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In-vitro drug transporter interaction studies with the outer membrane protein targeting anti-pseudomonal antibiotic murepavadin (POL7080)

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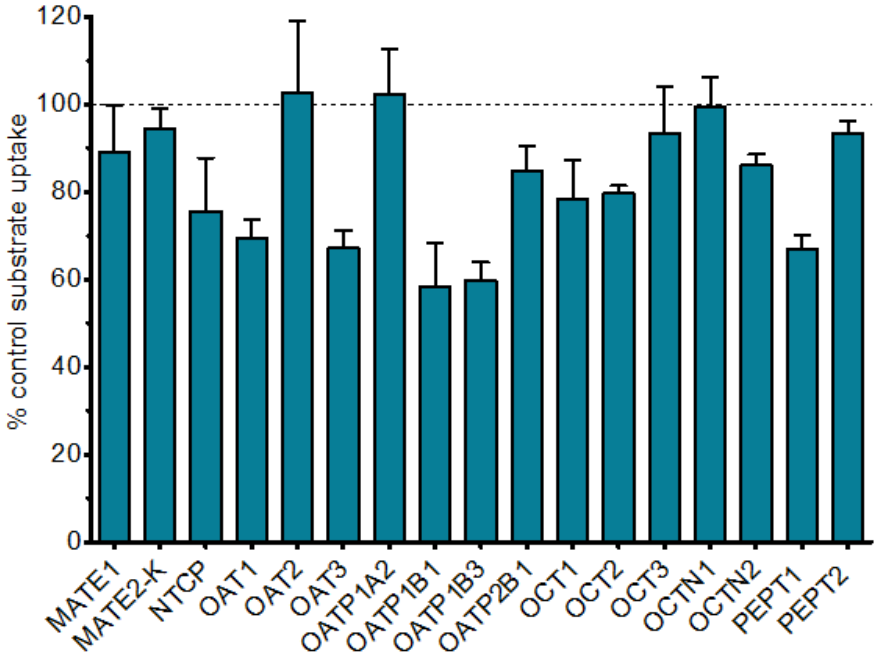
Background: Murepavadin (POL7080) represents the first member of a novel class of outer membrane protein targeting antibiotics. It specifically interacts with LptD and inhibits LPS transport. Murepavidin is being developed by Polyphor for the treatment of serious infections by Pseudomonas aeruginosa. POL7080 is the first in a new class of antibiotics not causing cell membrane lysis but acts through its binding to the outer membrane protein LptD, thereby disrupting membrane integrity. We have evaluated potential transporter based drug-drug interactions by investigating the extent of POL7080-dependent inhibition of several hepatic and renal transporters known to be involved in clinically relevant drug interactions.

Material/methods: Transporter inhibition studies were performed in CHO-K1, HEK293 or MDCKII cells over-expressing the human transporters MATE1, MATE2-K, NTCP, OAT1, OAT2, OAT3, OATP1A2, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, OCT3, OCTN1, OCTN2, PEPT1 and PEPT2 in a 96-well format at 37°C in assay buffer (pH 7.4). Control activity values were determined for each transporter by incubating cells in the absence of POL7080 with radio labeled probe substrates for between 2-10 minutes, depending on transporter. In addition, the effect of POL7080 on MDR1-mediated bidirectional digoxin transport was investigated in Caco-2 cells over 120 minute

incubations. Reference inhibitors provided positive controls. The effect of POL7080 (0.3-300 □M) on radiolabel probe substrate uptake was evaluated and was expressed as % control substrate uptake.

Results: The positive controls produced between 74-100% inhibition of probe substrate uptake. POL7080 did not significantly inhibit probe substrate accumulation by MATE-1, MDR1, OAT2, OATP1A2, OATP2B1, OCT2, OCT3, OCTN1, OCTN2 or PEPT2. POL 7080 showed no inhibition of digoxin permability or efflux by Caco-2 monolayers. At the top concentration used (300 □M), POL7080 slightly inhibited NTCP (31%), OAT1 (30%), OAT3 (33%), OATP1B1 (41%), OATP1B3 (40%) and OCT1 (25%) and PEPT1 (33%). It was not possible to calculate IC50 values for POL7080 any of the transporter systems tested.



Conclusions: The moderate inhibition of several transporters by POL7080 at 300 μM suggests that it is unlikely to cause drug-drug interactions mediated through these transporter mechanisms at predicted clinical exposures (<13 μM).