MARINE BIOLOGY

Florida Red Tide Brews Up Drug Lead for Cystic Fibrosis

Among the nasty compounds produced by the organism responsible for Florida's red tides is one with some surprising properties

Karenia brevis packs a powerful punch for a tiny organism. The culprit behind Florida's notorious red tides, the dinoflagellate produces a dozen toxins. And when a red tide coincides with an onshore breeze, emergency rooms brace for an influx of patients: The organism's airborne poisons, collectively known as brevetoxins, constrict bronchioles and send asthmatics and others with breathing difficulties scrambling for treatment. So the last thing you might expect from this nasty organism is a compound that alleviates wheezing and shortness of breath and helps clear mucus from the lungs. Yet one oddball in *K. brevis*'s armamentarium, a compound called brevenal, does just that, at least in sheep. It's being evaluated as a potential treatment for the debilitating lung disorder cystic fibrosis (CF), which afflicts 30,000 people in the United States, and researchers are poised to test it on Florida's endangered manatees next time some of the mammals are poisoned by a red tide.

Brevenal's surprising properties have been under investigation since the compound was first discovered in 2004 at the Center for Marine Science (CMS) at the University of North Carolina, Wilmington. New findings reported at the Society of Toxicology meeting in Charlotte, North Carolina, in late March indicate that the compound binds to a novel receptor in the lung, and that a synthetic version seems to work as well as the natural compound in laboratory and animal tests. Yet to be determined, however, is just why *K. brevis* produces a compound that counteracts some of the effects of its own fearsome suite of toxins. But then again, it's not clear why it produces those toxins either, notes CMS Director Daniel Baden.

From beach to bedside?

The oceans have long been touted as a potential source of new drug candidates, and researchers have systematically scoured sponges, corals, and marine microorganisms for likely compounds. Brevenal wasn't found that way: A shortage of guppies for routine toxicology screening led to its serendipitous discovery.

CMS pharmacologist Andrea Bourdelais was measuring the lethality of extracts isolated from brevetoxins by adding a tiny bit of test material to a beaker containing water and a guppy. If the fraction is toxic, the fish dies. Toxicologists usually retire fish that survive such tests to prevent subsequent chemical interactions, but the laboratory's supply of guppies was running low, so Bourdelais reused the survivors. When she added a known toxic fraction to beakers with leftover guppies, to her surprise, they did not die. "I had a spontaneous gut feeling—a gee-whiz moment—that the first material was an antidote to the second one," Bourdelais recalls.

Bourdelais subsequently showed that the mysterious extract (later named brevenal) protects guppies from death by brevetoxins in a dose-dependent fashion. The lab already had discovered that brevetoxins act on sodium channels, so Bourdelais used a standard lab test to check whether brevenal prevents the toxins from binding to the sodium channel receptor. It did. Bourdelais then sent the mysterious compound to William Abraham, research director at Mount Sinai Medical Center in Miami Beach, Florida, who had determined that all brevetoxins set off bronchoconstriction in a sheep model of asthma. Brevenal, he discovered, suppresses this effect.

Defective sodium transport is a hallmark of CF; it draws water away from airway surfaces, making mucus drier and stickier. Sodium channels are therefore a primary target for CF drugs, so Abraham compared brevenal to the CF drug amiloride in the sheep model. In the January 2005 *American Journal of Respiratory and Critical Care Medicine*, he reported that brevenal not only blocks bronchoconstriction, but it also increases mucus clearance—and it does so at concentrations 1 million–fold lower than amiloride. "We were excited that brevenal may have potential as a CF drug," says Abraham, based on its apparent potency compared to amiloride, which has a mediocre track record in the clinic. Also intrigued was AAI Pharma Inc., a company headquartered in Wilmington, North Carolina. It negotiated an exclusive license in 2004 to explore brevenal's potential as a treatment for CF.

Since then, Baden, Bourdelais, Abraham, and their colleagues have continued to probe brevenal's modus operandi. At the toxicology meeting, they reported that it acts on a new drug target: It binds a novel receptor in lung tissue associated with voltage-gated sodium channels; amiloride binds a related receptor, the epithelial sodium channel receptor. Baden also

Split personality. *Karenia brevis* (*inset*), which causes Florida's red tides (*above*), produces an antidote to its own bronchoconstricting toxins.

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reported that chemists in the laboratory of Makoto Sasaki at Tohoku University in Sendai, Japan, have synthesized brevenal from cheap starting materials. Dubbed ME-1, the synthetic agent performs as well as natural brevenal in receptor-binding assays and in preventing bronchoconstriction and clearing lung mucus in sheep, Baden reported.

Promises of new therapies for CF surface regularly, but many fizzle out. And in spite of its early promise, brevenal still has a long way to go. Steve Fontana, vice president of legal affairs at AAI Pharma, says the company's scientists are evaluating brevenal and its derivatives for safety and biological activity. Once they find the best drug candidate, the company will file an Investigational New Drug application with the U.S. Food and Drug Administration (FDA), but clinical trials are several years out.

In fact, humans may not be the first test subjects for brevenal's therapeutic potential. That honor may go to Florida's endangered manatees.

