. "Maybe to get better results, we need to try again but use more antibodies. We just don't know yet."

The second Brazilian team, led by molecular biologist Carla Fernandes of the Oswaldo Cruz Foundation, a biomedical-research institute in Porto Velho, tested a different technique. The researchers used a phage-display library — a method of studying interactions between proteins — to make synthetic versions of antibodies that llamas produced when they were injected with *B. jararacussu* snake venom. Giving these antibodies to snakebite victims would eliminate the need to use animal plasma. It also could leave less muscle damage and tissue death at the site of the bite than conventional antivenoms, because the synthetic antibodies are smaller and better able to penetrate into tissue.

The path to newer antivenoms is not straight, but researchers think that moving quickly is key. "There has been significant, rapid progress in this area, but it needs to be fast. There are too many people dying from what is essentially a preventable disease," says Harrison.

To Boyer, however, the antivenom shortage is not caused by a lack of science. "It costs 14 bucks to make a vial of antivenom that costs $14,000 in the US," she says. "You're not going to get cheaper than that. The expensive parts aren't the science — it's everyone wanting a cut of the profits that drives the price up and puts it out of reach." ■


1. Ramos, H. R. *et al. PLoS Negl. Trop. Dis.* **10,** e0004484 (2016).
2. Prado, N. D. R. *et al. PLoS ONE* **11,** e0151363 (2016).
3. Harrison, R. A., Hargreaves, A., Wagstaff, S. C., Faragher, B. & Lalloo, D. G. *PLoS Negl. Trop. Dis.* **3,** e569 (2009).




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