MedicalXpress

Novel non-antibiotic agents against MRSA and common strep infections

September 12 2012

Menachem Shoham, PhD, associate professor of biochemistry at Case Western Reserve University School of Medicine, has discovered novel antivirulence drugs that, without killing the bacteria, render Methicillin Resistant *Staphylococcus Aureus* (MRSA) and *Streptococcus pyogenes*, commonly referred to as strep, harmless by preventing the production of toxins that cause disease. The promising discovery was presented this week at the Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco.

MRSA infections are a growing public health concern, causing 20,000 to 40,000 deaths per year in the United States alone. It is the most prevalent bacterial pathogen in hospital settings and in the community at large, with about one million documented infections per year nationally, costing an estimated $8 billion annually to treat.

The problem has become increasingly severe as the bacteria have developed a resistance to antibiotics. As result, health care providers are running out of options to treat patients suffering from antibiotic-resistant infections, like MRSA and strep, 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," says Dr. Shoham. "We have discovered potential antivirulence drugs that block the production of toxins, thus rendering the bacteria harmless. Contrary to antibiotics, these new antivirulence

drugs do not kill the bacteria. 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 turning on 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 libraries of many thousands of "drug-like" compounds and finding out which compounds would fit best into the activation site on AgrA. Subsequently, about 100 of the best scoring compounds were 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 so-called "lead" compounds.

Optimization of the initial "lead" compounds was performed by chemical synthesis of 250 new compounds bearing small but important chemical modifications on one of the initial leads. More than a dozen active compounds have been discovered by this method. The best drug candidate reduces red blood cell rupture by 95 percent without affecting bacterial growth.

Beginning this fall, Dr. Shoham and colleagues will begin testing the drug candidate in animal models.

"It is possible to inhibit virulence of MRSA without killing the bacteria," continues Dr. Shoham. "Such antivirulence drugs may be used for

prophylaxis or therapy by themselves or in combination with an antibiotic. Antivirulence therapy may resensitize bacteria to antibiotics that have become ineffective by themselves."

Provided by Case Western Reserve University