IDWeek 2022 | Poster #P1676

Activity of SPR206 and Comparator Agents Against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* Causing Infections in United States Hospitals

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Introduction

- Non-fermentative Gram-negative bacilli (NF-GNB) are opportunistic organisms that have emerged as important healthcare-associated pathogens, mainly in immunocompromised patients.
- These organisms are innately less susceptible and/or resistant to many antimicrobial classes due to the presence of intrinsic genes encoding β-lactamases and efflux pumps.
- SPR206 is a next generation polymyxin under clinical development to treat pneumonia, bloodstream, and urinary tract infections caused by GNB multidrug-resistant (MDR) pathogens.
- The *in vitro* activity of SPR206 and comparators was monitored against GNB pathogens causing infection in US and European hospitals during 2021 as part of the SENTRY Antimicrobial Surveillance Program.
- This study reports the *in vitro* activity of SPR206 and comparator agents against *Acinetobacter baumannii-calcoaceticus* species complex (described here as *A. baumannii*) and *Pseudomonas aeruginosa* recovered from patients hospitalized in the USA.

Materials and Methods

Bacterial organisms

- This study included 238 *A. baumannii* and 450 *P. aeruginosa* recovered from patients hospitalized in medical centers in 9 US Census Divisions during 2021. Only consecutive isolates (1 per patient infection episode) responsible for documented infections according to local criteria were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) guidelines.
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories (North Liberty, IA, USA) and contained cation-adjusted Mueller-Hinton broth as per CLSI guidelines.
- Quality assurance was performed by sterility checks, colony counts, and testing CLSI-recommended quality control reference strains. MIC interpretations were performed using CLSI breakpoints for comparators. A susceptible breakpoint of ≤2 mg/L was used for SPR206 for comparison purposes.

Subset definitions

- MDR was defined as any isolate resistant to ≥3 classes of antibiotics, whereas an extensively drug-resistant (XDR) phenotype was any isolate susceptible to ≤2 classes of antibiotics.

Results

- A total of 34.9% (83/238) and 14.7% (35/238) of *A. baumannii* displayed an MDR or XDR phenotype, respectively (Table 1).
- Overall, SPR206 had $MIC_{50/90}$ of 0.12/0.5 mg/L against all *A. baumannii* and MIC_{50} and MIC_{90} values of 0.12 mg/L and 0.25-1 mg/L against resistant subsets, respectively (Table 1).
- Various antimicrobial agents showed *in vitro* activity (≥91.4% susceptible) against the non-MDR subset of *A. baumannii*. In contrast, only SPR206 ($MIC_{50/90}$, 0.12/0.25-1 mg/L) and colistin ($MIC_{50/90}$, 0.5/1 mg/L) remained active against the resistant subsets (Table 2).
- A total of 17.8% (80/450) and 8.0% (36/450) of *P. aeruginosa* displayed an MDR or XDR phenotype, respectively (Table 1).
- MIC_{50}, MIC_{90}, and MIC_{100} of 0.25 mg/L, 0.25 mg/L, and 2 mg/L were obtained for SPR206 against all *P. aeruginosa*, respectively (Table 1).
- All agents had good *in vitro* activity (≥91.1% susceptible) against the non-MDR subset of *P. aeruginosa*, except for piperacillin-tazobactam (88.9% susceptible) and levofloxacin (82.4% susceptible) (Table 3).
- SPR206 ($MIC_{50/90}$, 0.25/0.5 mg/L) and colistin ($MIC_{50/90}$, 1/1 mg/L) remained active against the resistant subsets, whereas other comparator agents had MIC_{90} values ≥16 mg/L (Table 3).

