candidate molecule is recombinant human plasma gelsolin (rh-pGSN), an abundant normal blood protein whose levels fall proportionally with disease severity. Pretreatment with rh-pGSN has beneficial effects in many pre-clinical models of inflammation and injury, including pneumonia. We evaluated the effects of delaying therapy with rh-pGSN up to 48 hours after lethal intra-nasal pneumococcal challenge in a murine model to mimic more realistic clinical circumstances.

**Methods.** Adult Bl/6 mice were inoculated intra-nasally with S. pneumoniae strain type 3 on day 0, followed by subcutaneous rh-pGSN 24 hours later for evaluation of bacterial clearance in lavage fluids. To assess effects on survival, rh-pGSN was administered on days 2 and 3 after infection and effects monitored for 10 days. No antibiotics or other interventions were given.

**Results.** Treatment with rh-pGSN at 24 hours after infection improved bacterial clearance, seen as reduction of bacterial CFU in bronchoalveolar lavage fluid at 48 hours (% of initial inoculum, vehicle vs. rh-pGSN: dose range 0.5–2 mg): 30 ± 13 vs. 13 ± 7, n = 6 mice/group inocula ranging 0.3–1.8 x 10^5 CFU 3 mice/group (trial, P < 0.01). In 3 separate trials, pGSM (0.5 mg s.c.) reduced weight loss and mortality (% survival, vehicle vs. pGSM: 40 vs. 80, 20 vs. 45; n = 16/group, P = 0.02). Increasing the dose to 1 mg further improved survival from 17 to 71%.

**Conclusion.** rh-pGSN can substantially improve survival in a murine model of fatal pneumococcal pneumonia, even when administered as single doses on days 2 and 3 after infection without antibiotics. The data support further evaluation of pGSM as adjunctive therapy for serious infections with diverse pathogens and in models of antibiotic-resistant pneumonia.

**Disclosures.** Z. Yang, BioAegis: Shared NIH grant to study plasma gelsolin, we receive plasma gelsolin for our lab studies; S. Levinson, BioAegis: BioAegis shares a grant to investigate plasma gelsolin with HSPh, Employee and Shareholder, Salary; T. Stool, BioAegis: Consultant and Shareholder, portion of royalties from Hospital IP licensed to BioAegis; M. DiNubile, BioAegis: Employee and Shareholder, Consulting fee; L. Kobzik, BioAegis: Collaborator and We share a NIH grant on pGSM with BioAegis, we receive plasma gelsolin for our lab studies

1520. **In Vivo Efficacy of Humanized Exposures of Cefiderocol Compared with Ceftazidime (FEP) and Meropenem (MEM) Against Gram-Negative Bacteria in a Murine Thigh Model**

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

**Friday, October 6, 2017: 12:30 PM**

**Background.** Cefiderocol (S-649266) is a novel siderophore cephalosporin under development by Shionogi (Osaka, Japan). Previous studies have demonstrated cefiderocol efficacy against a diverse population of Gram-negative bacteria with MICs ≤ 4 μg/mL. Our aim was to further define the agent’s clinical role by comparing the efficacy of humanized regimens of cefiderocol, FEP and MEM against a subset of these Gram-negative isolates.

**Methods.** 15 Gram-negative isolates were studied. MICs were determined by broth microdilution in triplicate, using reference CLSI methods. Pharmacokinetic studies were conducted to reproduce the humanized exposures of cefiderocol 2g q8h (3h inf.), FEP 2g q8h (3h inf.), and MEM 2g q8h (3 hours inf.). Antibiotics were started 2h post thigh infection with efficacy similar to that of LAMB. Higher doses of APX0104 at 156 mg/kg did not enhance survival vs. placebo. Further, APX0104 at 104 mg/kg and LAMB reduced pulmonary and brain fungal burden by 1 log and 1.5 log vs. placebo, respectively (P < 0.05, Wilcoxon rank-sum). The 52 and the 156 mg/kg APX0104 doses also reduced tissue fungal burden vs. placebo mice (P = 0.5–1.0 log).

**Conclusion.** APX0104 protected immunosuppressed mice from R. delemar infection with efficacy similar to that of LAMB. Higher doses of APX0104 were not protective despite lowering fungal burden. Continued investigation of APX0104 as a novel antifungal agent against mucormycosis is warranted.

**Disclosures.** K. J. Shaw, Amplex Pharmaceuticals Inc: Employee, Salary; Linnaeus: Consultant, Consulting fee

1522. **Fungal Cytological Profiling of Candida albicans Exposed to Diverse Antifungal Agents Including the Novel Gwt1 inhibitor APX001A**

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Fungal cytological profiling accelerates drug discovery efforts by determining the mechanism of action (MOA) of newly developed antifungal agents. Our goal was to adapt this technology to the identification and study of the MOA of APX001A, a novel fungal compound currently under development. Here we explore the utility of Fungal Cytological Profiling (FCP) of C. albicans in revealing changes in morphology over time using fluorescence labeled compounds that specifically stain a variety of subcellular structures including DNA and membranes. Included in the analysis was the novel broad spectrum Gwt1 inhibitor APX001A, the active moiety of the prodrug APX0104 which is currently in clinical trials for invasive fungal infections.

