P1310
Paper Poster Session
New antibiotics against Gram-negative bacteria

TP-6076 is efficacious in a mouse pneumonia model with carbapenem-resistant Acinetobacter baumannii (CRAB) and retains potency against common tetracycline-resistance mechanisms

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Background: TP-6076, a novel synthetic tetracycline, previously demonstrated potent activity *in vitro* against carbapenem-resistant *Enterobacteriaceae* (CRE) and CRAB, and efficacy against KPC-producing *Klebsiella pneumoniae* (KP) in a mouse pneumonia model. TP-6076 was evaluated in a mouse pneumonia model with CRAB and tested *in vitro* against *Enterobacteriaceae* and *A. baumannii* (AB) expressing tetracycline-specific (*tet*) and intrinsic resistance mechanisms.

Material/methods: Female CD-1 mice (n=5/group) rendered neutropenic with cyclophosphamide were infected intranasally with 6.98 $\log_{10}$ colony forming units (CFU)/mouse of CRAB strain AB1709. TP-6076 was administered IV BID at 5, 15 or 40 mg/kg for 72 hours, starting at 2 hours post-infection. Tigecycline was given at 50 mg/kg IV BID as a control. Lung CFUs were quantified at pre-dose (2 hr), 24, 48 and 72 hrs. Strains with defined tetracycline- and tigecycline-resistant mechanisms in *Escherichia coli* (EC), AB and KP were evaluated for susceptibility using broth microdilution CLSI methodology.

Results: TP-6076 was bactericidal *in vivo* against CRAB, as defined by a ≥3-$\log_{10}$ reduction in mean lung CFUs versus pre-dose (6.50 $\log_{10}$ CFU/lung), at 24 hrs for the 15 mg/kg and 40 mg/kg doses (3.26 and 2.47 $\log_{10}$ CFU/lung, respectively), and at 48 and 72 hrs for all three doses (≤2.35 to 2.62 $\log_{10}$ CFU/lung). At 48 and 72 hrs, TP-6076 showed ≥7 $\log_{10}$ CFU reductions versus concurrent untreated controls (9.53 and 9.61 $\log_{10}$ CFU/lung, respectively). In contrast, tigecycline at 50 mg/kg produced $\log_{10}$ CFU reductions of 0.59, 1.37, and 2.93,versus pre-dose lung CFUs, at 24, 48 and 72 hrs, respectively. TP-6076 activity was minimally impacted by recombinant overexpression of the most common *tet* determinants in EC DH10B (*tet*(A), (B), (K) efflux; *tet*(M), *tet*(Q) ribosomal protection; and *tet*(X) covalent inactivation, showing MIC values ranging from ≤0.004 to 0.25 µg/mL against all *tet* determinants. TP-6076 was potent against panels of clinical isolates containing *tet*(A) (AB, n=3; EC n=46; KP, n=34) , *tet*(B) (AB, n=18; EC, n=76; KP, n=5), *tet*(D) (EC, n=3; KP, n=34), *tet*(M) genes (EC, n=5), showing a maximum MIC_{90}=1 µg/mL. The TP-6076 MIC increased 16-fold to 0.125 µg/mL in an AB *adeS* mutant but returned to within 2-fold the parental MIC in an *adeS adeB* double mutant, confirming that TP-6076 is a substrate for the AdeABC pump. TP-6076 was potent against KP986 overexpressing *ramA (*MIC= 1µg/mL), and showed an $MIC_{50/90}$ =1/2 µg/mL against a panel of isolates (n=29) with *ramR* sequence variations. The $MIC_{50/90}$ of TP-6076 was 1/4 against tigecycline-resistant KP (n=47) µg/mL.

Conclusions: TP-6076 showed potent bactericidal activity *in vivo* against CRAB in a mouse pneumonia model, and was ≥4-fold more potent than tigecycline against AB, EC and KP isolates expressing common tetracycline-specific and intrinsic multidrug-resistance mechanisms.