Ceftolozane-tazobactam (CLT), Ceftazidime-avivactam (CZA).

Anything else ?

L. Dubreuil
Lille- Tourcoing

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Mécanismes de résistance acquise à ceftolozane-tazobactam chez *Pseudomonas*

Mutations (2 à 4) sur Amp C → **sur**production de AmpC

large amount of mutations on ampC genes was required for development of high-level resistance (Cabot et al., 2014).

Mutation de l'Oxacillinase

duplication AA D149 sur OXA 2 devenant OXA 135

Absence de la PLP4

Mécanismes de résistance acquise à ceftazidime – avibactam

- Plasmide de KPC3 variant apparaissant après 10 à 19j de traitement de KPC

- Mutations en 164 ou 179 sur KPC2 empêche la fixation (binding) de l'inhibiteur sur la ß-lactamase

- Variants de SHV-1 et KPC-2: une seule mutation isolée

Association imperméabilité ompK 36 et surproduction AmpC

The expression of additional ESBLs along with an ompK36 (porin loss) mutation also contributes to elevated CAZ/AVI MICs when in the presence of KPC-2 expression (Shields et al., 2015).

929 Shields

novel ST258, clade II sublineage, which are not hypermutators

Ceftazidime-avibactam resistance

10% of patients (8/77) treated for CRE infections developed ceftazidime-avibactam resistance

14% of patients (8/59) treated for CR-Kp infections developed ceftazidime-avibactam resistance

Patient	Days of C-A	Infection Type	Location	Treatment regimen	RRT*	Outcome at 30 days
1	10	PNA	MICU	Monotherapy	No	Failure
2	19	IAI	SICU	Monotherapy	CRRT	Failure
3	15	PNA	SICU	Monotherapy	No	Success w/ relapse
4	15	PNA	CTICU	+ inhaled gent	CRRT	Failure
5	15	PNA	MICU	Monotherapy	HD	Failure
6	7	PNA	MICU	Monotherapy	No	Failure
7	21	PNA	10G	Monotherapy	HD	Failure
8	31	PNA	CTICU	+ inhaled/IV gent	CRRT	Failure

* Independent risk factor for resistance (OR: 11.70, 95% CI: 1.79 – 76.0; *P*=0.003)

Resistance to CAZ-AVI by KPC-2 Variants

prevent avibactam from binding to and inhibiting the ß-lactamase.