Table 1. MIC distribution of SPR206 obtained against *A. baumannii* and *P. aeruginosa* and resistant subsets

Organism/	No. and cumulative % of isolates inhibited at MIC (mg/L) of:												MIC$_{50}$	MIC$_{90}$
Group (no. of isolates)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
A. baumannii (238)	3 (1.3)	73 (31.9)	82 (66.4)	48 (86.6)	15 (92.9)	7 (95.8)	5 (97.9)	3 (99.2)	0 (99.2)	2 (100.0)			0.12	0.5
Non-MDR (155)	1 (0.6)	42 (27.7)	57 (64.5)	37 (88.4)	10 (94.8)	2 (96.1)	3 (98.1)	2 (99.4)	0 (99.4)	1 (100.0)			0.12	0.5
MDR (83)	2 (2.4)	31 (39.8)	25 (69.9)	11 (83.1)	5 (89.2)	5 (95.2)	2 (97.6)	1 (98.8)	0 (98.8)	1 (100.0)			0.12	1
XDR (35)		17 (48.6)	11 (80.0)	5 (94.3)	1 (97.1)	0 (97.1)	0 (97.1)	0 (97.1)	0 (97.1)	1 (100.0)			0.12	0.25
P. aeruginosa (450)	3 (0.7)	14 (3.8)	123 (31.1)	284 (94.2)	22 (99.1)	2 (99.6)	2 (100.0)						0.25	0.25
Non-MDR (370)	3 (0.8)	8 (3.0)	105 (31.4)	237 (95.4)	14 (99.2)	1 (99.5)	2 (100.0)						0.25	0.25
MDR (80)		6 (7.5)	18 (30.0)	47 (88.8)	8 (98.8)	1 (100.0)							0.25	0.5
XDR (36)		3 (8.3)	9 (33.3)	19 (86.1)	5 (100.0)								0.25	0.5

MDR, multidrug-resistant (resistant to ≥3 classes); XDR, extensively drug-resistant (susceptible to ≤2 classes).

Table 2. Antimicrobial activity of SPR206 and comparator agents against *A. baumannii* and resistant subsets

Antimicrobial agent	MIC (mg/L)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
Non-MDR (155)						
SPR206	0.12	0.5	≤0.03 to 16	98.1[a]		
Colistin	0.5	1	0.12 to >8		97.4	2.6
Ampicillin-sulbactam	2	8	1 to 16	97.4	2.6	0.0
Meropenem	0.25	1	0.12 to 2	100.0	0.0	0.0
Ceftazidime	4	8	1 to >32	96.1	1.9	1.9
Ceftazidime-avibactam	8	16	2 to 32			
Piperacillin-tazobactam	≤0.06	16	≤0.06 to >128	91.4	3.3	5.3
Amikacin	4	4	1 to >32	98.7	0.0	1.3
Tobramycin	1	1	0.25 to >16	98.1	0.0	1.9
Tigecycline	0.25	0.5	0.12 to 4			
Levofloxacin	0.12	0.5	0.06 to 16	96.8	1.3	1.9
MDR (83)						
SPR206	0.12	1	≤0.03 to 16	97.6[a]		
Colistin	0.5	1	0.12 to >8		96.4	3.6
Ampicillin-sulbactam	32	>64	4 to >64	20.5	15.7	63.9
Meropenem	>32	>32	0.25 to >32	9.6	1.2	89.2
Ceftazidime	>32	>32	4 to >32	16.9	12.0	71.1
Ceftazidime-avibactam	32	>32	0.5 to >32			
Piperacillin-tazobactam	>128	>128	8 to >128	3.6	13.3	83.1
Amikacin	8	>32	1 to >32	56.6	4.8	38.6
Tobramycin	4	>16	0.5 to >16	51.8	6.0	42.2
Tigecycline	2	4	0.12 to >8			
Levofloxacin	16	>32	0.25 to >32	4.8	3.6	91.6
XDR (35)						
SPR206	0.12	0.25	0.06 to 16	97.1[a]		
Colistin	0.5	1	0.12 to >8		91.4	8.6
Ampicillin-sulbactam	32	>64	16 to >64	0.0	11.4	88.6
Meropenem	>32	>32	16 to >32	0.0	0.0	100.0
Ceftazidime	>32	>32	16 to >32	0.0	17.1	82.9
Ceftazidime-avibactam	>32	>32	8 to >32			
Piperacillin-tazobactam	>128	>128	64 to >128	0.0	2.9	97.1
Amikacin	>32	>32	1 to >32	22.9	8.6	68.6
Tobramycin	>16	>16	0.5 to >16	17.1	8.6	74.3
Tigecycline	4	4	1 to >8			
Levofloxacin	16	>32	4 to >32	0.0	2.9	97.1

MDR, multidrug-resistant (resistant to ≥3 classes); XDR, extensively drug-resistant (susceptible to ≤2 classes).
[a] Criteria as published by CLSI (2022). A susceptible breakpoint of ≤2 mg/L was used for SPR206 for comparison purposes.

