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 potential clinical scenarios.

**Methods.** Adult Bl/6 mice were inoculated intra-nasally with *S. pneumoniae* 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. 11 ± 7, n = 6; *P* = 0.02 for inocula ranging 0.3–1.8 ± 10^7 CFU, 3 mice/group/trial. CR mice were set as control (P = 0.01). In 3 separate trials, pGSN (0.5 mg s.c.) reduced weight loss and mortality (% survival, vehicle vs. pGSN: 40 vs. 80, vs. 25, vs. 17; n = 16/group, P = 0.02). Increasing the dose to 1 mg further improved survival from 17 to 71%.

Conclusions. Rh-pGSN can substantiate 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 pGSN 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: BixoAegis shares a grant to investigate plasma gelsolin with HSPH, Employee and Shareholder, Salary; T. Councill, 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 pGSN with BioAegis, we receive plasma gelsolin for our lab studies.

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

Marguerite Monogue, PharmD1; Masakatsu Tsuji, Ph.D2; Yoshihito Yamano, Ph.D2; Roger Echols, MD, FIDSA1 and David P. Nicolau, Ph.D1; 1Center for Anti-Infective Research and Development at Hartford Hospital, McKinney, Texas; 2SHIONOGI & CO., LTD., Osaka, Japan, Tokyo, Connecticut, 3Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut

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

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

**Background.** In the face of a multidrug-resistant (MDR) Gram-negative pandemic, cefiderocol (APX001) is currently in phase III trials, with the potential to restore the clinical utility of β-lactams against Enterobacteriaceae, A. baumannii, and P. aeruginosa with phenotypic resistance to the comparator β-lactams. These studies support the potential clinical utility of cefiderocol against these difficult-to-treat multidrug-resistant pathogens.

**Disclosures.** M. Tsuji, Shionogi & Co.: Employee, Salary; Y. Yamano, Shionogi & Co.: Employee, Salary; R. Echols, Shionogi & Co.: Employee, Salary; D. P. Nicolau, Shionogi & Co.: Research Contractor, Research support

### 1521. APX001A Protects Immunosuppressed Mice from Rhizopus delemar Infection

T. Celegiros, Kobe University Graduate School of Medicine, Kobe, Japan; S. Akhtar, Shionogi & Co., Ltd., Osaka, Japan; D. P. Nicolau, Ph.D1; 1Center for Anti-Infective Research and Development at Hartford Hospital, Hartford, Connecticut, 2Department of Immunology, Shionogi Research Institute at Harbor-UCLA Medical Center, Torrance, California, 3Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, California, 4UT Health San Antonio, San Antonio, Texas, 5Amplyx Pharmaceuticals Inc., San Diego, California, 6Bowling Green Medical Research Institute at Harbor UCLA Medical center, Torrance, California

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

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

**Background.** Mucormycosis is a life-threatening infection with high mortality that occurs predominantly in immunocompromised patients. APX001A is an antifungal agent that targets Gwt1, an early step in the conserved glycosylphosphatidylinositol (GPI) post-translational modification pathway of surface proteins in eukaryotic cells. Inhibition of inositol acylation by APX001A results in pleiotropic effects such as inhibition of maturation of GPI-anchored proteins necessary for growth and virulence and results in lethality. APX001A has in vitro activity against Mucorales. Here we assessed the in vivo activity of APX001A against *Rhizopus delemar* (MIC = 0.25 µg/mL). All mice treated with APX001A produced with meropenem (MEM) and cortisone acetate (500 mg/kg) on days -2, +3, and +8 relative to intratracheal infection with 2.5 × 10^6 cells of *R. delemar* 99–88%. 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). APX001A treatment started on day +1 through day +8 for APX001A and through day +4 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 fungal burden (by qPCR) served as efficacy endpoints.

**Results.** APX001 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 more protective than LAmB treatment (n = 20) (20% vs 100%; P = 0.02) and 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 2 and 156 mg/kg APX001A doses also reduced tissue fungal burden vs. placebo mice 0.5–1.0 log.

**Conclusion.** APX001 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.

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

### 1522. Fungal Cytological Profiling of Candida albicans Exposed to Diverse Antifungal Agents Including the Novel Gw1 Inhibitor APX001A

M. Sharp, PhD1,2; Quindy S. Solovey, PhD2; Karen Jay Shaw, PhD2; and Joseph Pogliano, PhD2; 1Linnaeus Bioscience, San Diego, California, 2Amplyx Pharmaceuticals Inc., San Diego, California

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

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

**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 new antifungal compounds. We explore the utility of Cytological Profiling (FP) of C. 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. Included in the analysis was the novel broad-spectrum Gw1 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 methodology. For FCP, antifungals were added to cultures (1 × 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 nikkomycin (3.33 µg/mL) incubated at 35°C with shaking. At 4 hours (1 µg/mL) and nikkomycin (3.33 µg/mL) incubated at 35°C with shaking. At 4 hours 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 nikkomycin (3.33 µg/mL) incubated at 35°C with shaking. At 4 hours.