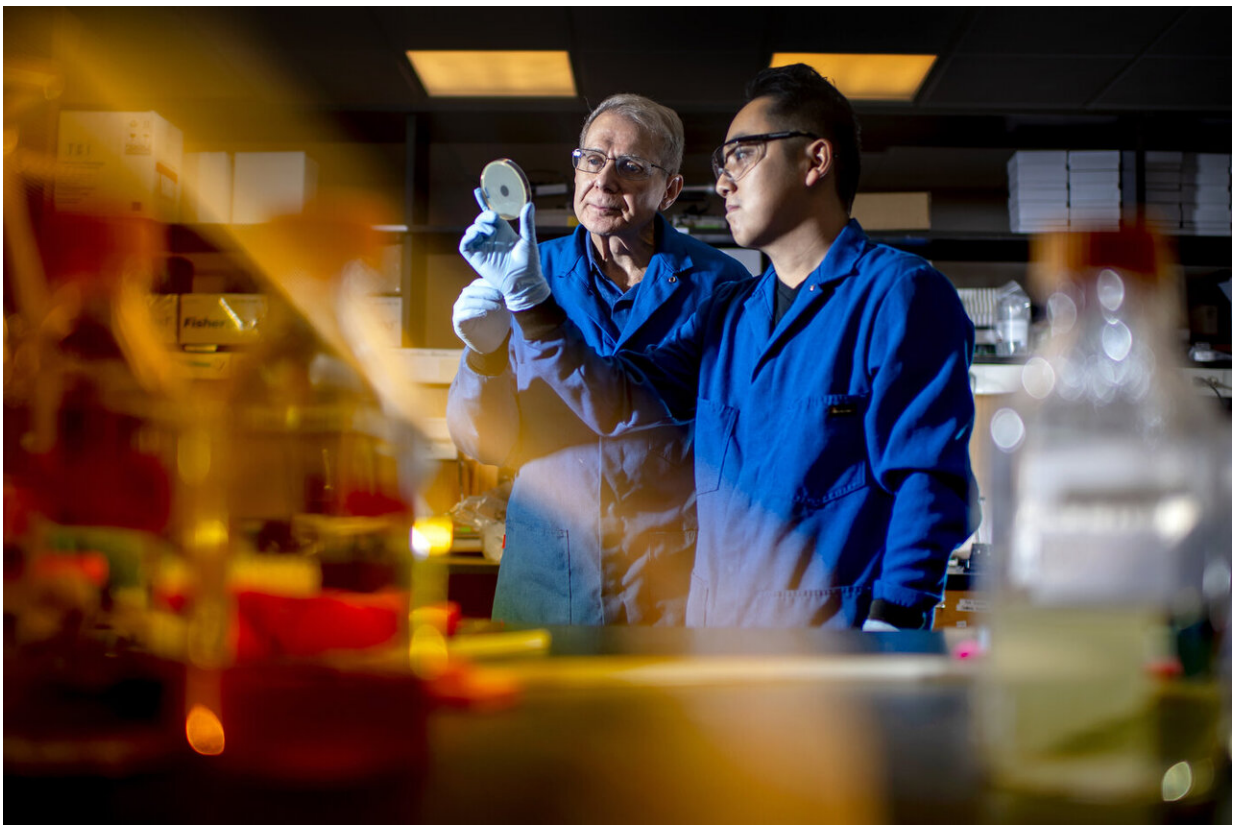
A new antibiotic has been hiding in the gut of a tiny worm. It may be our best weapon against drug-resistant bacteria.

November 21 2019, by Roberto Molar Candanosa



Kim Lewis, University Distinguished Professor of biology in the College of Science, and Yu Imai, a postdoctoral research associate at Lewis' lab, discovered a new class of antibiotics that could help fight drug-resistant gram-negative bacteria. Credit: Matthew Modoono/Northeastern University

Researchers at Northeastern have discovered a new antibiotic that could treat infections caused by some of the nastiest superbugs humanity is facing in the antibiotic resistance crisis.

After two years of work, a team of researchers led by Kim Lewis, University Distinguished Professor of biology, announced their discovery of darobactin, which can kill resistant microbes known as gram-negative bacteria.

The discovery, published today in *Nature*, promises to be a much-needed weapon in the war on drug-resistant bacteria, which are estimated to cause 700,000 deaths each year worldwide.

"We are running out of antibiotics," says Lewis, who directs the Antimicrobial Discovery Center, where the discovery of darobactin was made. "We need to be looking for novel compounds with no pre-existing resistance in the clinic or the population."