Table 3. Antimicrobial activity of SPR206 and comparator agents against *P. aeruginosa* and resistant subsets

Antimicrobial agent	MIC (mg/L)			CLSI[a]		
	50%	90%	Range	%S	%I	%R
Non-MDR (370)						
SPR206	0.25	0.25	≤0.03 to 2	100.0[a]		
Colistin	1	1	0.12 to 4		99.7	0.3
Meropenem	0.5	2	≤0.015 to 16	92.7	4.6	2.7
Ceftazidime	2	8	0.25 to >32	91.1	1.9	7.0
Ceftazidime-avibactam	2	4	0.03 to >32	99.2		0.8
Piperacillin-tazobactam	4	32	0.12 to >128	88.9	5.7	5.4
Amikacin	4	8	≤0.25 to 16	100.0	0.0	0.0
Tobramycin	0.5	1	≤0.12 to >16	98.4	0.0	1.6
Levofloxacin	0.5	2	≤0.015 to >32	82.4	9.2	8.4
Ceftolozane-tazobactam	0.5	1	≤0.12 to >16	99.2	0.3	0.5
MDR (80)						
SPR206	0.25	0.5	0.06 to 1	100.0[a]		
Colistin	1	1	0.12 to 2		100.0	0.0
Meropenem	8	32	0.25 to >32	17.5	11.2	71.2
Ceftazidime	32	>32	4 to >32	25.0	13.8	61.2
Ceftazidime-avibactam	8	16	1 to >32	75.0		25.0
Piperacillin-tazobactam	64	>128	8 to >128	11.2	42.5	46.2
Amikacin	4	32	0.5 to >32	85.0	5.0	10.0
Tobramycin	1	16	≤0.12 to >16	78.8	8.8	12.5
Levofloxacin	4	32	0.12 to >32	21.2	15.0	63.8
Ceftolozane-tazobactam	2	8	0.5 to >16	86.2	7.5	6.2
XDR (36)						
SPR206	0.25	0.5	0.06 to 0.5	100.0[a]		
Colistin	1	1	0.25 to 2		100.0	0.0
Meropenem	16	32	0.5 to 32	5.6	13.9	80.6
Ceftazidime	32	>32	4 to >32	5.6	11.1	83.3
Ceftazidime-avibactam	8	32	1 to >32	66.7		33.3
Piperacillin-tazobactam	128	>128	16 to >128	8.3	30.6	61.1
Amikacin	8	>32	1 to >32	77.8	5.6	16.7
Tobramycin	1	>16	0.25 to >16	63.9	13.9	22.2
Levofloxacin	8	32	0.5 to >32	5.6	13.9	80.6
Ceftolozane-tazobactam	2	16	0.5 to >16	72.2	13.9	13.9

MDR, multidrug-resistant (resistant to ≥3 classes); XDR, extensively drug-resistant (susceptible to ≤2 classes).
[a] Criteria as published by CLSI (2022). A susceptible breakpoint of ≤2 mg/L was used for SPR206 for comparison purposes.

Conclusions

- SPR206 showed potent *in vitro* activity against these recent collections of *A. baumannii* and *P. aeruginosa* from the USA. SPR206 potency was consistently greater than clinically available in-class and other comparator agents.
- These results, plus favorable safety and tolerability profiles of SPR206 in Phase 1 studies, support the clinical development of SPR206 for difficult-to-treat infections caused by these pathogens and their resistant subsets.

Acknowledgements

This research and poster presentation were sponsored by Spero Therapeutics, which was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Joint Warfighter Medical Research Program under Award No. W81XWH-19-1-0295.

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