In vitro activity of PLG0206 against isolates commonly found in periprosthetic joint infections (PJI)

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Introduction

- PLG0206 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections.
- PLG0206 is a broad-spectrum antimicrobial agent with activity against multidrug resistant organisms, has rapid activity against biofilms, and does not have significant local or systemic toxicity in animal models (1,2).
- In this study, the activity of PLG0206 was evaluated by broth microdilution against 104 isolates of *Staphylococcus epidermidis*, 53 other coagulase-negative staphylococci (CoNS), and 66 Gram-negative isolates consisting of Enterobacterales, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii*.

Methods

- 223 test organisms consisted of reference strains from the American Type Culture Collection, the Centers for Disease Control Antibiotic Reference Bank and clinical isolates from the Micromyx repository.
- Imipenem, levofloxacin, tigecycline, linezolid, vancomycin, oxacillin, ceftazidime, colistin, and amikacin were tested as comparators.
- Testing was conducted in accordance with guidelines from the Clinical and Laboratory Standards Institute (3,4).
- The media employed for testing in the broth microdilution MIC assay for all organisms were cation-adjusted Mueller Hinton Broth (CAMHB) and for PLG0206 only included RPMI-1640 medium supplemented with 0.002% P-80 due to precipitation/flocculation of PLG0206 observed in CAMHB.

Methods

- A standardized inoculum of each organism was prepared per CLSI methods (3, 4).
- Suspensions were prepared in PBS to equal a turbidity of a 0.5 McFarland standard that yielded a final cell density in the plates of approximately 5 x 10^5 CFU/mL.

Results

- Activity of PLG0206 and comparators against CoNS and resistant Gram-negative pathogens are shown in the Table.

Organism	Drug	MIC Range	Mode	MIC_{50}	MIC_{90}	%S	%R
All *S. epidermidis* (104)	PLG0206 CAMHB	0.25 - 4	1	1	1	NA	NA
	PLG0206 RPMI	0.03 - 0.12	0.12	0.12	0.12	NA	NA
	Imipenem	<0.008 - >8	0.015	0.06	>8	44.2%	55.8%
	Levofloxacin	0.12 - >4	>4	4	>4	47.1%	52.9%
	Tigecycline	0.12 - 2	0.25	0.25	1	NA	NA
	Vancomycin	1 - 4	2	2	2	100%	0%
	Linezolid	0.5 - >8	2	2	2	98.1%	1.9%
	Oxacillin	0.06 - >16	0.12	1	>16	44.2%	55.8%
MSSE (46)	PLG0206 CAMHB	0.25 - 4	1	1	1	NA	NA
	PLG0206 RPMI	0.03 - 0.12	0.12	0.12	0.12	NA	NA
	Imipenem	<0.008 - 0.06	0.015	0.015	0.015	100%	0%
	Levofloxacin	0.12 - >4	0.25	0.25	>4	84.8%	15.2%
	Tigecycline	0.12 - 2	0.25	0.25	1	NA	NA
	Vancomycin	1 - 4	2	2	2	100%	0%
	Linezolid	0.5 - 4	2	2	2	100%	0%
	Oxacillin	0.06 - 0.25	0.12	0.12	0.25	100%	0%
MRSE (58)[1]	PLG0206 CAMHB	0.25 - 4	1	1	1	NA	NA
	PLG0206 RPMI	0.03 - 0.12	0.12	0.12	0.12	NA	NA
	Imipenem	<0.008 - >8	>8	2	>8	0%	100%
	Levofloxacin	0.12 - >4	>4	>4	>4	17.2%	82.8%
	Tigecycline	0.12 - 1	1	0.5	1	NA	NA
	Vancomycin	1 - 4	2	2	2	100%	0%
	Linezolid	1 - >8	2	2	4	96.6%	3.4%
	Oxacillin	0.5 - >16	>16	16	>16	0%	100%
CoNS non-*epidermidis* (53)[2]	PLG0206 CAMHB	<0.12 - 4	0.25	0.25	1	NA	NA
	PLG0206 RPMI	0.015 - 2	0.06	0.06	0.06	NA	NA
	Imipenem	<0.008 - >8	0.03	0.03	0.25	52.8%	47.2%
	Levofloxacin	0.12 - >4	0.5	0.5	>4	83.0%	17%
	Tigecycline	0.25 - 2	0.5	0.5	1	NA	NA
	Vancomycin	0.5 - 2	1	1	1	100%	0%
	Linezolid	1 - 4	2	2	4	100%	0%
	Oxacillin	0.12 - >16	0.12	0.5	8	52.8%	47.2%

