Scientists target 'molecular machine' in the war against antimicrobial resistance

Annie Slinn reports on interesting research targeting bacteria to address antimicrobial resistance.

Scientists have studied a new target for antibiotics in the greatest detail yet – in the fight against antibiotic resistance.

The 'molecular machine' flagellum is essential for bacteria to cause infection, allowing bacteria to 'swim' around the bloodstream until finding something to infect. But it could also be a target for antibiotics.

Impairing the flagellum would deliver a critical, but not fatal, blow to bacteria. This is a new approach and contrasts to traditional antibiotics, which are designed to kill all bacteria in their path.

Keeping bacteria alive could help to tackle, or at least significantly slow down the rate of antibiotic resistance. This is because there is less pressure for the bacteria to adapt and develop resistance to survive.

To develop this new approach, scientists first need to understand the enemy. Answering the call, researchers at King's College London, have now studied the flagellum in its greatest detail to date.

The new study, published in Nature Microbiology today, addresses one of the most significant challenges to modern healthcare, antibiotic resistance. Drug-resistant infections are expected to claim more than 39 million lives between now and 2050 without further policy action, according to the Global Research on Antimicrobial Resistance Project.

Molecular structure of the bacterial flagellum – a new target in the war against antimicrobial resistance

Lead author Dr Julien Bergeron, King's College London, said: "The flagellum is perhaps the most studied cellular machine, acting as a propeller, through the rotation of a long filament. It is also a major reason why bacteria cause disease; flagella give bacteria a competitive edge at causing disease and the presence of this molecule alone contributes to more than 100,000s deaths annually.

"We knew how important it was to study this 'molecular machine', as we investigate it as a potential target in our quest to neutralise the threat of bacteria.

"The bacterial flagellum has long fascinated scientists and the wider public alike. Yet, despite being extensively studied for over 70 years, the molecular details of its architecture have so far eluded researchers. This is because we simply haven't had the tools."

Dr Bergeron and his team used a state-of-the-art type of technique called cryo-electron microscopy – which reveals images of cells at an atomic level in impressive molecular detail. This enabled the team to understand how the flagellum forms, identifying areas to target with drugs. They had access to one of the most powerful electron microscopes, based at the Francis Crick Institute, available for scientists tackling some of the biggest challenges in healthcare – from antibiotic resistance to cancer.

Dr Bergeron explained: "In this study, we have used the world's most advanced electron microscope to reveal the complete architecture of the bacterial flagellum, down to atomic levels of details. This unearthed unexpected intricacies in its structure. Critically, we were able to visualise the individual steps involved in the assembly of the flagellum, a process that until now had largely remained unexplained."

Co-author Professor Marc Erhardt, from the Max Planck Unit for the Science of Pathogens and the Humboldt-Universität zu Berlin, Germany, also developed a vital 'genetic trick', enabling scientists to study a very short section of flagella in great detail. He said: "It was an extraordinary experience to capture snapshots of the flagellum forming that had previously remained hidden. Observing how individual flagellin molecules are folded and inserted into the growing filament was like decoding a molecular ballet."

Further research is needed to fully understand how the flagellum forms, for example what triggers the initial process of its development. Scientists believe, however, it could be a key target to stop infections without driving resistance.

Dr Bergeron added: "This study will undoubtedly open new avenues towards the development of new treatments for bacterial infections. With the right funding and support this could become reality within a couple of years. However, realistically I think it would be more like a decade and we would need support from industry to help us in this fight against antimicrobial resistance."

Read the study: https://www.biorxiv.org/content/10.1101/2024.09.25.614892v1

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