A synthetic antibiotic may help turn the tide against drug-resistant pathogens

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A new antibiotic, synthesized at The Rockefeller University and derived from computer models of bacterial gene products appears to neutralize even drug-resistant bacteria. The compound, named cilagicin, works well in mice and employs a novel mechanism to attack MRSA, C. diff, and several other deadly pathogens, according to a study published in *Science*.

The results suggest that a new generation of antibiotics could be derived from computational models. "This isn't just a cool new molecule, it's a validation of a novel approach to [drug discovery](#)," says Rockefeller's Sean F. Brady. "This study is an example of computational biology, [genetic sequencing](#), and synthetic chemistry coming together to unlock the secrets of bacterial evolution."

Acting on eons of bacterial warfare

Bacteria have spent billions of years evolving unique ways to kill one another, so it's perhaps unsurprising that many of our most powerful antibiotics are derived from bacteria themselves. With the exceptions of penicillin and a few other notables derived from fungi, most antibiotics were first weaponized by bacteria to fight off fellow bacteria.

"Eons of evolution have given bacteria unique ways of engaging in warfare and killing other bacteria without their foes developing resistance," says Brady, the Evnin Professor and head of the Laboratory of Genetically Encoded Small Molecules. Antibiotic drug discovery once largely consisted of scientists growing streptomyces or bacillus in the lab and bottling their secrets to treat human disease.

But with the rise of antibiotic-resistant bacteria, there is an urgent need for new active compounds—and we may be running out of bacteria that are easy to exploit. Untold numbers of antibiotics, however, are likely hidden within the genomes of stubborn bacteria that are tricky or impossible to study in the lab. "Many antibiotics come from bacteria, but most bacteria can't be grown in the lab," Brady says. "It follows that we're probably missing out on most antibiotics."

An alternative method, championed by the Brady lab for the past fifteen years, involves finding antibacterial [genes](#) in soil and growing them within more lab-friendly bacteria. But even this strategy has its

limitations. Most antibiotics are derived from genetic sequences locked within clusters of bacterial genes, known as biosynthetic gene clusters, that function as a unit to collectively code for a series of proteins. But those clusters are often inaccessible with current technologies.

"Bacteria are complicated, and just because we can sequence a gene doesn't mean we know how the bacteria would turn it on to produce proteins," Brady says. "There are thousands and thousands of uncharacterized gene clusters, and we have only ever figured out how to activate a fraction of them."

A new pool of antibiotics

Frustrated with their inability to unlock many bacterial gene clusters, Brady and colleagues turned to algorithms. By teasing apart the genetic instructions within a DNA sequence, modern algorithms can predict the structure of the antibiotic like compounds that a bacterium with these sequences would produce. Organic chemists can then take that data and synthesize the predicted structure in the lab.

It may not always be a perfect prediction. "The molecule that we end up with is presumably, but not necessarily, what those genes would produce in nature," Brady says. "We aren't concerned if it is not exactly right—we only need the synthetic molecule to be close enough that it acts similarly to the compound that evolved in nature."

Postdoctoral associates Zonggiang Wang and Bimal Koirala from the Brady lab began by searching through an enormous genetic-sequence database for promising bacterial genes that were predicted to be involved in killing other bacteria and hadn't been examined previously. The "cil" gene cluster, which had not yet been explored in this context, stood out for its proximity to other genes involved in making antibiotics. The researchers duly fed its relevant sequences into an algorithm, which

proposed a handful of compounds that cil likely produces. One compound, aptly dubbed cilagicin, turned out to be an active antibiotic.

Cilagicin reliably killed Gram-positive bacteria in the lab, did not harm human cells, and (once chemically optimized for use in animals) successfully treated bacterial infections in mice. Of particular interest, cilagicin was potent against several drug-resistant bacteria and, even when pitted against bacteria grown specifically to resist cilagicin, the synthetic compound prevailed.

Brady, Wang, Koirala and colleagues determined that cilagicin works by binding two molecules, C55-P and C55-PP, both of which help maintain bacterial cell walls. Existing antibiotics such as bacitracin bind one of those two molecules but never both, and bacteria can often resist such drugs by cobbling together a cell wall with the remaining molecule. The team suspects that cilagicin's ability to take both molecules offline may present an insurmountable barrier that prevents resistance.

Cilagicin is still far from human trials. In follow-up studies, the Brady lab will perform further syntheses to optimize the compound and test it in animal models against more diverse pathogens to determine which diseases it may be most effective in treating.

Beyond the clinical implications of cilagicin, however, the study demonstrates a scalable method that researchers could use to discover and develop new antibiotics. "This work is a prime example of what could be found hidden within a gene cluster," Brady says. "We think that we can now unlock large numbers of novel natural compounds with this strategy, which we hope will provide an exciting new pool of drug candidates."

More information: Zongqiang Wang et al, Bioinformatic prospecting and synthesis of a bifunctional lipopeptide antibiotic that evades

resistance, *Science* (2022). DOI: 10.1126/science.abn4213.
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