Accumulation of a novel inhaled azole, PC945 in alveolar cells in temporally neutropenic immunocompromised mice infected with *Aspergillus fumigatus*

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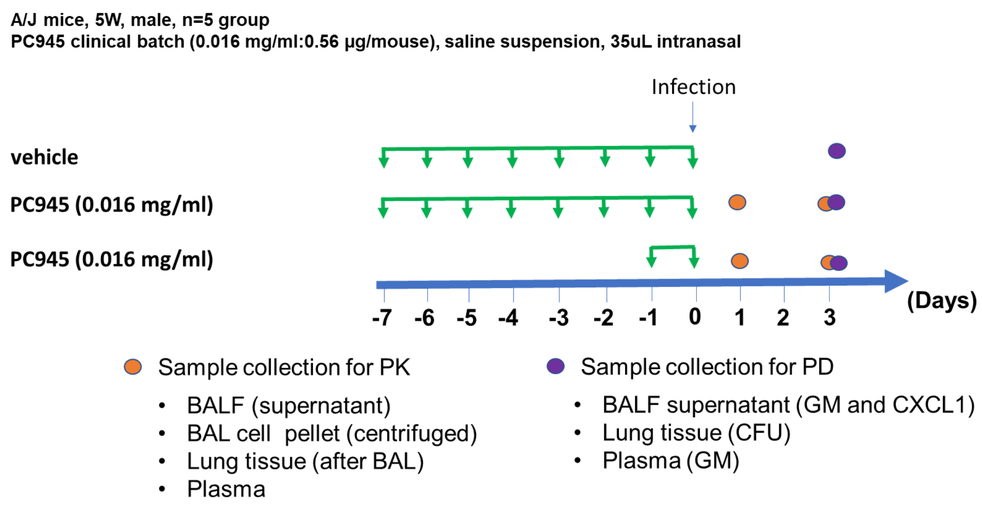
Introduction/Aim

PC945 is a novel inhaled antifungal agent[1,2], whose profile maximises the likelihood of clearing a pulmonary *Aspergillus* infection, while minimising the risk of either direct toxicity or toxicity/medical complications arising from unwanted drug-drug interactions. Since the target of PC945 is pulmonary *Aspergillus* infections, attempts to develop a useful pharmacokinetic (PK): pharmacodynamic (PD) model to aid clinical development have focused on exploring the relationship between local concentrations of PC945 in the lung and antifungal effects.

Methods

A/J mice (males, 5 weeks old) were dosed with hydrocortisone (125 mg/kg, sc,) on days 3, 2 and 1 before infection, and with cyclophosphamide (250 mg/kg, ip) 2 days before infection to induce temporary neutropenia. On day 0, animals were infected intranasally with 30 µL of the spore suspension of *Aspergillus fumigatus* (*A. fumigatus*) (ATCC 13073) at a concentration of 1.67 × 10^8 spores /mL in physiological saline. PC945 (0.016 mg/mL) was treated intranasally on days -7 to 0 (8 days) or Day -1 to 0 (2 days), and animals were culled on day 3 post *Aspergillus fumigatus* intranasal inoculation. Bronchoalveolar lavage fluid (BALF), lung and plasma were collected 24 or 72 hrs post the last dose (post infection) for biomarker and PK analysis. BAL cell pellet (alveolar cells) and BALF supernatant were collected separately after centrifugation of BALF samples (Figure 1).

Figure 1. Treatment schedule



Results

Intranasally dosed PC945 showed much stronger antifungal effects (CFU in lung, galactomannan (GM) in BALF and plasma) with 8 days rather than than 3 days of prophylaxis (Figure 2).

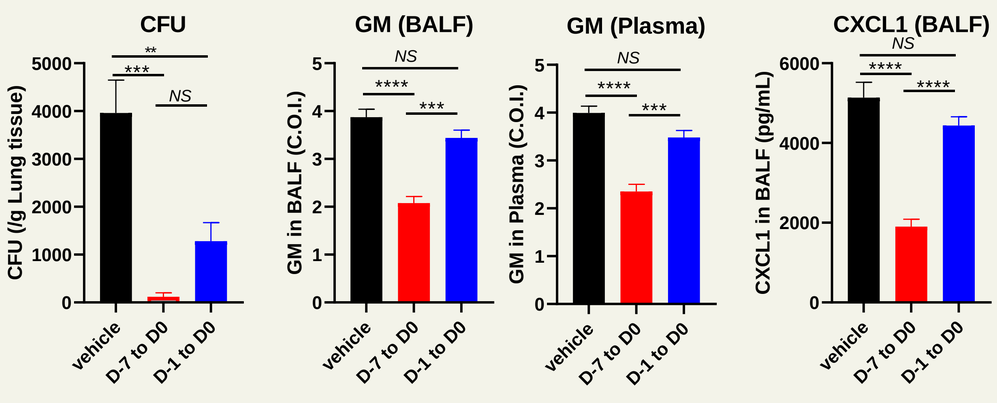


Figure 2. Summary of pharmacodynamics of extended prophylaxis treatment with PC945 in *A. fumigatus* infected immunocompromised A/J mice

