# Fighting antibiotic resistance with 'molecular drill bits'

March 17 2014

In response to drug-resistant "superbugs" that send millions of people to hospitals around the world, scientists are building tiny, "molecular drill bits" that kill bacteria by bursting through their protective cell walls. They presented some of the latest developments on these drill bits, better known to scientists as antimicrobial peptides (AMPs), at the 247th National Meeting & Exposition of the American Chemical Society (ACS).

One of the researchers in the search for new ways to beat pathogenic bacteria is Georges Belfort, Ph.D. He and his team have been searching for a new therapy against the bacteria that cause tuberculosis (TB). It's a well-known, treatable disease, but resistant strains are cropping up. The World Health Organization estimates that about 170,000 people died from multidrug-resistant TB in 2012.

"If the bacteria build resistance to all current treatments, you're dead in the water," said Belfort, who is at Rensselaer Polytechnic Institute.

To avoid this dire scenario, scientists are developing creative ways to battle the disease. In ongoing research, Belfort's group together with his wife, Marlene Belfort, and her group at the University at Albany are trying to dismantle bacteria from within. They also decided to attack it from the outside.

In their search for a way to do this, they came upon AMPs. Although these naturally occurring, short strings of amino acids are not new—all

classes of organisms from humans to bacteria produce them as part of their natural defense strategy—the fight against drug-resistant pathogens has heightened attention on these protective molecules.

Researchers began studying them in earnest in the 1980s. By 2010, they had identified nearly 1,000 unique AMPs from many sources, including fly larvae, frog skin and mammalian immune system cells. The molecules come in different shapes, lengths and with other varying traits. But one thing they all have in common is that they somehow break through bacterial cell walls, the tough outer layers that provide structural support and protection. When Belfort found out about AMPs' mode of action, he aptly dubbed them "molecular drill bits."

Intrigued by their potential, Belfort scoured recent work on the peptides and discovered a database filtering technique developed by another group, reported in 2012. It's a kind of design-your-own-AMP model.

Using the database filtering technology, Belfort's lab designed and synthesized three novel AMPs designed to drill into the thick walls of tuberculosis cells. When they tested them in the lab against *Mycobacterium tuberculosis* and another similar bacteria, all three AMPs killed the bacteria. One worked better than the others—but not as well as kanamycin, which is one of several antibiotics in the arsenal against TB that some strains have developed resistance against.

Belfort's team is now focused on improving their designs and understanding exactly how AMPs work. The group is also developing a laboratory test that will allow them to tell within hours rather than weeks if an AMP is working against *Mycobacterium tuberculosis*.

If developed into pharmaceuticals, AMPs could have the additional benefit of overcoming the very challenge they're designed to meet: drug-resistance. AMPs attack bacteria's walls, or cell membranes, which have

been conserved through a long history of evolution.

"It's going to be much more difficult for a bacterium that's been around for millions of years to reconfigure its membrane," Belfort said. "That's the core protective structure that has helped it survive this long."

**More information:** Molecular drill bits as antibiotics:


## Abstract

Antibiotic resistance is increasing at an alarming rate. Disrupting bacterial but not mammalian outer membrane integrity with peptides is an alternate strategy to destroy toxic bacteria and assess selectivity. New potent stable antimicrobial peptides (AMPs) together with a fundamental understanding of their mechanism of cell disruption are urgently needed. By combining a new de novo design approach, Database Filtering, protein engineering and rational design with several complementary measurement methods, we synthesize and test AMPs and derive structure-activity relationships for the most potent stable AMPs. Our first generation AMPs are toxic to both M. smegmatis and Mycobacterium tuberculosis. We also investigate the mechanism of membrane disruption of another class of AMPs, picidin 1 and 3, and discuss these finding.


Provided by American Chemical Society