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BIOTECH

Can Science Rob Snakes of Their Deadliest Weapon?

Biotech companies are on the prowl for newer, better antivenoms

By Usha Lee McFarling, STAT on March 21, 2017

A krait snake is milked for its venom, which is collected into a vial. The venom will be used in creating a serum against the venom.
Credit: Jeffery L. Rotman *Getty Images*

IRVINE, Calif. — Even in a test tube, snake venom is terrifying.

Mix a few beads of venom from a deadly Indian krait with blood cells and, within an instant, the clear liquid will turn bright red as toxins blast through the cells, rupturing

their membranes. One look tells you more than you want to know about the excruciating pain of a snakebite.

That's why synthetic chemist Jeffrey O'Brien was so startled, and so excited, when he tried lacing a test tube full of blood cells with a compound he had created to neutralize snake venom. He dropped in the krait's secretions and waited. The solution stayed clear. The blood cells were fine.

That work, in a chemistry lab here at the University of California, Irvine, could, perhaps, lead to a universal antidote to snake venom. And it's just one of several new high-tech efforts — coming from an unlikely cast of characters far outside the pharmaceutical mainstream — to tackle the staggering toll of death and disability caused by snakebite worldwide.

Those in the hunt for newer, better antivenoms include an emergency physician in San Francisco so keen to push ahead in his research that he had himself paralyzed in order to test an experimental drug; a 29-year-old biotech entrepreneur so hip he's been dubbed "Denmark's coolest engineer"; and an Indian physician who sought out advanced degrees in nanomedicine in Ireland so he could help prevent snakebite deaths in his home state of Tamil Nadu.

Backing them: investors ranging from the Pentagon to the Talking Heads's Jerry Harrison.

They're taking on a serious problem. Estimates suggest some 5 million people are bitten, more than 100,000 are killed, and 400,000 are left maimed or crippled each year from snakes like cobras, kraits, taipans, and black mambas. Most victims live in the developing world; many are children out playing or young men who cross paths with the wrong snake while farming.

Untreated, some bites cause patients to hemorrhage so badly, their deaths are mistaken for Ebola. Other venoms contain paralyzing neurotoxins, or destroy so much skin and muscle they can leave limbs blackened. Some victims are so desperate to stop the pain, they drink gasoline or electrocute themselves.

Antivenoms do exist — and have been saving lives for more than a century — but they can have serious side effects and are often unavailable or unaffordable for the poor, rural people most likely to be bitten in India, Southeast Asia, and sub-Saharan Africa.

The new crop of scientists rushing into the field have all sorts of biotech wonders at their disposal: nanoparticles, monoclonal antibodies, DNA vaccines — not to mention old-fashioned determination. Yet snake toxin is so chemically complex — "a pandemonium of molecules," says one scientist — that it's proved frustratingly difficult to engineer a good antidote.

"Many would consider snake venom the most complex drug target known to man," said Andreas Hougaard Laustsen, a researcher at the Technical University of Denmark whose lab (and startup company, VenomAb) has created the first recombinant antivenom.

Those in this little-known field of toxinology face another obstacle, too. It's been hard to grab the attention of the public, or of world health leaders, even though snakebites claim so many more victims than such high-profile threats as Ebola and land mines.

"Snakebite needs a Princess Diana," said Dr. Matt Lewin, a physician and researcher in San Francisco who is eagerly searching for new treatments. "If the pope sent one tweet about this, the world would snap to."

A 19TH CENTURY RECIPE LIVES ON

The basic recipe for creating antivenom was invented in 1894, and at first glance it does seem medieval: Milk snakes for their venom, inject it into horses, then bleed the horses to collect antibodies to the venom.

Decades of technical advances in the field of "venomics" and other areas have led to safer, purer, and more effective antivenoms. But the treatments still carry a host of problems.

Recipients can suffer allergic reactions, kidney damage, and even shock in response to the animal cells or pathogens found in some antivenoms. Some work only for a specific species of snake or related group of snakes; others require refrigeration, meaning it can be difficult to have the correct — or any — antivenom on hand in remote regions.

And there's a robust market in fake therapies throughout the developing world: Some jars sold as antivenom contain simple sugar water.

The field is plagued by strange economics, too. Hospitals in the West have been known to charge thousands of dollars per vial for the rattlesnake and coppermouth antivenom

CroFab — and patients can need up to 20 vials after a bite. Yet companies making such drugs rarely see strong profits because they're mostly reaching poor patients in the developing world.

In recent years, in fact, two major pharmaceutical companies — Wyeth (now Pfizer) and Sanofi — withdrew from the antivenom market, citing the inability to make a profit.

Sanofi stopped production of Fav-Afrique, an antivenom effective against the bites of black mambas, spitting cobras, and eight other African snakes. There are alternative products, but Sanofi's decision drew a scathing rebuke in 2015 from Médecins Sans Frontières, which publicly accused Sanofi of having "slithered" its way out of the market, risking "an Ebola-scale disaster."

Pfizer, meanwhile, stopped making a treatment for venom from the coral snake. Dr. Leslie Boyer, a pathologist, pediatrician, and antivenom developer who founded the University of Arizona's VIPER Institute, has engineered an alternative but can't find any drug company to manufacture it.

"The FDA put out a desperate call for help to pharmaceutical companies and basically got laughed out of the room," she said.

So she's watching helplessly as the last supplies of the Pfizer treatment run out. A coral snake bite isn't always fatal, but it often causes paralysis — and unless they get antivenom, victims can face weeks on a respirator until they can once again breathe on their own.

