Image of new antibiotic in action opens up new opportunities to combat antibacterial resistance

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Detailed pictures published today reveal how a new type of experimental antibiotic can kill bacteria that are already resistant to existing treatments. The findings could ultimately help scientists to develop new antibiotics to tackle the bacteria responsible for many hospital and community-acquired infections.

Using an imaging technique called x-ray crystallography, a team of researchers from GlaxoSmithKline (GSK) captured a snapshot of the new compound latched on to the enzyme topoisomerase. This enzyme is part of the bacteria's internal machinery and helps the bacteria produce proteins and replicate. Stopping this enzyme prevents the bacteria from reproducing. Medicines, known as the quinolones, that target the enzyme have been used successfully as antibiotics since 1962, however bacteria are increasingly developing resistance to this class of drugs.

By looking at x-ray images, the team have demonstrated that the new investigational medicine attaches to the enzyme in a different place to the quinolones, enabling it to stop the same bacteria that are resistant to these older treatments. The research is published today in the journal *Nature*, and is the result of two unique collaborations between GSK and the Wellcome Trust's Seeding Drug Discovery initiative and the U.S. Defense Threat Reduction Agency (DTRA).

"We already knew that targeting this enzyme was clinically proven to

stop bacteria in their tracks, we just needed to be a bit more inventive in how we attacked it," said Michael Gwynn, from GSK's Infectious Diseases research group. "These images and the data showing the efficacy of this compound against a range of bacteria validate our approach, demonstrating that the enzyme can still be blocked even in bacteria already resistant to other antibiotics that work against this same enzyme."

The study also reports the potency of the new compound, called GSK 299423, against antibiotic-resistant strains of bacteria such as Staphylococus aureus, including methicillin resistance S. aureus (MRSA), and against gram negative bacteria like E. coli, Pseudomonas, Klebsiella and Acinetobacter. Gram-negative bacteria are particularly difficult to attack as they have an outer membrane surrounding the bacterial cell wall which interferes with drug penetration. New medicines must not only be toxic to the pathogen, but must first overcome the barriers to entry into the cell.

Commenting on the importance of the findings, Ted Bianco of the Wellcome Trust said: "This is an important step forward in the race against antibiotic resistance. By solving the new structure of this important bacterial enzyme, and understanding how these drugs work, the team has opened the door for targeted drug design of new antibiotics, which are urgently needed."

The particular compound from this study is one of a group that is currently being worked on in order to develop the best compounds in terms of efficacy and safety. This should help identify drug candidates that could be taken forward into early stage trials in humans.

Development of the new drug class to tackle gram-negative infections is supported as part of the Trust's Seeding Drug Discovery initiative. The collaboration provides GSK with a £4 million award from the Trust with

GSK matching the contribution in staff, equipment, and other programme costs. The research collaborations with the Trust and with DTRA are aimed at developing an entirely new class of antibacterials to tackle hospital-acquired infections and potential bio-threat outbreaks.

"The Wellcome Trust has recently announced a five-year extension to the Seeding Drug Discovery initiative, enabling us to continue to support drug development in areas of unmet medical need," added Rick Davis, Business Development Manager at the Wellcome Trust.

More information: Bax B, Chan P, Eggleston D et al. Type lla topoisomerase inhibition by a new class of antibacterial agents. Nature, 2010 [Epub ahead of print].

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