A small molecule outclasses larger ones in combating drug-resistant bacteria that cause skin infections

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Electron micrograph of Methicillin-resistant Staphylococcus aureus (MRSA), which is becoming increasingly difficult to treat due to increased drug resistance. A*STAR researchers have designed a small molecule containing four amino acids that is effective in killing such bacteria quickly and efficiently. Credit: A*STAR Experimental Therapeutics Centre and IMB-IMCB Joint Electron Microscopy Suite

A promising drug candidate to address the growing problem of antibiotic-resistant skin infections has been discovered by A*STAR researchers.

Bacteria known as Methicillin-resistant Staphylococcus aureus (MRSA) (see image) is the primary cause of human skin infections and is now
endemic in many hospitals worldwide. Such infections are becoming harder to treat because an increasing number of MRSA strains are becoming resistant to standard antibiotics. Besides causing painful and unsightly skin conditions, MRSA infections can lead to more severe complications, such as surgical wound and catheter-related infections, blood poisoning, bone infections and pneumonia.

The arsenal available to fight the disease is rapidly shrinking for two reasons. Firstly, standard antibiotics have become less effective as the bacteria develop resistance to them and secondly, pharmaceutical companies are reluctant to invest in the costly search for new antibiotics due to the perceived low profitability in this research area.

Brian Chia of the A*STAR Experimental Therapeutics Centre and his co-workers have now designed and synthesized a new potential weapon in the battle against MRSA — a very short antimicrobial peptide.

Peptides are organic polymers made up of amino acid building blocks linked in a chain by peptide bonds. By designing peptides with specific amino acid sequences, researchers can tune peptides to target and disrupt bacterial membranes. Because antimicrobial peptides quickly disrupt bacterial membranes, bacteria have little time to mutate and develop drug resistance.

A major hurdle in developing antimicrobial peptides as drugs is that their relatively large molecular sizes make them expensive to manufacture on a large scale. The team solved this problem by designing an ultra-short peptide that consists of only four amino acids. In contrast, the shortest antimicrobial peptide currently in clinical trials, Omiganan, consists of 12 amino acids.

The researchers compared the MRSA-killing ability of their antimicrobial peptide with other antimicrobial peptide clinical
candidates as well as anti MRSA antibiotics currently prescribed by doctors.

The results were highly encouraging. "Our antimicrobial peptide far exceeded our initial expectations," says Chia. "Our four-residue peptide has an anti MRSA potency on par with that of the current shortest antimicrobial peptide — but it is three times shorter. Plus, because it consists of only two types of amino acids, drug manufacturing cost and time should be drastically reduced."

The team is currently working on formulating the antimicrobial peptide into a topical gel for pre-clinical studies.


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