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Paper Poster Session
New antibiotics against Gram-negative bacteria

Metabolism and excretion of the novel macrocycle antibiotic POL7080

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Background: POL7080 is a novel antimicrobial macrocycle peptide being for the treatment of serious infections by *Pseudomonas aeruginosa*, such as those causing ventilator-associated pneumonia (VAP). POL7080 functions through a novel mode-of-action by interacting with Lipopolysaccharide transport protein D (LptD), a bacterial target critical for outer membrane biogenesis. As POL7080 is a member of a new class of antibiotics, little is known about its disposition.

Material/methods: A quantitative whole body autoradiography (QWBA) and excretion study was performed in rats using ^{14}C-POL7080. In vitro experiments examined potential CYP interactions and potential involvement of a wide range of transporters.

Results: POL7080 is polybasic and displays low passive permeability. It is stable in vitro in S9 and microsomal fractions from human liver, kidney and lung, with slight turnover over several hours seen only in lung microsomes. POL7080 was also stable in rat, mouse and human plasma (10 µg/mL; 88%-93% still available after 4 hours) and based on *in vitro* data a hydrolysis of RG7929 due to human renal membrane dipeptidase (DHP-1) is unlikely. POL7080 also displayed no inhibition against CYP-P450 metabolic enzymes, suggesting minimal interaction potential. A QWBA study has shown rapid uptake of radioactivity into the tissues of rats dosed intravenously with ^{14}C-POL7080, with major uptake into the kidney. Investigations with a wide range of clinically relevant drug transporters did not identify any significant interactions with POL7080. However, POL7080 was found to be a substrate for megalin receptor-mediated endocytosis and inhibited megalin-mediated uptake of gentamicin *in vitro* using opossum kidney cells (IC50 5.84 µM). The megalin receptor-mediated uptake of POL7080 was strongly inhibited by colistin (IC50 = 3.07 ± 1.38 µM) and somewhat less by gentamicin (IC50 = 37.43 ± 7.55 µM).

Conclusions: POL7080 was stable *in vitro* using several test conditions used to investigate drug metabolism of small molecule and peptides. *In vivo* POL7080 undergoes glomerular filtration, reabsorption in the proximal tubule, probably involving the megalin-cubulin complex, which is commonly observed for small proteins and peptides that undergo glomerular filtration. These results are supportive of POL7080 as a potential antimicrobial agent and warrant further clinical investigations.