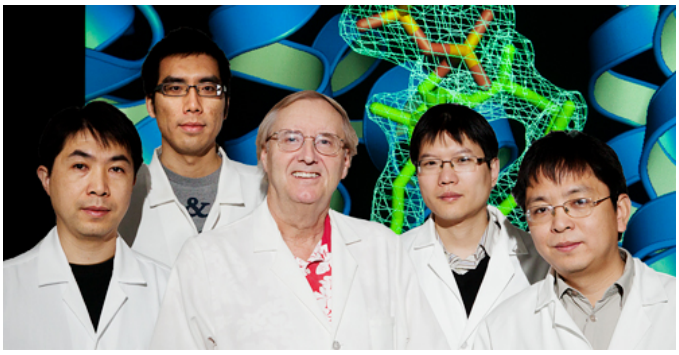
Chemists document workings of key staph enzyme – and how to block it



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L. Brian Stauffer

Chemists led by Illinois professor Eric Oldfield, center, determined the structure of a key enzyme that could lead to more efficient drugs to treat staph infections, parasites and high cholesterol. The research team, from left, research scientist Yonghui Zhang, graduate student Fu-Yang Lin, research scientist Rong Cao and postdoctoral associate Ke Wang.

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CHAMPAIGN, Ill. — Researchers have determined the structure and mechanism of an enzyme that performs the crucial first step in the formation of cholesterol and a key virulence factor in staph bacteria.

Chemists at the University of Illinois and collaborators in Taiwan studied a type of enzyme found in humans, plants, fungi, parasites, and many bacteria that begins the synthesis of triterpenes – one of the most abundant and most ancient classes of molecules. Triterpenes are precursors to steroids such as cholesterol.

“These enzymes are important drug targets,” said chemistry professor Eric Oldfield, who co-led the study. “Blocking their activity can lead to new cholesterol-lowering drugs, antibiotics that cure staph infections, and drugs that target the parasites that cause tropical maladies such as Chagas disease – a leading cause of sudden death in Latin America.”

For the study, the team picked a representative enzyme, dehydrosqualene synthase (CrtM), from the *Staphylococcus aureus* bacterium. Staph is one of the most common, yet notoriously hard to kill, bacterial infections. A key reason for staph’s resilience is a golden-colored coating called staphyloxanthin that protects it from the body’s immune system. CrtM catalyzes the first reaction in making staphyloxanthin, so inhibiting it would strip the bacteria of their protective coats and leave them vulnerable to attack by white blood cells.

The researchers already knew what CrtM looked like and its end product, but they didn’t know how the enzyme did its job. Uncovering the mechanism of action would enable scientists to design better inhibitors, and even tailor them to other targets.

The team crystallized the enzyme and soaked it with intermediates and inhibitors. They then studied the complex structures by X-ray crystallography using the synchrotron at the Advanced Photon Source at Argonne National

Laboratory.

They found that CrtM performs a two-step reaction, individually removing two diphosphate groups from the substrate. The substrate switches between two active sites within the enzyme as the reaction progresses. The most effective inhibitors bind to both sites, blocking the enzyme from any action.

“The leads that people have been developing for treating these diseases really haven’t had any structural basis,” said Oldfield, also a professor of biophysics. “But now that we can see how the protein works, we’re in a much better position to design molecules that will be much more effective against staph infections and parasitic diseases, and potentially, in cholesterol-lowering.”

The researchers’ inhibitor technologies have been licensed to AuricX Pharmaceuticals, which recently received a grant from the Texas Emerging Technology Fund for preclinical testing in staph infections.

The team published its work in the Proceedings of the National Academy of Sciences. The work was sponsored by the National Institutes of Health and the National Science Council. Co-authors were U. of I. graduate students Fu-Yang Lin and Yi-Liang Liu, research scientists Rong Cao and Yonghui Zhang, and postdoctoral associate Ke Wang. Taiwan collaborators included Chia-I Liu, Wen-Yih Jeng, Tzu-Ping Ko and Andrew H. Wang.

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The paper, “Mechanism of Action and Inhibition of Dehydrosqualene Synthase,” is available online.

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