

POL7001 IS HIGHLY EFFICACIOUS IN THE MURINE NEUTROPENIC LUNG INFECTION MODEL

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Objective

POL7001 represents a member of a novel class of outer membrane protein targeting antibiotics. Like murepavidin POL7001 is a pathogen-specific antibiotic with a very potent and selective antibacterial activity¹.

POL7001 specifically interacts with LptD and inhibits LPS transport². The MIC of POL7001 towards the infecting organisms covered a range from 0.063 mg/L to 0.25 mg/L which covers the MIC₉₀ range of POL7001 against this organism (0.125 mg/L).

In these studies the efficacy of POL7001 was assessed in neutropenic murine models of pneumonia due to UDR and MDR *Pseudomonas aeruginosa* clinical isolates.

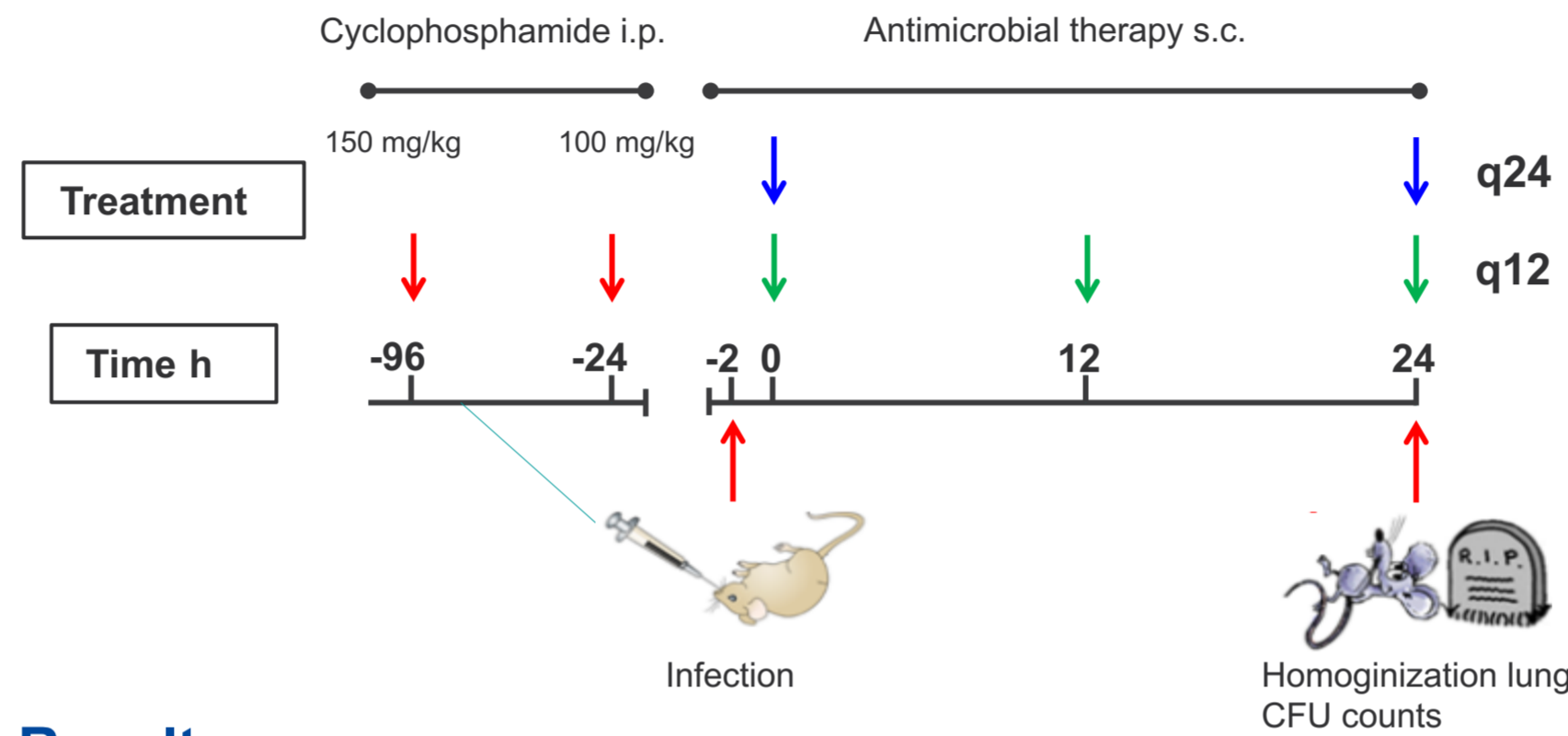
Methods

- All isolates were tested by the CLSI broth microdilution method (M07-A8³, 2009) in cation-adjusted Mueller-Hinton broth.
- CD-1 mice were inoculated intranasally with a pipette with 0.05 mL of bacteria suspension containing approximately 10⁶ CFU.
- The mice were treated subcutaneously in the neck region with a single dose at 2 hour post infection or with b.i.d dosing at 2 and 14 hours post infection.
- The total daily dose ranged from 1.88 mg/kg given as a single dose to 60 mg/kg given b.i.d. Comparator antibiotics were used.
- The mice were then euthanized; the lungs were collected for determining the CFU counts.
