Newly engineered enzyme is a powerful staph antibiotic

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(PhysOrg.com) -- In the past decade, methicillin-resistant Staphylococcus aureus, or MRSA, has ushered in a new era in the fight between man and bug. By harnessing the power of nature's own antibiotics, scientists have engineered an enzyme known as a lysin that not only kills MRSA in mice but also works synergistically with antibiotics that were once powerless against the formidable organism.

With their best chemical antibiotics slowly failing, scientists are increasingly looking to nature for a way to control deadly staph bacteria — the culprit behind most hospital infections. Naturally toxic for bacteria, enzymes called lysins have the promising ability to obliterate staph, but the problem is producing large enough quantities of them to study how they work. Rockefeller University scientists have now overcome this barrier by engineering a lysin that not only kills multidrug-resistant Staphylococcus aureus (MRSA) in mice, but also works synergistically with traditional antibiotics that have long been shelved due to resistance.

For the past five years, Vincent A. Fischetti, head of the Laboratory of Bacterial Pathogenesis and Immunology, and his colleagues have tried to clone a lysin that specifically targets staph, but they always ran into the same problem. Although hundreds of thousands of lysins could be expressed in an engineered cell, they all would stick together forming an insoluble clump, rendering them inactive. "They were useless; a real thorn in our side," says Fischetti. "We've come across some problems cloning lysins for other bacteria, such as strep, but nothing to this

extent."

Lysins, proteins derived from the viruses that have been infecting bacteria for billions of years, have two basic components. One acts as a recognition system to identify the specific bacteria species it has evolved to target; the other works like a molecular power drill that bores holes through the bacterium's cell wall, killing the organism. Together, these two components work so quickly and so efficiently that bacteria have no time to develop resistance.

To develop a functional lysin, Fischetti's team, including Anu Daniel and Chad Euler, a former postdoc and a senior graduate fellow in the lab, respectively, took advantage of the modular nature of lysins. In a series of progressive and logical steps, the team mixed and matched the two segments from 20 to 25 different staph-specific lysins until they created a chimera that, when expressed in sufficient numbers, didn't stick together. They then tested the chimeric lysin — named chimeric lysin for staphylococci, or ClyS — to see if it would behave like one that had evolved in nature.

"It's as if this chimeric lysin evolved on its own," says Fischetti. "It resists neutralization by antibodies that treat it as a foreign invader and it is highly, highly effective."

By combining nature's forces with technological power, Fischetti and his team have not only come up with an alternative way to defeat MRSA but have potentially breathed new life into drugs that are no longer effective against the organism. Used alone, ClyS is able to kill all staph species, including strains of MRSA, in both culture and in mice. But the researchers also found that when using ClyS together with the antibiotic oxacillin (an antibiotic to which MRSA is resistant), the synergistic effect allowed them to administer both in very low doses, allowing a previously shelved and inexpensive antibiotic to be used again.

“This work came out of sheer persistence and hard, tedious work,” says Fischetti. “But it also speaks to the power of nature and technology working together to help us win this battle of antibiotic resistance.”

More information: Antimicrobial Agents and Chemotherapy online: January 19, 2010. Synergism between a novel chimeric lysin and oxacillin protects against infection by methicillin-resistant Staphylococcus aureus, Anu Daniel, Chad Euler, Mattias Collin, Peter Chahales, Kenneth Gorelick and Vincent A. Fischetti

Provided by Rockefeller University