Anti-infectives to combat antibiotic resistance

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Pharmaceuticals

Problem

With antibiotic-resistant "superbugs" projected to cause approximately 40 million deaths over the next 25 years, the healthcare industry faces a dire need for innovative solutions. This resistance is driving up global healthcare costs, which could reach over US$1 trillion annually by 2050, as well as other economic areas such as livestock production. The escalating crisis underscores the urgency for novel interventions that can effectively address this growing public health threat.

The highest proportion of the threat comes from Gram-negative bacteria, which are inherently resistant due to their complex cell envelope that impedes the entry of antibiotic drugs. Current antibiotics primarily target intracellular processes and struggle to penetrate the double-membrane structure of Gram-negative bacteria. This limitation, combined with the bacteria's ability to eject antibiotics through efflux pumps, results in ineffective treatments and contributes to the rise in antibiotic-resistant strains.

Solution

Our research has identified the Two-Partner Secretion (TPS) systems as critical therapeutic targets that are druggable and found on all relevant Gram-negative pathogens. These systems are conserved and essential for most Gram-negative bacteria to establish infection and cause disease. TPS systems are also are surface-exposed, making them accessible to inhibitors that do not need to cross the bacterial envelope. By inhibiting TPS systems, we can disarm the bacteria without killing them, potentially reducing the emergence of resistance, and extending the drugs' clinical lifespan on the market.

We've designed potent inhibitors targeting components of the TPS system. *In vitro* studies have shown that our inhibitors bind to their target resulting in inhibition of secretion of tested virulence factors.

This innovative approach offers a unique opportunity to develop a new class of anti-infectives. This novel therapeutic strategy is less likely to disrupt the beneficial microbiome and, therefore, may have fewer side effects compared to traditional antibiotics. We have determined that that the inhibitors are active against *Bordetella* species that infect mammals including, the causative agent of Whooping Cough, preventing the release of an essential adhesin and an essential immune avoidance toxin. Due to conserved target structures, the potential is high for these inhibitors to be designed as pan-species virulence inhibitors. Our findings suggest that these inhibitors can serve as a foundation for the development of next-generation therapeutics.

Beside human health, the inhibitors may also be useful in agriculture because pathogenic bacteria that infect livestock and staple crops produce TPS systems that can be targeted with this approach.

Intellectual Property Status

This invention is the subject of a PCT patent application, PCT/AU2025/050953.

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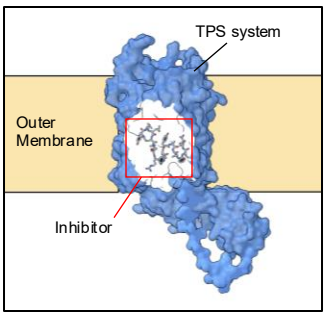

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