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).

	Strain	MIC (mg/L)	Static Dose (mg/kg)	Stasis Ave 24 hours tAUC/MIC	Stasis Ave 24 hours fAUC/MIC	1 log kill dose (mg/kg)	1 log kill Ave 24 hours tAUC/MIC	1 log kill Ave 24 hours fAUC/MIC
CA	K-1	0.008	2.52	3426	44.5	5.26	6435	83.6
	580	0.016	1.20	948	12.3	2.03	1429	18.6
	98–17	0.06	1.34	274	3.6	2.73	490	6.4
	98–210	0.016	1.06	868	11.3	2.28	1574	20.5
CG	10956	0.5	6.29	120	1.6	17.3	301	3.9
	5592	0.06	0.03	21.7	0.3	0.51	114	1.5
	35315	0.25	0.34	17.9	0.2	2.39	105	1.4

Conclusion. CD101 demonstrated in vivo potency in the neutropenic murine disseminated candidiasis model against select CA and CG strains. Similar to studies with other echinocandins, AUC/MIC fit the exposure-response data well and CG targets were numerically lower than CA. However, while CA target range was similar, CG target range was almost 10-fold lower compared with other echinocandins.

Disclosures. **B. Vanscoy**, Cidara: Research Contractor, Research support; **P. G. Ambrose**, Cidara: Research Contractor, Research support; **D. R. Andes**, Cidara: Grant Investigator, Research support

1529. Efficacy of Oral APX001 in a Murine Model of Cryptococcal Meningitis

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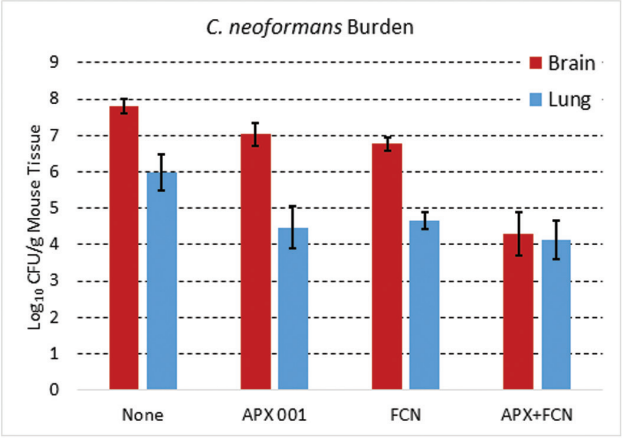
Background. APX001 is a first-in-class intravenous and orally available broad spectrum antifungal inhibitor of Gwt1, a protein involved in glycosylphosphatidylinositol anchor biosynthesis. This study evaluated efficacy of APX001, alone and in combination with fluconazole (FCN), in a mouse model of cryptococcal meningitis.

Methods. Mice (10/group) infected via tail vein with *Cryptococcus neoformans* received APX001, FCN, both, or neither, for 7 days. APX001 was given orally as 390mg/kg thrice daily. FCN was given intraperitoneally as 80mg/kg/day. Brain and lung were cultured to determine tissue burden. Data were evaluated by unpaired *t*-test.

Results. In brain, the burden of *C. neoformans* in mice receiving combined therapy was 3.52 log lower than in untreated control mice. The burden in mice receiving APX001 alone was 0.78 log lower than in untreated mice. The burden in mice receiving FCN alone was 1.04 log lower than in untreated mice. In lung, the burden in mice receiving combined therapy was 1.84 log lower than in untreated control mice. The tissue burden for mice receiving APX001 alone was 1.58 log lower than in untreated mice. The tissue burden in mice receiving FCN alone was 1.3 log lower than untreated mice.

Conclusion. Activity in murine brain: (i) Combined therapy of APX001 with FCN significantly inhibited growth of *C. neoformans* H99 compared with untreated control mice ($P < 0.0001$), and was significantly more active than monotherapy with APX001 or FCN ($P < 0.0001$ and $P < 0.0003$, respectively). (ii) APX001 and FCN each, alone, significantly inhibited growth of *C. neoformans* H99 in brain tissue compared with untreated control mice ($P < 0.0001$). Activity in murine lung: (i) Combined therapy of APX001 with FCN performed somewhat better than FCN alone ($P = 0.0297$), but no better than APX001 alone ($P = 0.2500$). (ii) APX001 and FCN each, alone, significantly inhibited growth of *C. neformans* H99 in lung tissue compared with untreated control mice ($P < 0.0001$). (iii) Significant potentiation of APX001 in combination with FCN in this model with *C. neoformans* H99 was observed within the brain, and further investigation is warranted to determine whether APX001 in combination with FCN has potential to be an effective oral regimen for treating cryptococcal meningitis.