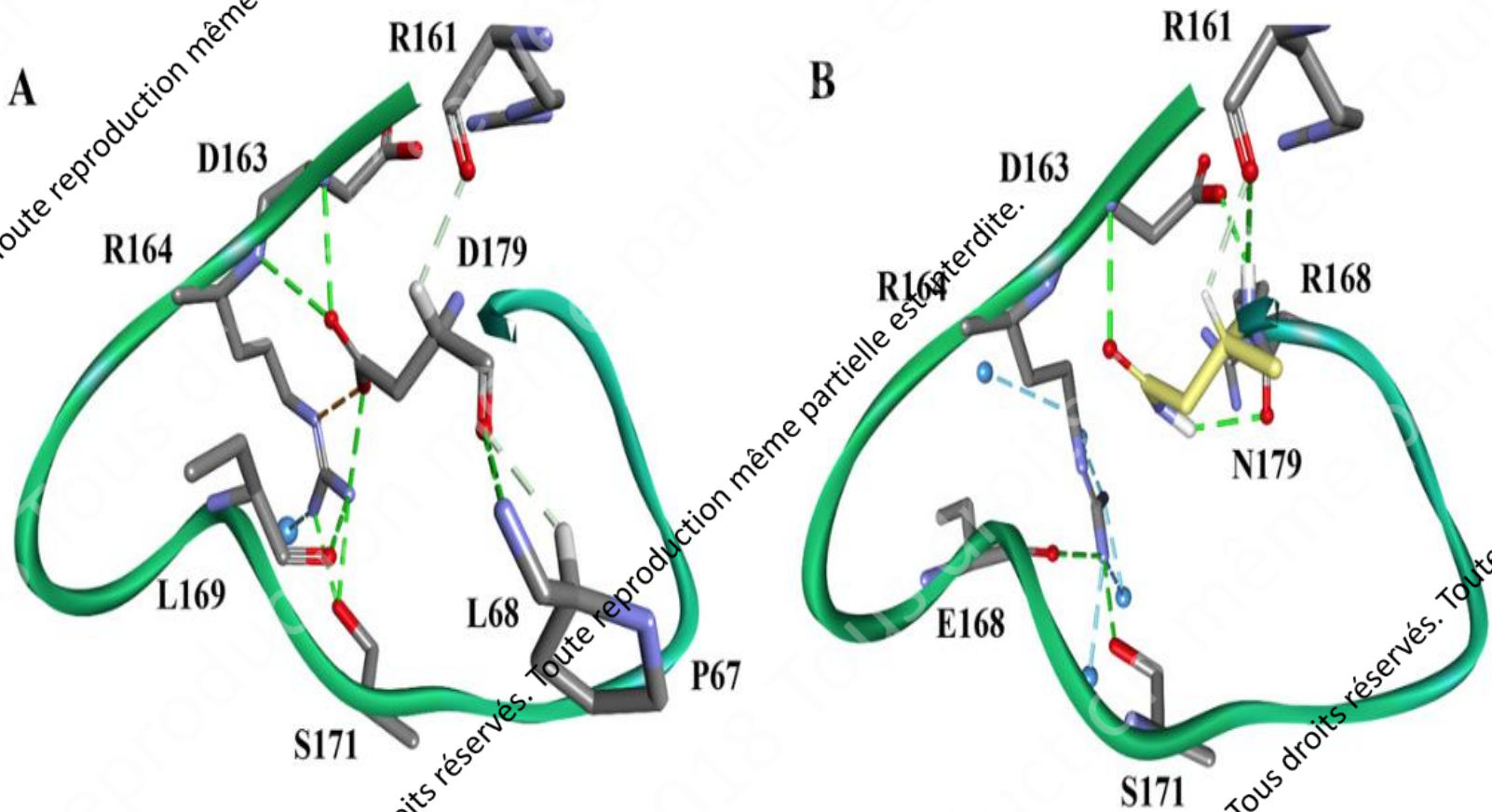

FIG 1 Ω-Loop hydrogen bond networking changes due to the aspartate (D) to-asparagine (N) substitution at Ambler position 179 in KPC-2. (A) KPC-2. (B) Asp179Asn (D179N) variant.

Is the reported early development of resistance a unique flaw of ceftazidime/avibactam or might it be seen withother new ß-lactam/ß-lactamase inhibitor combinations?

How commonly will the mechanisms causing this phenotype be found in the clinic?

Tremendous new !

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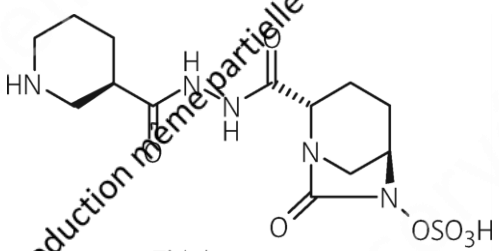
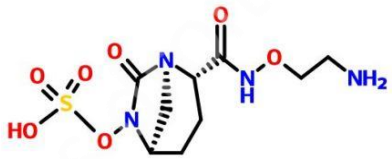
bicyclo-acyl hydrazide = BCH

