Activity of Investigational Polymyxin-B-Like Compound (SPR206) against Set of Gram-Negative Bacilli Responsible for Human Infections

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Introduction

- Gram-negative bacilli (GNB) are opportunistic organisms that have emerged as important healthcare-associated pathogens, mainly in the immunocompromised patient population
- GNB producing extended-spectrum β-lactamase (ESBL) and/or carbapenemase enzymes that show resistance to many antibiotics have been steadily increasing to alarming levels in hospital and community settings
- SPR206 is a polymyxin derivative compound being clinically developed for treating serious infections caused by GNB (Figure 1)
- This study evaluated the *in vitro* potency of SPR206 and compared its potency to those of polymyxin-B and colistin against a current collection of GNB, including carbapenem-resistant organisms

Materials and Methods

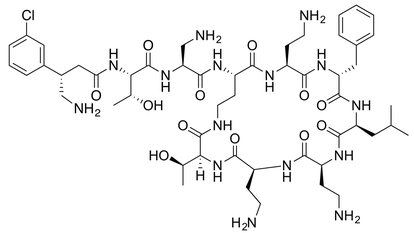
Bacterial isolates

- A total of 930 recent clinical *Enterobacteriaceae* isolates (2016–2017) were randomly selected through the SENTRY Antimicrobial Surveillance Program from 40 medical centers in 21 European (EUR) nations (n=339), 82 medical centers located in North America (NA; n=486), 17 medical centers from 9 Asia-Pacific (APAC) nations (n=68), and 16 medical centers from 11 Latin American (LATAM) nations (n=90) (Table 1)
- Isolates were responsible for bloodstream (30%), urinary tract (26%), pneumonia (20%), skin and skin structure (15%), and other infections (9%)
- An additional set of 53 meropenem-nonsusceptible isolates was also included to investigate the drug activities against carbapenem nonsusceptible organisms (Table 2)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa)
- Bacterial isolate identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document against the following antimicrobial agents (ranges)
  - SPR206 (0.015 – 16 mg/L)
  - Colistin (0.06 – 64 mg/L)
  - Polymyxin-B (0.06 – 64 mg/L)
  - Ceftriaxone (0.12 – 8 mg/L)
  - Meropenem (0.12 – 8 mg/L)
- JMI Laboratories manufactured the frozen-form reference 96-well panels used in this study with Starstead polystyrene panels (product #82.1582.001)
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*E. coli* ATCC 25922, *E. coli* NCTC 13846, *K. pneumonia* ATCC 700603, and *P. aeruginosa* ATCC 27853)
- Breakpoint criteria for comparator agents were from the M100 CLSI (2018) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2018) documents
- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07 (2018) document against SPR206 and select comparator agents