Disclosures. **K. J. Shaw**, Amplyx Pharmaceuticals Inc.: Employee, Salary

1530. Diol-Based Polymer Microparticles for Treatment of Cutaneous Aspergillosis in an Immunocompromised Murine Model

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Background. Local delivery of antifungals may allow for high concentrations of therapeutic directly in wound beds infected with invasive fungi. In this work, microparticles (MPs) fabricated from a novel biodegradable polymer synthesized from 1,10-decanediol (DD) and fumaric acid were leveraged for the local delivery of voriconazole (VRC) in a murine model of cutaneous aspergillosis. In addition to controlled local delivery of VRC, the MPs also degrade into byproducts which themselves have bioactivity against fungal viability and promote host wound healing.

Methods. The *in vitro* release kinetics of VRC-loaded MPs were measured over 6 days in PBS at 37°C under mild agitation. Immunocompromised BALB/c mice with 5 mm full thickness cutaneous defects infected with *A. fumigatus* were treated with: Group 1) no infection, no treatment; Group 2) no treatment; Group 3) unloaded blank MPs; and Group 4) VRC-loaded MPs ($n = 10$ per group). Six days after treatment (nine days after initial infection), mice were euthanized. Wound bed size, fungal wound bed CFU, and histological presence of fungi were evaluated to determine the effects of MPs on wound healing and infection.

Results. MPs were capable of releasing VRC at concentrations above *A. fumigatus* MIC for at least six days. Mice treated with VRC-loaded MPs had significantly decreased wound size than mice with no treatment (64.2% vs. 19.4% wound reduction, $P = 0.002$) and were not significantly different than uninfected controls (64.2% vs. 58.1%, $P = 0.497$). Although wound healing was increased with VRC-loaded MPs, total fungal burden was not significantly different between infected groups.

Conclusion. Diol-based MPs are capable of local delivery of VRC to treat infected wound beds in an immunocompromised murine model of cutaneous aspergillosis. VRC-loaded MPs restored normal wound healing. As fungal burden was unchanged, the exact mechanism of enhanced wound healing needs to be further explored.

Disclosures. **D. P. Kontoyiannis**, Pfizer: Research Contractor, Research support and Speaker honorarium; Astellas: Research Contractor, Research support and Speaker honorarium; Merck: Honorarium, Speaker honorarium; Cidara: Honorarium, Speaker honorarium; Amplyx: Honorarium, Speaker honorarium; F2G: Honorarium, Speaker honorarium

1531. *In vivo* Pharmacodynamic Evaluation of Omadacycline (PTK 0796) against *Staphylococcus aureus* (SA) in the Murine Thigh Infection Model

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Background. Omadacycline is a novel aminomethylcycline antibiotic in development for acute bacterial skin and skin structure infection (ABSSSI) and community acquired bacterial pneumonia (CABP). The goal of the study was to determine the PK/PD targets in the murine thigh infection model against a diverse group of SA pathogens including MRSA.

Methods. 10 SA strains (4 MSSA, 6 MRSA) were utilized. MICs were determined using CLSI methods. Single dose murine plasma PK was previously determined in our lab and used for PK/PD analyses. The neutropenic murine thigh infection model was utilized for all treatment studies and drug dosing was by subcutaneous route. Four-fold increasing doses of omadacycline (0.25–64 mg/kg) were administered q12h to groups of mice infected with each strain. Treatment outcome was measured by determining organism burden in the thighs (CFU) at the end of each experiment (24 hours). The Emax Hill equation was used to model the dose–response data to the PK/PD index AUC/MIC. The magnitude of the PK/PD index AUC/MIC associated with net stasis and 1-log kill were determined in the thigh model for all strains.

Results. MICs ranged from 0.25–0.5 mg/L. At the start of therapy, mice had 7.1 ± 0.3 $\log_{10}$ CFU/thigh. In control mice, the organism burden increased 2.3 ± 0.3 $\log_{10}$ CFU/thigh over 24 hours. There was a relatively steep dose–response relationship observed with escalating doses of omadacycline. Maximal organism reductions were 4–5 $\log_{10}$ CFU/thigh compared with untreated controls. Stasis and 1 log-kill (from start of therapy) was observed against each strain. The AUC/MIC magnitude associated with stasis and 1-log kill endpoints are shown in the table.

SA Group (n = 10)	24 hours Static Dose (mg/kg)	Stasis AUC/MIC	24 hours 1 log kill Dose (mg/kg)	1 log kill AUC/MIC
Mean	13.9	23.7	45.7	78.1
Median	13.0	21.9	39.8	57.7
Std Dev	4.3	10.6	31.4	79.5

Conclusion. Omadacycline demonstrated in vivo potency against a diverse group of SA pathogens including MRSA strains. Stasis 24 hours AUC/MIC targets