Disperazol: treating catheter associated urinary tract biofilm infections

Michael Graz, Katrine Qvortrup*, Claus Moser, Tim Tolker-Nielsen, Michael Givskov
Costerton Biofilm Center, Univesity of Copenhagen, Denmark
*Department of Chemistry, Technical University of Denmark, Denmark

Disperazol is a SAR optimised, small molecule, non-traditional therapeutic for treating recalcitrant *Pseudomonas aeruginosa* biofilm infections. Our primary indication is hospital acquired catheter associated urinary tract infections (CAUTI).

Our focus are biofilms that are the central mode of all microbial life. In response to external cues, biofilm bacteria turn from a sessile to a planktonic mode, and vice-versa. In contrast to their planktonic counterparts, biofilm bacteria show a remarkable, overarching resistance antimicrobials, and as such represent an AMR mode of bacterial life. Modern medical procedures provide an unintended platform for the development of biofilm infections which in turn contributes to the alarming increase in AMR infections.

Our approach is to manipulate the c-di-GMP signalling pathway in *P.aeruginosa*. In general, high levels of c-di-GMP induce the formation of surface adhesins and exopolysaccharides that serve as extracellular matrix components and promote biofilm formation. Low c-di-GMP on the other hand activates degradation of c-di-GMP causing biofilms to dismantle and liberate susceptible bacteria. We identified BifA, which through c-di-GMP signalling operates as the life-mode master-switch in *P.aeruginosa*. BifA constitutes a non-lethal antimicrobial drug target. We designed Disperazol to manipulate the BifA switch. When biofilm dismantling is coupled with classic antibiotic treatments, it mitigates the overall AMR properties of the infection because it increases bacterial susceptibility to the conventional antibiotic.

Disperazol can be orally co-administered with Ciprofloxacin. We used a murine CAUTI model where catheters precoated with *P.aeruginosa* were installed in the bladders. 3µg Disperazol/g BW or 1µg Ciprofloxacin/g BW administered to mice revealed a 10-fold reduction in bacteria compared with the control group. In comparison, a combined oral administration of Disperazol and Ciprofloxacin proved to be 1000-fold more efficient than oral Ciprofloxacin alone.

Early ADME-Tox indicates that Disperazol is readily absorbed across the GIT, minimally binds plasma protein, has no effect on cellular ATP levels and a little effect on Cytochrome: CYP1A, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

We are now looking to raise $6 million to validate Disperazol's action in a non-rodent model, and progress through toxicology and into a Phase 1 first in human trial in 2024.