Researcher discovers new 'anti-pathogenic' drugs to treat MRSA

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Menachem Shoham, PhD, associate professor and researcher in the department of biochemistry at the Case Western Reserve University School of Medicine, has identified new anti-pathogenic drugs that, without killing the bacteria, render Methicillin Resistant Staphylococcus Aureus (MRSA) harmless by preventing the production of toxins that cause disease.

Infections of MRSA are a growing public health problem causing 20,000 deaths per year in the U.S. alone. MRSA is the most prevalent bacterial pathogen in hospital settings and in the community at large. The problem has become increasingly severe due to the fact that the bacteria develop resistance to antibiotics. Currently, there are only two antibiotics available to treat MRSA (vancomycin and linezolid) and strains are emerging that are resistant even to these two remaining antibiotics. As result, healthcare providers are running out of options to treat patients suffering from antibiotic-resistant infections, creating a dire need for alternative treatments and approaches.

"Staph bacteria are ubiquitous and normally do not cause infections, however, occasionally these bacteria become harmful due to their secretion of toxins," said Dr. Shoham. "We have discovered potential "anti-pathogenic" drugs that block the production of toxins, thus rendering the bacteria harmless. Contrary to antibiotics, these new anti-pathogenic drugs do not kill the bacteria. And since the survival of the bacteria is not threatened by this approach, the development of resistance, like that to antibiotics, is not anticipated to be a serious

problem."

Dr. Shoham identified a bacterial protein, known as AgrA, as the key molecule responsible for the release of toxins. AgrA, however, needs to be activated to induce toxin production. His goal was to block the activation of AgrA with a drug, thus preventing the cascade of toxin release into the blood that can lead to serious infections throughout the body.

The screening for AgrA inhibitors was initially carried out in a computer by docking a library of 90,000 compounds and finding out which compounds would fit best into the activation site on AgrA. Subsequently, about one hundred of the best scoring compounds were acquired and tested in the laboratory for inhibition of the production of a toxin that ruptures red blood cells.

Seven of these compounds were found to be active. Testing compounds bearing chemical similarity to the original compounds lead to the discovery of additional and more potent compounds.

More than a dozen active compounds have been discovered by this method. The best drug candidate reduces red blood cell rupture to 12% of the value without the drug at a concentration of 10 μg/mL, without affecting bacterial growth..

"It is possible to inhibit virulence of MRSA without killing the bacteria," continued Dr. Shoham. "Such anti-pathogenic drugs may be used for prophylaxis or therapy by themselves or in combination with an antibiotic."

This research was carried out in the laboratory of Dr. Menachem Shoham in the Department of Biochemistry at the Case Western Reserve University School of Medicine in Cleveland, Ohio. Funding was

provided by grants from the Steris Corporation and from the American Heart Association.

The results were presented at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston Conference Center earlier this week.

Provided by Case Western Reserve University