Researchers Find New Way to Attack a Dangerous TB Strain

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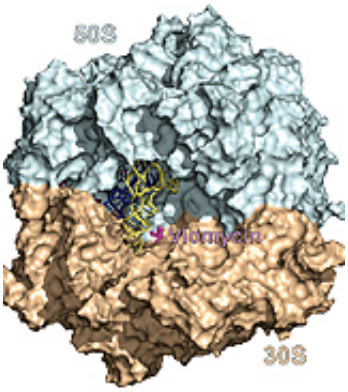

Antibiotic viomycin binds to TB ribosome, inhibiting the ability of the bacteria to function.

(PhysOrg.com) -- A Yale research team led by Nobel laureate Thomas A. Steitz has discovered how a family of tuberculosis-fighting antibiotics combats the deadly disease, a finding that may lead to new ways to combat a dangerous emerging drug-resistant form of TB.

The findings are reported online Feb. 14 in the journal Nature Structural and Molecular Biology.

Approximately 9 million new cases of tuberculosis are diagnosed every year, and the disease killed 2 million people in 2007 alone, according to the World Health Organization. Public health officials are particularly

concerned about the emergence of extensively drug-resistant tuberculosis , which does not respond to commonly used antibiotics.

“There is a concern this could spread worldwide,” Steitz said.

Over half of antibiotics work by inhibiting the function of ribosomes, the cellular protein-making machinery within bacterium such as Mycobacterium tuberculosis. Steitz, the Sterling Professor of Molecular Biophysics and Biochemistry and professor of chemistry at Yale, was awarded the 2009 Nobel Prize in Chemistry for his work describing the structure and function of the large ribosomes. He is also an investigator for the Howard Hughes Medical Institute.

The Yale team hopes that by finding exactly how current antibiotics block activity within the TB ribosome, scientists could design new drugs to combat resistant forms of the disease. Using technology called X-ray crystallography, Steitzand his team describe where the antibiotics viomycin and capreomycin bind - at a site between the large and small subunits of the ribosome. They note this binding spot is close to two sites where two other families of antibiotics interact with the ribosome.

Knowing this structure, it may be possible to design an antibiotic that would block actions of currently drug resistant forms of tuberculosis and other infections, said Susan Froshauer, president and CEO of Rib-X Pharmaceuticals Inc., a New Haven-based biotechnology company.

The company has already used the knowledge of ribosome structure developed by Steitz, a scientific co-founder of Rib-X, and other scientists to develop a new generation of antibiotics to treat such infections as methicillin-resistant Staphylococcus aureus (MRSA). The company has four new antibiotics under development, two of which are in clinical trials.

The research was funded by the National Institutes of Health, HHMI and the Agouron Institute.

Other Yale authors of the paper include Gregor Blaha, Robert L. Grodzicki and Michael D. Strickler. Lead authors are Blaha and Robin E. Stanley, formerly of Yale and now with the National Institute of Diabetes and Digestive and Kidney Diseases.

Provided by Yale University