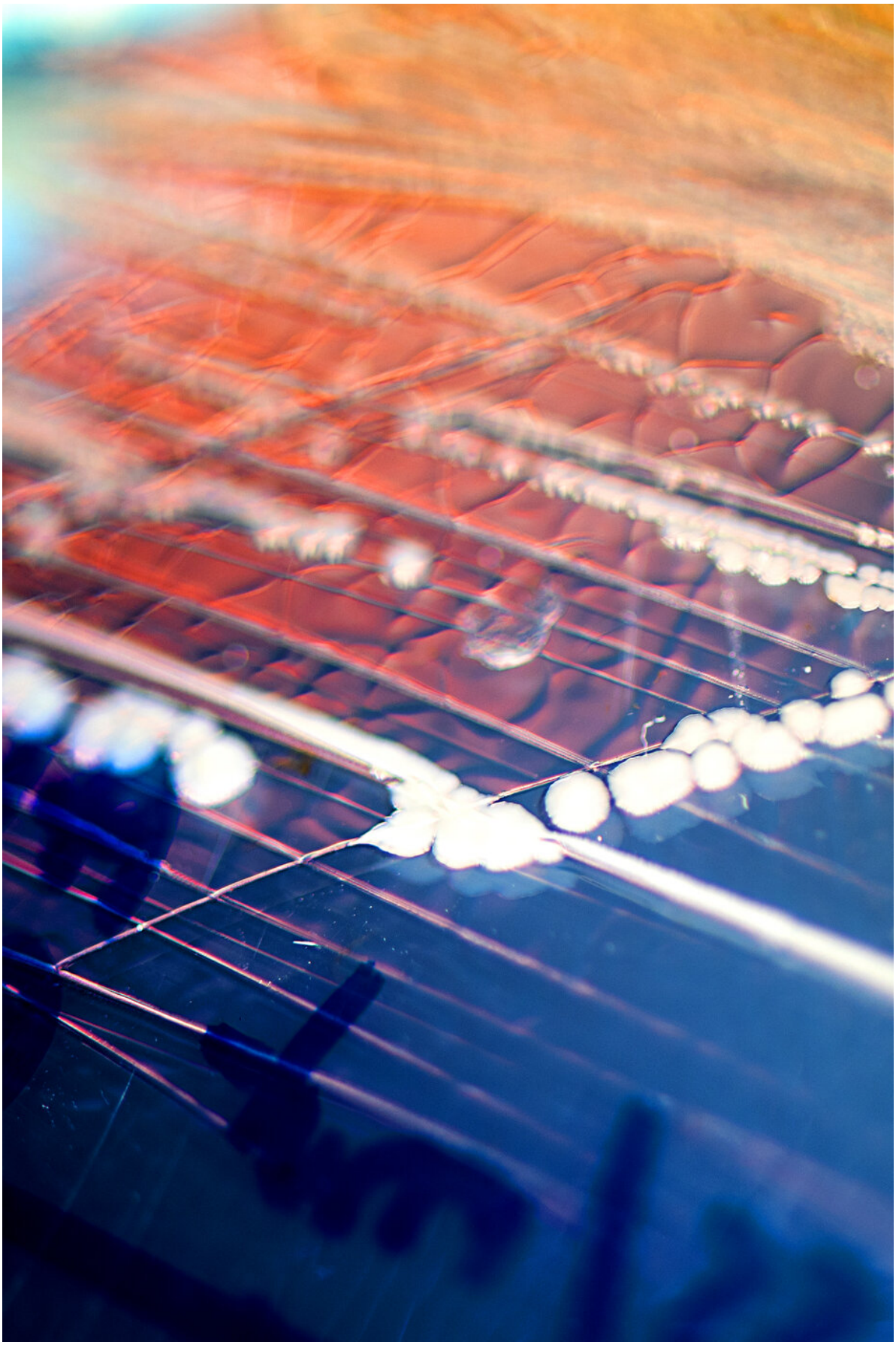
Yu Imai, a postdoctoral research associate in Lewis' lab, discovered the compound from Photorhabdus bacteria that live inside the gut of a nematode, a tiny parasitic worm found in soil. It's the first time, Lewis says, that the animal microbiome was found to harbor an antibiotic that promises to be useful for humans.

In experiments using mice conducted by Kirsten Meyer, also a postdoctoral research associate in Lewis' lab, darobactin cured E. coli and Klebsiella pneumoniae infections, with no signs of toxicity.

The newly discovered compound breathes new life into the search for a solution to the antimicrobial resistance crisis. The molecule has a unique structure and an unusual mode of action that make it particularly effective against gram-negative bacteria.

"We have never seen anything remotely similar to that before among antibiotics," Lewis says.

