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Scientists use nature against nature to develop an antibiotic with reduced resistance

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A new broad range antibiotic, developed jointly by scientists at The Rockefeller University and Astex Pharmaceuticals, has been found to kill a wide range of bacteria, including drug-resistant *Staphylococcus* (MRSA) bacteria that do not respond to traditional drugs, in mice. The antibiotic, Epimerox, targets weaknesses in bacteria that have long been exploited by viruses that attack them, known as phage, and has even been shown to protect animals from fatal infection by *Bacillus anthracis*, the bacteria that causes anthrax.

Target selection is critical for the development of new antimicrobial agents. To date, most approaches for target selection have focused on the importance of bacterial survival. However, in addition to survival, the Rockefeller scientists believe that molecular targets should be identified by determining which cellular pathways have a low probability for developing resistance.

"For a billion years, phages repeatedly have infected populations of bacteria, and during this period of time they have identified weaknesses in the bacterial armor," says senior author Vincent A. Fischetti, professor and head of the Laboratory of Bacterial Pathogenesis and Immunology. "We're taking advantage of what phage have 'learned' during this period for us to identify new antibiotic targets that we believe will escape the problem of resistance found for other antibiotics."

The path to identification of this new target spanned more than seven years of effort. Fischetti and his colleagues used a phage-encoded

molecule to identify a bacterial target enzyme called 2-epimerase, which is used by *Bacillus anthracis* to synthesize an essential cell wall structure. In 2008, Fischetti's lab, with Rockefeller's Erec Stebbins and his colleagues in the Laboratory of Structural Microbiology, solved the crystal structure of this enzyme. Based on this work, the researchers identified a previously unknown regulatory mechanism in 2-epimerase that involves direct interaction between one substrate molecule in the enzyme's active site and another in the enzyme's allosteric site. Fischetti and his colleagues chose to target the allosteric site of 2-epimerase to develop inhibitory compounds, because it is found in other bacterial 2-epimerases but not in the human equivalent of the enzyme.

Through the collaboration with Astex, an inhibitor of 2-epimerase named Epimerox was developed. Raymond Schuch, a former postdoctoral researcher in Fischetti's lab, tested the inhibitor in mice infected with *Bacillus anthracis*. He found that not only did Epimerox protect the animals from anthrax, but the bacteria did not develop resistance to the inhibitor. The researchers also found that Epimerox was able to kill methicillin-resistant *Staphylococcus aureus* (or MRSA) with no evidence of resistance even after extensive testing. Their work was published this week in *PLOS One*.

"Since nearly all Gram-positive bacteria contain 2-epimerase, we believe that Epimerox should be an effective broad-range antibiotic agent," says Fischetti. "The long-term evolutionary interaction between phage and bacteria has allowed us to identify targets that bacteria cannot easily change or circumvent. That finding gives us confidence that the probability for developing resistance to Epimerox is rather low, thereby enabling treatment of infections caused by multi-drug-resistant bacteria such as MRSA. It is a very encouraging result at a time when antibiotic resistance is a major health concern."