Development of divalent LecA ligands as antivirulence agents against Pseudomonas aeruginosa

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The Gram-negative bacterium *Pseudomonas aeruginosa* is a critical threat for mankind. Chronic infections are characterized by biofilm formation, a major virulence factor of P. aeruginosa, which leads to extensive drug resistance. The tetrameric *P. aeruginosa* lectin LecA is a virulence factor and an anti-biofilm drug target. Increasing the overall binding affinity by multivalent presentation of binding epitopes can enhance the weak carbohydrate–ligand interactions. Low-nanomolar divalent LecA inhibitors with up to 260-fold valency-normalized potency boost and excellent selectivity over human galectin-1 were synthesized from D-galactose pentaacetate and benzaldehyde-based linkers in four linear steps. However, these molecules displayed an intrinsic pH-dependent chemical instability due to their design for dynamic combinatorial assembly, and furthermore, a very low aqueous solubility. Therefore, the acylhydrazone linking motif was isosterically replaced with a more stable amide bond and the linking unit between two galactosides was also varied. The resulting optimized divalent LecA ligands retained low-nanomolar binding affinities, showed improved metabolic stability and were up to 1000-fold more soluble. The lead compound inhibited LecA adhesion to lung cells, restored wound closure in a scratch assay and reduced *P. aeruginosa* invasiveness to host cells *in-vitro*.

Bibliographic references:

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