PC945 was not detectable in plasma at either 24hrs or 72hrs post the last dose, and much higher levels of PC945 were detected in the lung at 24hrs post the last dose after 8 days (709±126 ng/g lung) than after 2 days prophylaxis (301±56 ng/g lung). Interestingly, little or no PC945 was detected in BAL supernatant (<10 ng/mL) but significantly higher levels were detected in BAL cell pellets (Figure 3). The concentrations in alveolar cell pellets show an impressive correlation with anti-fungal activity in the lung (Figure 4, Table 1).

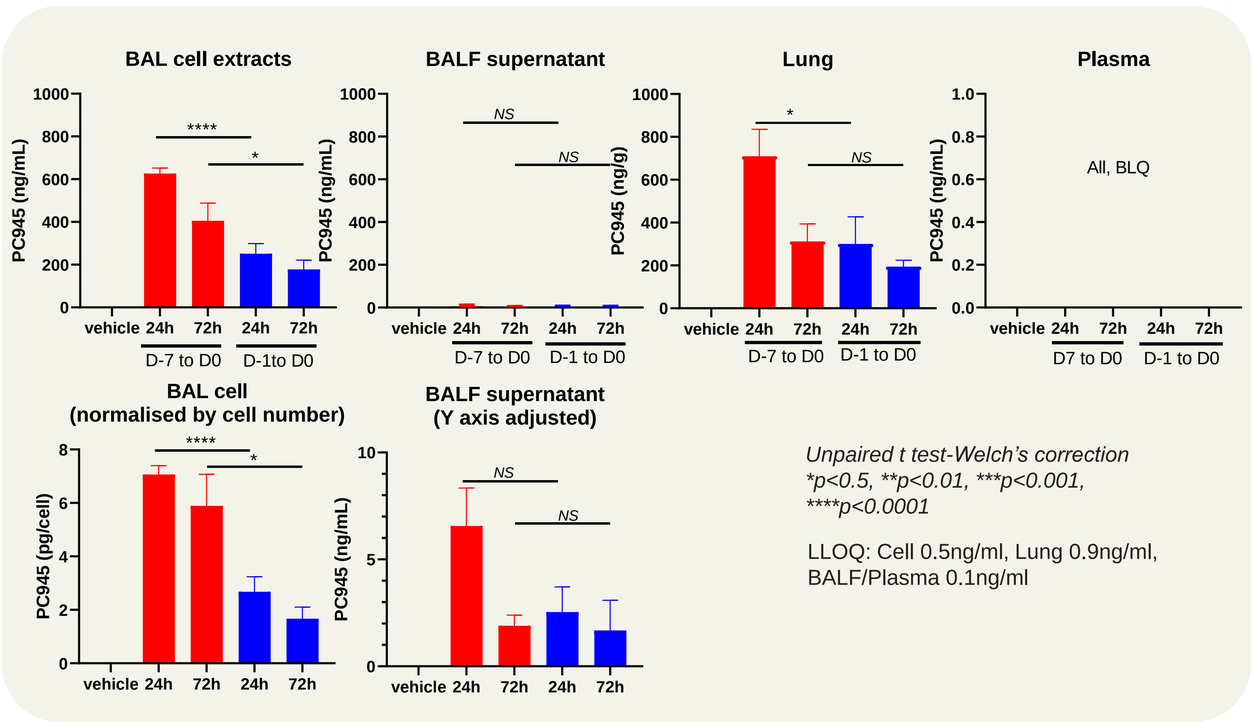


Figure 3. Summary of pharmacokinetics of extended prophylaxis treatment with PC945 in *A. fumigatus* infected immunocompromised A/J mice

