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Paper Poster Session I

New antibacterial drugs

S-649266, a novel siderophore cephalosporin: *in vivo* efficacy in murine infection model caused by multidrug-resistant Gram-negative bacteria

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Background: S-649266, is a novel catechol-substituted siderophore cephalosporin with potent activity against Gram-negative pathogens including multidrug-resistant (MDR) isolates. In this *in vivo* study, the efficacy of S-649266 was evaluated using neutropenic murine infection model caused by various MDR strains.
Methods: *In vivo* efficacy was determined in pulmonary infection models with five weeks old neutropenic ICR male mice (n=5). Administration was initiated at 2 hours post infection and repeated every 3 hours. Colistin and tigecycline were administered at 2 and 14 hours post infection. Viable cells in lungs at 24 hours after the initiation of treatment were evaluated. Tested strains were carbapenem-resistant strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae including NDM or KPC-producing strains and/or ST258 sequence type strains of *Klebsiella pneumoniae*. $T_{f>MIC}$ of S-649266 was calculated with MIC obtained using iron-deficient ISB (Iso-sensitest broth), which was prepared by pre-treating with the metal chelating resin, Chelex (Bio-Rad).
Results: In murine pulmonary infection, S-649266 decreased viable cells to 10^3 cfu/lungs against KPC-producing *P. aeruginosa* and IMP-1 and OXA-58 co-producing MDR *A. baumannii* at 300 and 30 mg/kg (q3h), where the $T_{f>MIC}$ values achieved with clinical dosage, respectively. However, colistin and tigecycline did not decrease viable cells at 20 and 10 mg/kg, respectively, which represent AUC in human dosage. S-649266 also showed potent efficacy and induced significant reduction in viable cells in lungs of KPC-producing *K. pneumoniae.* Meropenem alone and combination therapy of meropenem and colistin did not reduce the viable cells of KPC-producing *K. pneumoniae*. S-649266 also showed potent efficacy against NDM-1 producing Enterobacteriaceae.
Conclusion: S-649266 showed potent efficacy against carbapenem resistant *P. aeruginosa*, *A. baumannii*, Enterobacteriaceae in murine lung infection model reflecting the potent *in vitro* activity under infection simulated iron limited conditions.