IBM lab designs molecule to kill drug-resistant superbugs

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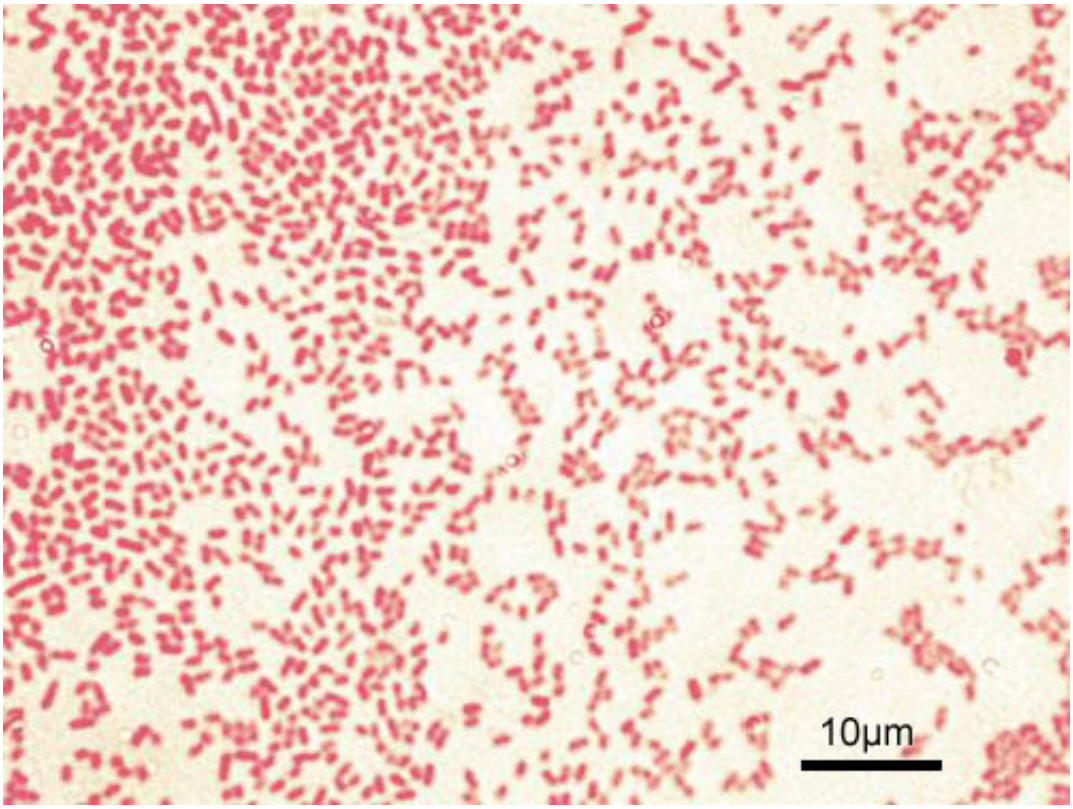

Gram-stained P. aeruginosa bacteria (pink-red rods) Credit: Wikipedia

As a scientist at IBM's Almaden Research Laboratory, James Hedrick was well aware of the global problem of antibiotic-resistant bacteria, which can turn a minor scrape into a death sentence.

But the threat turned personal after he had routine knee surgery. Sudden

excruciating pain signaled infection, demanding emergency hospitalization. Hedrick was lucky: the medications worked, the infection cleared and he went home eight days later.

Hedrick's close call inspired his research team to design a new molecule, called a polymer, that targets five deadly types of drug-resistant microbes and kills them like ninja assassins. Their research, a collaboration with Singapore's Institute of Bioengineering and Nanotechnology, was reported recently in the journal *Nature Communications*.

If commercialized, the polymer could boost the fight against "superbugs" that can fend off every antibiotic that doctors throw at them. An estimated 700,000 people worldwide die every year from these untreatable infections.

"It could be part of the physician's arsenal in case of a really bad infection," said Hedrick. "A last line of defense."

