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In Vitro Activity Evaluation of a Next-Generation Polymyxin, SPR206, against Non-Fermentative Gram-Negative Bacilli Responsible for Human Infections

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Introduction

- Non-fermentative gram-negative bacilli (NFGNB) are opportunistic organisms that have emerged as important healthcare-associated pathogens, mainly in the immunocompromised patient population
- These organisms are innately resistant to many antimicrobial classes due to the presence of intrinsic genes encoding β-lactamases and decreased permeability
- SPR206 is a polymyxin derivative compound being clinically developed for treating serious infections caused by gram-negative organisms (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 NFGNB

Materials and Methods

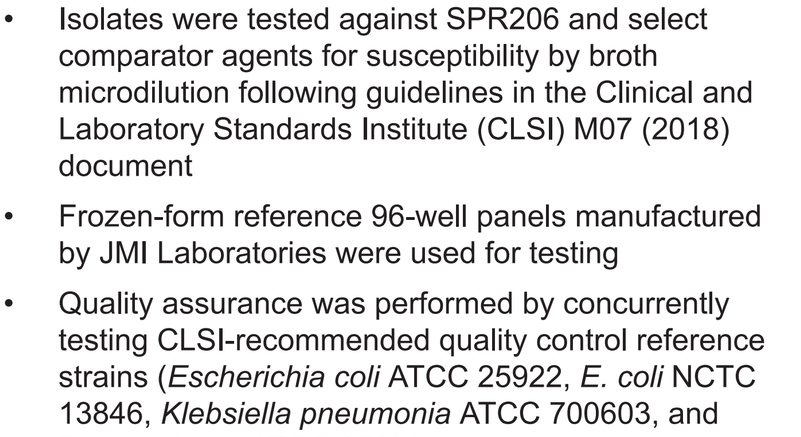
Bacterial isolates

- A total of 389 randomly selected isolates (182 *Pseudomonas aeruginosa*, 185 *Acinetobacter* spp., and 22 *Stenotrophomonas maltophilia*) representing current antimicrobial susceptibility profiles for the respective species were included
- In addition, a subset of 53 and 130 meropenem-nonsusceptible *P. aeruginosa* and *Acinetobacter* spp., respectively, were analyzed separately
- These isolates originated from the SENTRY Antimicrobial Surveillance Program (2016-2017) bank of organisms and were recovered from 37 medical centers in 20 European nations (n=163), 64 medical centers in the United States (n=203), 12 medical centers from 8 Asia-Pacific nations (n=32), and 12 medical centers from 8 Latin American nations (n=32)
- Isolates were collected from patients with pneumonia (55.4%), skin and skin structure infections (24.7%), bloodstream infections (12.8%), and other infections (7.2%)

Antimicrobial susceptibility testing

- Isolates were tested against SPR206 and select comparator agents for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document
- Frozen-form reference 96-well panels manufactured by JMI Laboratories were used for testing
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*Escherichia coli* ATCC 25922, *E. coli* NCTC 13846, *Klebsiella pneumonia* ATCC 700603, and *P. aeruginosa* ATCC 27853)
- Breakpoint criteria for comparator agents were those available in the CLSI M100 (2018) document

Figure 1 Structure of SPR206



Results

- 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)
- Similar MIC results for the respective compounds were obtained against carbapenem-nonsusceptible *P. aeruginosa* compared with the randomly selected set (Table 2)
- Against *A. 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)
  - 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 showed potent *in vitro* activity against a current collection of NFGNB, and its potency was consistently greater than the clinically available in-class comparator agents
- The *in vitro* results obtained for SPR206 warrant additional investigations to explore its clinical utility for treating infections caused by commonly multidrug-resistant gram-negative pathogens

Table 1 Antimicrobial activity of SPR206 and comparators tested against a random selection of non-fermentative gram-negative bacilli

Organism (no. of isolates) / Antimicrobial agent	Number and cumulative % of isolates inhibited at MIC (mg/L) of [a]: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	%S[c]
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	4 93.0	3 94.6	3 96.2	1 96.8		6 100.0	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	4 90.9	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 number of tested isolates within each row that display the indicated MIC value.
[b] Greater than the highest concentration tested.
[c] Susceptible breakpoints were those from CLSI/EUCAST (2018).

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

Organism (no. of isolates) / Antimicrobial agent	Number and cumulative % of isolates inhibited at MIC (mg/L) of [a]: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	> [b]	MIC_{50}	MIC_{90}	%S[c]
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 number of tested isolates within each row that display the indicated MIC value.
[b] Greater than the highest concentration tested.
[c] Susceptible breakpoints were those from CLSI/EUCAST (2018).

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