Gram-negative bacteria, which include E. coli and Salmonella, have an additional, outer membrane that shields them from many types of antibiotics. This extra protection is why gram-negative bacteria are at the top of a list of "priority" pathogens that need to be targeted with new antibiotics, compiled by the World Health Organization.



Using soil-dwelling organisms, Lewis' team found a new antibiotic that can target some of the toughest drug-resistant bacteria. Credit: Matthew Modoono/Northeastern University

Bacteria can also acquire additional resistance mechanisms from other microorganisms, which can make them largely impervious to currently available antibiotics. In a process biologists call horizontal gene transmission, bacteria pick up DNA from the environment and incorporate it into their genomes. These new genes can then be passed down to future generations.

This ability to pick and choose DNA is also how Photorhabdus bacteria, which have been around for hundreds of millions of years, acquired the genes coding for darobactin, Lewis says.

"What were they doing for the last 370 million years?" Lewis says. "I think these bacteria screened the entire biosphere for antibiotics of use to us."

Nematodes and Photorhabdus bacteria have a symbiotic relationship that helps them prey on different kinds of insects, such as caterpillars. Inside a caterpillar, nematodes release Photorhabdus bacteria, which in turn release toxins that kill the caterpillar and turn it into dinner.

But as the symbionts dine, the Photorhabdus also have to fend off freeloaders from the environment, which might also want to feast on the dead caterpillar. These opportunistic microbes can come from the nematode's own gut, which happens to be full of the same gram-negative bacteria that attack humans.

"Since Photorhabdus bacteria live in the nematode, and the nematode is an animal just like we are, whatever they make has to be non-toxic [for us]," Lewis says. "These compounds also have to move through and survive in the tissues of the caterpillar, which is also an animal and is actually very similar to us."

More than 50 years have passed since the introduction of the last class of antibiotics that target gram-negative bacteria.

The restrictive outer membrane of gram-negative bacteria is built with the help of an essential protein that sits on the surface of the cell. This protein, called BamA, works like a gumball machine that opens and closes a gate to dispense chewing gum. In these bacteria, BamA opens and closes a gate periodically, taking in freshly made proteins and inserting them into the protective membrane. That open-and-close mechanism is the vulnerability of these bacteria, Lewis says.

"Darobactin binds to that [BamA] protein and jams it, so it cannot open anymore," he says. "The bacteria cannot build a proper cell envelope, and that causes death."

Using soil-dwelling organisms, Lewis' team found a new antibiotic that can target some of the toughest drug-resistant bacteria. Credit: Matthew Modoono/Northeastern University

When Lewis' team tested E. coli that had developed resistance to darobactin, the bacteria lost their ability to infect mice. That means gram-negative bacteria cannot change the BamA protein without losing their ability to infect.

Eric Brown, Distinguished University Professor of biochemistry and biomedical sciences at McMaster University in Hamilton, Ontario, says the discovery of darobactin is an example of research "from soup to nuts" in terms of finding a compound from natural sources, figuring out a target, doing animal studies, and sorting out the way the organism

makes that compound.

"They didn't set out to find the BamA inhibitor, they just kind of stumbled on it," Brown says. "It's just kind of a master class on how to find a unique natural product antibiotic."

It's not the first time Lewis' lab has made a remarkable find by digging up soil bacteria. In 2015, Lewis and Slava Epstein, a professor of biology at Northeastern, working with NovoBiotic Pharmaceuticals, a biotech startup they founded together, announced the discovery of teixobactin, another promising class of antibiotics. Teixobactin targets gram-positive bacteria, another major class of microbes that includes MRSA, a deadly strain of staph.

Brown, who emphasized that darobactin shows promise as a potential new antibiotic, says it's difficult to predict whether the newly discovered compound will be safe and effective in people.

"It's pretty promising to see efficacy in infection models with more than one pathogen, and they report a lack of toxicity in those experiments, at least apparent, because it's not an extensive toxicity test by any stretch," Brown says. "It certainly is a very long road to a new antibiotic [for humans], but I'm of the view that you really need shots on goal. [And this] is another shot on goal for a field that desperately needs options."

Lewis expects darobactin to follow in the steps of teixobactin, which is on track to enter clinical trials. And, he says, there might be more antibiotics waiting to be discovered, including additional ones that target BamA.

"There's a trillion species of bacteria on the planet," Lewis says. "It is hard for me to imagine that we found the only molecule that exists on the planet that targets this [BamA] protein."

More information: Yu Imai et al. A new antibiotic selectively kills Gram-negative pathogens, *Nature* (2019). DOI: 10.1038/s41586-019-1791-1

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