Delayed Therapy with Plasma Gelsolin Improves Survival in Murine Pneumococcal Pneumonia

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1517. ZTI-01 Treatment Improves Survival of Animals Infected with Multidrug Resistant Pseudomonas aeruginosa
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**Background.** ZTI-01 (fosfomycin, FOS, for injection) is currently under US development to treat complicated urinary tract infections. ZTI-01 is unique compared to other antimicrobials in that it inhibits an early step in cell wall synthesis via covalent binding to MurA. ZTI-01 demonstrates broad in vitro activity against Gram-negative (GN) and -positive (GP) bacteria, including multidrug-resistant (MDR) organisms. Our study goals were to determine the efficacy of ZTI-01 as a monotherapy or in combination with meropenem against MDR Pseudomonas aeruginosa in a preclinical model of pulmonary infection.

**Methods.** 8 week old neutropenic mice were infected with a MDR strain of P. aeruginosa via intubation-mediated intratracheal (IMIT) instillation. 3 hours after instillation, mice received treatment with ZTI-01, meropenem, or ZTI-01 plus meropenem (combination therapy) q6h for 5 days. Mice were monitored every 8 hours for 7 days for development of disease and morbidity and animals were euthanized. Lungs and spleens were harvested at euthanasia, or at 7 days for survivors, and processed for bacterial enumeration and development of pathology.

**Results.** Mice were challenged with a lethal dose of P. aeruginosa UNC-13. Mock treated animals succumbed to infection within 36 hours post-infection. Animals that received 6 kg/kg/day ZTI-01 showed an increase in the MTD (52 hours) and 25% of the cohort were protected from lethal disease. Combining ZTI-01 with meropenem resulted in a significant increase in survival (≥75% of cohorts survived infection at the end of the study). Combining ZTI-01 with meropenem resulted in a significant increase in survival (≥75% of cohorts survived infection at the end of the study) compared to meropenem alone. CD101 demonstrated broad antifungal activity against C. auris blastospores and moderate antifungal activity against C. auris hyphae. CD101 showed an average 3 log reduction in kidney CFU compared with fluconazole, amphotericin B, and vehicle treated groups, which was statistically significant (P = 0.03, 0.03, and 0.04, respectively). At the end of the study, percent survival of mice in CD101, fluconazole, amphotericin B, vehicle, and untreated groups was 80, 30, 20, and 0%, respectively (Figure 1).

**Conclusion.** Taken together, our findings show that CD101 possesses potent antifungal activity against C. auris infection in a disseminated model of candidiasis. Additionally, treatment with CD101 resulted in a significantly higher overall percent survival. Further investigation of this drug is warranted.

Figure 1. Survival curve of mice in all treatment groups after 14 days.
Cefiderocol (S-649266) is a novel siderophore cephalosporin under development by BioAegis and Amplyx Pharmaceuticals Inc., targeting Gram-negative bacteria. It demonstrates activity similar to MEM and FEP for susceptible pathogens, while also displaying activity 1.5 ± 0.4 log10 CFU at 24h compared with 0 hour controls. Against FEP and MEM susceptible isolates, cefiderocol achieved 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 cefiderocol as adjunctive therapy for serious infections with diverse pathogens and in models of antibiotic-resistant infections.

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. Stossel, BioAegis: Consultant and Shareholder, portion of royalties from Hospital IP licensed to BioAegis; M. DiNubile, BioAegis: Employee and Shareholder, Consulting fee; L. Kozbik, BioAegis: Collaborator and We share a NIH grant on pGnS with BioAegis, we receive plasma gelsolin for our lab studies;

1520. In Vivo Efficacy of Humanized Exposures of Cefiderocol Compared with Ceferazime (FEP) and Meropenem (MEM) against Gram-negative Bacteria in a Murine Thigh Model
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Background. Bacterial cytological profiling accelerates drug discovery efforts by determining the mechanism of action (MOA) of newly developed antibacterial agents. Our goal was to adapt this technology to the identification and study of the MOA for new fungal compounds. We explore the utility of Cytological Profiling (PCP) of f. albicans in revealing changes in morphology over time using for 6 antifungal agents with unique MOA using fluorescently labeled compounds that specifically stain a variety of subcellular structures including DNA and membranes. Inhibited in the analysis was the novel broad spectrum Gwt1 inhibitor APX001A, the active moiety of the prodrug APX001 which is currently in clinical trials for invasive fungal infections.

Methods. The MICs of 6 antifungals vs. C. albicans were determined by CLSI methods. For FCP, antifungals were added to cultures (1 x 10^7 cells/mL) in RPMI 1640 (buffered with MOPS) at concentrations near MIC: APX001A (0.064 µg/mL); caspofungin (1 µg/mL); fluconazole (2 µg/mL); fluconazole (2 µg/mL); amphotericin B (1 µg/mL) and nystatin (3.33 µg/mL) incubated at 35°C with shaking. At 4 hours post inoculation, cells were harvested, washed, and resuspended with caspofungin and then stained examined under the fluorescence microscope. Dyes included FM 4–64 (membrane stain with 2.5 x 10^5 cells of R. delemar 99–880. For survival studies, treatment with APX001A (prodrug) at 52, 104, or 156 mg/kg (twice daily, po), was compared with liposomal amphotericin B (LAMB) at 15 mg/kg (once daily). Treatment started on day +1 through day +8 for APX001A and day +8 for LAMB. Placebo mice received vehicle control. For fungal burden studies, dosing started 8 hours post infection through day +3. Mice were sacrificed on day +4. Survival time, and tissue fungal burden (by qPCR) served as efficacy endpoints.

Results. APX001A treatment at either 52 or 104 mg/kg prolonged survival of mice vs. placebo (n = 20 per arm) (21-day survival of 0% for placebo, 30% for 52 mg/kg, 45% for 104 mg/kg, P < 0.05 by Log Rank test). APX001A at 104 mg/kg was superior to 52 mg/kg at day +1. APX001A at 156 mg/kg did not enhance survival vs. placebo. Further, APX001A 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, by Wilcoxon rank-sum). The 52 and the 156 mg/kg APX001A doses also reduced tissue fungal burden vs. placebo mice 0.5–1.0 log.

Conclusion. APX001A protected immunosuppressed mice from R. delemar infection with efficacy similar to that of LAMB. Higher doses of APX001A were not protective despite lowering fungal burden. Continued investigation of APX001A as a novel antifungal agent against mucormycosis is warranted.