Activity of the novel engineered antimicrobial peptide PLG0206 against Enterobacterales isolates

David Huang[1], Jonathan Steckbeck[1], Dean Shinabarger[2], Ian Morrissey[3], Stephen Hawser[4] ; [1]Peptilogics, Pittsburgh, PA, USA.; [2]Microbiologics, Kalamazoo, MI, USA; [3]Antimicrobial Focus, Sawbridgeworth, UK; [4]IHMA Europe, Monthey, Switzerland

Peptilogics

INTRODUCTION

- PLG0206 is an investigational, engineered cationic antimicrobial peptide designed to overcome the shortcomings of other natural AMPs, such as toxicity and limited activity (1,2). PLG0206 has recently been shown to be well tolerated and safe in a phase 1 study (3).
- The current study evaluated the activity of PLG0206 and comparator antimicrobials against Enterobacterales isolates collected from various world-wide locations in 2019.

MATERIALS AND METHODS

- Isolates tested included *Citrobacter* spp. (151), *Enterobacter cloacae* (152), *Escherichia coli* (300), *Klebsiella pneumoniae* (300), *Morganella morganii* (43), *Proteus* spp. (152), *Providencia* spp. (61) and *Serratia marcescens* (45). The isolates were collected in 2019, with approximately one-third from Europe and the remainder from other regions (Figure 1). The isolates originated from a variety of infection types (Figure 2)
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology (4) in cation-adjusted Mueller Hinton broth (CA-MHB), except for PLG0206 which was tested in MOPS RPMI-1640 medium supplemented with 0.004% Tween-80 due to precipitation of PLG0206 observed in CAMHB.
- The susceptibility of comparator antimicrobials was determined using the 2022 CLSI breakpoints (5). Multi-drug-resistance (MDR) was defined as resistance to 3 or more of the antimicrobials tested by class of antimicrobial including aminoglycosides (amikacin, gentamicin or tobramycin), cephems (cefepime, cefpodoxime or ceftazidime), fluoroquinolones (levofloxacin or ciprofloxacin) and tetracyclines (doxycycline or eravacycline [non-susceptible]) or by individual antimicrobial for aztreonam, colistin, ceftazidime/avibactam, meropenem, and meropenem/vaborbactam.

FIGURE 1. Geographical location of the Enterobacterales tested.

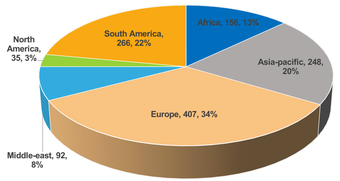

FIGURE 2. Infection source for the Enterobacterales tested.

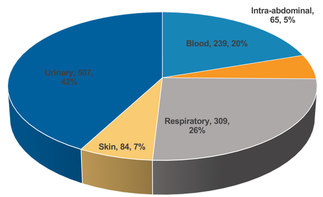

FIGURE 3: Cumulative % MIC distribution for PLG0206 against Enterobacterales isolates.

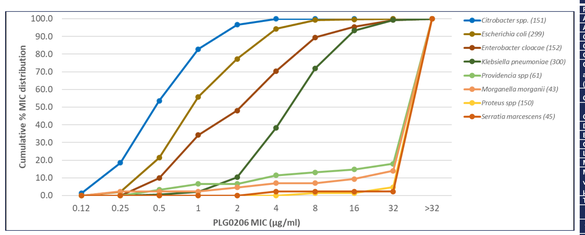

TABLE 1: Summary activity of PLG0206 and comparators against *Citrobacter* spp

Antimicrobial	*Citrobacter spp.* (n=151)*					*C. freundii* (n=91)					*C. koseri* (n=55)				
	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R
PLG0206	0.5	2	-	-	-	1	2	-	-	-	0.5	0.5	-	-	-
Amikacin	2	4	98.7	0.0	1.3	2	4	97.8	0.0	2.2	2	4	100.0	0.0	0.0
Aztreonam	0.12	64	76.2	1.3	22.5	0.25	64	69.2	2.2	28.6	0.06	16	89.1	0.0	10.9
Cefepime	0.06	>32	82.1	4.0	13.9	0.06	>32	78.0	5.5	16.5	0.03	>32	89.1	0.0	10.9
Cefpodoxime	2	>32	60.3	10.6	29.1	4	>32	42.9	17.6	39.6	0.25	>32	89.1	0.0	10.9
Ceftazidime	0.5	>64	78.1	0.7	21.2	1	>64	69.2	1.1	29.7	0.25	2	90.9	0.0	9.1
Ceftazidime-avibactam (4 µg/mL)	0.12	0.5	94.7	-	5.3	0.12	1	92.3	-	7.7	0.12	0.25	98.2	-	1.8
Colistin	0.25	0.5	-	100.0	0.0	0.25	0.5	-	100.0	0.0	0.12	0.25	-	100.0	0.0
Doxycycline	2	16	82.8	6.6	10.6	2	16	76.9	7.7	15.4	0.5	4	90.9	5.5	3.6
Eravacycline	0.25	0.5	93.4	-	-	0.25	1	89.0	-	-	0.12	0.5	100.0	-	-
Gentamicin	0.5	8	89.4	0.7	9.9	0.5	32	85.7	1.1	13.2	0.5	0.5	94.5	0.0	5.5
Levofloxacin	0.06	2	80.8	5.3	13.9	0.25	2	72.5	6.6	20.9	0.03	0.5	92.7	3.6	3.6
Meropenem	≤0.06	≤0.06	93.4	0.0	6.6	≤0.06	0.12	91.2	0.0	8.8	≤0.06	≤0.06	96.4	0.0	3.6
Meropenem-vaborbactam (8 µg/mL)	≤0.03	≤0.03	95.4	0.7	4.0	≤0.03	0.06	93.4	1.1	5.5	≤0.03	≤0.03	98.2	0.0	1.8
Tobramycin	0.5	8	86.8	3.3	9.9	0.5	16	82.4	4.4	13.2	0.5	4	92.7	1.8	5.5
$MIC_{50/90}$: concentration (µg/mL) required to inhibit 50/90% of the bacteria tested;															
%S/I/R: % susceptible/intermediate/resistant according to CLSI breakpoints															
*Includes 91 *C. freundii*, 55 *C. koseri*, 2 *C. braakii*, 2 *C. sedlakii* & 1 *C. farmeri*															

