of Gram-negative bacterial species and the infection sites. The PK/PD analysis for 3 strains, which had large different MIC between two conditions (16, 2 and 2 mg/mL in ID-CAMHB and 128, 32 and 32 mg/mL in CAMHB, respectively) showed that the fT>MIC required for 1 $\log_{10}$ reduction ranged from 71.7% to 89.0% using the MIC in ID-CAMHB. On the other hand, these values were significantly lower (ranging from 10 to 50%) using the MIC in CAMHB.

Conclusion. The PK/PD analysis using murine thigh/lung infection models showed that ID-CAMHB is the appropriate media for MIC determination for the prediction of *in vivo* efficacy irrespective of infection sites and bacterial species.

Disclosures. **Y. Yamano**, SHIONOGI & CO., LTD.: Employee, Salary; **R. Nakamura**, SHIONOGI & CO., LTD.: Employee, Salary; **T. Sato**, SHIONOGI & CO., LTD.: Employee, Salary; **M. Tsuji**, Shionogi & Co.: Employee, Salary; **R. Echols**, Shionogi & CO., LTD: Consultant, Consulting fee

1525. Efficacy Evaluation of Iclaprim in a Neutropenic Rat Lung Infection Model with Methicillin-Resistant *Staphylococcus aureus* Entrapped in Alginate Microspheres

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Background. The objective of this study was to demonstrate the effect of iclaprim, a new generation diaminopyrimidine, in a neutropenic rat lung infection model with methicillin resistant *Staphylococcus aureus* (MRSA).

Methods. *S. aureus* strain AH1252, a thymidine knockout of the MRSA wild type AW6 strain, was utilized for this study. The bacterial strain was diluted in a 2% alginate buffer, which was added dropwise in a ratio of 1:5 into 50 mM MgCl to form alginate beads. The alginate beads reduce the efficacy of bacterial clearance similar to that seen in the cystic fibrosis population. A 5.25×10^4 bacterial inoculum was administered intratracheally to groups of 9 rats with prepared alginate bacteria suspensions, under isoflurane anesthesia. Beginning 2 hours post infection, rats received either iclaprim or vancomycin for 3 days via subcutaneous injection every 12 hours. Twelve hours after the last treatment, rats were euthanized and lungs collected for CFU determination.

Results. The Table below shows survival, CFU/gram of lung, and change in CFUs (Standard Error of the Mean (S.E.M.) from baseline by treatment or vehicle group.

Conclusion. In this rat lung infection model increased survival was observed in both iclaprim and vancomycin treatment groups, compared with the infection controls. Rats receiving iclaprim demonstrated a 5.34 $\log_{10}$ CFU reduction from the 72 hour infection whereas vancomycin-treated rats showed a 3.38 $\log_{10}$ CFU reduction from the 72 hour infection controls.#8232;Based on these data, further evaluation of iclaprim for *S. aureus* lung infections among the cystic fibrosis population is warranted.

Disclosures. **D. Huang**, Motif Bio: Employee, Salary

1526. Discovery of a Series of Potent and Selective Nucleotide Prodrug Inhibitors of Respiratory Syncytial Virus (RSV) Replication

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Background. RSV can cause severe respiratory tract infections in infants and the elderly. Current experimental therapies include polymerase and fusion inhibitors, but their clinical use may be limited by toxicity or rapid emergence of viral resistance. Here we report new nucleotide prodrugs that are selective for and highly active against RSV replication *in vitro*.

Methods. Novel nucleotide prodrugs were synthesized and tested for their ability to inhibit RSV replication in 3-dimensional preparations of differentiated normal human bronchial epithelial (dNHBE) cells. Drug selectivity was assessed in the anti-RSV assays at concentrations up to 100 μg/mL, and in 14-day exposures with human bone marrow stem cells and 3-day exposures with human induced pluripotent (iPS) cardiomyocytes at concentrations up to 100 μM. The formation and half-lives ($t_{½}$) of analog triphosphates (TPs) of selected prodrugs were measured in phytohaemagglutinin-stimulated human peripheral blood mononuclear cells (PBMCs) incubated with 100 μM prodrug. After 8 hours, medium was replaced with fresh medium without drug and cell extracts were prepared at various time points and analyzed for intracellular levels of TPs. After single oral dosing of Golden Syrian hamsters with selected prodrugs (~60 mg/kg), plasma pharmacokinetics and lung levels of TPs were determined at 4 and 24 hours or at 24 and 72 hours post dose.

Results. The most potent nucleotide prodrugs inhibited RSV replication by 90% at concentrations (EC_{90}) as low as 0.021 μM. None of the prodrugs tested showed significant cytotoxicity with dNHBE cells, bone marrow stem cells or cardiomyocytes. The $t_{½}$ of the TPs formed in human PBMCs ranged from 1.3 to >5 days. In hamsters, plasma parent drug levels were ≤1 ng/mL, yet significant levels of the corresponding TPs were detected in lung tissue. Furthermore, the highest TP concentrations (up to 1344 ng/g) were observed at the latest sampling time point (up to 72 hours).

