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P1665 Outer membrane protein targeting antibiotics (OMPTAs): in vivo characterization of a novel class of compounds with respect to pharmacokinetics, efficacy and renal toxicity

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Background: The OMPTAs (outer membrane protein targeting antibiotics) are a new class of antibiotics being developed for the treatment of serious Gram-negative infections. Here we investigated the pharmacokinetics, *in vivo* activity when tested against *E. coli* in the neutropenic thigh infection model and the potential for renal toxicity

Materials/methods: In the PK study, male CD1 mice 7-8 weeks were dosed subcutaneous with 10 mg of compound. Blood were obtained and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). Renal toxicity was evaluated in CD1 mice (5 mice/group) were dosed subcutaneous at 12 mg/kg, 6 times a day (every 2h) and clinical signs were monitored. At termination all animals were subjected to gross necropsy and tissues examined macroscopically. The kidneys were histopathologically examined as previously described (Roberts *et a*l, 2015). Colistin and colistin-nonapeptide were used as controls. *In vivo* efficacy was evaluated in neutropenic CD1 mice. Mice were infected with *E. coli* from frozen stock diluted to an optimal concentration with PBS. The inoculum concentration was ~1.35 x 10^7 cfu/mL (6.75 x 10^5 cfu/thigh). Polymyxin B and meropenem were used as control antibiotics

Results: The $t_{1/2}$ of the compounds ranged between 0.9-1.3h, the C_{max} from 2-5 mg/L and the AUC between 5-10 mg*h/L. In the renal toxicity assay colistin demonstrated a mild to moderate toxicity with histological score of 24, whereas the colistin nonapeptide was significantly less toxic with a histological score of 6. The OMPTA compounds showed a range of activities with the lead compounds having a very low histological scores of 1-2. The OMPTA compounds are active in the thigh infection model with 1-2 log decrease in CFUs, Polymyxin B showed a 1-log decrease whereas meropenem had no effect.

Conclusions: The OMPTA compounds show potent *in vitro* and *in vivo* antimicrobial activity towards both WT and MDR organisms. When evaluated for nephroptoxicity, the lead OMPTA's had little effect on the mouse kidney *in vivo*, suggesting a significantly lower nephrotoxic potential compared to colistin. The novel OMPTA class of antibiotics has a significant potential to provide novel antibiotics against clinically-relevant Gram-negative pathogens for which there are currently limited treatment options.