'SNAKEBITE JESUS' TAKES ON VENOM

The new breed of snakebite entrepreneurs insist science — and possibly startups — can save the day.

"I was so perplexed when I found out antivenom was still produced by ancient methods. I expected it would be more advanced," said VenomAb's Laustsen, who was dubbed "Snakebite Jesus" by the Danish media after he returned from a lengthy research stay in Costa Rica with long hair and a sunburn. (He's also the one named "Denmark's coolest engineer" by the Danish alliance Engineer the Future.)

His antivenom uses recombinant human antibodies produced by cultivating cells in fermentation tanks — the same technology used to produce blood factors and insulin.

“It’s like brewing beer,” he said.

Because no animal cells are involved, the antivenom should cause fewer side effects, such as “serum sickness.” And, in theory at least, they can be designed to neutralize a venom’s worst toxins. But his group is still working on finding the right combination of antibodies.

Lausten himself acknowledged that the path ahead will be long. Even if he can hold down development and manufacturing costs, he may have a hard time turning profits, given that the main market is in low-income nations. “I don’t think you can justify [venture capital] investment” in the hopes of churning out a blockbuster drug, he said. “I think it has to be semi-philanthropic.”

Other promising techniques include work by the UC Irvine group, led by chemistry professor Ken Shea and his doctoral student Jeffrey O’Brien, both specialists in creating bioreactive synthetic nanoparticles.

They jumped into the game after the Defense Department put out a call for research to develop a “universal antivenom” to help protect soldiers. Shea had spent the last decade working on synthetic particles to counteract melittin, an active ingredient in bee venom, and thought his approach might have a wider use.

Their strategy was to engineer a nanoparticle that toxins in snake venom would bind to instead of cell membranes. Their target: a family of proteins called PLA2s that are common in snake, bee, and scorpion venoms. The PLA2 proteins are known to burst through cells, causing massive tissue damage and bleeding.

The scientists are patenting their particle and working with an Irvine-based startup called 300 Cells to develop it. But they’re quick to warn that any human treatment is a long way off, and will likely require creating additional synthetic particles to handle different components of venom. They say they have much lab work to do before testing starts, even in mice.

A HEART DRUG WITH SNAKEBITE POTENTIAL

Lewin, the San Francisco physician, thinks he's found a way around many of those development and cost hurdles. He's not starting from scratch. Instead, he's been sifting through pharmaceutical rejects for drugs that failed in their intended therapies but might be useful against snakebite because they target proteins in venom.

Lewin has seen the toll of snakebite firsthand in the community hospital in Tamil Nadu where he works as a visiting physician with his antivenom research partner, Dr. Stephen Samuel, a nanotechnologist and doctor who works in the UK but regularly returns home to India to treat snake victims.

The two, said Lewin, have treated the "deep, angry bites" of Russell's viper, the invisible but paralyzing bites of kraits, and patients "bleeding like crazy" from snakes they could not even name.

Lewin is so committed to the cause that he tried one potential treatment — the antiparalytic nose spray neostigmine — to reverse paralysis he'd had induced during an experiment run by anesthesiologists at a San Francisco hospital. Lewin survived, but he's since moved on to something he thinks is more promising: the drug varespladib.

Varespladib targets the same family of enzymes — PLA2 — that the Irvine group sees as promising. Better yet, it has already passed through Phase 1 and 2 clinical testing as a potential drug to treat sepsis and acute coronary syndrome, meaning it may prove safe for humans in emergency use.

"Varespladib blocks every snake venom PLA2 we've ever tested — 35 of them from six continents," said Lewin. And it keeps mice injected with venoms alive. He and his partners are now working to get access to the clinical trial data on the drug, in hopes of planning a study on its use as a snakebite treatment.

The name of Lewin's company? Ophirex. It means Snake King.

TENSION AT A GLOBAL SNAKEBITE CONFERENCE

While they're excited about the new research, veterans of the field warn it could be decades before new synthetic treatments are available for snakebite. Some fear the growing hype over barely tested research amounts to a not-so-subtle bashing of current antivenom therapy — which is commonly dismissed as "from the 19th century."

The old treatments may be flawed, but they do save lives in the here and now.

“Research is great,” said Boyer, “but this is like getting excited about the latest cancer immunotherapy when there are no surgeons available to remove the tumors first.”

That tension erupted last summer at the annual World Health Assembly meeting in Geneva, where the world’s snakebite experts — there are just a few dozen — gathered in a small conference room. Some called new biotech antivenom projects a distraction; others worried that any therapies developed by for-profit startups will be ruinously expensive.

Experts from Africa noted that even the lowest-tech solutions — like cheap plastic boots to shield the bare ankles of poor farmers — would save more lives today than any recombinant or synthetic therapy.

One person who is watching the new research closely — and playing a role in creating some of it — is toxinologist José Maria Gutiérrez, who has worked quietly on antivenoms for some 40 years at Costa Rica’s Instituto Clodomiro Picado and is credited with many of the field’s advances, including a potent new antivenom that works against numerous African snake species and can be freeze-dried so it does not require refrigeration. It’s sold at very low cost to countries that need it.

He calls the debate over new versus old technology “a false dichotomy.”

Snakebite, Gutiérrez said, is a major public health issue. While it needs new high-tech solutions, it also desperately needs better production and distribution streams so traditional antivenoms can get where they’re needed. Also important: More public and medical education. “We need innovation at many different levels,” he said.

“People think technology will bring solutions in one to two years and we should forget about horses, but these avenues are still very early in their development,” Gutiérrez said. “Right now, we have very good antivenoms, and for many years they will be the only treatment available.”

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