1529. Efficacy of Oral APX001 in a Murine Model of Cryptococcal Meningitis
Wiley A. Schell, PhD*; Charles Giamberardino, M.R.; Karen J. Shaw, PhD; and John R. Perfect, MD, FIDSA; 1 Medicine, Duke University Medical Center, Durham, North Carolina, 2 Infectious Diseases, Duke University Medical Center, Durham, North Carolina, 3 Amylyx Pharmaceuticals Inc., San Diego, California, 4 Medicine, Duke University School of Medicine, Durham, North Carolina.

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

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. Brain and lung of mice 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 in mice receiving FCN alone was 1.3 log lower than in untreated mice. The tissue burden in mice receiving APX001 alone was 1.58 log lower than in 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 = 0.0397), but no better than APX001 alone (P = 0.2590). (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 was observed within the first 24 hours, 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.

1530. Dial-Based Polymer Microparticles for Treatment of Cutaneous Aspergillosis in an Immunocompromised Murine Model
Alexander Tatara, PhD*; Nathanial Albert, MSc; Emma Watson, BS; Antoninos Mikos, PhD and Dimitrios P. Kontoyiannis, MD, ScD, PhD (Hon), FACP, FIDSA, FEMM, FAAM, Medicine, Baylor College of Medicine, Houston, Texas, 2 MD Anderson Cancer Center, Houston, Texas, 3 Bioengineering, Rice University, Houston, Texas. 4 The University of Texas MD Anderson Cancer Center, Houston, Texas

Session: 167. Preclinical Study with New Antibiotics and Antifungals
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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 by atom transfer radical polymerization (ATRP) and functionalized for targeting of 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, fungoidal 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 untreated 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. 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.

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