"A red tide event spreads like a wildfire and poisons birds, fish, sea turtles, manatees, and dolphins," says Andrew Stamper, a veterinarian at Disney's Animal Programs in Lake Buena Vista, Florida. In March and April of this year, about 30 manatees died following a red tide spike, and 150 died in 1996 from red tide poisoning. Only 3000 of the mammals are estimated to live along Florida's coast.

In February, Stamper received a "compassionate use" permit from FDA to evaluate the safety and effectiveness of brevenal in manatees. Stamper's colleague, veterinarian David Murphy of Lowry Park Zoo in Tampa, Florida, will test brevenal on rescued manatees brought to the zoo's rehabilitation center. When poisoned by brevetoxins, manatees become paralyzed and drown because they cannot hold their head above water to breathe. Murphy straps lifejackets underneath rescued manatees and supports their half-ton bodies in shallow tanks. Normal breathing resumes in a few days, but full recovery takes months. Brevenal "will add a new weapon in our arsenal," Murphy says. The next time a red tide hits, "we'll be ready to go," says Stamper.

–CAROL POTERA

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GEOPHYSICS

Stalking a Volcanic Torrent

The setting of the climax of the *Lord of the Rings*, New Zealand's Mount Ruapehu is earning a second reputation as a laboratory for understanding killer mudslides

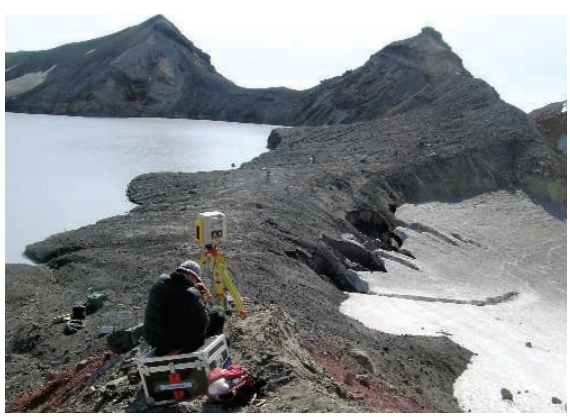
MOUNT RUAPEHU, NEW ZEALAND—From a helicopter, the steaming lake nestled in the snowy crater below looks inviting, like a giant Jacuzzi for Maori gods. But taking a dip would be a bad idea: Mount Ruapehu's rocky chalice burbles with scalding sulfuric acid. The otherworldly volcano was used for scenes of the hobbit Frodo ascending perilous Mount Doom in the *Lord of the Rings*. But the real Mount Doom is a killer, too. Cradling a deep lake between its 2500-meter peaks, Ruapehu is prone to lahar flows, one of the most dangerous—and least understood—volcanic hazards. In 1953, a lahar (an Indonesian word meaning mudslide) here knocked out a train bridge; 5 minutes later, a passenger train plummeted into a gorge, killing 151 people.

Earlier this year, Ruapehu's acidic lake was unleashed again. Noxious waters blasted down the slopes, picking up rocks as big as cars along the way. But this time, not a single person was hurt.

Not only was the lahar predicted by an early warning system, but the event also generated "orders of magnitude more data than for any other lahar event anywhere in the world," says Vernon Manville, a volcanologist at the Institute of Geological and Nuclear Sciences (GNS) in Taupo, New Zealand. "This has been a 10-year experiment in the making." The information mother lode should help scientists better protect the millions of people who live in the path of lahar-generating volcanoes around the world.

Wiring up Mount Doom

In 1995, Ruapehu's roughly 50-year cycle of eruptions kicked in again. Gobs of lava burped up from the bottom of the crater, adding 7 meters of loose ash and stones, called tephra, to the rim. The deepened crater soon filled with snowmelt from above and sulfuric acid and other material from fumaroles below. One of Ruapehu's grumbles late last year triggered an earthquake that whipped the lake into a frenzy, slamming the crater walls with 6-meter waves. "It was clear that it was only a matter of time" before the tephra rim failed and caused a lahar, says Manville.



Bracing for the big one. Readying for a world first: recording data from a volcanic lahar in action.

CREDIT: GNS SCIENCES

But exactly when the big one would strike was unknown. The inherent unpredictability of lahars is what makes them so dangerous, says Cynthia Gardner, a geologist at the Cascades Volcano Observatory in Vancouver, Washington. Most eruptions are preceded by a telltale increase in underground vibrations, swelling of the slopes, and changes in the composition of vented gases. But a lahar "can occur without warning," Gardner says. Besides eruptions and earthquakes, even a heavy rain can be enough to loosen unstable material at the top of many steep volcanoes. Gravity does the rest.

Another deadly aspect of lahars is the great distances they can travel down river valleys, sometimes hundreds of kilometers from a volcano. "Imagine," says Gardner, "a rushing surge of water coming toward you that's tens of meters thick" and carrying boulders, trees, and even houses. The best chance of survival is to get out of the way—only lahars are too fast to outrun. The deadliest lahar in recent history occurred in 1985, when an eruption of the Nevado del Ruiz volcano in Columbia triggered mudslides 50 meters thick that buried a town 70 kilometers away, killing 23,000 people.

To warn of an impending lahar at Ruapehu, a team led by Harry Keys, an engineer at the New Zealand Department of Conservation, wired up the mountain. His group installed underground microphones, called geophones, at the lake's rim to record

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