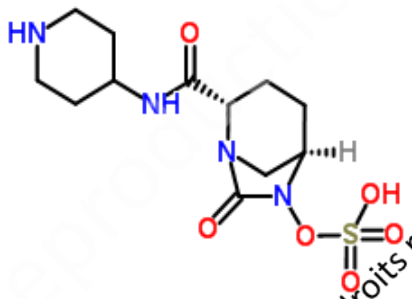


Zidebactam

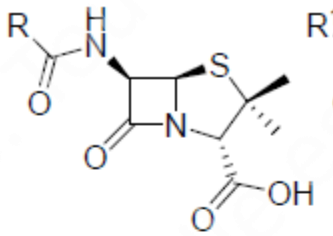
Diazabicyclooctanes= DBO



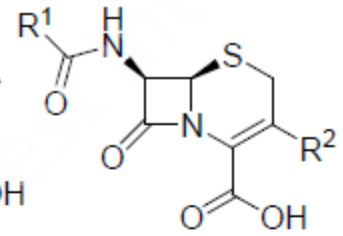
Nacubactam



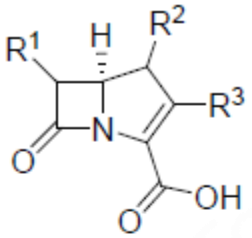
Relebactam



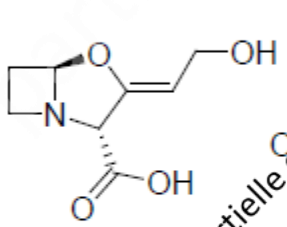
Penicillin



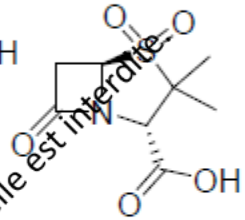
Cephalosporin



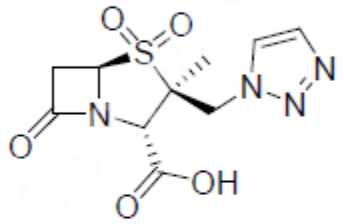
Carbapenem



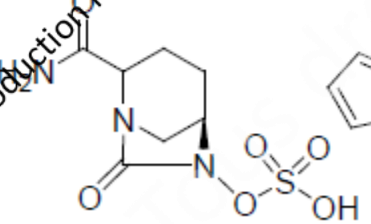
Clavulanic acid



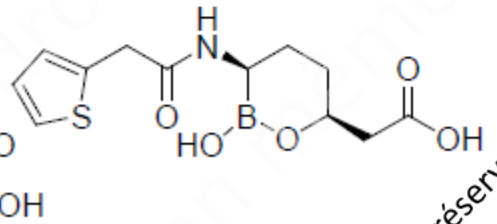
Sulbactam



Tazobactam



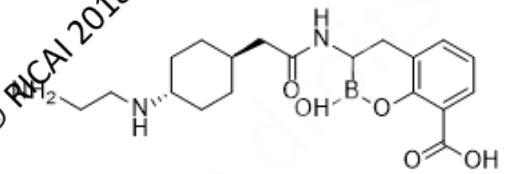
Avibactam (NXL-104)



RPX-7009 = Vaborbactam

Figure 1: β-Lactam antibiotics and β-lactamase inhibitors.

VNRX 5133



Lab: MSD

Designed for *Pseudomonas aeruginosa*

Relebactam (+ imipenem/cilastatin)

- Triple combination (includes cilastatin DHP-1 inhibitor)
- Relebactam is more stable to hydrolysis by KPC-2 than avibactam
- Potentiates activity of imipenem against some CRPA (potential advantage vs vaborbactam/meropenem)

