Monday, January 5, 2026

Poster abstract submission

Approval Status Not Started

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Poster title

In vitro and in vivo activity of the novel siderophore-cephalosporin AR-2126 against carbapenem-resistant Pseudomonas aeruginosa and A. baumannii

Poster abstract

Background: AR-2126 is a novel siderophore-cephalosporin that hijacks the iron uptake systems for entry into Gram-negative cells. This study investigated the in vitro and in vivo activity of AR-2126 against P. aeruginosa and A. baumannii and the in vivo activity of nebulized AR-2126 in a carbapenem-resistant (CR) P. aeruginosa lung infection model in mice.

Materials: MIC testing was conducted by broth microdilution using CAMHB according to CLSI (M07, 2018) using regular and iron-depleted (ID) CAMHB. Bacterial isolates were collected from hospital-acquired and ventilator acquired bacterial pneumonia patients or patients with cystic fibrosis (CF) or non-CF exacerbations. The in vivo activity of AR-2126 was determined in a lung infection model in neutropenic BALB/c mice (n=6 per group) infected with CR P. aeruginosa B1020 at 1x104 CFU/animal. At T=1 h and T=5 h post infection animals were treated with aerosolized AR-2126, aztreonam, amikacin and moxifloxacin for 10 min at doses ranging from 1 to 10 mg/kg.

Results: AR-2126 displayed potent antibacterial activity against the tested P. aeruginosa (MIC50/90 of 0.25/2 mg/L), A. baumannii (MIC50/90 of 0.12/0.5 mg/L) isolates and was as good as or even more potent than the tested comparators cefiderocol, cefepime, ceftazidime, ceftolozane/tazobactam, meropenem and tobramycin.
High lung penetration was achieved in mice upon inhalation of AR-2126 aerosolized with a nebulizer (PariBoy®), a device that is typically used by CF patients for inhalation of aztreonam or amikacin.
PK directly translated into potent in vivo efficacy in a CR P. aeruginosa lung infection model in mice following inhalation of aerosolized AR-2126 and comparators. While the living cell counts in the lungs increased by 4-5 log10 CFU/lung in the untreated control, AR-2126 significantly reduced the CFU/lung in a dose-dependent manner reaching -2 log10 at the highest tested dose of 16 mg/mL BID (Figure 1).

Conclusions: This study demonstrated the potent in vitro activity of AR-2126 against P. aeruginosa and A. baumannii and the in vivo PoE for inhalation treatment of a carbapenem-resistant P. aeruginosa lung infection. Inhalation treatment of infectious diseases is appealing to both outpatients and hospitalized

patients because it delivers high concentrations of medication directly to the site of infection (the lungs) with minimal systemic side effects, allowing for more efficient treatment across outpatient and inpatient settings.

Research topic

Small molecule therapeutics

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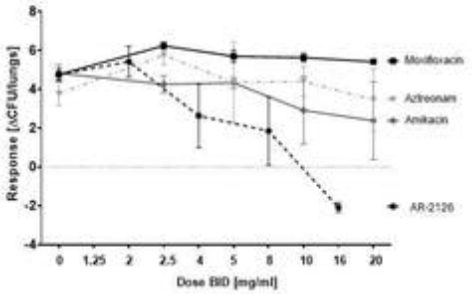
Figure 1. *In vivo* efficacy of inhaled AR-2126 in a carbapenem-resistant *P. aeruginosa* lung infection model in mice. Aerosolized antimicrobials were administered by inhalation for 10 min at the indicated doses at T=0 h and T=5 h post infection. CFU/lungs were determined at T=24 h post infection and compared with the untreated early control (inoculum, dotted line).



	MIC (µg/mL)
AR-2126	0.25
Amikacin	2 (S)
Aztreonam	32 (R)
Moxifloxacin	32 (R)
Meropenem	16 (R)