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
\( \text{IC}_{50} \) required for 1 log 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/leg 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.** S. Good, Arex Pharmaceuticals, Inc.; Employee and Shareholder, Salary;
A. Moussa, Arex Pharmaceuticals, Inc.; Employee and Shareholder, Salary; J. C. Meillon,
Oxeltis; Employee and Shareholder, Salary; X. J. Zhou, Arex Pharmaceuticals, Inc.;
Employee and Shareholder, Salary; R. Pietropolo, Arex Pharmaceuticals, Inc.; Board Member,
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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 carbapenem-
ase producing Klebsiella pneumoniae (KPC) are associated with high mortality rates.
New methods to prevent or treat these infections are needed. Candida antitoxigen Hyr1p is
predicted to share structural and sequence homology with the hemagglutinin/hemolysin
protein (FhaB) and siderophore-binding protein of GNIB including AB and KPC, respectively.
Indicative 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
protect 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
12h-release assay. The efficacy of mAb in protecting against AB- or KPC-induced
The pneumonia was studied in neutropenic or immunocompetent CD1 mice by adminis-
teracting 30 µg of mAb (i.p.), on Day 1 + 4 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% of mAb reduced 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
ABMDR and KPC. Our results warrant the further development of these mAb as novel
immunotherapies against MDR GNB.

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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, and current antiviral 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 (dNHB) 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 (t1/2) of
analogue triphosphates (TPs) of selected prodrugs were measured in phytohaemagglutini-
stimulated human peripheral blood mononuclear cells (PBMCs) incubated with
100 µM prodrug. After 8 hours, medium was replaced with fresh medium without drug
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 pro-
drugs (~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 (EC50) as low as 0.021 µM. None of the prodrugs tested showed
significant cytotoxicity with dNHB cells, bone marrow stem cells or cardi-
omyocytes. 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 concen-
trations (~1,344 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 t1/2 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, Arex Pharmaceuticals, Inc.; Employee and Shareholder, Salary;
A. Moussa, Arex Pharmaceuticals, Inc.; Employee and Shareholder, Salary; J. C. Meillon,
Oxeltis; Employee and Shareholder, Salary; X. J. Zhou, Arex Pharmaceuticals, Inc.;
Employee and Shareholder, Salary; R. Pietropolo, Arex Pharmaceuticals, Inc.; Board Member,
Employee and Shareholder, Salary.

1526. In vivo Pharmacokinetic/Pharmacodynamic (PK/PD) Target Characterization of the Novel Echinocandin CID101 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. gla-
brata (CG) using the murine neutropenic disseminated candidiasis model.

**Methods.** Six 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 µg/mL (CA) or 6.2 ± 0.2 µg/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 aseptic-
ally 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
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1529. Efficacy of Oral APX001 in a Murine Model of Cryptococcal Meningitis
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The tissue burden in mice receiving FCN alone was 1.3 log lower than untreated mice. The tissue burden for mice receiving APX001 alone was 1.58 log lower than in untreated mice. Mice receiving combined therapy was 1.84 log lower than in untreated control mice. The tissue burden in mice receiving FCN alone was 1.3 log lower than untreated mice. 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 infected controls (64.2% vs. 58.1%, P = 0.497). Although wound healing was increased with VRC-loaded MPs, total fungaloadered 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.

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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, fungaloadered wound bed, and fungal 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 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 infected 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. K. J. Shaw. Amplyx Pharmaceuticals Inc.: Employee, Salary.

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 PK/PD of the studied compounds 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 associated with net stasis was determined for each strain. The exact mechanism of enhanced wound healing needs to be further explored.

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

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

| Strains | SA | 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 |
| Std Dev | 3.3 | 5.7 | 13.7 | 24.7 |
| Median  | 13.0 | 21.9 | 30.6 | 79.5 |

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