- The lung bacterial burden was determined at 2 and 26 hrs post inoculation.

References

- ¹Cigana et al, Antimicrob. Agents Chemother, 2016, 60: 4991-5000
- ²Srinivas et al, Science, 2010, 327: 1010-1013
- ³CLSI. M07-A8. Clinical Laboratory Standards Institute, 2009. Wayne PA

Figure 1: A diagram of the procedures followed



Results

Table 1: MICs of the strains evaluated *in vivo*

Strain / MIC = mg/L	POL7001	Polymyxin B	Aztreonam	Ceftazidime	Cefepime	Imipenem	Meropenem	Doripenem	Piperacillin tazobactam	Ciprofloxacin	Levofloxacin	Gentamicin	Tobramycin	Amikacin
ATCC 27853	0.063	2	8	8	4	8	8	4	32	0.125	0.5	2	0.5	4
ATCC BAA 2113	0.125	2	16	4	4	0.5	0.5	0.25	16	0.125	0.5	1	0.5	2
NCTC 13437	0.125	1	>16	>32	>16	>8	32	>4	32	>4	>4	>8	>8	32
X11045	0.063	2	2	1	2	2	1	0.25	2	0.25	0.5	4	1	16
9	0.25	1	4	1	4	0.5	0.25	0.25	4	0.25	0.5	2	0.5	4
12	0.125	2	16	16	8	8	4	4	64	>4	>4	>8	>8	4
15	0.125	2	>16	32	8	8	4	4	>64	>4	>4	>8	>8	4
16	0.125	1	16	4	4	8	8	>4	32	>4	>4	≤0.5	≤0.125	0.5
22	0.125	1	8	32	16	4	4	4	16	>4	>4	>8	>8	>32

- From the 9 isolates tested 5 are considered MDR.
- The MICs of the isolates ranged from 0.063 to 0.25 mg/L of which 6 were equal to the MIC₉₀
- POL7001 displays a potent in vitro activity towards these isolates
- The models displayed a robust infection with generally a 3-log growth from start of treatment
- Comparator antibiotics often showed little effect in this model

