# Q&A: A potential new weapon in the war against superbugs

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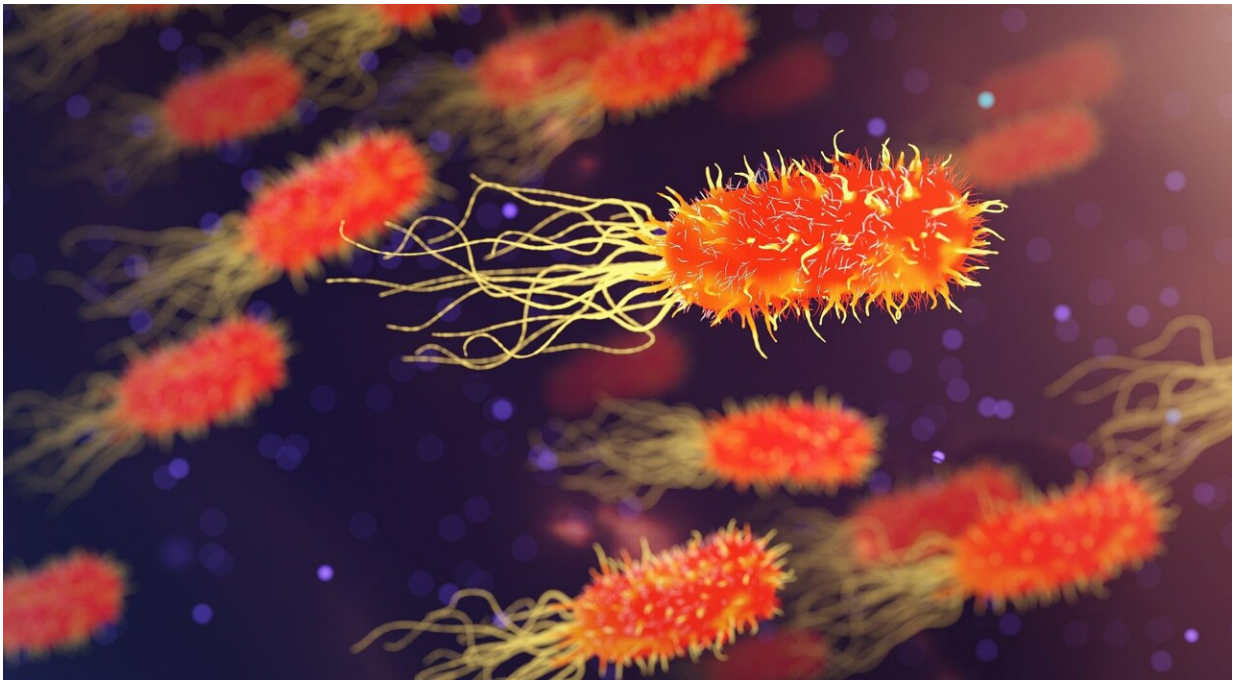

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For nearly 25 years, Dr. James Kirby has worked to advance the fight against infectious diseases by finding and developing new, potent antimicrobials, and by better understanding how disease-causing bacteria make us sick. In a recent paper published in *PLOS Biology*, Kirby and colleagues investigated a naturally occurring antimicrobial agent discovered more than 80 years ago.

"The end of modern medicine as we know it." That's how the then-director general of the World Health Organization characterized the creeping problem of antimicrobial resistance in 2012. Antimicrobial resistance is the tendency of bacteria, fungus and other disease-causing microbes to evolve strategies to evade the medications humans have discovered and developed to fight them. The evolution of these so-called "super bugs" is an inevitable natural phenomenon, accelerated by misuse of existing drugs and intensified by the lack of new ones in the development pipeline.

Without antibiotics to manage common bacterial infections, small injuries and minor infections become potentially fatal encounters. In 2019, more than 2.8 million antimicrobial-resistant infections occurred in the United States, and more than 35,000 people died as a result, according to the Centers for Disease Control and Prevention (CDC). In the same year, about 1.25 million people died globally. A report from the United Nations issued earlier this year warned that number could rise to ten million global deaths annually if nothing is done to combat antimicrobial resistance.

Using leading-edge technology, Kirby's team demonstrated that chemical variants of the antibiotic, called streptothricins, showed potency against several contemporary drug-resistant strains of bacteria. The researchers also revealed the unique mechanism by which streptothricin fights off bacterial infections. What's more, they showed the antibiotic had a therapeutic effect in an animal model at non-toxic concentrations. Taken together, the findings suggest streptothricin deserves further pre-clinical exploration as a potential therapy for the treatment of multi-drug resistant bacteria.

We asked Dr. Kirby to tell us more about this long-ignored antibiotic and how it could help humans stave off the problems of antimicrobial resistance a little longer.

## Q: Why is it important to look for new antimicrobials? Can't we preserve the drugs we have through more judicious use of antibiotics?

Stewardship is extremely important, but once you're infected with one of these drug-resistant organisms, you need the tools to address it.

Much of modern medicine is predicated on making patients temporarily—and sometimes for long periods of time—immunosuppressed. When these patients get colonized with these multidrug-resistant organisms, it's very problematic. We need better antibiotics and more choices to address multidrug resistance.