The research is part of IBM's ongoing effort to develop synthetic polymers for medical uses, based on a technology discovered in 2012 when exploring new ways to etch silicon wafers used in semiconductor chips. In 2016, the team showed they could be used to combat deadly viral diseases.

Hedrick and his team have extensive experience with synthetic polymers, long repeating chains of connected molecules that can be found in pretty much everything around us, including plastic trash bags, paints, styrofoam cups, plastic bottles, adhesives and computers.

It was at a conference about polymers, in fact, when Hedrick felt his knee ache. He had recently undergone successful surgical repair of his knee cap after a basketball injury, and it had been feeling fine. He was

returning home from Hawaii when the pain turned awful.

"My leg was freezing up and was extraordinarily painful," he recalled. "On the way to the airport, I went to the hospital. They confiscated my ticket, told me I'd have surgery in a few hours. I was there eight days."

"Had the bacteria been a superbug, resistant to medication, my story might have had a different ending," he said.

Antibiotics have been a critical public health tool since the discovery of penicillin in 1928, saving the lives of millions of people around the world. But the emergence of drug-resistant bacteria is reversing the miracles of these medicines, with drug choices becoming increasingly limited, expensive, and, in some cases, nonexistent.

The resistance occurs after repeated exposure to an antibiotic, when a few hardy bugs survive—and proliferate.

There are not nearly enough new antibiotics in development to replace those that are now ineffective, according to a September 2017 World Health Organization report. Of an estimated 33 antibiotics being tested, only eight are innovative in a way that will be beneficial against the superbugs, the report found. The other 25 are merely tweaks to existing treatments that are, ultimately, short-term solutions.

The Obama Administration provided a road map to guide the development of new drugs through the pipeline, but because of the resistance problem, "with each new drug we have to be very diligent stewards of its appropriate use," said Dr. Susan Casey Bleasdale of the Infectious Diseases Society of America.

"This is a significant potential breakthrough in the battle against antibiotic resistance," said Bleasdale, who is medical director of

infection control at the University of Illinois Hospital & Health Sciences System and responsible for guiding the development of hospital-wide infection control protocols and procedures. "If this proves true in clinical trials and is validated as safe and effective, this has the potential to be a game changer."

Earlier versions of synthetic polymers created problems because they essentially exploded the bacteria, releasing dangerous toxins into the bloodstream. While other scientists are researching different approaches to avoid resistance, most involve finding new molecules or proteins. IBM's synthetic molecule employs a completely different strategy.

It carries a negative electrical charge, so is drawn—like a magnet—to the positively charged surfaces of infectious cells. Then it binds to the cell, pierces the membrane, enters it and turns the inner liquid contents into solids. The new ninja polymer kills bacteria so quickly, they don't have time to mutate.

The eventual goal, said Hedrick, is to create an entirely new class of therapeutics that could treat a spectrum of infectious diseases with a single mechanism—without the onset of resistance.

Hedrick's team tested the polymers on mice infected with five hard-to-treat, multi-drug resistant bacteria: Acinetobacter baumannii; E. coli; Klebsiella pneumoniae; methicillin-resistant Staphylococcus aureu and Pseudomonas aeruginosa. These superbugs are commonly acquired by hospital patients, and can cause systemic infections that lead to septic shock and multiple-organ failure.

The bacteria were killed. No toxic side effects were seen. Within three days, the polymers decayed and were eliminated from the body.

Significantly, the team found that the bacteria did not show any

development of resistance even after multiple treatments with the polymer. That's because it acts so quickly, the bacteria don't evolve.

The next phase of the research is to show that the polymer doesn't build up in the body. Then IBM hopes to team up with pharmaceutical companies to develop the polymer into a specific therapy, test it in patients and, hopefully, bring it to market.

It won't be cheap; a lab-engineered polymer will likely cost more to make than traditional antibiotics.

But it could offer a critical new weapon when there are no options left, Hedrick said.

"Superbugs that are resistant to antibiotics are a serious health threat," he said. "The medical community needs more choices in treating patients."

More information: Willy Chin et al. A macromolecular approach to eradicate multidrug resistant bacterial infections while mitigating drug resistance onset, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03325-6