PACE Award Profile: Ineos Oxford Institute

Optimising a new class of broad-spectrum cell-wall transpeptidase inhibitors

Project title: Next generation, broad spectrum cell wall targeting antibiotics

The development of penicillin was a world-changing advance for medicine. Ever since then, the penicillins and related β-lactam-containing antibiotics have been a mainstay of treatment strategies for bacterial infection. β-lactam antibiotics inhibit a family of enzymes, the cell-wall transpeptidases, that are crucial to bacterial survival. The β-lactam ring has been considered vital to the mode of action of the penicillins, but it is also their Achilles heel. Over time, bacteria have evolved serine and metallo-β-lactamase enzymes that can degrade the lactam ring, causing worrying levels of antimicrobial resistance globally.

The Ineos Oxford Institute for antimicrobial research (IOI) is tackling this challenge by developing a new class of small-molecule transpeptidase inhibitor that does not contain a β-lactam unit. Assays with isolated enzymes and extensive microbiological studies have already shown that these new inhibitors are not degraded by many β-lactamases, and that they have excellent activity against a broad spectrum of Gram-negative bacteria, including strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* currently found in clinical settings.

With funding and close collaborative support from PACE, the IOI will continue this research by optimising their novel series of transpeptidase inhibitors. As well as synthetic chemistry work, the project will involve studies into the underlying biochemistry and microbiology, in order to progress the inhibitors towards preclinical development and ultimately to clinical development.

If successful, the project could deliver a new class of antibiotics active against a very well-studied (and therefore attractive) bacterial enzyme. This would enable more effective treatment of serious bacterial infections – such as urinary tract infections that are becoming increasingly resistant to the β-lactams including the cephalosporins and the ‘last-resort’ carbapenems.