TABLE 2: Summary activity of PLG0206 and comparators against *E. coli*, *E. cloacae* and *K. pneumoniae*

Antimicrobial	*E. coli* (n=299)*					*E. cloacae* (n=152)					*K. pneumoniae* (n=300)				
	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R
PLG0206	1	4	-	-	-	4	16	-	-	-	8	16	-	-	-
Amikacin	2	8	98.7	0.7	0.7	2	4	96.7	0.7	2.6	2	32	89.3	1.0	9.7
Aztreonam	0.12	>64	66.2	3.7	30.1	0.12	>64	63.2	0.7	36.2	0.25	>64	56.0	1.7	42.3
Cefepime	0.06	>32	66.9	3.0	30.1	0.12	>32	71.1	1.3	27.6	0.5	>32	54.7	1.0	44.3
Cefpodoxime	0.5	>32	60.2	0.3	39.5	2	>32	50.7	3.9	45.4	1	>32	52.3	0.0	47.7
Ceftazidime	0.25	64	69.6	2.7	27.8	0.5	>64	59.9	1.3	38.8	1	>64	52.7	2.7	44.7
Ceftazidime-avibactam (4 µg/mL)	0.12	0.25	97.7	-	2.3	0.25	2	91.4	-	8.6	0.12	1	93.3	-	6.7
Ciprofloxacin	Not tested					Not tested					0.25	>32	50.0	5.0	45.0
Colistin	0.25	0.25	-	100.0	0.0	0.25	2	-	90.8	9.2	0.25	0.5	-	96.3	3.7
Doxycycline	2	32	55.5	19.4	25.1	2	16	80.3	8.6	11.2	2	32	61.0	8.0	31.0
Eravacycline	0.25	0.25	99.7	-	-	0.5	1	89.5	-	-	0.25	1	85.7	-	-
Gentamicin	0.5	>32	76.6	0.7	22.7	0.5	>32	77.0	0.0	23.0	0.5	>32	67.3	1.0	31.7
Levofloxacin	0.5	16	56.2	2.3	41.5	0.03	8	78.9	3.3	17.8	0.5	>32	58.0	5.3	36.7
Meropenem	≤0.06	≤0.06	97.3	0.0	2.7	≤0.06	0.25	92.1	0.7	7.2	≤0.06	32	84.3	1.0	14.7
Meropenem-vaborbactam (8 µg/mL)	≤0.03	≤0.03	97.3	0.3	2.3	≤0.03	0.06	93.4	1.3	5.3	≤0.03	16	89.3	0.3	10.3
Tobramycin	1	16	76.9	7.4	15.7	0.5	32	75.7	2.6	21.7	0.5	>32	59.0	7.3	33.7
$MIC_{50/90}$: concentration (µg/mL) required to inhibit 50/90% of the bacteria tested;															
%S/I/R: % susceptible/intermediate/resistant according to CLSI breakpoints															
*One *E. coli* was unable to grow in RPMI															

