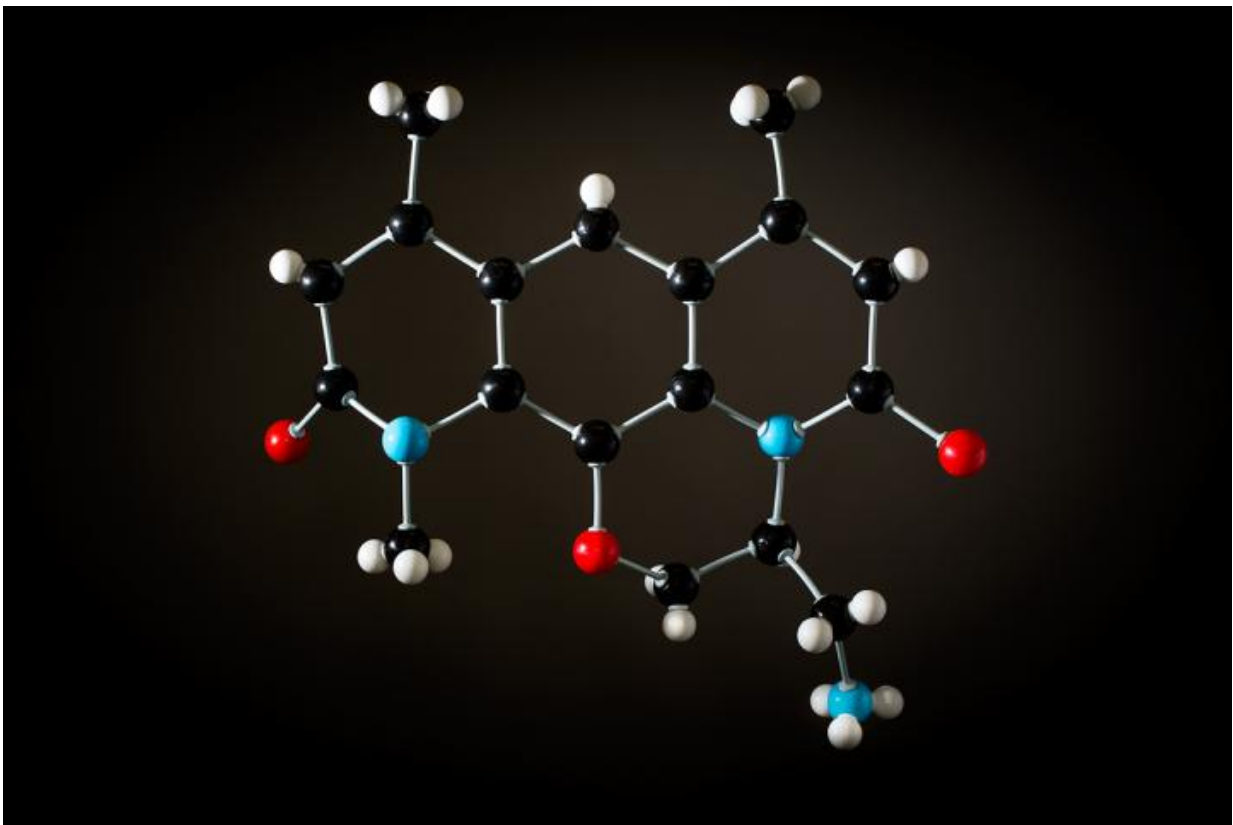


Antibiotic breakthrough: Team discovers how to overcome gram-negative bacterial defenses

May 10 2017



6DNM-amine is a proof of concept that the new approach can transform gram-positive antibiotics to drugs that can also kill gram-negative microbes. Credit: L. Brian Stauffer

Scientists report that they now know how to build a molecular Trojan horse that can penetrate gram-negative bacteria, solving a problem that for decades has stalled the development of effective new antibiotics against these increasingly drug-resistant microbes. The findings appear in the journal *Nature*.

