PACE Award Profile: Oxford Drug Design

Developing a novel mode of action, bladder-targeted, small-molecule, for oral therapy of urinary tract infections

Project title: Leucyl-tRNA synthetase inhibitor for oral therapy of urinary tract infections

Urinary tract infections (UTIs) are the most common bacterial infection worldwide. By far the most numerous are the so-called 'uncomplicated' UTIs, which are nevertheless of concern because of their increasing drug resistance. This is exacerbated by using antibiotics that act through the whole body, with the added problem of collateral damage to the body's microbiome.

Oxford Drug Design is addressing this challenge by developing a small-molecule oral antibiotic that accumulates in the bladder, where the infection generally resides, and which uses a different mode of action from current UTI therapies. Previous work has identified three potent and selective series of inhibitors of a bacterial leucyl-tRNA synthetase active against several Gram-negative pathogens that frequently occur in UTIs. These inhibitors have activity in physiological models of infection, as well as oral bioavailability.

PACE funding and support will help this work to progress, with key objectives being characterisation of the three inhibitor series, improvement of potency and the pharmacokinetic profile, and evaluation of safety and efficacy. This work will prioritise leads active against *E. coli* and *Klebsiella pneumoniae*, including those that produce extended-spectrum β-lactamases and those resistant to carbapenems.

Success in this project will provide an oral antibiotic of a completely novel class and mechanism of action designed with uncomplicated UTIs specifically in mind. Importantly, by being targeted to the bladder, such an antibiotic would reduce the risk of resistance while also minimising damage to the microbiome – which is particularly relevant to patients with recurring UTIs.