Published in final edited form as:
Science. 2007 June 15; 316(5831): 1561–1562. doi:10.1126/science.316.5831.1561.

Florida Red Tide Brews Up Drug Lead for Cystic Fibrosis

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Abstract

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 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.

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