Led by University of Illinois chemistry professor Paul Hergenrother, the scientists tested their approach by modifying a drug that kills only gram-positive bacteria, which lack the rugged outer cell membrane that characterizes gram-negative microbes and makes them so difficult to combat. The modifications converted the drug into a broad-spectrum antibiotic that could also kill gram-negatives, the team reports.

Gram-negative bacteria include pathogenic strains of *Escherichia coli*, *Acinetobacter*, *Klebsiella* and *Pseudomonas aureginosa*, all of which, according to the Centers for Disease Control and Prevention, are becoming "increasingly resistant to most available antibiotics."

The effort to find [new antibiotics](#) to combat these pathogens has failed again and again simply because almost all new drugs are unable to penetrate the gram-negative bacterial cell wall, Hergenrother said.

"We have a handful of classes of antibiotics that work against gram-negatives, but the last class was introduced 50 years ago, in 1968," Hergenrother said. "Now, the bacteria are developing resistance to all of them."

The void of new antibiotics is not due to lack of effort. In 2007, for example, a large pharmaceutical company screened roughly 500,000 synthetic [compounds](#) for activity against *E. coli*, none of which led to a new drug, the researchers wrote.

"These microbes have an outer membrane that is basically impermeable

to antibiotics or would-be antibiotics," Hergenrother said. "Any drugs that work against them almost always are going through a special gateway, called a porin, that lets in amino acids and other compounds the bacteria need to live."

Rather than using commercial chemical libraries, Hergenrother's group turned to its own collection of complex molecules. These were the natural products of plants and microbes that the scientists had modified in the lab.

"A few years ago, we found that through a series of organic chemistry steps we could change natural products into molecules that look very different from the parent compounds," Hergenrother said. The new molecules were more diverse than most available commercially, he said. The team has produced more than 600 new compounds using this approach.

The researchers tested these compounds individually against [gram-negative bacteria](#), looking for those that successfully accumulated inside the cells.

"The few that got in all had amines on them, so we started building out from there," Hergenrother said. Amines are molecular components that contain the element nitrogen.

The researchers tested more compounds with amines, and their success rate increased. But this was not the only trait needed to break into the gram-negative cells.

"Having an amine was necessary but not sufficient," Hergenrother said.

Using a computational approach, the team discovered three key traits required for access: To get in, a compound must have an amine that is

not hindered by other molecular components; it must be fairly rigid (floppy compounds are more likely to get stuck in the porin gateway), and it must have "low globularity," which, more simply, means it must be flat, not fat.

To test these guidelines, the team added an amine group to deoxynybomycin, a compound created in the 1960s by Kenneth Rinehart Jr., at the time a chemistry professor at the U. of I. They chose this compound because it is a potent killer of [gram-positive bacteria](#) and has the other desirable traits: rigidity and low globularity. By adding an amine to the right place on the molecule, the researchers converted DNM into a [broad-spectrum antibiotic](#) that they are calling 6DNM-amine.

"The point is not necessarily this compound, which may or may not be a good candidate as a drug used in human health," Hergenrother said. "It's more important as a demonstration that we understand the fundamentals at play here. Now, we know how to make collections of compounds where everything gets in."

Finding compounds that penetrate the membrane is important, but [antibiotics](#) also must kill the bacteria. Previous research suggests that only about one in 200 random compounds that penetrate gram-negative bacteria are also likely to kill the [bacteria](#), Hergenrother said.

"These are workable odds," he said. "Much better than zero in 500,000."

More information: Michelle F. Richter et al, Predictive compound accumulation rules yield a broad-spectrum antibiotic, *Nature* (2017). [DOI: 10.1038/nature22308](https://doi.org/10.1038/nature22308)

Provided by University of Illinois at Urbana-Champaign

Citation: Antibiotic breakthrough: Team discovers how to overcome gram-negative bacterial defenses (2017, May 10) retrieved 10 April 2024 from

<https://medicalxpress.com/news/2017-05-antibiotic-breakthrough-team-gram-negative-bacterial.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.