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Scientists Learning to Target Bacteria Where They Live

By Kari Lydersen
Washington Post Staff Writer
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CHICAGO -- In the arms race between humans and bacteria, the ability to form "biofilms" -- large aggregations of microbes embedded in a slimy matrix -- has been one of the weapons the organisms use to defeat the immune system, antibiotic drugs and other threats. But scientists, who only recently recognized the role that biofilms play in antibiotic resistance, may be closing in on promising prospects for defeating pathogens.

Scientists have learned that bacteria that are vulnerable when floating around as individual cells in what is known as their "planktonic state" are much tougher to combat once they get established in a suitable place -- whether the hull of a ship or inside the lungs -- and come together in tightly bound biofilms. In that state, they can activate mechanisms like tiny pumps to expel antibiotics, share genes that confer protection against drugs, slow down their metabolism or become dormant, making them harder to kill.

The answer, say researchers, is to find substances that will break up biofilms.

"Since the time of Pasteur, we've been working on trying to kill off and control planktonic bacteria, but we've made very little progress in the control and understanding of biofilm bacteria," said David Davies, a biofilm expert at the State University of New York at Binghamton. "Now we're very good at getting rid of acute bacterial infections, which used to be a real scourge of mankind, but we have this incredible number of chronic, debilitating bacterial infections" often linked to biofilms.

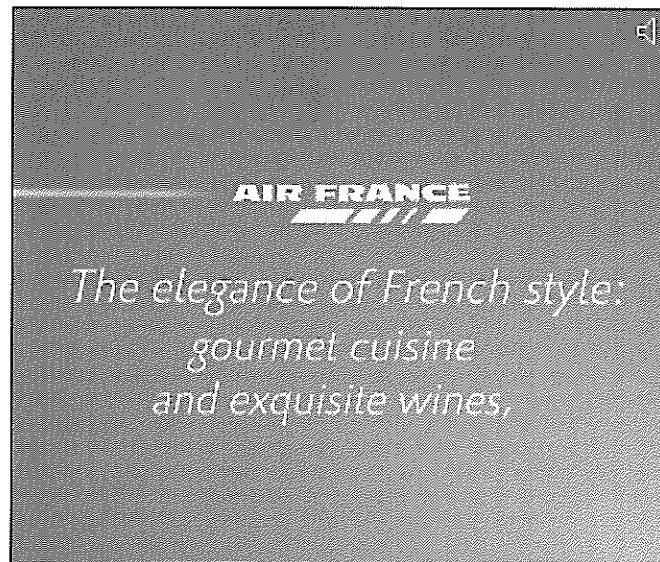
Notorious biofilm infections come from the bacterium *Pseudomonas aeruginosa*, which often affects lungs and can debilitate and kill cystic fibrosis sufferers, and methicillin-resistant *Staphylococcus aureus* (MRSA), which can spread quickly through prisons, hospitals and even beaches. *Acinetobacter baumannii* infections, which plague wounded soldiers, are also probably caused by biofilms, as are more mundane afflictions such as sinusitis and ear infections.

A successful means of dispersing biofilms, Davies said, would be a medical breakthrough akin to the discovery of penicillin in 1928.

The March edition of the *Journal of Bacteriology* features Davies's research on forcing biofilm dispersion by using bacteria's own chemical signals against them. Biofilm colonies disperse naturally in response to environmental factors or to spread and form new colonies. Davies and his colleagues have discovered a chemical signal, in the form of a fatty acid that tells bacteria it is time to break up.

He hopes this naturally occurring molecule, cis-2-decenoic acid or CDA, which is approved by the Food and Drug Administration as a food additive, could be used to fight infection. Because it does not kill bacteria, he says, it should not trigger the development of resistant bacteria, which could happen through natural selection if the chemical killed its targets.

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At North Carolina State University in Raleigh, two chemistry professors say they might have found a potential key to biofilm dispersion in the oceans, which scientists are mining for a variety of new drugs. When John Cavanagh and Christian Melander saw photos of the sea sponge *Agelas conifera* looking clean and healthy on a coral reef smothered by bacterial biofilms, they had a eureka moment.

"We were looking at that and said this sponge probably has it figured out," Cavanagh said. "It has no immune system, but it's found a way to defend itself against all the biofilms in the ocean, where there is a lot of nasty stuff floating around."

Melander said "a throwaway sentence in an obscure journal" -- the Bulletin of the Chemical Society of Japan -- gave them another clue. They isolated a compound from the sponge that disperses biofilms and figured out how to synthesize it quickly and cheaply.

The professors said that in laboratory tests, the compound, paired with an antibiotic, has effectively dispersed and killed previously antibiotic-resistant forms of MRSA, *A. baumannii* and other bacteria, though the scientists do not know how it works.

Although they hope to pair it with antibiotics to be taken orally, Melander and Cavanagh first plan to impregnate the compound in implanted medical devices that are prone to bacterial contamination, such as catheters, stents and artificial limbs.

Similar projects are in the works at other labs worldwide.

"In the last 15 years or so, we've really seen things take off. There will be lots of novel technologies coming out," said Rodney Donlan, team leader of the biofilm lab at the Centers for Disease Control and Prevention. The agency is experimenting with using phages -- viruses that can kill bacterial cells -- to prevent biofilm formation on medical devices

The Canadian company Kane Biotech plans to submit plans to the FDA this year for a wound gel containing a natural enzyme found in human mouths that disperses biofilms, which it has named DispersinB. The enzyme is nontoxic but makes biofilms susceptible to antibiotics and immune responses.

"The world is now turning their attention to the fact we just can't keep developing more and more drugs," said Gord Froehlich, Kane Biotech's president and chief executive. "We have to look at how the bacteria actually live and survive rather than just shooting more bullets."

University of Florida molecular biologist Tony Romeo describes the research as still in its nascent stages and said that discovering exactly why and how biofilms form is crucial.

"By understanding the factors that are needed for biofilms to develop, we hope to identify chinks in the armor that can lead to novel ways to treat or prevent such kinds of infections," Romeo said.

But dispersing biofilms without understanding all the ramifications could be a "double-edged sword," Romeo warned, because some bacteria in a biofilm could wreak worse havoc once they disperse.

"Simply inducing biofilm dispersion without understanding exactly how it will impact the bacterium and host could be very dangerous, as it might lead to spread of a more damaging acute infection," he said.

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