Figure 2: Effect of POL7001 in the murine neutropenic lung infection model

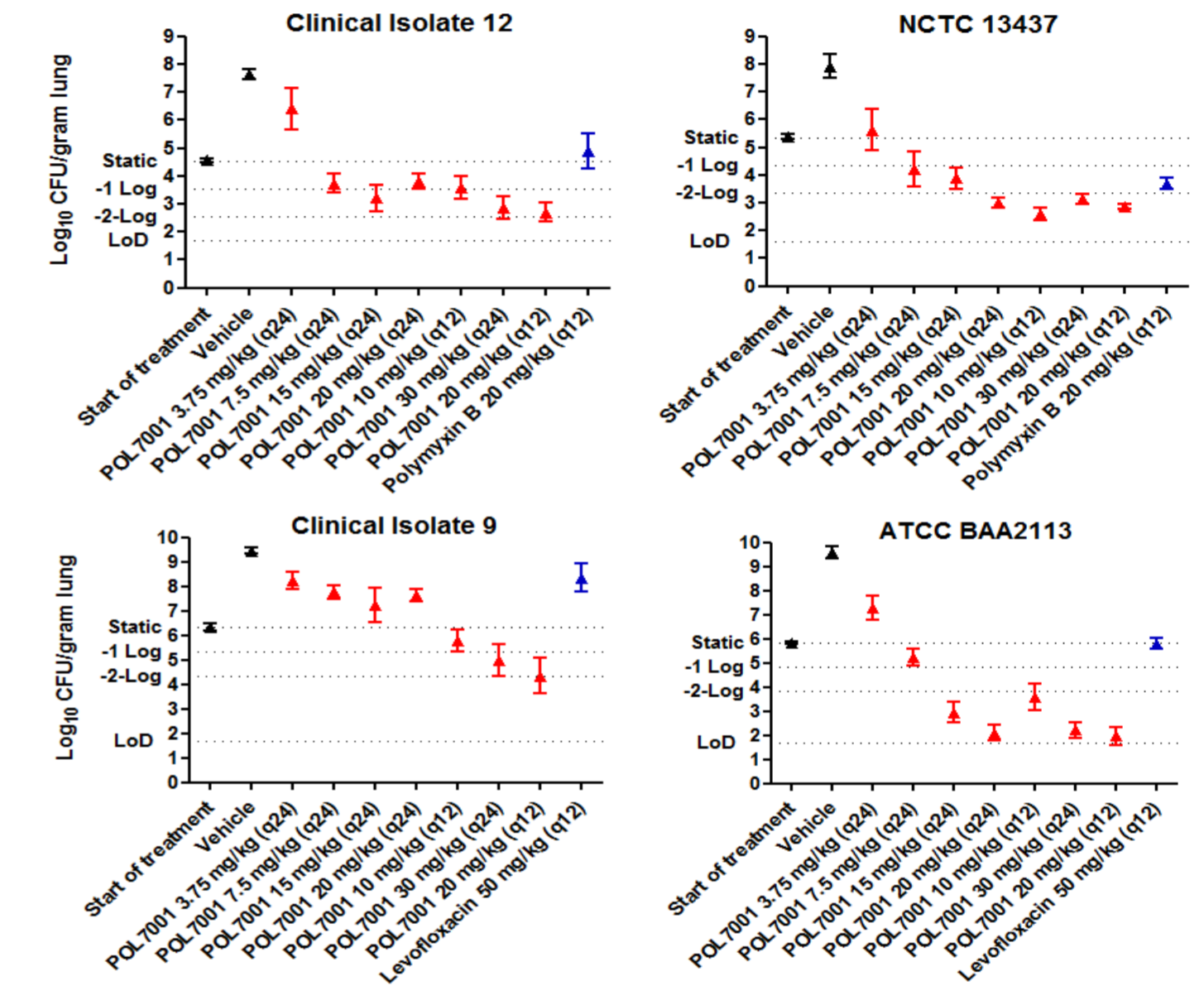


Table 2: Efficacy of POL7001 against isolates in the murine neutropenic lung infection model

Effect (mg/kg)	ATCC 27853	ATCC BAA 2113	NCTC 13437	X11045	9	12	15	16	22
Static*	3.75	7.5	7.5	7.5	20	7.5	3.75	3.75	7.5
1-log reduction*	7.5	15	7.5	40	30	15	7.5	3.75	7.5
2-log reduction*	7.5	15	20	30	40	40	7.5	3.75	20

*Lowest dose required for the effect in CFU reduction from pre-treatment levels.

Conclusion

- POL7001 is highly efficacious in the neutropenic murine pneumonia model against both non-MDR and MDR *P. aeruginosa*