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Poster abstract submission

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Poster title

Multiparameter Optimization of pathoblockers targeting elastase (LasB) for the treatment of Pseudomonas aeruginosa lung infections

Poster abstract

Infections caused by Pseudomonas aeruginosa are becoming increasingly difficult to treat due to the rise of antimicrobial resistance. This poses a particular threat to patients suffering from e.g. hospital-acquired or ventilator-associated pneumonia (HAP/VAP), cystic fibrosis (CF) or non-cystic fibrosis bronchiectasis (NCFB). To develop novel, non-traditional treatments targeting P. aeruginosa virulence, the secreted protease elastase (LasB) represents a prime target due to its key role in bacterial virulence and its extracellular localization. [1,2]
We have recently discovered a potent and selective phosphonate-based scaffold of LasB inhibitors, which we are optimizing towards novel treatment options for lung infections. [3,4] In the frame of this medicinal chemistry optimization campaign, we are applying an in house screening cascade for in vitro ADMET properties, such as metabolic stability, Calu-3 permeability, plasma protein binding and cytotoxicity. Applying this multiparameter approach together with in vivo pharmacokinetic profiling, we rationalized compound properties that lead to favorable bioavailability in the lung after both inhalative and systemic administration. These findings could be translated into in vivo efficacy in combination with standard-of-

care antibiotics in murine in vivo infection models.

[1] Luyt, C.-E., et al. (2018) Curr. Opin. Crit. Care. 24(5), 332-338. [2] Everett, M. J., Davies, D. T. (2021) Drug Discov. Today. 26(9), 2108-2123. [3] Konstantinovic et al. (2023) ACS Cent. Sci. 9(12):2205-2215. [4] WO 2022/043322 A1.

Research topic

Small molecule therapeutics