Figure 1 Structure of SPR206



Results

- Against *Enterobacteriaceae*, SPR206 ($MIC_{50/90}$, 0.06/0.12 mg/L) was more potent than colistin and polymyxin-B ($MIC_{50/90}$, 0.25/0.25 mg/L; Table 1, Figure 2)
  - SPR206 inhibited 93.2% of all *Enterobacteriaceae* at ≤0.12 mg/L, while colistin and polymyxin-B inhibited 38.3% and 33.1%, respectively, at ≤0.12 mg/L (Table 1)
- SPR206 had an MIC_{50} of ≤2 mg/L against *Escherichia*, *Citrobacter*, *Salmonella*, and *Shigella* species (Table 1 and data not shown)
- Ceftriaxone displayed a bimodal MIC distribution ($MIC_{50/90}$, ≤0.12/>8 mg/L) against all *Enterobacteriaceae* isolates and 77.4% were susceptible at the CLSI and EUCAST breakpoints of ≤1 mg/L
  - Meropenem was very active ($MIC_{50/90}$, ≤0.12/≤0.12 mg/L) against these isolates and 97.0%/97.2% were susceptible at the CLSI/EUCAST breakpoints, respectively (Table 1)
- Against a CRE challenge set, SPR206 ($MIC_{50/90}$, 0.06/0.12 mg/L) showed MIC values 4-fold lower than colistin and polymyxin-B ($MIC_{50/90}$, 0.25/0.5 mg/L; Table 2)
  - Isolates included bla_{KPC}, bla_{OXA-48}, bla_{VIM}, and bla_{NDM-1} genotypes
  - MIC results similar to the random selection set are seen in Table 1
  - As expected, ceftriaxone ($MIC_{50/90}$, >8/>8 mg/L) and meropenem ($MIC_{50/90}$, >8/>8 mg/L) showed little activity against this challenge set (Table 2)
- SPR206 inhibited all randomly selected *P. aeruginosa* at ≤2 mg/L and showed MIC results ($MIC_{50/90}$, 0.25/0.5 mg/L) 2-fold lower than colistin ($MIC_{50/90}$, 0.5/1 mg/L) and polymyxin B ($MIC_{50/90}$, 0.5/1 mg/L) (Table 1, Figure 3)
- Similar MIC results for the respective compounds were obtained against carbapenem-nonsusceptible *P. aeruginosa* compared with the randomly selected set (Table 2)
- Against *Acinetobacter baumannii*, SPR206 ($MIC_{50/90}$, 0.12/0.25 mg/L) was 2- to 8-fold more potent than polymyxin-B ($MIC_{50/90}$, 0.25/1–2 mg/L) and 4- to 32-fold more potent than colistin ($MIC_{50/90}$, 0.5/4–8 mg/L) (Tables 1 and 2, Figure 4)
  - In addition, SPR206 inhibited 95.7% of randomly selected *Acinetobacter* spp. or 93.1% of all tested *Acinetobacter* spp. at ≤2 mg/L
- SPR206 ($MIC_{50/90}$, 0.25/4 mg/L) and polymyxin-B ($MIC_{50/90}$, 0.5/4 mg/L) showed similar MIC values against *S. maltophilia*, and these compounds had MIC results 4- to 16-fold lower than colistin ($MIC_{50/90}$, 4/16 mg/L) (Table 1)

Conclusions

- Overall, SPR206 was highly potent against a contemporary collection of *Enterobacteriaceae* and non-fermentative GNB
- Based on $MIC_{50/90}$ results, SPR206 potency was consistently 2- to 4-fold greater than the potency of clinically available in-class comparator agents colistin and polymyxin-B
- Against a challenge set of isolates with increased carbapenem MIC values
  - SPR206 MIC results were not adversely affected when compared with the MIC values obtained against randomly selected organisms
  - SPR206 MIC values were consistently lower than colistin and polymyxin-B
- These *in vitro* results obtained for SPR206 warrant its further development as an option for treating gram-negative infections

Acknowledgements

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Table 1 Antimicrobial activity of SPR206 and comparators tested against the main organisms and organism groups for non-challenge isolates

