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In Vivo Efficacy of SPR206 in Murine Lung and Thigh Infection Models Caused by Multidrug Resistant Pathogens *Pseudomonas aeruginosa* and *Acinetobacter baumanii*

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REVISED ABSTRACT

Background: The emergence and spread of multidrug-resistant (MDR) *Pseudomonas aeruginosa* (Pa), and *Acinetobacter baumannii* (Ab) are limiting available treatment options. SPR206 is a polymyxin analogue that exhibits potent *in vitro* activity against key Gram-negative pathogens Ab, Pa, *Escherichia coli* and *Klebsiella pneumoniae*, including MDR variants. Here, we describe the efficacy of SPR206 in murine lung and thigh infection models using either Pa14 (*lads* mutant; hypervirulent) or Ab NCTC13301 (Ab13301) (OXA-23+; carbapenem resistant).

Material/methods: Neutropenic mice were infected by inoculating into the thigh (IM) or into the lungs by intratracheal (IT) or intranasal (IN) administration. SPR206 and PMB were dosed at various concentrations by either subcutaneous (SC) or intravenous (IV) administration, every 8 hours (q8h) or every 4 hours (q4h). Mice were euthanized at either 16 h or 24 h. Lung or thigh tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

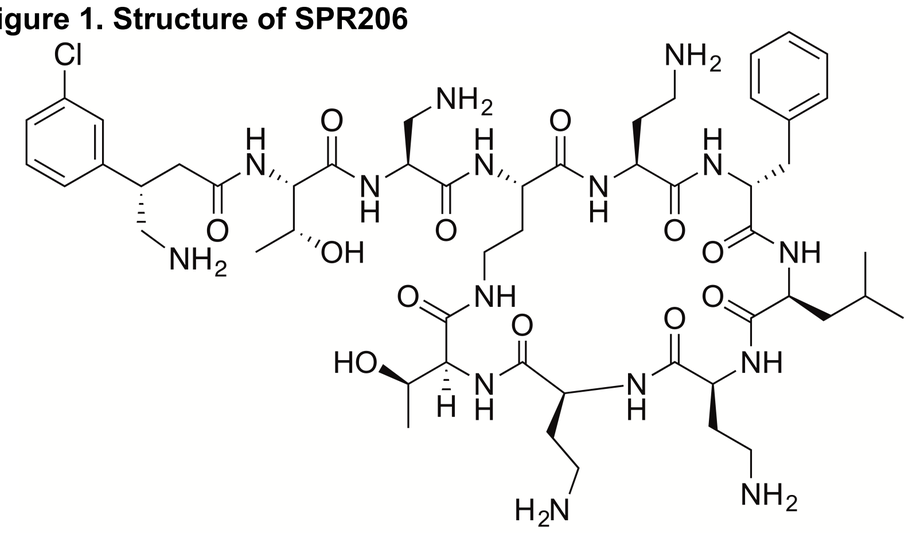
Results: The MIC values of SPR206 and PMB for Pa14 are 0.13 mg/L and 0.13 mg/L, respectively and 0.13 mg/L and 0.25mg/L for Ab13301, respectively. In lung tissue, Ab13301 and Pa14 grew from 1.9 to 3 log CFU/g between 2 h and 16 h or 24 h. In the lung model, administration of PMB (25 mg/kg) and SPR206 (30 mg/kg) q8h SC reduced the burden of Pa14 by 1.5 and 3.6 log CFU/mL compared to 2 h control. Administration of PMB and SPR206 at 20 mg/kg q4h SC, also in the lung model, reduced the burden of Ab13301 by 2.8 and 4.6 log CFU/mL compared to 2 h control. In the thigh model, administration of PMB and SPR206 at 4 mg/kg IV q4h reduced the burden of Ab13301 by 3.4 and 4.3 log CFU/g compared to 2h control.

Conclusions: The *in vivo* pharmacology studies described herein demonstrate that SPR206 exhibits similar or superior, efficacy to PMB in both murine thigh and lung infections. These data support the continued development of SPR206 for IV administration in the hospital setting for the treatment of serious Gram-negative infections.

