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A synthetic antibiotic, lolamicin, attacks harmful bacteria while sparing friendly microbes.
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An Antibiotic That Distinguishes Friend from Foe

A novel compound targets an essential transport system found only in disease-causing bacteria, leaving commensal bacteria unharmed.

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Animals house thousands of commensal bacterial species in their guts, which play an important role in maintaining the host's health.[1] However, antibiotic treatment indiscriminately wipes out both helpful and harmful gut bacteria, causing an imbalance in the local microbiota and paving the way for gastrointestinal infections. Antibiotics that selectively target pathogenic bacteria could bypass such complications, yet they are scarce.

In a new study, researchers have identified a compound that kills pathogenic bacteria while sparing friendly gut microbes.[2] The paper, published in *Nature*, presents a strategy for selectively targeting harmful bacteria, offering a framework

for developing other microbiome-sparing antibiotics.

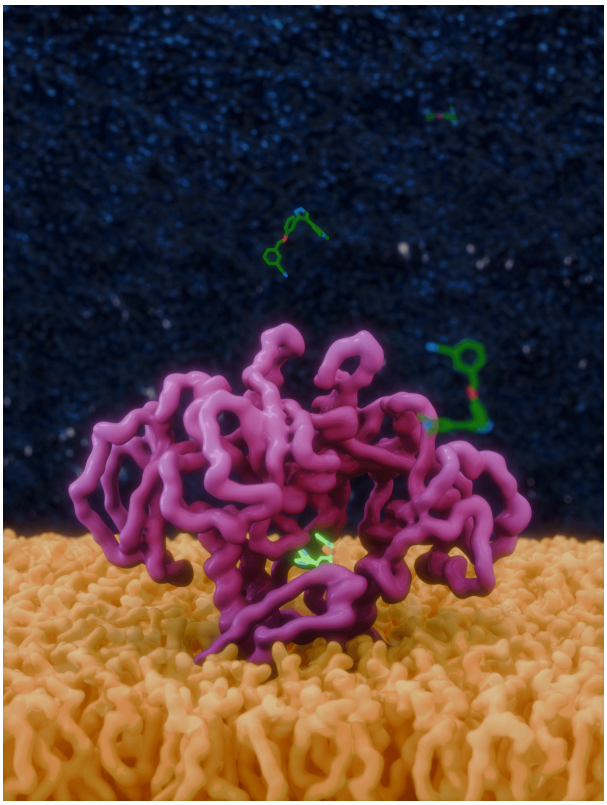
“Antibiotics have selectivity for bacteria over human cells, but most of them cause great devastation to our microbiome,” said Paul Hergenrother, a chemist at the University of Illinois Urbana-Champaign and a study coauthor.

Bacteria are classified as either Gram-negative or Gram-positive based on their cell wall structure—Gram-negative bacteria have a thick layer of protection, making them difficult to kill. Most antibiotics either only target Gram-positive bacteria or they are broad-spectrum, killing both types. However, few drugs target only Gram-negative bacteria.[3]

Researchers had previously identified that a lipoprotein transport system called Lol is exclusively present in Gram-negative bacteria.[4] When Hergenrother and his team sequenced the genomes of different Gram-negative commensals and pathogens, they found that the Lol system was genetically different between the two types of bacteria. This led the team to speculate that drugs targeting the Lol system could be effective if they could find a compound that specifically targeted the version of the system found in the pathogenic Gram-negative bacteria.[5]

The team wondered whether any known Lol inhibitors might do the trick. After screening available compounds, they identified two—pyridinepyrazole and pyridineimidazole—that inhibited the Lol complex that is essential for Gram-negative bacteria survival. They modified the inhibitors by adding amine groups in different combinations until they found one variant that showed evidence of antibacterial activity. They named this compound lolamicin.

When Hergenrother’s team tested lolamicin against laboratory and multidrug-resistant strains of common Gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, it wiped out each of these pathogens. However, lolamicin did not affect lab-grown strains of Gram-negative commensals or Gram-positive bacteria, indicating its specificity against Gram-negative pathogens. In contrast, commonly used broad spectrum antibiotics like clindamycin and amoxicillin killed all kinds of bacteria.



Lolamicin molecules (green) bind to their target, the Lol complex (pink) on phospholipids in the Gram-negative bacterial inner membrane (yellow).

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To test lolamicin in vivo, the researchers infected mice with multidrug-resistant Gram-negative pathogens and treated them with the novel compound. While nearly all the untreated mice died within three days of bacterial exposure, most of the mice that received lolamicin, either orally or intraperitoneally, survived.

To assess lolamicin's effect on the gut microbiome, the researchers treated healthy mice with lolamicin or conventional antibiotics and sequenced the DNA from their feces. Clindamycin and amoxycillin caused significant shifts in the makeup of the gut microbial population. In contrast, lolamicin did not disrupt the normal gut microflora.

To further explore its effect on the gut microbiome, the researchers treated mice with either lolamicin or a conventional antibiotic before exposing them to *Clostridium difficile*, a bacterium that typically infects guts with disrupted microbiota.[6] Mice treated with amoxycillin or clindamycin developed a *C. difficile* infection, but those treated with the novel compound did not, indicating that lolamicin does not disturb normal gut microflora.

"We're excited about [the results]," said Hergenrother. "We hope that by showing that you can get a Gram-negative selective compound that doesn't disturb the gut microbiome, more researchers will pursue this line of inquiry."

"This is a welcome example," said Kim Lewis, a microbiologist at Northeastern University who was not involved in the study, who hopes that these results stimulate similar efforts to look for selective antibiotics.

One of the limitations, though, is that targeted bacteria could eventually develop

resistance to the drug compound, Kim noted. “But further modifications of the compound can help diminish the frequency of resistance,” he added.

Hergenrother said that the team plans to optimize the compound. “[But] resistance is inevitable,” he said. The only way to delay it is by improving antibiotic stewardship, he noted. The team’s next goal is to study lolamicin more thoroughly in preclinical models.

Lewis estimated that it will take at least eight years for such a compound to reach the clinic. But he noted that the last time a Gram-negative selective antibiotic was introduced for human use was in the 1960s. “By comparison, eight years doesn’t sound as foreboding,” he added.

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