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

Wiley A. Schell, MD; Charles Giamberardino, M.R.; Karen J. Shaw, PhD; and John R Perfect, MD, FIDSA

**Background.** APX001 is a first-in-class intravenous and orally available broad-spectrum antifungal inhibitor of Gwlt, a protein involved in glycolysophosphatidylinositol 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 in triplicate and used for PK/PD analyses. The neutropenic murine thigh infection model was used to determine the effects of APX001 on fungal burden and infection.

**Results.** APX001 was significantly more active than monotherapy with APX001 (P < 0.0001), and was significantly more active than fluconazole monotherapy (P < 0.0001). APX001 and FCN in combination 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 = 0.0397), but no better than APX001 alone (P = 0.2500). (ii) APX001 and FCN each, alone, significantly inhibited growth of C. neoformans 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 first 24 hours, but further investigation is warranted to determine whether APX001 in combination with FCN has potential to be an effective oral regimen for treating cryptococcal meningitis.

**Conclusion.** APX001 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.** P. G. Ambrose, Cidara: Research Contractor, Research support; R. D. Andes, Cidara: Grant Investigator, Research support; Wiley A. Schell, Cidara: Research Contractor, Research support; P. G. Ambrose, Cidara: Research Contractor, Research support; R. D. Andes, Cidara: Grant Investigator, Research support.

---

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

Alexander Tataria, PhD; Nathaniel Albert, MS; Emma Watson, BS; Antoninos Mikos, PhD and Dimitrios P. Kontoyiannis, MD, ScD, PhD (Hon), FACP, FIDSA, FIMMM, FAAM, MD, Medicine, Baylor College of Medicine, Houston, Texas, MD Anderson Cancer Center, Houston, Texas, MD Anderson Cancer Center, Houston, Texas, MD Anderson Cancer Center, Houston, Texas

**Background.** Local delivery of antifungals may allow for high concentrations of therapeutics directly in wound beds infected with invasive fungi. In this work, microparticles (MPs) fabricated from a novel biodegradable polymer synthesized by a dialysis/10-deacetylation (DD) and fungal acidic 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 by 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, 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 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 untreated 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.** Dial-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.
were approximately 24. This is very similar to previous studies of omadacycline against S. pneumoniae (stasis AUC/MIC 18) and other PK/PD evaluations of tetracycline-class antibiotics. 1-log kill targets were only 2–3 fold more than stasis targets for each strain. This data should provide useful in the dose-regimen optimization of omadacycline.

Disclosures. D. R. Andes, Paratek: Grant Investigator, Research support

1532. Human Target Attainment Probabilities for Delafloxacin against Escherichia coli and Pseudomonas aeruginosa

Randall Hoover, PhD1; Andrea Marra, PhD1; Erin Duffy, PhD1 and Sue K. Cammarata, MD2; Melinta Therapeutics, New Haven, Connecticut, 1Pharmacology, Melinta Therapeutics, New Haven, Connecticut, 2Melinta Therapeutics, New Haven, Connecticut, Melinta Therapeutics, Inc., New Haven, Connecticut

Session: 167. Preclinical Study with New Antibiotics and Antifungals Friday, October 6, 2017: 12:30 PM

Background. Delafloxacin (DLX) is a broad-spectrum fluoroquinolone antibiotic under FDA review for the treatment of ABSSSI. Previous studies determined DLX bacterial stasis and 1-log bacterial reduction free AUC0–24/MIC (AUC0–24/MIC) targets for Escherichia coli (EC) and Pseudomonas aeruginosa (PA) in a mouse thigh infection model. The resulting PK/PD targets were used to predict DLX target attainment probabilities (TAP) in humans.

Methods. Monte Carlo simulations were used to estimate TAP with DLX 300 mg IV, q12hr. Human DLX plasma pharmacokinetics were determined in patients with ABSSSI in a Phase 3 clinical trial. Individual AUC values were analyzed and determined to be log-normally distributed. The parameters of the AUC distribution were used to simulate random values for AUC0–24, which were then combined with random MIC values based on 2014–2015 US distributions of skin and soft tissue isolates of EC (n = 108) and PA (n = 40), to calculate PK/PD TAPS.