Organism group (no. of isolates) / Antimicrobial agent	No. and cumulative % of isolates at MIC (mg/L) of [a]: 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	%S[c]
Enterobacteriaceae (541)[d]																
SPR206	47 8.7	370 77.1	87 93.2	15 95.9	3 96.5	1 96.7	1 96.9	0 96.9	1 97.0	3 97.6			13 100.0	0.06	0.12	
Colistin		1 0.2	206 38.3	293 92.4	18 95.7	3 96.3	1 96.5	2 96.9	0 96.9	1 97.0	4 97.8	2 98.2	10 100.0	0.25	0.25	96.5
Polymyxin-B		1 0.2	178 33.1	310 90.4	25 95.0	6 96.1	4 96.9	0 96.9	3 97.4	1 97.6	3 98.2	2 98.5	8 100.0	0.25	0.25	
Ceftriaxone			348 64.3	42 72.1	21 76.0	8 77.4	3 78.0	3 78.6	6 79.7				110 100.0	≤0.12	>8	77.4
Meropenem			516 95.4	6 96.5	3 97.0	0 97.0	1 97.2	0 97.2	1 97.4				14 100.0	≤0.12	≤0.12	97.2
E. coli (182)																
SPR206	15 8.2	134 81.9	30 98.4	1 98.9	1 99.5	0 99.5	1 100.0							0.06	0.12	
Colistin			39 21.4	135 95.6	7 99.5	0 99.5	0 99.5	1 100.0						0.25	0.25	99.5
Polymyxin-B			56 30.8	114 93.4	8 97.8	3 99.5	1 100.0							0.25	0.25	
K. pneumoniae (181)																
SPR206	9 5.0	146 85.6	19 96.1	4 98.3	0 98.3	0 98.3	0 98.3	0 98.3	0 98.3	2 99.4			1 100.0	0.06	0.12	
Colistin			85 47.0	90 96.7	2 97.8	1 98.3	0 98.3	0 98.3	0 98.3	0 98.3	2 99.4	1 100.0		0.25	0.25	98.3
Polymyxin-B			60 33.1	108 92.8	7 96.7	2 97.8	1 98.3	0 98.3	1 98.9	1 99.4	1 100.0			0.25	0.25	
E. cloacae species complex (94)																
SPR206	5 5.3	57 66.0	14 80.9	4 85.1	1 86.2	0 86.2	0 86.2	0 86.2	1 87.2	1 88.3			11 100.0	0.06	>16	
Colistin			41 43.6	37 83.0	2 85.1	0 85.1	1 86.2	0 86.2	0 86.2	1 87.2	2 89.4	1 90.4	9 100.0	0.25	64	86.2
Polymyxin-B			27 28.7	48 79.8	4 84.0	1 85.1	1 86.2	0 86.2	2 88.3	0 88.3	2 90.4	2 92.6	7 100.0	0.25	32	
P. aeruginosa (182)																
SPR206		1 0.5	19 11.0	113 73.1	43 96.7	5 99.5	1 100.0							0.25	0.5	
Colistin			15 8.2	82 53.3	80 97.3	3 98.9	2 100.0							0.5	1	98.9
Polymyxin-B			22 12.1	139 88.5	20 99.5	1 100.0								0.5	1	100.0
Meropenem			25 13.7	36 33.5	35 52.7	28 68.1	17 77.5	8 81.9	12 88.5				21 100.0	0.5	>8	77.5
Acinetobacter spp. (185)																
SPR206		53 28.6	90 77.3	25 90.8	8 95.1	1 95.7	0 95.7	0 95.7	1 96.2	1 96.8			6 100.0	0.12	0.25	
Colistin				38 20.5	78 62.7	40 84.3	8 88.6	4 90.8	6 93.0	3 94.6	3 96.2	1 96.8	10 100.0	0.5	4	88.6
Polymyxin-B			9 4.9	91 54.1	35 73.0	32 90.3	6 93.5	2 94.6	4 96.8	2 97.8	3 99.5	0 99.5	1 100.0	0.25	1	93.5
Meropenem			1 0.5	25 14.1	21 25.4	11 31.4	7 35.1	3 36.8	4 38.9				113 100.0	>8	>8	35.1
S. maltophilia (22)																
SPR206		1 4.5	8 40.9	4 59.1	1 63.6	1 68.2	1 72.7	4 90.9	1 95.5	1 100.0				0.25	4	
Colistin			1 4.5	0 4.5	3 18.2	2 27.3	4 45.5	2 54.5	4 72.7	2 90.9	4 100.0	2 100.0		4	16	
Polymyxin-B			2 9.1	6 36.4	5 59.1	1 63.6	4 81.8	3 95.5	1 100.0					0.5	4	
Meropenem													22 100.0	>8	>8	

[a] The intensity of shading is proportional to the % of tested isolates within each row that display the indicated MIC value.
[b] Greater than the highest dilution tested.
[c] Susceptible breakpoints were those from CLSI/EUCAST (2018).
[d] Organisms include: *Citrobacter* species (19), *Enterobacter aerogenes* (22), *E. cloacae* species complex (94), *Escherichia coli* (182), *Klebsiella oxytoca* (19), *K. pneumoniae* (181), *Salmonella* species (13), and *Shigella* species (11)

Figure 2 Comparison of colistin (A) or polymyxin-B (B) to SPR206 when tested against 573 *Enterobacteriaceae* isolates

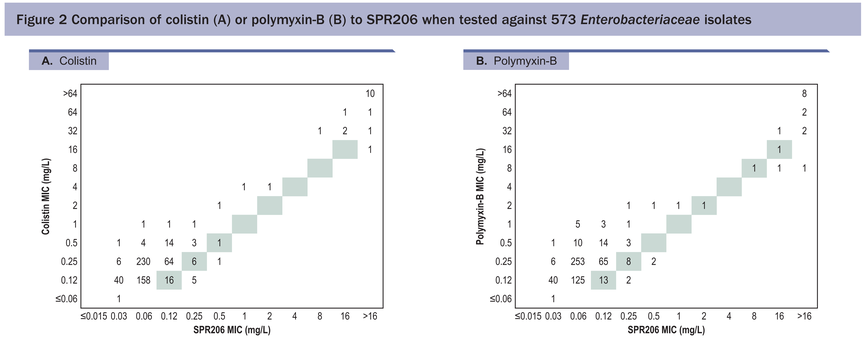

Figure 3 Comparison of colistin to SPR-206 when tested against 182 *Pseudomonas aeruginosa* isolates

