New approach may render disease-causing staph harmless

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Researchers at the University of Illinois helped lead a collaborative effort to uncover a completely new treatment strategy for serious Staphylococcus aureus ("Staph") infections. The research, published Feb. 14 in *Science Express* comes at a time when strains of antibiotic-resistant Staph (known as MRSA, for methicillin-resistant S. aureus) are spreading in epidemic proportions in hospital and community settings.

Among the deadliest of all disease-causing organisms, Staph is the leading cause of human infections in the skin, soft tissues, bones, joints and bloodstream, and drug-resistant Staph infections are a growing threat. By federal estimates, more than 94,000 people develop serious MRSA infections and about 19,000 people die from MRSA in the U.S. every year. MRSA is believed to cause more deaths in the U.S. than HIV/AIDS.

The multi-institutional team exploited a chemical pathway that allows the Staph bacterium to defend itself against an immune response. The researchers showed that a compound (BPH-652) originally designed to lower cholesterol blocks a key enzyme in that pathway, weakening the organism's defenses and allowing the body's immune cells to prevail against the infection.

A golden-colored pigment called a carotenoid gives the S. aureus bacterium its edge. "Aureus" is Latin for "golden." The carotenoid acts as an antioxidant for the bacterium, allowing it to evade attack by the body's immune cells. By crippling production of the carotenoid, the

compound strips Staph of one of its key defenses.

The new research builds on a recent discovery by scientists at the University of California, San Diego. The UCSD team, led by Dr. Victor Nizet, a professor of pediatrics and pharmacy, showed that knocking out a gene for an enzyme in the chemical pathway that produced the Staph carotenoid reduced its virulence.

When he read about this finding, University of Illinois chemistry professor Eric Oldfield realized that the chemical precursors of the Staph carotenoid were identical to those that led to production of cholesterol in humans. Oldfield, who is the senior author of the paper, had spent decades exploring this pathway, which has implications for the treatment of some cancers, as well as fungal and parasitic diseases. He noted that an enzyme in the human pathway, squalene synthase, was strikingly similar to one that led to the production of the carotenoid in Staph. He also knew that many compounds already had been developed to block the human enzyme.

“I thought there was a good chance that squalene synthase inhibitors developed early on as cholesterol lowering agents might also work on this other pathway,” he said. “Current cholesterol-lowering drugs like statins work in a completely different way and would be ineffective.”

The researchers began by testing dozens of new compounds for their activity against the Staph enzyme. This allowed them to narrow the field of potential candidates to eight. When they tested these drugs on Staph cells, they found that BPH-652 was the most effective at getting into the cells. A tiny dose impaired the cells’ ability to produce the carotenoid. The cells, once golden, turned white.

“We have found that the same golden armor used by Staph to thwart our immune system can also be its Achilles’ heel,” said Nizet, a study co-

author, who is affiliated with the Skaggs School of Pharmacy and Pharmaceutical Sciences at UCSD.

Preliminary studies were conducted in the laboratories of Nizet and Dr. George Liu, a professor of pediatrics at Cedar-Sinai Medical Center. Exposure to BPH-652 also markedly reduced bacterial levels in a mouse model of severe Staph infection.

The key to the compound's success is that the human and bacterial enzymes it targets are so similar. Andrew Wang and his colleagues at Academia Sinica and the National Taiwan University, both in Taipei, used X-ray crystallography to determine the structure of the enzyme and how it interacts with the inhibitors.

"Our structural studies pinpointed how these drug candidates bound to the bacterial enzyme to shut off pigment production," Wang said.

The new findings are particularly promising because BPH-652 already has been used (as a cholesterol-lowering agent) in human clinical trials, reducing the cost and time for development.

"This research is an excellent example of how discoveries at the lab bench can lead to clinical advances," said Dr. Elias A. Zerhouni, the director of the National Institutes of Health, which supported the research. "By following their scientific instinct about a basic biological process, the researchers found a promising new strategy that could help us control a very timely and medically important health concern."

Source: University of Illinois at Urbana-Champaign