

P1666 **Outer membrane protein targeting antibiotics (OMPTAs): a novel class with potent in vitro and in vivo activity against E. coli-harboring mcr-1 and/or mcr-3 genes**

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Background: The OMPTAs (outer membrane protein targeting antibiotics) are a new class of antibiotic being developed for the treatment of Gram-negative infections belonging to the clinically relevant ESKAPE pathogens. The OMPTAs are active against multidrug-resistant Gram-negative organisms including those resistant to colistin through chromosomal mutations or possession of the mcr colistin resistance genes. Here we investigated the in vitro activity of OMPTAs towards several strains as well as the *in vivo* activity of the compounds when tested against *E. coli* harboring mcr-1 and/or mcr-3 genes.

Materials/methods: The activity of the OMPTA antibiotics was tested against a panel of fifteen recent isolates of *E. coli* harboring the mcr-1 and/or mcr-3 genes. All isolates were tested by the CLSI broth microdilution method (M07-A10) in cation-adjusted Mueller-Hinton broth and the EUCAST interpretive criteria were used to determine susceptibility for comparators. To evaluate the OMPTA's *in vivo*, mice were rendered neutropenic with injections with cyclophosphamide day -4 and -1. On Day 0, mice were infected by IP administration of either 1.4×10^7 cfu/mL *E. coli* AF45 (mcr-1) or 3.3×10^7 cfu/mL *E. coli* SNTR36B6 (mcr-3). The cfus in the peritoneal wash were counted at the start of treatment and at the end of treatment. The OMPTA compounds were dosed at 30 mg/kg q12h (*E. coli* AR45 (mcr-1) and 10 mg/kg (*E. coli* SNTR36B6 (mcr-3)) and the control antibiotics for the studies were tigecycline (40 mg/lkg) or meropenem (40 mg/kg) respectively.

Results: The OMPTA antibiotics show broad and very potent coverage against *E. coli* harboring mcr-1 and/or mcr-3 genes. The MIC values for the OMPTA's were between 0.03 and 0.5 mg/L for the organisms tested. *In vivo* the OMPTA compounds showed a 2-log reduction in CFUs compared to start of treatment and were moderately more potent than the comparator antibiotics tested.

Conclusions: The OMPTA antibiotics display potent activity against *E. coli* harboring the mcr-1 and/or mcr-3 genes both *in vitro* and *in vivo*. This class therefore has a significant potential to provide novel antibiotics against clinically-relevant Gram-negative pathogens for which there are currently limited treatment options.