University of Sheffield

PACE Award Profile: University of Sheffield

Advancing small-molecule inhibitors of flap endonucleases in *Pseudomonas aeruginosa* for treatment of pneumonia

Project title: Towards new drugs for a novel target in *Pseudomonas aeruginosa*

The Gram-negative bacterium *Pseudomonas aeruginosa* is a leading cause of hospital-acquired pneumonia but has developed resistance to most antibiotics. The Sayers laboratory at the University of Sheffield aims to tackle this by targeting a family of enzymes called flap endonucleases (FENs) with essential roles in DNA replication, repair and recombination.

The team has already developed selective, highly potent, rapidly bactericidal FEN inhibitors active against bacteria in the genus *Neisseria*, with MICs of <0.5 µg/mL. Work has started on translating this experience to *P. aeruginosa*, with the results of an initial biochemical inhibitor screen providing small-molecule hits with IC_{50} values down to 380 nM. One of these was capable of killing *P. aeruginosa* cells and had an MIC of ~8 µg/mL.

With funding and support from PACE, the team will initiate a hit-to-lead program, aided by X-ray structural studies of FEN–inhibitor co-complexes and an already-established biochemical assay. The outcome should be the demonstration of a proof-of-concept for the efficacy of these compounds in a physiological model of infection. Given the existing work on *Neisseria*, the novel mode-of-action and rapid bactericidal activity, low resistance frequencies are expected.

Success in this project will result in delivery of a series of compounds that can be progressed towards the treatment of hospital- and ventilator-acquired pneumonia caused by *P. aeruginosa*, for which patients currently have limited treatment options. By targeting an essential component of the bacterial reproductive cycle, resistance is much less likely to develop, and the rapid action should improve cure rates and result in shorter treatment periods.