Taking the Resistance Out of Drug-Resistant Infections

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(PhysOrg.com) -- It started out as a research project focused on getting rid of harmful bacterial accumulations called biofilms. Now it has the potential to make conventional antibiotics work against stubborn, drug-resistant bacteria.

This unexpected development might have come as a surprise to the North Carolina State University researchers involved in the project, Dr. Christian Melander, assistant professor of chemistry, and Dr. John Cavanagh, William Neal Reynolds Distinguished Professor of Molecular and Structural Biochemistry.

What's not surprising, however, is the researchers' willingness to try seemingly unusual or unconventional methods to solve common problems. After all, getting rid of biofilms meant figuring out something odd to people who aren't chemists: how to safely and efficiently mimic a sea sponge.

Sponging Away Biofilms

Bacteria have a number of ways of protecting themselves from antibiotics, including casing themselves in a protective barrier known as a biofilm. Biofilms comprise about 80 percent of the world's microbial environment and are, according to statistics from the National Institutes of Health and the Centers for Disease Control, responsible for up to 80 percent of all bacterial infections.

In addition to medical concerns - certain biofilms in the lung kill cystic fibrosis patients, for example - biofilms also have enormous impacts in agriculture and industry. Biofilms destroy crops, foul ship's hulls and coat medical devices. Biofilms also coat - don't be alarmed - your teeth. As anyone who has had plaque scraped from their teeth knows, getting rid of biofilms once they adhere to a surface is really difficult.

To create chemical compounds that can scrub away biofilms, Melander and Cavanagh looked to a particular sea sponge, Agelas conifera, that lives in the Caribbean Sea.

"Somehow, this sponge that can't run away and that has no immune system stays remarkably clean while everything around it is covered in biofilms, so the sponge has some molecular way of keeping them at bay," Cavanagh said. "We've never seen a sea sponge up close, but we understand the chemical processes going on. So Christian devised chemical compounds to mimic the sponge compound, ageliferin, that keeps the sponge free of biofilms. Our compounds are not toxic to mammals like ageliferin is, though, and we can make the compounds in enormous quantities."

The NC State chemical compounds don't kill biofilms outright, but cause them to revert to their single-celled form. Common antibiotics are then able to do their job of eliminating the single-celled bacteria.

Melander and Cavanagh have had great success achieving the original goal of their research, as every targeted biofilm has been defeated.

Working with researchers at Wake Forest University Medical School, for example, Melander and Cavanagh demonstrated they can break up deadly biofilms in a mimic of a cystic fibrosis lung. In collaboration with Dr. David Ritchie, professor of plant pathology at NC State, the researchers successfully eliminated bacterial spot disease from a field of

pepper plants. Melander and Cavanagh have also dissolved their compound in marine paint and, working with Dr. Peter Moeller at the National Oceanic and Atmospheric Administration, have shown in ocean tests that it assists in keeping marine biofilm growth to a minimum.

Rebooting Antibiotics

While thrilled with their successes, Melander and Cavanagh wondered if their compounds might do more than overcome biofilms. Could their molecules stop bacteria from protecting themselves in other ways? Was it possible to make multi-drug resistant bacteria susceptible to antibiotics once more?

"There are a lot of antibiotics lying around useless these days because bacteria have learned to resist them. We wondered if we could give antibiotics a new lease on life," Cavanagh says.

The researchers certainly didn't aim low. They decided to tackle two of the most insidious problems known today; methicillin resistant Staphylococcus aureus (MRSA) and multi-drug resistant Acinetobacter baumannii (MDRAB). MRSA needs no introduction - it is a widespread and dangerous infection resistant to more than a dozen common antibiotics, including methicillin, penicillin and amoxicillin. MDRAB is arguably scarier. Up to 1,000 times more resistant than MRSA, it is found in hospitals and attacks patients who have compromised immune systems. MDRAB has become notorious recently since it plagues the military. Wounded soldiers are taken to hospitals where they become infected with MDRAB, often with fatal results.

Melander and Cavanagh showed that their compounds were able to overcome the multi-drug resistance of two nasty strains of MRSA and MDRAB. The MRSA strain from a hospital in Portugal was resistant to 16 antibiotics. The MDRAB strain was taken from a Canadian

serviceman. In both cases, the NC State compounds enabled conventional antibiotics to work again. As Cavanagh puts it, "We have, in effect, taken the MR out of MRSA."

Now, Melander and Cavanagh have formed a start-up company called Agile Sciences that is producing more of the chemical compounds and partnering with several drug companies to do further testing. The Research Triangle Park company is the "vehicle for the masses - the way to get things out to the general public to see if we can help," according to Cavanagh, while he and Melander get back to work on "building a better mousetrap," or making the compounds even better. Is it possible to make a chemical compound that stops bacteria from forming biofilms, for example, or place a chemical on surfaces so biofilms don't attach? Those are the types of questions the NC State scientists are now examining.

"Meanwhile, there are a lot more biofilms to destroy," Melander says "and we need to see whether we can make even more antibiotics work again."

Provided by North Carolina State University