INTRODUCTION

- The emergence of multidrug-resistant (MDR) organisms has resulted in fewer available treatment options.
- SPR206 (Figure 1) is a polymyxin analogue that exhibits potent *in vitro* activity against key Gram-negative pathogens Ab, Pa, *Escherichia coli* (Ec) and *Klebsiella pneumoniae* (Kp), including MDR variants.
- Here, we describe the efficacy of SPR206 in murine lung and thigh infection models using either Pa14 (*lads* mutant; hypervirulent)[1] or Ab NCTC13301 (Ab13301) (OXA-23+; carbapenem resistant).

Figure 1. Structure of SPR206



METHODS

- The minimum inhibitory concentration (MIC) was determined for SPR206 and polymyxin B (PMB) using CLSI methodology[2].
- Neutropenia was induced in CD-1 female or male mice by administering cyclophosphamide by intraperitoneal injection on days -4 and -1 (150 and 100 mg/kg, respectively).
- Mice were infected by inoculating into the thigh (IM) or into the lungs by intratracheal (IT) or intranasal (IN) administration.
- SPR206 and PMB were dosed at various concentrations by either subcutaneous (SC) or intravenous (IV) administration, every 8 hours (q8h) or every 4 hours (q4h).
- Mice were euthanized at either 16 h or 24 h.
- Lung or thigh tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

Table 1. MIC of strains used in the studies

Strain	MIC (mg/L)			
	PMB	SPR206	LEVO	TIG
P. aeruginosa Pa14	0.125	0.125	0.125	NA
A. baumannii NCTC 13301	0.25	0.125	NA	2

