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# Trojan horse strategy defeats drug-resistant bacteria

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A new antimicrobial approach can kill bacteria in laboratory experiments and eliminate life-threatening infections in mice by interfering with a key bacterial nutrient, according to research led by a University of Washington scientist. The joint project, conducted at the UW, the University of Iowa, and the University of Cincinnati, will be featured in the April 2 issue of the *Journal of Clinical Investigation*.

Bacteria are increasingly resistant to antibiotics, and existing drugs work poorly against chronic infections like those that occur in wounds, on medical devices and in the lungs of people with cystic fibrosis. For these reasons, a great deal of research is focused on finding new antibiotic compounds.

In this study, researchers took a different approach. Rather than trying to find agents that best killed bacteria in test tubes, they sought to intensify the stress imposed on microbes by one of the body's own defense mechanisms.

"The competition for iron is critical in the struggle between bacteria and host," explained the study's senior author, Pradeep Singh, associate professor of medicine and microbiology at the UW. "The body has potent defense mechanisms to keep iron away from infecting organisms, and invaders must steal some if they are to survive."

Iron is critical for the growth of bacteria and for their ability to form biofilms, slime-encased colonies of microbes that cause many chronic

infections. "Because iron is so important in infection, we thought infecting bacteria might be vulnerable to interventions that target iron," explained Yukihiro Kaneko, senior fellow in microbiology at the UW and the study's lead author.

To accomplish this, the researchers used gallium, a metal very similar to iron.

"Gallium acts as a Trojan horse to iron-seeking bacteria," said Singh. "Because gallium looks like iron, invading bacteria are tricked, in a way, into taking it up. Unfortunately for the bacteria, gallium can't function like iron once it's inside bacterial cells."

The researchers showed that gallium killed microbes, and prevented the formation of biofilms. Importantly, gallium's action was intensified in low iron condition, like those that exist in the human body. Gallium was even effective against strains of Pseudomonas aeruginosa from cystic fibrosis patients that were resistant to multiple antibiotics. In mice, gallium treatment blocked both chronic and acute infections caused by this bacterium.

The idea of using gallium as a substitute for iron was developed by a group led by Bradley Britigan, a researcher at the University of Cincinnati and a co-author on this study. The general approach of targeting stresses already applied by natural defense mechanisms could be a promising new way to treat infections.

"We badly need new approaches to fight bacteria," said Singh. "The gallium strategy isn't ready for clinical use yet," he added. "However, we think this approach is promising, and we can't afford to leave any stone unturned."

Source: University of Washington