•Relebactam

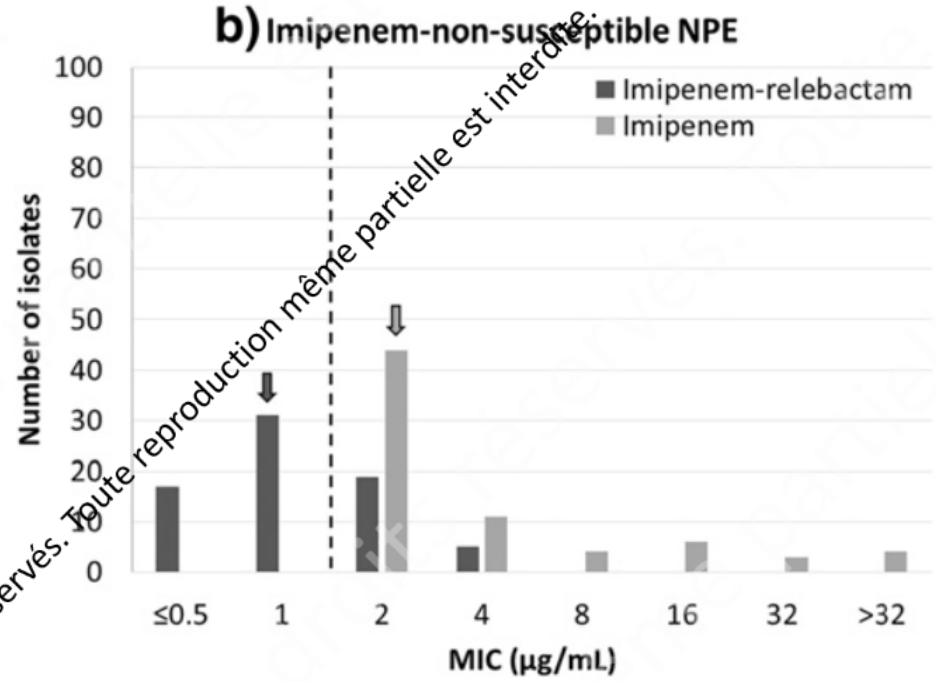
Organism	n	Drug	MIC (mg/L)							
			≤0.5	1	2	4	8	16	32	>32
P. aeruginosa	1065	IMI	20.8	58.3	64.1	68.9	81.4	**94.2**	97.4	100
		IMI/REL	69.9	80.9	**91.5**	93.7	96.2	96.9	97.8	100
P. aeruginosa, IMI-NS	331	IMI					40.2	81.3	**91.5**	100
		IMI/REL	9.7	40.2	72.5	79.8	87.6	**90.0**	93.1	100
NPE	1949	IMI	76.3	89.3	**94.0**	95.6	96.5	97.3	97.7	100
		IMI/REL	87.6	**95.7**	97.5	98.4	98.7	98.9	99.0	100
NPE, IMI-NS	116	IMI				26.7	40.5	55.2	61.2	**100**
		IMI/REL	39.7	46.6	58.6	73.3	78.4	81.9	83.6	**100**

Shaded area indicates susceptible by EUCAST 2015 imipenem breakpoint; MIC_{90} bolded; NPE, non-Proteeae *Enterobacteriaceae*; IMI, imipenem; REL, relebactam; NS, non-susceptible

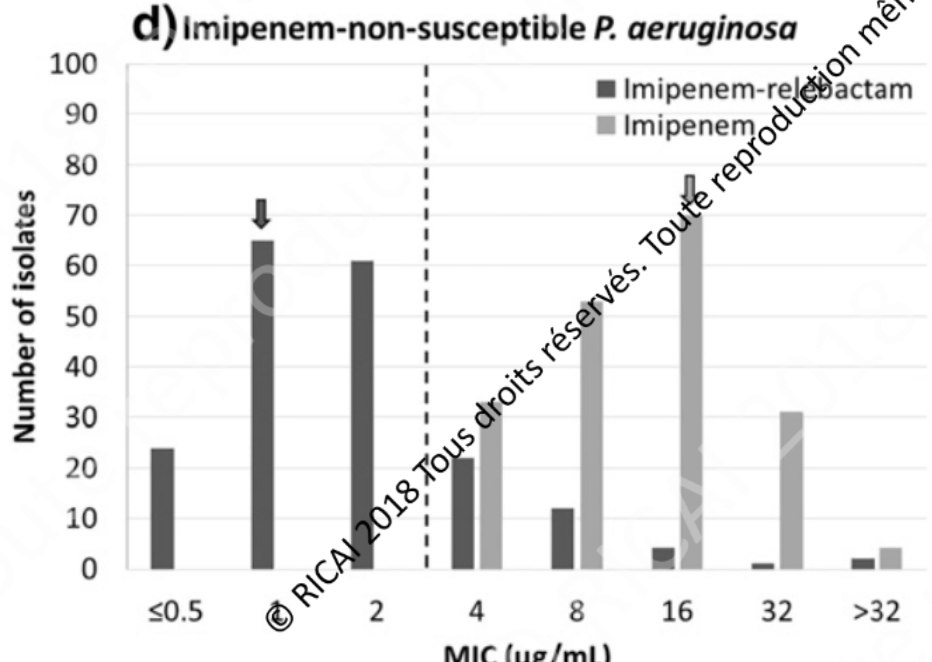
27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: P060 News on relebactam and vaborbactam