RESULTS

Figure 2. Lung infection Ab NCTC13301 – SPR206 vs PMB

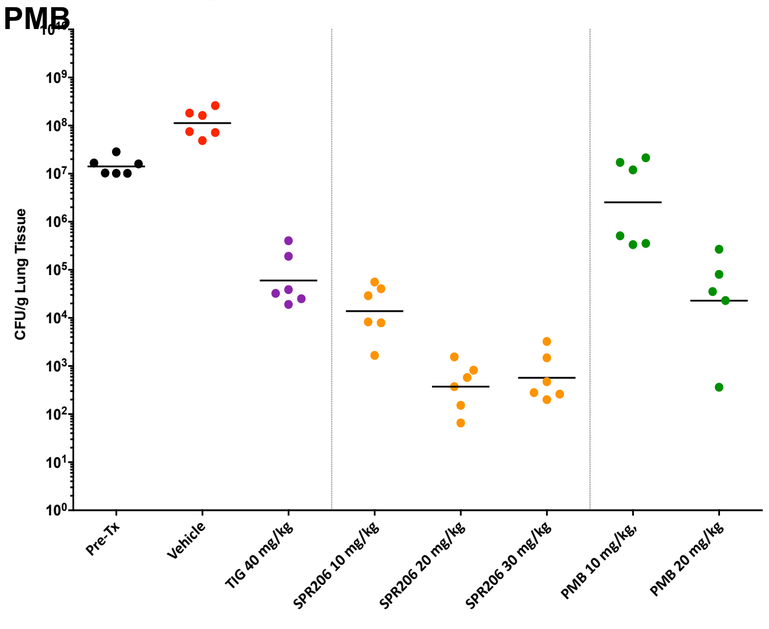


Figure 3. Lung infection Pa14 – SPR206 vs PMB

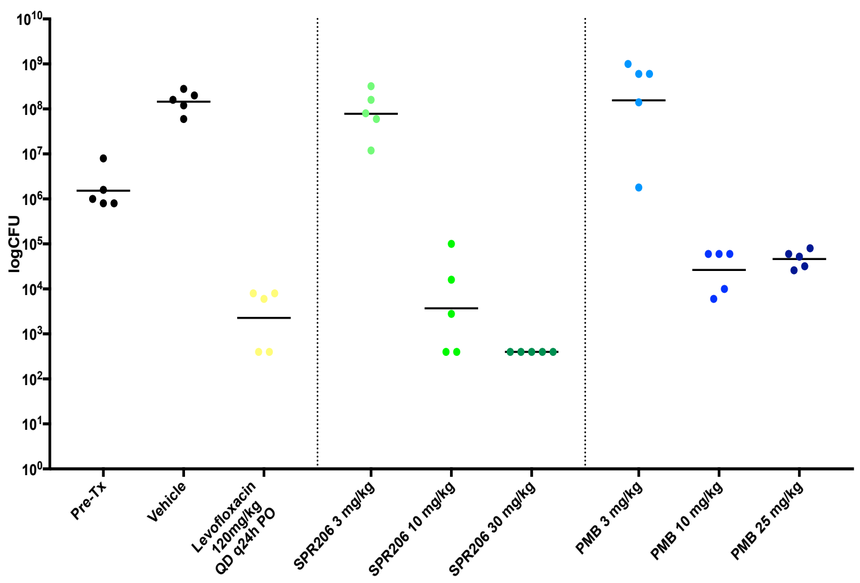


Figure 4. Thigh infection Ab NCTC13301 – SPR206 vs PMB

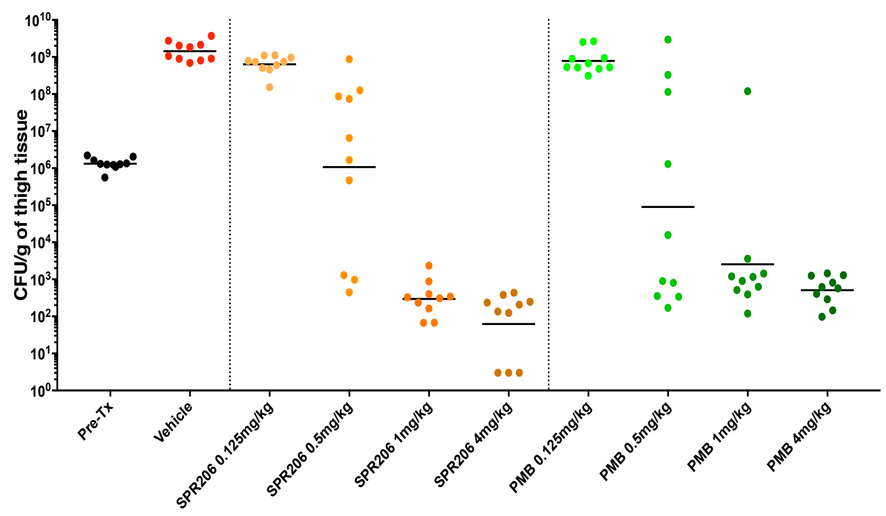


Table 2. Lung burden reduction in Ab NCTC13301 with SPR206 or PMB administration

Treatment (mg/kg q4h, SC) 16 hr duration	Log_{10} Geometric mean (CFU/g)	Log_{10} change from pre-treatment levels
Pre-treatment Control	7.15	NA
Vehicle Control	8.10	+0.90
TIG 40	4.78	-2.37
SPR206 10	4.10	-3.01
SPR206 20	2.60	-4.58
SPR206 30	2.80	-4.40
PMB 10	6.40	-0.75
PMB 20	4.36	-2.79

Table 3. Lung burden reduction in Pa14 with SPR206 or PMB administration

Treatment (mg/kg q8h, SC) 24 hr duration	Log_{10} Geometric mean (CFU/g)	Log_{10} change from pre-treatment levels
Pre-treatment Control	6.18	NA
Vehicle Control	8.16	+1.98
LEVO	3.35	-2.83
SPR206 3	7.89	-1.71
SPR206 10	3.57	-2.61
SPR206 30	2.60	-3.58
PMB 3	8.19	-2.01
PMB 10	4.42	-1.76
PMB 25	4.66	-1.52

Table 4. Thigh burden reduction in Ab NCTC13301 with SPR206 or PMB administration

Treatment (mg/kg q4h, IV) 16 hr duration	Log_{10} Geometric mean (CFU/g)	Log_{10} change from pre-treatment levels
Pre-treatment Control	6.12	NA
Vehicle Control	9.16	+3.04
SPR206 0.125	8.80	+2.68
SPR206 0.5	6.03	-0.09
SPR206 1	2.47	-3.65
SPR206 4	1.81	-4.31
PMB 0.125	8.89	+2.77
PMB 0.5	4.95	-1.17
PMB 1	3.41	-2.71
PMB 4	2.71	-3.41

CONCLUSIONS

- The *in vivo* studies described herein demonstrate that SPR206 exhibits similar or superior burden reductions compared to PMB
- These data support the continued development of SPR206 for the treatment of serious Gram-negative infections.

REFERENCES

[1]Mikkelson H (2011) The Pseudomonas aeruginosa reference strain PA14 displays increased virulence due to a mutation in ladS PLoS One. 6(12):e29113

[2]CLSI M07-A10: Methods for Dilution Antimicrobial Susceptibility Testing for Aerobic Bacteria

ACKNOWLEDGMENTS

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