Antimicrobial	*Citrobacter spp.* (n=26)*					*E. coli* (n=92)					*E. cloacae* (n=45)					*K. pneumoniae* (n=132)				
	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R	MIC_{50}	MIC_{90}	%S	%I	%R
PLG0206	1	2	-	-	-	1	2	-	-	-	1	16	-	-	-	8	16	-	-	-
Amikacin	4	16	92.3	0.0	7.7	4	8	95.7	2.2	2.2	4	16	91.1	2.2	6.7	4	>64	77.3	1.5	21.2
Aztreonam	64	>64	19.2	0.0	80.8	64	>64	9.8	2.2	88.0	64	>64	13.3	0.0	86.7	>64	>64	9.1	0.8	90.2
Cefepime	>32	>32	15.4	11.5	73.1	>32	>32	13.0	3.3	83.7	>32	>32	11.1	2.2	86.7	>32	>32	5.3	0.8	93.9
Cefpodoxime	>32	>32	3.8	0.0	96.2	>32	>32	4.3	0.0	95.7	>32	>32	0.0	0.0	100.0	>32	>32	2.3	0.0	97.7
Ceftazidime	>64	>64	15.4	3.8	80.8	32	>64	16.3	5.4	78.3	>64	>64	4.4	0.0	95.6	>64	>64	3.8	3.0	93.2
Ceftazidime-avibactam (4 µg/mL)	0.5	>32	69.2	-	30.8	0.25	4	92.4	-	7.6	1	>32	71.1	-	28.9	0.25	>32	84.8	-	15.2
Ciprofloxacin	Not tested					Not tested					Not tested					>32	>32	9.8	2.27	87.9
Colistin	0.25	0.5	-	100.0	0.0	0.25	0.25	-	100.0	0.0	0.25	>32	-	82.2	17.8	0.25	1	-	92.4	7.6
Doxycycline	8	>32	34.6	23.1	42.3	8	>32	29.3	20.7	50.0	4	>32	53.3	22.2	24.4	16	>32	32.6	13.6	53.8
Eravacycline	0.5	1	73.1	-	-	0.25	0.25	98.9	-	-	0.5	2	68.9	-	-	0.5	2	77.3	-	-
Gentamicin	8	>32	46.2	3.8	50.0	16	>32	41.3	2.2	56.5	32	>32	24.4	0.0	75.6	32	>32	28.0	1.5	70.5
Levofloxacin	2	16	23.1	23.1	53.8	8	32	7.6	0.0	92.4	4	>32	31.1	8.9	60.0	8	>32	24.2	8.3	67.4
Meropenem	≤0.06	64	61.5	0.0	38.5	≤0.06	0.5	91.3	0.0	8.7	0.12	32	73.3	2.2	24.4	≤0.06	>64	64.4	2.3	33.3
Meropenem-vaborbactam (8 µg/mL)	≤0.03	>32	73.1	3.8	23.1	≤0.03	0.5	91.3	1.1	7.6	≤0.03	32	77.8	4.4	17.8	≤0.03	>32	75.8	0.8	23.5
Tobramycin	16	>32	26.9	19.2	53.8	8	32	40.2	15.2	44.6	16	>32	20.0	8.9	71.1	16	>32	12.9	13.6	73.5
$MIC_{50/90}$: concentration (µg/mL) required to inhibit 50/90% of the bacteria tested;																				
%S/I/R: % susceptible/intermediate/resistant according to CLSI breakpoints																				
*Includes 21 *C. freundii* & 5 *C. koseri*																				

RESULTS SUMMARY

- PLG0206 was active against *Citrobacter* spp., *E. coli*, *E. cloacae*, and *K. pneumoniae*, but inactive against *Providencia* spp., *M. morganii*, *Proteus* spp. and *S. marcescens* (Figure 3).
- PLG0206 activity compared well with the other test antimicrobials with MIC_{90} values lower than most comparators (Tables 1 and 2).
- PLG0206 retained activity against MDR isolates of *Citrobacter* spp. (26), *E. coli* (92), *E. cloacae* (45), and *K. pneumoniae* (132) with virtually unchanged MIC_{50} or MIC_{90} (Table 3).

CONCLUSION

- PLG0206 was active against isolates from the family *Enterobacteriaceae*, including MDR strains. These data suggest that the novel antimicrobial peptide PLG0206 could be a potential treatment option against infections caused by *Enterobacteriaceae* isolates.

References

1. Deslouches, B. et al. Rational design of engineered cationic antimicrobial peptides consisting exclusively of arginine and tryptophan, and their activity against multidrug-resistant pathogens. Antimicrob Agents Chemother 2013:57, 2511–21.
2. Deslouches B, et al. Engineered cationic antimicrobial peptides to overcome multidrug resistance by ESKAPE pathogens. Antimicrob Agents Chemother. 2015;59:1329–33.
3. Huang, D et al. A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of a First-in-Human Engineered Cationic Peptide, PLG0206, Intravenously Administered in Healthy Subjects. Antimicrob Agents Chemother. 2022; 66:e0144121.
4. CLSI. 2018. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 11th ed. CLSI standard M07. CLSI, Wayne, PA, USA.
5. CLSI. 2022. Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI supplement M100. CLSI, Wayne, PA, USA.

Acknowledgments

Research reported in this press release is supported by CARB-X. CARB-X's funding for this project is sponsored by the Cooperative Agreement Number IDSEP160030 from ASPR/BARDA and by an award from Wellcome Trust. The content is solely the responsibility of the authors and does not necessarily represent the official views of CARB-X or any of its funders.