We have to realize that this is a worldwide problem, and organisms know no borders. So, a management approach for using these therapies may work well in Boston but may not in other areas of the world where the resources aren't available to do appropriate stewardship.

## Q: Your team investigated an antimicrobial discovered more than 80 years ago. Why was so little still known about it?

The first antibiotic, penicillin, was discovered in 1928 and mass produced for the market by the early 1940s. While a game-changing drug, it worked on only one of the two major classes of bacteria that infect people, what we call gram-positive bacteria. The gram-positive bacteria include staphylococcal infections and streptococcal infections which cause strep throat, skin infections and toxic shock. There still was not an antibiotic for the other half of bacteria that can cause human infections, known as gram-negative organisms.

In 1942, scientists discovered this antibiotic that they isolated from a soil bacterium called streptothricin, possibly addressing gram-negative organisms. A pharmaceutical company immediately licensed the rights to it, but the development program was dropped soon after when some patients developed renal or kidney toxicity. Part of the reason for not pursuing further research was that several additional antibiotics were identified soon thereafter which were also active against gram-negatives. So, streptothricin got shelved.

## Q: What prompted you to look at streptothricin specifically now?

It was partly serendipity. My research laboratory is interested in finding new, or old and forgotten, solutions to treat highly drug-resistant gram-negative pathogens like E. coli or Klebsiella or Acinetobacter that we commonly see in hospitalized, immunocompromised patients. The problem is that they're increasingly resistant to many if not all of the antibiotics that we have available.

Part of our research is to understand how these superbugs cause disease. To do that, we need a way to manipulate the genomes of these organisms. Commonly, the way that's done is to create a change in the organism linked with the ability to resist a particular antibiotic that's known as a selection agent. But for these super resistant gram-negative pathogens, there was really nothing we could use. These bugs were already resistant to everything.

We started searching around for drugs that we could use, and it turns out these super resistant bugs were highly susceptible to streptothricin, so we were able to use it as a selection agent to do these experiments.

As I read the literature on streptothricin and its history, I had the

realization that it was not sufficiently explored. Here was this antibiotic with outstanding activity against gram-negative bacteria—and we confirmed that by testing it against a lot of different pathogens that we see in hospitals. That raised the question of whether we could get really good antibiotic activity at concentrations that are not going to cause damage to the animal or person in treatment.

## Q: But it did cause kidney toxicity in people in 1942. What would be different now?

What scientists were isolating in 1942 was not as pure as what we are working with today. In fact, what was then called streptothricin is actually a mixture of several streptothricin variants. The natural mixture of different types of streptothricins is now referred to as nourseothricin.

In animal models, we tested whether we could kill the harmful microorganism without harming the host using a highly purified single streptothricin variant. We used a very famous strain of Klebsiella pneumoniae called the Nevada strain which was the first pan-drug-resistant, gram-negative organism isolated in the United States, an organism for which there was no treatment. A single dose cleared this organism from an infected animal model while avoiding any toxicity. It was really remarkable. We're still in the very early stages of development, but I think we've validated that this is a compound that's worth investing in further studies to find even better variants that eventually will meet the properties of a human therapeutic.

## Q. How does nourseothricin work to kill gram-negative bacteria?

That's another really important part of our study. The mechanism hadn't been figured out before and we showed that nourseothricin acts in a

completely new way compared to any other type of antibiotic.

It works by inhibiting the ability of the organism to produce proteins in a very sneaky way. When a cell makes proteins, they make them off a blueprint or message that tells the cell what amino acids to link together to build the protein. Our studies help explain how this antibiotic confuses the machinery so that the message is read incorrectly, and it starts to put together gibberish. Essentially the cell gets poisoned because it's producing all this junk.

In the absence of new classes of antibiotics, we've been good at taking existing drugs like penicillin for example and modifying them; we've been making variations on the same theme. The problem with that is that the resistance mechanisms against penicillin and other drugs already exist. There's a huge environmental reservoir of resistance out there. Those existing mechanisms of resistance might not work perfectly well against your new variant of penicillin, but they will evolve very quickly to be able to conquer it.

So, there's recognition that what we really want is new classes of antibiotics that act in a novel way. That's why streptothricin's action uncovered by our studies is so exciting. It works in a very unique way not seen with any other antibiotic, and that is very powerful because it means there's not this huge environmental reservoir of potential resistance.

## Q. You emphasize these are early steps in development. What are the next steps?

My lab is working very closely with colleagues at Northeastern University who figured out a way to synthesize streptothricin from scratch in a way that will allow us to cast many different variants. Then

we can look for ones that have the ideal properties of high potency and reduced toxicity.

We are also continuing our collaboration with scientists at Case Western Reserve University Medical Center, diving more deeply to understand exactly how this antibiotic works. Then we can use that fundamental knowledge in our designs of future variants and be smarter about how we try to make the best antibiotic.

We have great collaborators that have allowed us to pursue a project that crosses multiple fields. This work is an example of collaborative science really at its best.

**More information:** Streptothricin F is a bactericidal antibiotic effective against highly drug-resistant gram-negative bacteria that interacts with the 30S subunit of the 70S ribosome, *PLOS Biology* (2023). DOI: 10.1371/journal.pbio.3002091

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