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Poster abstract submission

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Poster title

A first-in-class c-di-GMP signalling inhibitor potentiates polymyxin activity against multidrug-resistant Pseudomonas aeruginosa and Escherichia coli

Poster abstract

Antimicrobial resistance in Gram-negatives is a critical unmet clinical need, particularly in multidrug-resistant Pseudomonas aeruginosa and Escherichia coli, for which treatment increasingly relies on last-line agents, such as polymyxins. Conventional antibiotics exert strong selective pressure by targeting bacterial survival, thereby accelerating the emergence of resistance. Targeting bacterial virulence pathways offers an alternative strategy to attenuate pathogenicity while enhancing the efficacy of existing antimicrobials.

We report the discovery and characterisation of a first-in-class small-molecule inhibitor that disrupts cyclic-di-GMP regulated lifestyle switching. Phenotypic screening identified a lead compound, VEI-0026, which potently inhibits swarming motility, a validated determinant of acute virulence, in multidrug-resistant Pseudomonas aeruginosa clinical isolates derived from respiratory, urinary, skin, wound, and bloodstream infections. VEI-0026 inhibited swarming with an IC50 of approximately 200 nM and demonstrated dose-dependent activity across all isolates tested. No minimum inhibitory concentration was observed at concentrations up to ten-fold higher than the swarming EC100, consistent with a predominantly non-bactericidal mechanism.

Transcriptomic analysis revealed broad suppression of clinically relevant virulence pathways, including flagellar systems, type III secretion, elastase expression, and other cyclic-di-GMP-regulated determinants associated with adverse clinical outcomes. Combination minimum inhibitory concentration studies demonstrated concentration-dependent potentiation of polymyxins, with VEI-0026 reducing the minimum inhibitory concentrations of colistin and polymyxin B against multidrug-resistant clinical isolates of Pseudomonas aeruginosa and Escherichia coli. Minimum inhibitory concentration reductions of 4–16-fold were observed in Pseudomonas aeruginosa, whereas more pronounced effects of at least 16-fold were

observed in Escherichia coli. When polymyxin B was substituted with polymyxin B nonapeptide, minimum inhibitory concentrations remained reduced, consistent with potentiation not solely attributable to canonical outer membrane permeabilisation.

Together, these findings position cyclic-di-GMP-directed virulence inhibition as a promising strategy to sensitise Gram-negative pathogens to last-line polymyxins, expand combination treatment options, and reduce selective pressure in multidrug-resistant infections.

Research topic

Small molecule therapeutics