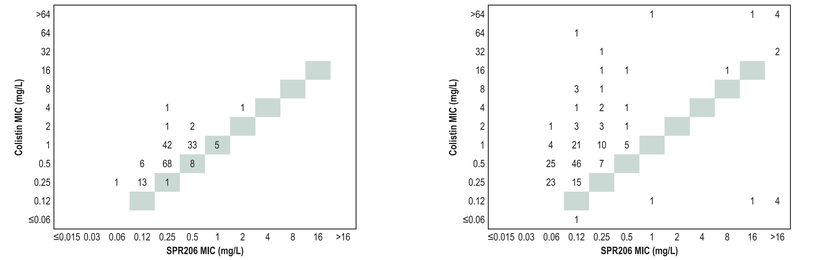

Figure 4 Comparison of colistin to SPR-206 when tested against 185 *Acinetobacter* spp. isolates

Table 2 Antimicrobial activity of SPR206 and comparators tested against meropenem-nonsusceptible gram-negative bacilli

Organism group (no. of isolates) / Antimicrobial agent	No. and cumulative % of isolates at MIC (mg/L) of [a]: 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	%S[c]
Carbapenem-resistant *Enterobacteriaceae* (32)[d]																
SPR206	1 3.1	23 75.0	8 100.0											0.06	0.12	
Colistin			13 40.6	14 84.4	5 100.0									0.25	0.5	100.0
Polymyxin-B			2 6.2	24 81.2	3 90.6	3 100.0								0.25	0.5	
Ceftriaxone							1 3.1	0 3.1	1 6.2				30 100.0	>8	>8	0.0
Meropenem						1 3.1	2 9.4	7 31.2	4 43.8				18 100.0	>8	>8	9.4
P. aeruginosa (53)																
SPR206			5 9.4	25 56.6	19 92.5	3 98.1	1 100.0							0.25	0.5	
Colistin				3 5.7	27 56.6	22 98.1	0 98.1	0 98.1	1 100.0					0.5	1	98.1
Polymyxin-B				8 15.1	35 81.1	9 98.1	1 100.0							0.5	1	100.0
Acinetobacter spp. (130)																
SPR206		40 30.8	64 80.0	13 90.0	4 93.1	1 93.8	0 93.8	0 93.8	1 94.6	1 95.4			6 100.0	0.12	0.25	
Colistin				22 16.9	54 58.5	27 79.2	6 83.8	4 86.9	4 90.0	3 92.3	3 94.6	1 95.4	6 100.0	0.5	8	83.8
Polymyxin-B			4 3.1	61 50.0	22 66.9	25 86.2	6 90.8	2 92.3	4 95.4	2 96.9	3 99.2	0 99.2	1 100.0	0.25	2	90.8

[a] The intensity of shading is proportional to the % of tested isolates within each row that display the indicated MIC value.
[b] Greater than the highest dilution tested.
[c] Susceptible breakpoints were those from CLSI/EUCAST (2018).
[d] Includes *Citrobacter freundii* species complex (4 isolates; 1 bla_{KPC-2}, 1 bla_{VIM-1}, 1 bla_{NDM-1}, and 1 bla_{OXA-48}), *E. cloacae* species complex (9 isolates; 1 bla_{KPC-2}, 2 bla_{NMC-A}, 1 bla_{KPC-2}, 3 bla_{NDM-1}, 1 bla_{NDM-1}, and 1 bla_{VIM-1}), *Escherichia coli* (9 isolates; 3 bla_{KPC-2}, 1 bla_{NMC-A}, 1 bla_{KPC-2}, 1 bla_{NDM-1}, 1 bla_{NDM-1} + $bla_{OXA-232}$, 1 bla_{NDM-1}, and 1 bla_{OXA-48}), *Klebsiella oxytoca* (1 isolate, bla_{KPC}), and *K. pneumoniae* (9 isolates; 1 bla_{KPC-2}, 3 bla_{KPC-2}, 2 bla_{NDM-1}, and 3 bla_{OXA-48}).

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