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Pharmacodynamics of APX001A, the active moiety of APX001, in pulmonary and nasal in vitro models of invasive aspergillosis

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Background: The treatment of invasive aspergillosis is problematic due to high lethality coupled with limited treatment options. Antifungal drugs have issues of toxicity, drug interactions and resistance, the latter being a prime example of the global AMR health problem. Thus, the development of new antifungal compounds is essential. APX001A is the active moiety of APX001 prodrug, a novel first-in-class antifungal agent that selectively inhibits Gwt1, an enzyme required for GPI anchor biosynthesis. APX001A has broad-spectrum activity *in vitro* against *Candida* and *Aspergillus,* including strains resistant to currently available antifungal drugs. The aim of this study was to evaluate the *in vitro* pharmacodynamics of APX001A against the most common pathogenic species of *Aspergillus, A. fumigatus* and *A. flavus*.

Material/methods: To evaluate the efficacy of APX001A against *A. fumigatus*, a well-characterised *in vitro* model of human pulmonary invasive aspergillosis was used. Briefly, a bilayer of human pulmonary artery endothelial cells and human alveolar epithelial cells were cultured on a semipermeable polyester membrane. The bilayer was inoculated with *A. fumigatus* conidial

suspension on the alveolar surface. Three strains of *A. fumigatus* were used: a triazole wild type (NIH4215) and two strains with different *CypA* amino acid substitutions (L98H and G138C) that confer resistance to triazole antifungal agents. An additional *in vitro* model that substitutes human nasal epithelial cells for the epithelial layer was developed to study the pharmacodynamics of APX001A against *A. flavus*. Two *A. flavus* clinical strains were used (LEMI764 and LEMI1024). Infected cell bilayers were then exposed to seven different APX001A concentrations ranging from 0.015 to 1mg/L for 48 hours. Media from the endothelial surface, as well as epithelial surface lavage, were analysed. In both models, galactomannan (GM) was used as the readout. Experiments were performed in triplicate.

Results: In the *A. fumigatus* pulmonary infection bilayer model, 0.25 mg/L of APX001A suppressed the GM index (<1) in the endothelial compartment infected with NIH4215. For strains L98H and G138C, suppression of GM was observed at only 0.03 mg/L and 0.125 mg/L, respectively. For the *A. flavus* nasal infection model, the lowest concentration of APX001A tested, 0.015mg/L, suppressed GM in the endothelial surface for both strains tested.

Conclusions: These findings suggest that APX001A is a potent antifungal agent against *A. fumigatus* and *A. flavus*. APX001A prevents invasion through cell bilayers and may prevent angioinvasion. APX001A induces a concentration-dependent decline in galactomannan. Further *in vivo* studies are required to fully characterise the pharmacodynamics of APX001A.