

ARREPATH

PACE Award Profile: ArrePath

Advancing small-molecule drug leads to inhibit a crucial enzyme in 'Enterobacterales' bacteria

Project title: Advancing a direct-acting, small molecule antibacterial with Gram negative specificity and a novel mechanism of action

Some of the most severe bacterial infections, especially in hospital settings, are caused by multi-drug resistance in the Gram-negative group of bacteria known as 'Enterobacterales', which includes *E. coli* and *Klebsiella pneumoniae*. ArrePath is tackling this challenge by using machine-learning approaches to find and optimise molecules with novel mechanisms of action against multi-drug-resistant pathogens. Using this platform, ArrePath identified a series of compounds that inhibit an essential enzyme that is highly conserved across Gram-negative bacteria and has never before been clinically exploited.

Currently, the lead program shows single-digit MIC values against multiple Enterobacterales strains, no *in vitro* cytotoxicity, and a favorable trajectory toward delivering an oral small molecule therapeutic. With funding and support from PACE, ArrePath aims to advance their project to the lead optimisation stage. They plan to do this by optimising the ADMET/pharmacokinetic properties of their inhibitors, demonstrating *in vivo* proof of concept for this novel target, and by broadening their spectrum by improving *in vitro* activity against additional members of the 'Enterobacterales' group.

Success for the project will mean delivery of an antibiotic that can treat some of the most serious multi-drug-resistant infections – specifically, complicated urinary tract infections, ventilator-associated bacterial pneumonia and bloodstream infections. In addition, if such an antibiotic is effective when administered orally as well as intravenously, that would help hospitalised patients switch to an easily-taken oral medicine when appropriate.