Conclusion. Efficacy of CFDC was demonstrated in this descriptive pathogen-focused study, including CREs, metallo-NDM producers and CR non-fermenters. Baseline imbalances of ICU and shock in the subset of infections with *Acinetobacter* spp. may have contributed to the mortality difference between CFDC and BAT arms.

Disclosures. Matteo Bassetti, MD, Shionogi Inc. (Advisor or Review Panel member) Roger Echols, MD, Shionogi Inc. (Consultant) Yuko Matsunaga, MD, Shionogi Inc. (Employee) Simon Portsmouth, MD, Shionogi Inc. (Employee) Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee) Kiichiro Toyoizumi, PhD, Shionogi & Co., Ltd. (Employee) Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee)

1272. Efficacy of a Non-Peptide, Small Molecule Mimic of Host Defense Proteins in Mouse Models of Disseminated Candidiasis and Aspergillosis

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Session: P-58. Novel Agents

Background. We are developing a series of small nonpeptide mimics of host defense proteins (smHDPs) for antifungal applications. MICs < 0.1 µg/ ml have been demonstrated against multiple yeast and mold species. Their potential therapeutic utility has been evaluated in animal models of disseminated fungal infections.

Methods. Susceptibility testing against clinical isolates of *Candida albicans* (CA) and *Aspergillus fumigatus* (AF) was done according to CLSI guidelines. Cytotoxicity (CC_{50}) in mouse 3T3 and human HepG2 cells was determined in an MTS assay (Promega Cell Titer 96). For candidiasis, neutropenic CD-1 mice were infected IV with 3.5 x 10^4 CFU CA and test agents were administered subcutaneously (SC) once (QD) or twice (BID) daily beginning 2 hrs post-infection (PI). The positive control was fluconazole (20 mg/kg PO QD). Kidney burdens were measured at 24 hrs PI (n = 5/grp) and survival was measured at 2 weeks after 5 days of treatment (n = 8/grp). For aspergillosis, neutropenic CD-1 mice were infected IV with 4.5 log10 spores AF and test agents were administered SC BID for 5 days beginning 24 hrs PI. The positive control was posaconazole (20 mg/kg PO QD). Liver and kidney fungal burdens were measured 24 hrs after the last dose (n = 10/grp).

Results. The lead smHDP, FC-5096, has MICs of 0.08 and 0.024 ug/ml, respectively, against the CA and AF clinical isolate strains used in the mouse efficacy studies. Selectivity for antifungal vs. mammalian cell cytotoxicity (MIC/CC_{50}) was >1,000 fold. In the disseminated candidiasis model, FC-5096 significantly reduced fungal kidney burdens relative to untreated mice to levels found at treatment onset ($P < 0.0001$). Full survival over 2 weeks was observed after 5 days of BID treatment with FC-5096. All untreated mice succumbed between days 3 – 6 PI. Efficacy was comparable to fluconazole. In the disseminated aspergillosis model, FC-5096 produced up to 2.5 log10 reductions in fungal liver burdens and efficacy was significantly better than posaconazole ($P = 0.0251$). In kidney, both FC-5096 and posaconazole caused > 1.6 log10 reductions in fungal burdens that exceeded the limit of detection.

Conclusion. The high antifungal potency, low cytotoxicity and robust *in vivo* efficacy support further study of FC-5096 for clinical development.

Disclosures. Richard W. Scott, PhD, Fox Chase Chemical Diversity Center (Employee) Simon DP Baugh, PhD, Fox Chase Chemical Diversity Center (Employee) Mark E Pulse, MS, Fox Chase Chemical Diversity Center (Independent Contractor)

1273. Efficacy of Cefiderocol against carbapenem-resistant A. baumannii and P. aeruginosa in ventilator-associated pneumonia mouse model

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Session: P-58. Novel Agents

Background. Cefiderocol (CFDC) is a novel cephalosporin with siderophore structure, characterized by transportation through siderophore receptor on outer membrane of Gram-negative bacteria and structural stability against beta-lactamase. The antimicrobial activity against multidrug resistant bacteria is demonstrated *in vitro* and *in vivo*. In this study, we aimed to elucidate the *in vivo* efficacy of CFDC using ventilator-associated pneumonia (VAP) mouse model.