Results. DLX/AUC0–24/MIC targets for bacterial stasis and 1-log bacterial reduction for EC were 14.5 and 26.2, and for PA were 3.81 and 5.02, respectively. The Monte Carlo simulations for EC predicted TAPs of 98.7% for stasis at an MIC of 0.25 µg/mL and 99.3% for 1-log bacterial reduction at an MIC of 0.12 µg/mL. The simulations for PA predicted TAPs of 97.3% for stasis and 86.5% for 1-log bacterial reduction at an MIC of 1 µg/mL.

E. coli MIC (µg/mL)

| Target | 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 |
|--------|-------|-------|------|------|------|------|----|--|
| Stasis | 100   | 100   | 100  | 100  | 100  | 97.8 | 50.4| 2.0|
| 1-Log Kill | 100  | 100   | 100  | 100  | 100  | 99.3 | 60.4| 5.0|

P. aeruginosa MIC (µg/mL)

| Target | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 5 |
|--------|------|------|------|------|----|---|---|---|---|
| Stasis | 100  | 100  | 100  | 100  | 100 | 97.3 | 45.9 | 1.7 | 0.5 |
| 1-Log Kill | 100 | 100  | 100  | 100  | 100 | 86.5 | 78.7 | 0.3 | 0.1 |

Conclusion. DLX 300 mg IV, q12hr, should achieve AUC24/MIC ratios that are adequate to treat ABSSSI caused by most contemporary isolates of EC and PA. For EC, isolates with DLX MICs ≤0.05 µg/mL comprised 73% of all isolates. For PA, isolates with DLX MICs ≤1 µg/mL comprised 88% of all isolates. Similar results would be expected for TAP with oral DLX 450 mg, q12hr.

Disclosures. R. Hooper, Melinta Therapeutics: Consultant, Consulting fee; A. Marra, Melinta Therapeutics: Employee, Salary; E. Duffy, Melinta Therapeutics: Employee, Salary; S. K. Cammarata, Melinta Therapeutics: Employee, Salary

1533. Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-Abdominal Abscess Model

Yanan Zhao, PhD3; Brendan Prideaux, PhD3; Yoji Nagasaki, MD3; Min H. Lee, MS3; Pei-Yu Chen, MS3; Landry Blanc, PhD3; Hansun Ho, PhD4; Cornelius J. Clancy, MD2; Min-Hong Nguyen, MD2; Yeronique Dartois, PhD2 and David Perlin, PhD4; 3Public Health Research Institute, New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, New Jersey; 4University of Pittsburgh, School of Medicine, Pittsburgh, PA

Session: 167. Preclinical Study with New Antibiotics and Antifungals Friday, October 6, 2017: 12:30 PM

Background. Intra-abdominal candidiasis (IAC) is a prominent invasive fungal infection associated with high mortality. Prompt antifungal therapy and source control are crucial for successful treatment. Echinocandin antifungal drugs are first-line agents. Yet, their clinical effectiveness is highly variable with known potential for breakthrough resistance, and little is known about drug exposure at the site of infection. Using matrix-assisted desorption/ionization (MALDI) mass spectrometry imaging as well as standard analytical techniques, we investigated the spatial and quantitative distribution in tissue lesions for two echinocandin drugs, micafungin and CD101, in a clinically relevant IAC mouse model.

Methods. Female 6–8 week old C57 mice weighing 18–22 g were infected intraperitonely (IP) with 1 × 10⁸ CFU of C. albicans SC5314 mixed with sterile stool matrix. Single IP doses of CD101 at 5 or 20 mg/kg (equivalent to humanized therapeutic dose) or micafungin at 5 mg/kg (therapeutic dose) were administered to mice at day 3 post-inoculation. Mice were sacrificed at just before antifungal treatment (n = 1), and at 1, 3, 6, 24, and 48 hours post-dose (n = 3 per group per time point). Liver and kidney lesions were collected for MALDI imaging. Laser capture microdissection (LCM) followed by liquid chromatography coupled tandem mass spectrometry (LC/MS-MS) was applied to 6 and 24 hours samples for drug exposure measurement. In a separate experiment, mice were treated with 2 or 3 doses of micafungin (5 mg/kg), or a single dose of CD101 (20 mg/kg). Drug accumulation was analyzed at 48 and 72 hours post the first dose.

