

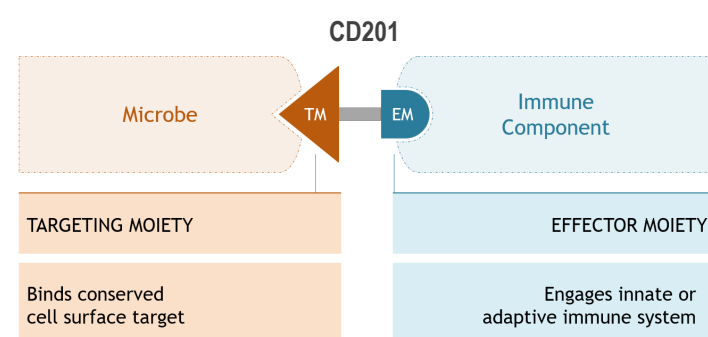
# Antibacterial activity of CD201, a novel lipopolysaccharide-binding antibacterial immunotherapy, against recent Gram-negative clinical isolates, including colistin-resistant strains



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## INTRODUCTION AND PURPOSE

CD201 is a member of a novel, lipopolysaccharide (LPS)-binding immunotherapy class of antibacterials that demonstrates bispecific activity to antibacterial and immunotherapeutic targets. CD201 is being developed for use against multidrug-resistant Gram-negative bacterial strains, including those resistant to colistin (COL) through chromosomal mutations or possession of the *mcr-1* COL<sup>R</sup> gene. Here we investigated the intrinsic antibacterial activity of CD201, independent of its immunotherapeutic activity, in MIC<sub>90</sub> panels comprising contemporary clinical isolates of key Gram-negative species, including strains resistant to COL.



## METHODS

MIC<sub>90</sub> panels were assembled from clinical isolates collected from US sites between 2012 and 2016 (Micromyx, LLC). Twenty-strain COL<sup>S</sup> panels were comprised of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. A 25-strain COL<sup>R</sup> panel was comprised of uncharacterized, chromosomal mutants of *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*. MIC assays (CLSI broth microdilution<sup>1</sup>) were performed for CD201 and comparators, including COL, polymyxin B (PMB), meropenem (MERO), tigecycline (TIG), amikacin (AMIK) and levofloxacin (LEVO). MIC values were called at 100% inhibition after 24 h incubation at 37°C and assessed by CLSI interpretive criteria.<sup>2</sup>

## RESULTS

Table 1. MIC<sub>90</sub> values and ranges for COL<sup>S</sup> and COL<sup>R</sup> isolate panels

Species (n)	MIC <sub>90</sub> (range) (µg/mL)						
	CD201	COL	PMB	MERO	TIG	AMIK	LEVO
<i>E. coli</i> (20)	2 (2 - 2)	0.5 (0.25 - 0.5)	0.5 (0.25 - 1)	0.03 (0.015 - 0.03)	0.5 (0.125 - 0.5)	8 (1 - 8)	>8 (0.03 - >8)
<i>K. pneumoniae</i> (20)	4 (2 - 8)	0.5 (0.25 - 0.5)	0.5 (0.5 - 1)	0.5 (0.03 - 8)	2 (1 - 8)	8 (≤0.5 - 32)	4 (0.03 - >8)
<i>P. aeruginosa</i> (20)	4 (2 - 8)	2 (0.5 - 4)	1 (0.5 - 1)	>8 (0.25 - >8)	>8 (>8 - >8)	16 (2 - 16)	4 (0.5 - >8)
<i>A. baumannii</i> (20)	4 (2 - 4)	2 (0.5 - 4)	1 (0.5 - 2)	>8 (0.25 - >8)	4 (0.5 - 8)	>64 (1 - >64)	>8 (0.06 - >8)
COL <sup>R</sup> : <i>Kp</i> , <i>Pa</i> , <i>Ab</i> (25)	16 (2 - 32)	>1024 (8 - >1024)	256 (1 - >1024)	>8 (0.03 - >8)	8 (0.5 - >8)	>256 (1 - >256)	128 (0.06 - >256)

