01117
05. New antibacterial agents, PK/PD & Stewardship
5a. Mechanisms of action, new compounds, preclinical data & pharmacology of antibacterial agents

PLG0206, a Novel Engineered Antibacterial Peptide, has Broad Spectrum Activity Against Bacteria, Including ESKAPE Pathogens

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Introduction

- PLG0206 is a novel engineered antibacterial peptide with rapid bactericidal and anti-biofilm activities that is being developed for the treatment of periprosthetic joint infections (PJI). 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). Precipitation of PLG0206 at ≥8 mg/L using cation-adjusted Mueller-Hinton (CAMHB) broth has prevented a full evaluation of its *in vitro* activity. In this study, RPMI-1640 broth supplemented with MOPS/Tween-80 was tested as an alternative medium for MIC testing of PLG0206.

Materials and Methods

- Worldwide clinical isolates from seven countries, with the largest representation from Europe (n=991), were collected in 2019 and are shown in Table 1.

Table 1. ESKAPE isolates by region

Count by Region	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Grand Total
E. faecium	5	12	29	20	4	3	2	75
S. aureus	31	48	100	73	21	12	16	301
K. pneumoniae	37	55	97	63	28	8	12	300
A. baumannii	38	48	106	66	20	9	11	298
P. aeruginosa	37	51	99	67	25	9	12	300
E. cloacae	18	27	52	37	8	5	5	152
Grand Total	173	253	511	344	111	49	62	1503

- Testing was conducted in accordance with guidelines from the Clinical and Laboratory Standards Institute (3,4), except that PLG0206 was tested in MOPS RPMI-1640 medium supplemented with 0.004% Tween-80 due to precipitation of PLG0206 observed in CAMHB.

Results

Table 2. PLG0206 and comparator antibiotics against ESKAPE pathogens.

Organism (N;phenotype)	Drug	MIC range	MIC_{50}	MIC_{90}	%S	%R
E. faecium (75) Note: 29 isolates did not grow in RPMI so PLG0206 data are from 46 isolates only.	PLG0206	≤0.03 - 0.5	0.06	0.25	-	-
	Azithromycin	0.5 - >32	>32	>32	-	-
	Clindamycin	0.06 - >32	>32	>32	-	-
	Daptomycin	0.06 - 4	2	2	0.0	100.0
	Doxycycline	0.03 – 0.16	4	16	62.7	13.3
	Levofloxacin	0.25 - >32	>32	>32	8.0	4.0
	Linezolid	1 - 8	1	2	98.7	0.0
	Penicillin	0.06 - >32	>32	>32	13.3	-
	Vancomycin	0.25 - >32	0.5	>32	77.3	0.0
S. aureus, MRSA (180) Note: 6 isolates did not grow in RPMI so PLG0206 data are from 174 isolates only.	PLG0206	0.12 - 2	0.5	1		
	Azithromycin	0.12 - >32	8	>32	47.8	50.6
	Clindamycin	0.06 - >32	0.12	>32	76.7	23.3
	Daptomycin	0.12 - 2	0.25	0.5	99.4	-
	Doxycycline	0.03 - 16	0.06	1	95.0	1.1
	Levofloxacin	0.12 - >32	4	32	47.2	52.2
	Linezolid	0.5 - 4	1	2	100.0	0.0
	Penicillin	0.06 - >32	32	>32	1.7	98.3
	Vancomycin	0.25 - 1	1	1	100.0	0.0
S. aureus, MSSA (121) Note: 3 isolates did not grow in RPMI so PLG0206 data are from 118 isolates only.	PLG0206	0.06 - 4	0.5	1		
	Azithromycin	0.25 - >32	1	>32	77.7	20.7
	Clindamycin	0.06 - >32	0.12	0.12	97.5	2.5
	Daptomycin	0.12 - 1	0.25	0.5	100.0	-
	Doxycycline	0.03 - 8	0.06	0.5	98.3	0.0
	Levofloxacin	0.06 - 8	0.25	4	89.3	10.7
	Linezolid	0.5 - 4	1	2	100.0	0.0
	Penicillin	≤0.03 - >32	4	32	13.2	86.8
	Vancomycin	0.5 - 2	1	1	100.0	0.0
K. pneumoniae (300)	PLG0206	0.5 - >32	8	16		
	Amikacin	0.5 - >64	2	32	89.3	9.7
	Aztreonam	≤0.03 - >64	0.25	>64	56.0	42.3
	Aztreonam/Avibactam (4 µg/mL)	≤0.016 – 0.5	0.03	0.25	-	-
	Cefepime	0.016 - >32	0.5	>32	54.7	44.3
	Cefpodoxime	≤0.03 - >32	1	>32	52.3	47.7
	Ceftazidime	0.06 - >64	1	>64	52.7	44.7
	Ceftazidime/Avibactam (4 µg/mL)	≤0.03 - >32	0.125	1	93.3	6.7
	Ciprofloxacin	0.008 - >32	0.25	>32	46.3	45.0
	Colistin	0.125 - 32	0.25	0.5	-	3.7
	Doxycycline	0.125 - >32	2	32	61.0	31.0
	Eravacycline	0.06 - 8	0.25	1	-	-
	Gentamicin	0.125 - >32	0.5	>32	67.3	31.7
	Levofloxacin	0.016 - 64	0.5	>32	58.0	36.7
	Meropenem	≤0.06 - >64	≤0.06	32	84.3	14.7
	Meropenem/Vaborbactam (8 µg/mL)	≤0.03 - >32	≤0.03	16	89.3	10.3
	Plazomicin	0.125 - >32	0.25	0.5	-	-
	Tobramycin	0.125 - >32	0.5	>32	59.0	33.7

Results

Table 2 continued. PLG0206 and comparator antibiotics against ESKAPE pathogens.

