Research could put penicillin back in battle against antibiotic resistant bugs that kill millions

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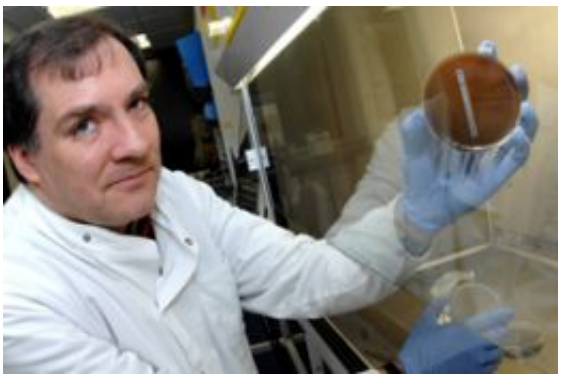

Dr Adrian Lloyd

Research led by the University of Warwick has uncovered exactly how the bacterium Streptococcus pneumoniae has become resistant to the antibiotic penicillin. The same research could also open up MRSA to attack by penicillin and help create a library of designer antibiotics to use against a range of other dangerous bacteria.

Worldwide Streptococcus pneumoniae causes 5 million fatal pneumonia infections a year in children. In the US it causes 1 million cases a year of pneumococcal pneumonia in the elderly of which up to 7% are fatal. This new research has completely exposed how Streptococcus pneumoniae builds its penicillin immunity and opens up many ways to

disrupt that mechanism and restore penicillin as a weapon against these bacteria.

The research was led by Dr Adrian Lloyd of the University of Warwick's Department of Biological Sciences along with other colleagues from the University of Warwick, the Université Laval, Ste-Foy in Quebec, and The Rockefeller University in New York. The research was funded by Welcome Trust and the MRC.

Penicillin normally acts by preventing the construction of an essential component of the bacterial cell wall: the Peptidoglycan. This component provides a protective mesh around the otherwise fragile bacterial cell, providing the mechanical support and stability required for the integrity and viability of cells of Streptococcus pneumoniae and other bacteria including MRSA.

The researchers targeted a protein called MurM that is essential for clinically observed penicillin resistance and has also been linked to changes in the chemical make up of the peptidoglycan that appear in penicillin resistant Streptococcus pneumoniae isolated from patients with pneumococcal infections.

The researchers found that MurM acted as an enzyme that was key to the formation of particular structures within the S. pneumoniae peptidoglycan called dipeptide bridges that link together strands of the peptidoglycan mesh that contributes to the bacterial cell wall. The presence of high levels of these dipeptide bridges in the peptidoglycan of Streptococcus pneumoniae is a pre-requisite for high level penicillin resistance.

The Warwick team were able to replicate the activity of MurM in a test tube, allowing them to define the chemistry of the MurM reaction in detail and understand every key step of how Streptococcus pneumoniae

deploys MurM to gain this resistance.

The results will allow the Warwick team, and any interested pharmaceutical researchers, to target the MurM reaction in Streptococcus pneumoniae in a way which will lead to the development of drugs which will disrupt the resistance of Streptococcus pneumoniae to penicillin.

The same research also offers exciting possibilities to disrupt the antibiotic resistance of MRSA which uses similarly constructed peptide bridges in the construction of the peptidoglycan component of its cell wall. Therefore, thanks to this research, even MRSA could now be opened up to treatment by penicillin.

A further spin-off from this new MurM research, is that the Warwick led researchers are also able to readily reproduce every precursor step the bacterial cell uses to create its peptidoglycan. The tools developed at Warwick open up each step of the creation of the peptidoglycan (MurA, MurB, MurC etc, etc) used by an array of dangerous bacteria. This provides a valuable collection of targets for pharmaceutical companies seeking ways of disrupting antibiotic resistance in such bacteria.

Source: University of Warwick