Conclusion. The data indicate that these potent new nucleotide prodrugs are metabolized to TPs that prevent RSV replication likely by inhibition of the viral RNA polymerase. Additionally, the long $t_{½}$ observed for many of the TPs suggest that it might be possible to cure RSV infections with a single dose. IND enabling studies are ongoing, targeting clinical evaluation in early 2018.

Disclosures. **S. Good**, Atea Pharmaceuticals, Inc.: Employee and Shareholder, Salary; **A. Moussa**, Atea Pharmaceuticals, Inc.: Employee and Shareholder, Salary; **J. C. Meillon**, Oxeltis: Employee and Shareholder, Salary; **X. J. Zhou**, Atea Pharmaceuticals, Inc.: Employee and Shareholder, Salary; **K. Pietropaolo**, Atea Pharmaceuticals, Inc.: Employee and Shareholder, Salary; **J. P. Sommadossi**, Atea Pharmaceuticals, Inc.: Board Member, Employee and Shareholder, Salary

1527. Novel Immunization Strategies Against Multi-drug-resistant Gram-negative Bacteria

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Background. Healthcare-related infections due to multi-drug resistant (MDR) Gram-negative bacteria (GNB) such as *Acinetobacter baumannii* (AB) and *carbapenemase producing Klebsiella pneumoniae* (KPC) are associated with high mortality rates. New methods to prevent or treat these infections are needed. *Candida*antigen Hyr1p is predicted to share structural and sequence homology with the hemagglutinin/hemolysin protein (FhaB) and siderophore-binding protein of GNB including AB and KPC, respectively. Indeed, active and passive immunization using Hyr1p as a target protect against AB infections in mice. Thus, we attempted to develop protective monoclonal antibodies (mAb) and test their efficacy against AB and KPC in vitro and in vivo.

Methods. Murine hybridomas were generated from Balb/c mice after vaccination with recombinant Hyr1p. The concentration and identification of the collected mAbs were determined using Bradford and SDS-PAGE. Binding ability of mAb was tested against AB and KPC using flow cytometry. In-vitro studies on the ability of these mAbs to kill KPC and AB were tested by quantitative culturing. The ability of these mAbs to protect from AB- or KPC-mediated alveolar epithelial cell (A549) damage was studied with ^{51}Cr-release assay. The efficacy of mAb in protecting against AB- or KPC-induced pneumonia was studied in neutropenic or immunocompetent CD1 mice by administering 30 μg of mAb (i.p.) on Day +1 and +4, relative to infection, respectively. Survival of mice served as an endpoint.

Results. Four different mAb-producing hybridoma cells generated IgM that bound to AB and KPC. 40–80 μg/mL of mAb resulted in 100% killing effect of AB or KPC in vitro. Two of mAb (25 μg/mL each) resulted in protecting A549 cells from AB- or KPC-induced damage by ~80% vs. cells incubated with isotype-matching Ab ($P < 0.05$). Finally, one of the mAb resulted in 70% or 100% long-term survival of mice infected with lethal doses of KPC or AB, respectively ($P < 0.05$).

Conclusion. We used *Candida* Hyr1p to generate cross-protective mAb against MDR AB and KPC. Our results warrant the further development of these mAb as novel immunotherapeutics against MDR GNB.

Disclosures. **All authors:** No reported disclosures.

1528. In vivo Pharmacokinetic/Pharmacodynamic (PK/PD) Target Characterization of the Novel, Long Acting Echinocandin CD101 against *C. albicans* and *C. glabrata* in the Neutropenic Murine Disseminated Candidiasis Model

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Background. CD101 is a novel, long acting echinocandin. The purpose of the study was to evaluate the PK/PD activity of CD101 against *C. albicans* (CA) and *C. glabrata* (CG) using the murine neutropenic disseminated candidiasis model.

Methods. 4 CA and 3 CG strains were used. MICs were determined by CLSI standards. Single dose plasma PK was determined in groups of three mice after IP doses of 1, 4, 16, and 64 mg/kg. For treatment studies, mice were rendered neutropenic via administration of cyclophosphamide at days -4, -1, +2 and +4. Mice were infected with 6.3 ± 0.1 CFU/mL (CA) or 6.2 ± 0.2 CFU/mL (CG) injected into the lateral tail vein. Treatment dose range was 0.016 – 64 mg/kg, given once by IP injection 2 hours after infection. Experiment duration was 7 days at which point kidneys were aseptically harvested for CFU counts. The Emax Hill equation was used to model the dose–response data to PK/PD index AUC/MIC. The static and 1-log kill doses, as well as associated total and free AUC/MIC values were determined for each isolate.

Results. CD101 MICs were 0.008–0.06 mg/L for CA and 0.06 – 0.5 mg/L for CG. Single dose plasma PK parameter ranges include: Cmax 2.6–77 mg/L, $AUC_{0-\infty}$ 93–4046 mg*hours/L, $T_{1/2}$ 28–41 hours. Dose-dependent cidal activity was observed with a maximal kill of over 2 $\log_{10}$ CFU/kidney. Average 24 hours AUC over 7 days was used to model AUC/MIC data and fit the treatment response data well (CA R^2 0.70, CG R^2 0.86). The static dose (SD) and 1-log kill dose and associated total and free AUC/MIC values are shown (Table).