Results. Drug accumulation within lesions was observed with both drugs at their humanized therapeutic dose. However, micafungin, even at steady-state, failed to approach the mutant prevention concentration (MPC) (16 µg/mL) of the infecting strain. CD101 demonstrated extensive penetration into the lesions after a single dose administration and persisted in lesions at above MIPC level of 29.7 µg/mL at 72 hours postdose.

Conclusion. These findings indicate that current echinocandin drugs may be limited by penetration at the site of infection, which have implications for clinical outcomes and emergence of resistance in patients with IAC.

Disclosures. C. J. Clancy, Merck: Received research funding, Research support; Astellas: Received research funding, Research support; CIDara: Received research funding, Research support; Astellas: Scientific Advisor, Advisory board; Merck: Scientific Advisor, Advisory board; CIDara: Scientific Advisor, Advisory board; D. Perlin, CIDara: Research Contractor and Scientific Advisor, Research grant; Amplyx: Research Contractor and Scientific Advisor, Research grant; Matnas: Scientific Advisor, Research support; Scynexis: Research Contractor and Scientific Advisor, Research grant; Merck: Research Contractor, Research grant; Astellas: Research Contractor, Research grant

1534. In Vitro Synergistic Activity of Biapenem Combination with Sulbactam, Colistin, and Fosfomycin Sodium Against Multidrug-resistant Acinetobacter baumannii Isolates from Tertiarycare Hospitals in Thailand

Jantana Houngsaitong, MS1; Preecha Montanakitkul, Assoc. Prof2; Taniya Paiboonvong, MS3; and Mullika Chomnawang, Assoc. Prof3; 1Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand, 2Faculty of Pharmacy, Mahidol University, Bangkok, Thailand, 3Faculty of Pharmacy, Siam University, Bangkok, Thailand, 4Department of Microbiology, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

Session: 167. Preclinical Study with New Antibiotics and Antifungals Friday, October 6, 2017: 12:30 PM

Background. Acinetobacter baumannii has become a major cause of nosocomial infections worldwide due to highly resistant to various groups of antibiotic agents. This in vitro study was determine the MICs for sulbactam, colistin, fosfomycin sodium individually and synergistic activity of both in combination with biapenem against multidrug-resistant A. baumannii.

Methods. The MICs and synergistic interaction of sulbactam, colistin, fosfomycin sodium and biapenem were determined according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2016) by the chequerboard technique. 40 clinical MDR-Acinetobacter baumannii isolates from 13 tertiarycare hospitals in Thailand were tested. The synergistic effect was evaluated by the fractional inhibitory concentration index (FICI).

Results. The MICs for MDR- Acinetobacter baumannii results of biapenem and other agents are shown in Figure 1. The FICI results showed all 40 strains (100%) had an FICI ≤ 0.5, suggesting a synergistic effect of colistin in combination with biapenem (Table 1). MICs of mostly strains were decreased two to four doubling dilutions for both antibiotics agents. Moreover, 95% of isolates have MICs to colistin and fosfomycin sodium lower than sensitivity breakpoint when combined with biapenem. The result showed no data on the antagonistic effect (FICI > 4) of all biapenem-based combination.

Conclusion. The combination of colistin or fosfomycin sodium show synergistic pattern and MIC improvements for all strains. For that reason, the use of colistin, fosfomycin sodium combined with biapenem could be a promising treatment option for MDR- Acinetobacter baumannii.

FIGURE 1. MIC for multidrug resistant Acinetobacter baumannii biapenem (n = 63), sulbactam (n = 40), colistin (n = 40), and fosfomycin sodium (n = 40).

Poster Abstracts • OFID 2017:4 (Suppl 1) • S479