**Methods.** The MICs of 6 antifungals vs. C. albicans were determined by CLSI methodology. FCP, antifungals were added to cultures (1 x 10^5 cells/mL) in RPMI 1640 (buffered with MOPS) at concentrations near MIC: APX0104A (0.064 μg/mL); caspofungin (1 μg/mL); fluconazole (2 μg/mL); fluconazole (2 μg/mL); amphotericin B (1 μg/mL) and nikkomycin (3.33 μg/mL) incubated at 35°C with shaking. At 4 hours p.s. (time of infection), we stained for membranes and DNA and examined fluorescence microscopy. Dyes included FM 4-64 (membranes), DAPI (DNA), and Sytox Green (cell viability). High-resolution fluorescent microscopy, image analysis and quantitation of cytological parameters (cell length, width, shape, DNA content) were used to create a cytological profile for each condition.
Results. Unique cytological signatures strongly correlated with antifungal MOA: FCZ resulted in rounded cells that lacked lypophil forms; APX001A resulted in abundant intracellular membrane labeling at 4 hours, consistent with an endoplasmic reticulum stress response, with cell death (Sytox Green Staining) at 24 hours.

Conclusion. FCP is a rapid and accurate method to establish MOA and distinguish between antifungals that inhibit specific biosynthetic pathways (e.g., cell wall and sub-pathways (glucan vs. chitin synthesis). In addition, this technology can be useful in drug discovery programs to determine on-target vs. off-target activity of newly synthesized molecules.

Disclosures. M. Sharp, Linnaeus: Employee, Salary. Q. Soltow, Amplyx Pharmaceuticals Inc.: Employee, Salary. K. J. Shaw, Amplyx Pharmaceuticals Inc.: Employee, Salary. Linnaeus: Consultant, Consulting fee. J. Pogliano, Linnaeus: Employee, Salary.

1523. Fosfomycin (FOS) Plus Meropenem (MER) Suppresses Resistance Emergence Against P. aeruginosa (PA) PAO1 in the Hollow Fiber Infection Model (HFIM)

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Background. FOS (ZTI-01, fosfomycin for injection) is an epoxide antibiotic that covalently binds MurA, an earlier step in cell wall synthesis inhibition. FOS has demonstrated synergistic killing with other classes of agents, including carbapenems. PA, among other non-fermentors, are difficult to treat pathogens and combination therapy is important to ensure killing and suppress emergence of resistance. Here, we examine the combination of FOS + MER in the HFIM against PA.

Methods. The experimental design was fully factorial (3 FOS and 3 MER arms and all combinations). Simulated FOS doses were 4, 6 and 8 g 8 hourly (Q8). MER doses were 0.5, 1 and 2 g Q8. The experiment lasted 10 days. Concentrations from the central compartment were measured in all arms by LC/MS/MS. Total bacterial burden and resistant subpopulations for both drugs were measured. Resistance plates were infused with 3XBaseline MIC. Starting inoculum was 6.86 Logs.

Results. FOS/MER MICs were 64 mg/L (broth) and 0.5 mg/L. Mutational frequency to resistance were -5.27 (FOS) and -6.7 (MER). There were 15 drug-containing arms and a no-treatment control. All drug arms had concentration-time profiles accurately reproduced. All FOS alone arms had rapid resistance emergence. MER 0.5 gm alone had resistance emerge at Day1. FOS 4 g + MER 0.5 g allowed resistance to both agents as did FOS 6g + MER 0.5g. FOS 6 g + MER 1 g allowed MER resistance, but not FOS. All other combination regimens fully suppressed all resistant mutants. The effect of combination therapy is shown in Figures 1–3. MICs for MER-resistant isolates were 2 mg/L early and up to 16 mg/L late (day4 and after). FOS-resistant isolates generally had MIC values between 128 and >1024 mg/L.

Conclusion. The combination of FOS + MER is promising for therapy of a wild-type PA. Doses of FOS and 8 g Q8 tended to suppress resistance emergence to either agent when combined with 1 or 2 g Q8 of MER. We intend on examining the impact of resistance mutations to MER (oprD downregulated and MexAB upregulated) with this combination to identify any potential therapeutic advantage of this combination regimen.

Disclosures. G. L. Drusano, Zavante: Scientific Advisor, Consulting fee.

1524. Good Correlation of Cefiderocol Between In Vivo Efficacy Murine Thigh/ Lung Infection Models and MIC Determined in Iron-Depleted Conditions

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Background. Cefiderocol (S-649266) is a novel siderophore cephalosporin active against a wide variety of carbapenem-resistant Gram-negative bacteria such as Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii and Stenotrophomonas maltophilia. This potent activity is mainly due to its efficient penetration through the outer membrane via active iron transporter systems and its high stability to both serine- and metallo-carbapenemases. The antibacterial activity is evaluated under iron-deficient conditions to mimic the infection sites in human. In this study, the efficacy in murine infection models was evaluated in order to show that the MIC under iron-deficient conditions is more predictive for the in vivo efficacy.

Methods. A total of 19 strains of E. coli, K. pneumoniae, P. aeruginosa and A. baumannii were used for the in vivo efficacy studies using neutropenic murine thigh or lung infection models. The efficacy was evaluated by the bacterial reduction at 24 hours after treatment by subcutaneous q3h administration of cefiderocol which was initiated at 2 hours post-infection. MIC of cefiderocol was determined by broth microdilution methods according to CLSI instruction using both CAMHB and iron-depleted CAMHB (ID-CAMHB). The PK/PD analysis was conducted by calculating the percentage T>MIC value of free plasma concentrations (FT>MIC) in infected mice.

Results. The efficacy in murine thigh and lung infection models were evaluated by using 12 and 15 strains, respectively. The average FT>MIC value required for static effect and 1 log<sub>10</sub> reduction was shown to be 75% and 85%, respectively irrespective