Results

Organism	Drug	MIC Range	Mode	MIC_{50}	MIC_{90}	%S	%R
Enterobacterales (22)[3]	PLG0206 CAMHB	1 - >8	8	8	>8	NA	NA
	PLG0206 RPMI	<0.12 - >128	0.5	0.5	32	NA	NA
	Imipenem	2 - >8	>8	>8	>8	0%	95.5%
	Levofloxacin	0.06 - >4	>4	>4	>4	14%	86%
	Tigecycline	0.25 - 4	0.5	0.5	2	95.4%	0%
	Ceftazidime	0.12 - >32	>32	>32	>32	5%	86%
	Colistin	0.06 - >16	0.25	0.12	16	NA	NA
	Amikacin	1 - >64	>64	16	>64	55%	32%
P. aeruginosa (20)	PLG0206 CAMHB	8 - >8	8	8	>8	NA	NA
	PLG0206 RPMI	0.5 - 4	1	1	2	NA	NA
	Imipenem	4 - >8	>8	>8	>8	0%	90%
	Levofloxacin	0.5 - >4	>4	>4	>4	10%	90%
	Tigecycline	8 - >16	>16	>16	>16	NA	NA
	Ceftazidime	4 - >32	>32	>32	>32	10%	85%
	Colistin	0.12 - 2	0.5	0.5	1	100%	0%
	Amikacin	0.5 - >64	8	8	>64	55%	30%
A. baumannii (24)	PLG0206 CAMHB	2 - 8	4	4	8	NA	NA
	PLG0206 RPMI	0.25 - 0.5	0.25	0.25	0.5	NA	NA
	Imipenem	1 - >8	>8	>8	>8	8.3%	87.5%
	Levofloxacin	4 - >4	>4	>4	>4	0%	96%
	Tigecycline	1 - 16	4	4	4	NA	NA
	Ceftazidime	>32 - >32	>32	>32	>32	0%	100%
	Colistin	0.12 - >16	0.25	0.25	4	83%	17%
	Amikacin	2 - >64	>64	>64	>64	21%	79%

MSSE, methicillin-susceptible *S. epidermidis*. MRSE, methicillin-resistant *S. epidermidis*. CoNS, coagulase-negative staphylococci. NA, not applicable. %S, percentage of isolates that are susceptible according to established CLSI breakpoints (tigecycline FDA breakpoints used where applicable). %R, percentage of isolates that are resistant according to established CLSI breakpoints (tigecycline FDA breakpoints used where applicable).

[1] For testing PLG0206 in RPMI one isolate did not grow; data for PGL0206 RPMI is based on 57 isolates.

[2] Species breakdown for non-*epidermidis* CoNS- *S. hominis* (10), *S. haemolyticus* (10), *S. warneri* (8), *S. capitis* (4), *S. simulans* (5), *S. lugdunensis* (4), *S. caprae* (4), *S. saprophyticus* (7), and *S. pettenkoferi* (1).

[3] Species breakdown for Enterobacterales *E. coli* (8), *K. pneumoniae* (8), *P. mirabilis* (2), *E. cloacae* (2), *K. oxytoca* (1), *C. freundii* (1).

- Overall, the PLG0206 MIC values were much lower when the organisms were tested in RPMI relative to CAMHB. For example, the MIC50 and MIC90 values were 4 to 16-fold lower in RPMI than CAMHB for the tested groups of organisms (CoNS, Enterobacterales, *P. aeruginosa,* and *A. baumannii*) (**Table 1**).
- Methicillin-resistance in *S. epidermidis* did not affect the MIC50/MIC90 values or MIC distribution of PLG0206.

Conclusions

•PLG0206 was found to have potent antimicrobial activity against CoNS; activity in RPMI was more potent than CAMHB. There was no impact of methicillin-resistance among CoNS on the activity of PLG0206.

•PLG0206 had varying activity against resistant Gram-negative bacilli. Among Enterobacterales, PLG0206 was most active against *E. coli*, *E. cloacae*, and *C. freundii*, was comparatively less active against *Klebsiella* spp., and was inactive against *P. mirabilis*.

•Despite the high degree of drug resistance among the evaluated *P. aeruginosa* and *A. baumannii*, PLG0206 had potent activity when evaluated in RPMI. As with CoNS, PLG0206 MIC values were several-fold higher in CAMHB relative to RPMI when testing Gram-negative bacilli.

References

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