Methods. The minimum inhibitory concentration (MIC) of CFDC and meropenem (MEPM) against the test *Acinetobacter baumannii* (Ab) and *Pseudomonas aeruginosa* (Pa) isolates were measured by broth microdilution assay. Iron depleted medium was used for CFDC. For VAP mouse models, neutropenia was induced by cyclophosphamide intraperitoneal administration, followed by intubation of sterile tube in the trachea and inoculation of bacterial suspension. PK analysis were performed in infected mice, in order to determine treatment regimens to achieve targeted time above MIC (TAM) of free concentrations in plasma. Treatment was initiated 3 hours post infection and continued up to 120 h for survival analysis. To investigate the bactericidal effect, the mice were sacrificed to count bacterial load in the lung at 48 h and 24 h for VAP-Ab and Pa, respectively.

Results. MICs(mg/L) of CFDC and MEPM against Ab were 0.5 and 128, and Pa were 0.008 and 16, respectively. The treatment regimens to achieve target MIC were shown in Table 1. In order to assess dose dependency of CFDC, required doses to achieve TAM of 70%, 90%, and 100% were calculated. These doses used in the studies were achievable in human for CFDC, but not for MEPM due to high MICs of the test strains. In treatment study for VAP-Ab, bactericidal effect was achieved at TAM > 70% in CFDC groups, as well as TAM 30% in MEPM group. In VAP-Pa, bactericidal effect was observed at TAM > 90% in CFDC groups, as well as TAM 30% in MEPM group.

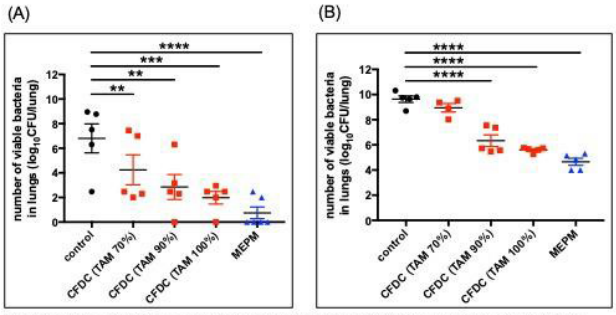
Table 1.Treatment regimen and free TAM against VAP-Ab and Pa

VAP-Ab	dose	interval	f TAM
CFDC	55 mg/kg	6h	70.1 %
	210 mg/kg		90.5 %
	390 mg/kg		100 %
MEPM	1,100 mg/kg	6h	30.0 %

VAP-Pa	dose	interval	f TAM
CFDC	3 mg/kg	8h	76.0 %
	10 mg/kg		90.5 %
	30 mg/kg		100 %
MEPM	110 mg/kg	8h	30.0 %

MEPM was administered with the same amount of cilastatin.

Figure 1. Bacterial load in the lungs of VAP-Ab and Pa



Bacterial load in the lung of mice with VAP-Ab (A) and VAP-Pa (B) are shown. Dunnett's multiple comparisons test is performed. A *P* value < 0.05 is considered statistically significant. Five mice per group were used. ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

Conclusion: The efficacy of CFDC against VAP-Ab and Pa were demonstrated in this study. Although 90% free TAM was required for bactericidal effect, CFDC was shown to be effective against carbapenem-resistant Gram-negative pathogens at the recommended clinical dosing regimen.

Disclosures. Katsunori Yanagihara, MD, PhD, Shionogi & Co.,Ltd. (Grant/Research Support)

1274. Evaluating the Activity of SPR719, a Novel Aminobenzimidazole, against Nontuberculous Mycobacteria

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Session: P-58. Novel Agents

Background. Pulmonary infections caused by Nontuberculous Mycobacteria (NTM) are increasing in prevalence and are associated with high mortality and morbidity. Members of the *Mycobacterium avium* complex (MAC; primarily *M. avium* and *M. intracellulare*) and *M. abscessus* are most commonly associated with NTM pulmonary disease. Treatment options are limited and new agents with potent activity are needed. In this study, the activity of SPR719, a novel aminobenzimidazole, against NTM is reported.