Table 2. MIC values for individual isolates from the COL<sup>R</sup> panel

#	Species	Strain	MIC (µg/mL)						
			CD201	COL	PMB	MERO	TIG	AMIK	LEVO
1	<i>K. pneumoniae</i>	6949	4	>1024	>1024	16	1	16	128
2	<i>K. pneumoniae</i>	6951	16	1024	256	32	8	64	256
3	<i>K. pneumoniae</i>	6952	4	64	32	8	1	64	128
4	<i>K. pneumoniae</i>	6953	4	64	32	16	1	32	128
5	<i>K. pneumoniae</i>	6955	4	256	32	32	8	16	128
6	<i>K. pneumoniae</i>	6956	32	64	64	256	2	32	256
7	<i>K. pneumoniae</i>	6958	2	256	32	32	2	64	16
8	<i>K. pneumoniae</i>	6961	16	128	64	32	4	16	64
9	<i>K. pneumoniae</i>	6964	4	32	16	16	1	16	128
10	<i>K. pneumoniae</i>	6269	16	128	64	32	1	16	32
11	<i>K. pneumoniae</i>	6382	4	16	1	0.03	0.5	1	0.06
12	<i>K. pneumoniae</i>	8811	4	256	64	64	2	64	64
13	<i>P. aeruginosa</i>	7874	2	16	16	1	>8	4	0.5
14	<i>P. aeruginosa</i>	6977	8	1024	256	8	>8	32	>256
15	<i>A. baumannii</i>	8537	2	256	16	128	4	16	32
16	<i>A. baumannii</i>	8644	2	8	2	64	4	4	16
17	<i>A. baumannii</i>	8990	32	256	64	128	4	8	16
18	<i>A. baumannii</i>	6971	2	128	8	64	4	2	128
19	<i>A. baumannii</i>	6973	4	>1024	256	16	2	>256	8
20	<i>A. baumannii</i>	6975	2	32	8	32	4	>256	8
21	<i>A. baumannii</i>	8381	4	512	32	64	4	>256	8
22	<i>A. baumannii</i>	8383	8	>1024	256	8	4	>256	16
23	<i>A. baumannii</i>	8384	4	>1024	256	16	2	>256	8
24	<i>A. baumannii</i>	8386	4	64	8	32	2	>256	8
25	<i>A. baumannii</i>	6338	2	8	2	32	2	4	16

- CD201 MIC<sub>90</sub> values for *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* ranged between 2 and 4 µg/mL, compared to 0.5 - 2 µg/mL for COL and 0.5 - 1 µg/mL for PMB
- MERO and TIG possessed greater activity against the COL<sup>S</sup> *E. coli* and *K. pneumoniae* panels than AMIK and LEVO
- COL<sup>S</sup> *P. aeruginosa* and *A. baumannii* isolates demonstrated much higher levels of resistance to comparator agents than the COL<sup>S</sup> *E. coli* and *K. pneumoniae* isolates
- Cross-resistance with COL and PMB was observed for some strains in the chromosomal mutant COL<sup>R</sup> panel, however, CD201 maintained >64-fold and 16-fold MIC<sub>90</sub> potency advantages over COL and PMB, respectively
- All but one of the isolates in the COL<sup>R</sup> panel (*K. pneumoniae* 6382) was also resistant to one or more of the MERO, TIG, AMIK, and LEVO comparators
- For the three comparator agents where interpretive criteria are available, MERO, AMIK, and LEVO, resistance was observed at 92%, 40%, and 92%, respectively among the COL<sup>R</sup> panel isolates

## CONCLUSIONS

- CD201 maintained consistent activity against panels of contemporary, clinically-relevant Gram-negative species
- CD201 showed potency advantages over COL and PMB against multidrug-resistant COL<sup>R</sup> isolates
- These MIC data demonstrate the intrinsic, LPS-binding-based antibacterial activity of CD201
- This promising in vitro activity of CD201 is independent of potential added benefits from CD201 immunotherapeutic activity

## REFERENCES

- 1) CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-10<sup>th</sup> Edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA, USA, 2015.
- 2) CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 27<sup>th</sup> Informational Supplement. CLSI document M100-S27. CLSI, Wayne, PA, USA, 2016.

## DISCLOSURES

- This study was funded by Cidara Therapeutics. The authors are employees and shareholders of Cidara Therapeutics
- Bacterial isolates were obtained from Micromyx, LLC (Kalamazoo, MI, USA)
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