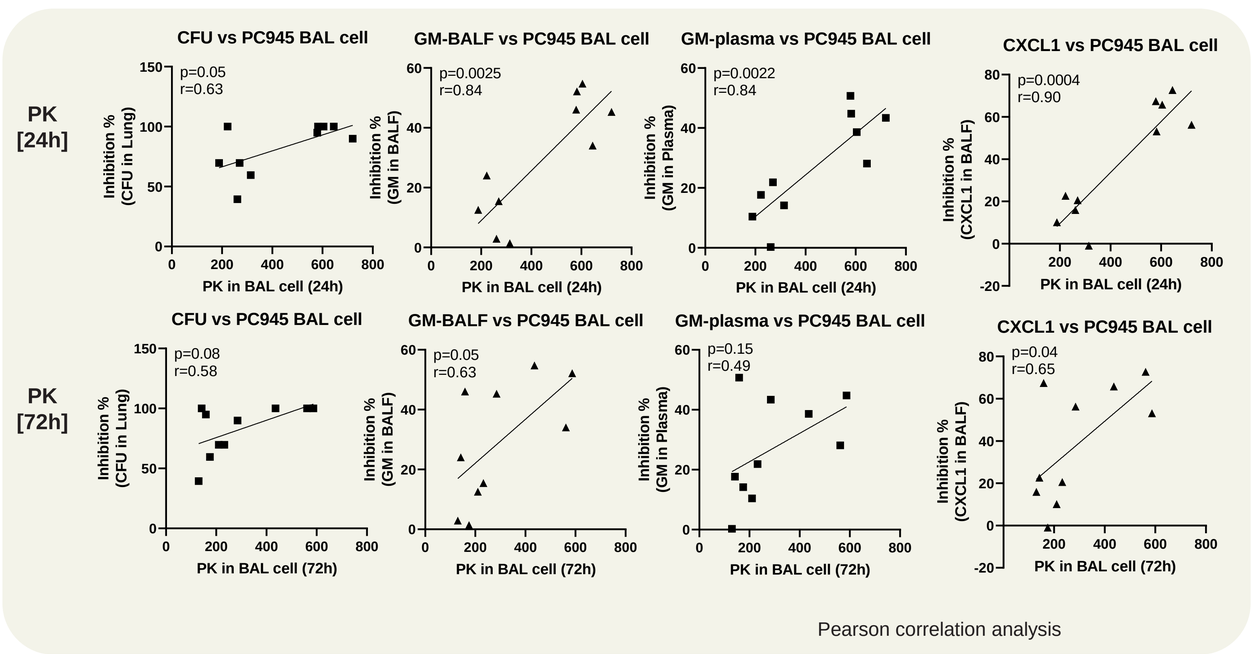


Figure 4. PK (BAL cell)-PD analysis : Better correlation with PK [24h]

Table 1. Correlation between PK (BAL cell)-PD analysis

	PK BAL cell (24h)	PK BAL cell corrected (24h)	PK Lung (24h)
CFU	r= 0.63, p=0.05	r= 0.62, p=0.06	r= 0.47, p=0.17
GM-BALF	r= 0.84, p=0.0025	r= 0.83, p=0.0027	r= 0.51, p=0.062
GM=Plasma	r= 0.84, p=0.0022	r= 0.85, p=0.0019	r= 0.45, p=0.19
CXCL1	r=0.90. p=0.004	r=0.90. p=0.004	r= 0.77, p=0.0091
	PK BAL cell (72h)	**PK BAL cell corrected (72h)**	**PK Lung (72h)**
CFU	r=0.58, p=0.05	r=0.63, p=0.05	r= 0.41, p=0.23
GM-BALF	r=0.63, p=0.05	r=0.72, p=0.018	r= 0.49, p=0.15
GM=Plasma	r=0.49, p=0.15	r=0.59, p=0.074	r= 0.40, p=0.25
CXCL1	r=0.65, p=0.04	r=0.72, p=0.018	r= 0.37, p=0.30

- The correlations with lung PK are poorest across the board. Whether that's because lung PK is inherently less predictive of PD activity or because the estimates of lung drug concentrations are more variable than those in BAL cells is unclear.
- For all 3 PK parameters the correlation of PD activity with drug concentration is better using 24 hour than 72 hour data.
- The best correlation (24 and 72 hour) is with corrected BAL cell PK.

Conclusion

Intranasally dosed PC945 accumulated in alveolar cells. These observations will be pursued, and it is intended that BAL cell concentrations of PC945 be measured in the future clinical study rather than standard BALF measurement.

References

1. Colley T et al., Antimicrob Agents Chemother. 2017 Apr 24;61(5). pii: e02280-16.
2. Kimura G et al., Antimicrob Agents Chemother. 2017 Aug 24;61(9). pii: e00124-17.