Recupération 66.5%



Recupération 81 %

S.H. Lob et al. / Diagnostic Microbiology and Infectious Disease 88 (2017) 171–176

IMI /REL synergie maximale 4 mg/L

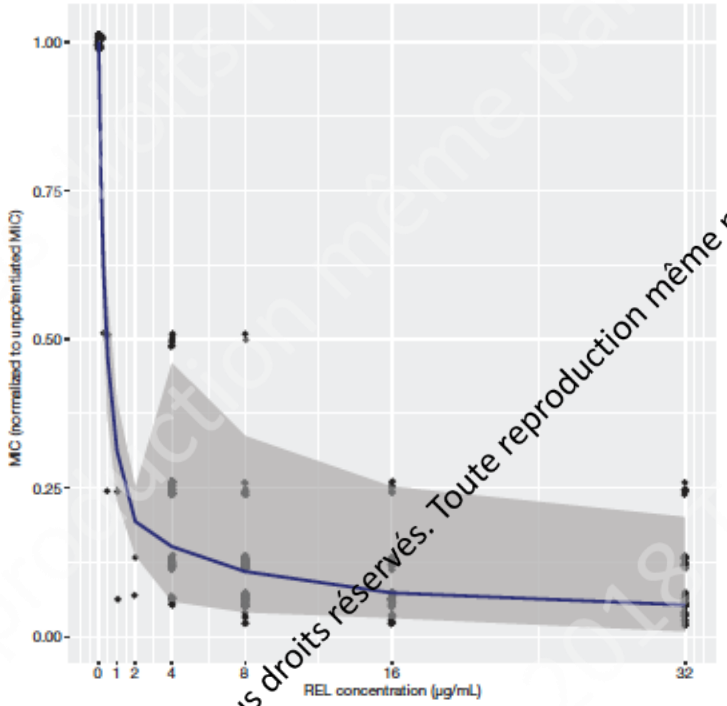


FIG 4 Relationship between IMI imipenem MIC and the REL concentration in static checkerboard experiments from a total of 1,185 data points from 93 strains of *P. aeruginosa* overlaid with the model fit drug concentration at which the maximum effect is observed (E_{max}) (symbols, experimental data; blue line, median model fit; shaded area, minimum-maximum model fit). REL, relebactam.

In **P. aeruginosa**, there was an MIC reduction in **OprD-deficient** strains from 16–64 mg/L to 1–4 mg/L.

A minimal effect of **relebactam** was seen in OXA-48 producing isolates. Isolates with an initial carbapenem MIC >64 mg/L had an MIC reduction to 16 mg/L with the addition of high dose 32mg/L relebactam.

Relebactam does not induce ampC as did avibactam

Inactivation of the porin protein OmpK36 in *K. pneumoniae* has been reported to confer resistance to both imipenem–relebactam and meropenem–vaborbactam.