Organism (N;phenotype)	Drug	MIC range	MIC_{50}	MIC_{90}	%S	%R
A. baumannii (298)	PLG0206	0.125 - 4	0.5	1		
	Amikacidin	1 - >64	>64	>64	39.9	57.7
	Ampicillin/Sulbactam (2:1)	0.5 - >32	32	>32	29.2	66.4
	Cefepime	0.5 - >32	>32	>32	26.2	71.5
	Ceftazidime	1 - >32	>32	>32	29.5	68.8
	Ciprofloxacin	≤0.03 - >32	>32	>32	27.2	72.5
	Colistin	0.125 - >32	0.25	0.5	-	2.7
	Doxycycline	≤0.25 - >128	4	64	57.0	37.9
	Gentamicin	0.25 - >32	>32	>32	38.3	58.4
	Levofloxacin	≤0.06 - >32	16	>32	28.2	66.4
	Meropenem	≤0.06 - >64	64	>64	29.9	68.8
	Meropenem/Vaborbactam (8 µg/mL)	≤0.06 - >32	>32	>32	-	-
	Piperacillin/Tazobactam (4 µg/mL)	≤0.5 - >128	>128	>128	26.8	70.1
	Sulbactam	0.5 - >32	16	>32	-	-
	Tetracycline	1 - >32	32	>32	33.6	55.4
	Tobramycin	≤0.06 - >32	16	>32	45.3	52.7
P. aeruginosa (300) Note: 3 isolates did not grow in RPMI so PLG0206 data are from 297 isolates only.	PLG0206	0.06 - 4	1	2	-	-
	Amakacin	0.125 - >64	4	64	85.3	12.3
	Aztreoman	≤0.06 - >16	8	>16	69.3	19.7
	Aztreonam/Avibactam (4 µg/mL)	≤0.03 - >16	4	>16	-	-
	Cefepime	0.125 - >32	4	>32	75.7	17.3
	Ceftazidime	0.125 - >32	4	>32	71.3	22.7
	Ceftazidime/Avibactam (4 µg/mL)	≤0.06 - >16	2	>16	87.3	12.7
	Ciprofloxacin	≤0.03 - >32	0.125	16	76.0	20.0
	Coliston	0.125 - 8	0.5	1	0.0	0.3
	Doxycycline	0.5 - >128	8	32	-	-
	Gentamicin	≤0.06 - >32	1	>32	82.7	14.3
	Levofloxacin	≤0.06 - >32	0.5	32	69.3	21.7
	Meropenum	≤0.06 - >64	0.5	32	77.7	15.3
	Meropenem/Vaborbactam (8 µg/mL)	≤0.06 - >32	0.5	32	-	-
	Piperacillin/Tazobactam (4 µg/mL)	≤0.5 - >128	8	128	73.7	14.3
	Tetracycline	0.5 - >32	8	32	-	-
	Tobramycin	≤0.06 - >32	0.5	>32	84.7	14.7
E. cloacae (152)	PLG0206	0.5 - >32	4	16	-	-
	Amikacin	1 - >64	2	4	96.7	2.6
	Aztreonam	≤0.03 - >64	0.125	128	63.2	36.2
	Aztreonam/Avibactam (4 µg/mL)	≤0.016 - 8	0.06	0.5	-	-
	Cefepime	0.03 - >32	0.125	64	71.1	27.6
	Cefpodoxime	0.125 - >32	2	64	50.7	45.4
	Ceftazidime	0.125 - >64	0.5	128	59.9	38.8
	Ceftazidime/Avibactam (4 µg/mL)	≤0.03 - >32	0.25	2	91.4	8.6
	Colistin	0.125 - >32	0.25	2	-	9.2
	Doxycycline	0.5 - >32	2	16	80.3	11.2
	Eravacycline	0.125 - 4	0.5	1	-	-
	Gentamicin	0.25 - >32	0.5	64	77.0	23.0
	Levofloxacin	0.008 - >32	0.03	8	78.9	17.8
	Meropenem	≤0.06 - >64	≤0.06	0.25	92.1	7.2
	Meropenem/Vaborbactam (8 µg/mL)	≤0.03 - >32	≤0.03	0.06	93.4	5.3
	Plazomicin	0.25 - >32	0.25	0.5	-	-
	Tobramycin	0.25 - >32	0.5	32	75.7	21.7

Summary

•Broad-spectrum activity was demonstrated *in vitro* for PLG0206 including most of the ESKAPE group.

•29/75 *E. faecium*, 9/301 *S. aureus*, and 3/300 *P. aeruginosa* were unable to grow in RPMI.

•PLG0206 was most active against the enterococci and staphylococci, including MRSA.

Conclusions

•The activity of PLG0206, in RPMI-1640 broth medium, warrants continued evaluation for treatment of the so-called ESKAPE group of pathogens that are a major cause of nosocomial life-threatening infections and are on the WHO's "priority pathogen" list.

References

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