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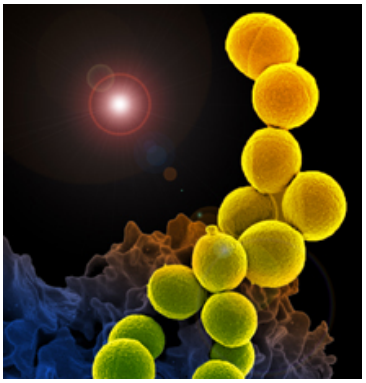
New Drug Effective Against MRSA in Mice

Scientists identified an effective new drug for mice with methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterial infection that is very hard to treat. The findings may lead to new antibiotics for people infected with the resistant bacteria.



Surface of a white blood cell fighting MRSA. Credit: Frank DeLeo, NIAID.

Antibiotic resistance is a growing public health problem. Many diseases, including tuberculosis, gonorrhea and *S. aureus* ("Staph"), have become difficult to treat because the microbes responsible have evolved resistance to the drugs used to treat them. Decades of widespread use have encouraged the spread of bacteria with resistance to multiple antibiotics. Recent data from the U.S. Centers for Disease Control and Prevention suggest that antibiotic resistance costs the nation an estimated $20 billion a year in excess health care costs.

Many antibiotics used for treating infections, including penicillin and methicillin, are designed to target late stages of bacterial cell wall synthesis. Cell walls are essential to bacterial survival, but the structures don't exist in humans. An enzyme called undecaprenyl diphosphate synthase (UPPS) is needed for early-stage cell wall synthesis. Since UPPS isn't produced by humans, it's a potential target for drug development. Earlier studies had already identified some compounds that inhibit UPPS.

A team led by Dr. Eric Oldfield of the University of Illinois at Urbana-Champaign and Andrew McCammon of the University of California, San Diego, set out to build on the previous work to develop UPPS inhibitors that could potentially be used as new antibacterial drugs. The study was partly funded by NIH's National Institute of Allergy and Infectious Diseases (NIAID), National Institute of General Medical Sciences (NIGMS) and National Cancer Institute (NCI). It appeared on January 2, 2013, in *Proceedings of the National Academy of Sciences*.

The researchers used computer screening programs to identify diverse compounds with activity against UPPS. They then used X-ray crystallography to analyze the 3-D structures of the compounds bound to the enzyme. The researchers found that the 10 identified compounds bound to at least 1 of 4 previously identified UPPS binding sites. The strongest of the inhibitors, they discovered, bound to a site that is surprisingly outside the region responsible for the enzyme's activity.

The researchers confirmed in laboratory cultures that the strongest inhibitors were active against both *E. coli* and a strain of MRSA. One of the most potent compounds also increased the effectiveness of methicillin against a MRSA strain. The scientists next tested this compound on mice infected with MRSA.

"Twenty out of 20 animals survived if they were treated with this drug lead, and zero survived if they weren't treated," Oldfield says.

his research may pave the way for more effective antibacterial drugs. Additional studies will be needed to know whether these inhibitors or others like them can be used to treat people with resistant infections.

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