

PACE Award Profile: Justus-Liebig-University Giessen with Infex Therapeutics

Optimisation of a membrane-targeting bicyclic heptapeptide for treatment of KAPE infections

Project title: BamA inhibitors – Novel drugs against Gram-negative bacterial pathogens

New antibiotics are urgently needed against Gram-negative pathogens in the 'KAPE' group – *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*. A highly conserved chaperone-like protein, BamA (which is involved in the synthesis of essential outer membrane proteins) is an appealing target, which was considered undruggable by small molecules until recently.

However, the identification of Darobactin A, a natural product that selectively targets BamA, and the elucidation of the biosynthetic route to the bicyclic heptapeptide, has allowed the team at Justus-Liebig-University Giessen to make a number of modified lead compounds, which showed improved activity and successfully reduced bacterial loads of *K. pneumoniae* and *P. aeruginosa* in physiological models of lung infection. They have now teamed up with Infex Therapeutics, a clinical-stage anti-infectives development company, to accelerate the onwards development of the program.

The funding and support from PACE will allow the co-development team to continue these efforts. The primary objective will be optimisation of the lead structure using *in vitro* and *in vivo* profiling, with the aim of supporting nomination of a candidate for preclinical studies. The focus will be on developing a drug effective against complicated urinary tract infections, while also assessing efficacy against lower respiratory tract infections.

Success would result in a new class of antibiotics that target a range of multi-drug-resistant Gram-negative pathogens, and do not show cross-resistance to existing treatments. With the novel mode of action and favourable toxicity profile, such antibiotics should address unmet patient needs and be a highly effective option for treating life-threatening hospital-acquired infections.