KPC-2 vs. KPC-3 Activity

KPC Producing K. pneumoniae (n=62)	Imipenem-Relebactam Median MIC (range)		Ceftazidime-Avibactam Median MIC (range)	
	Median MIC (range)	P-value	Median MIC (range)	P-value*
KPC-3 variant	0.25 (0.125-0.5)	0.31	128 (16-512)	0.0001
No KPC-3 variant	0.5 (0.125-4)		2 (0.25-16)	

*p<0.0001 by multivariate analysis

1. Humphries et al AAC 2015; 59:6605. 2. Humphries et al AAC 2016; 61:e00537. 3. Nelson et al AAC 2017; 61:e00989. 4. Shields et al, AAC 2017; 61:e2097. 5. Haidar et al AAC2017; 61:e2534. 6. Haidar et al. AAC 2017; 61: e00642-17.

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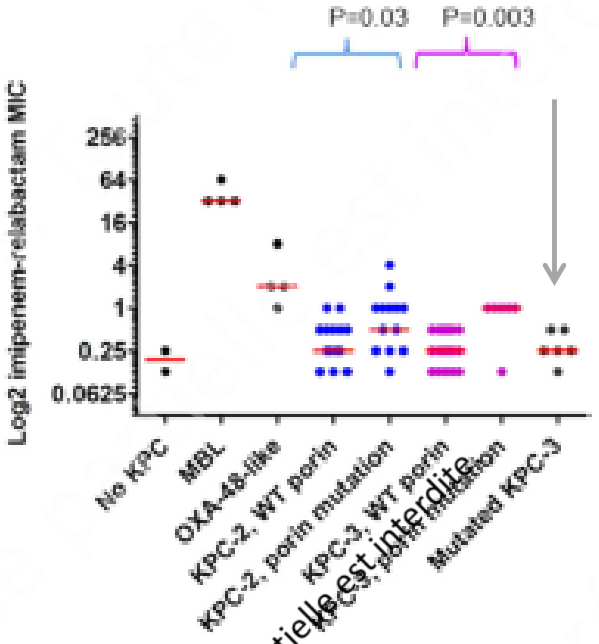
Identifying Spectra of Activity and Therapeutic Niches for Ceftazidime-Avibactam and Imipenem-Relebactam against Carbapenem-Resistant *Enterobacteriaceae*

Ghady Haidar,[a] Cornelius J. Clancy,[b,c,d] Liang Shen,[e] Palash Samanta,[a] Ryan K. Shields,[a,b,c] Barry N. Kreiswirth,[e] M. Hong Nguyen[a,b,c]

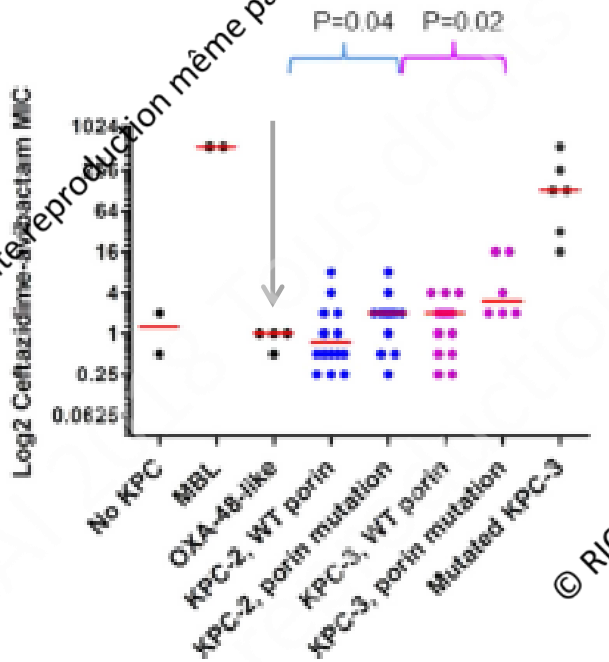
TABLE 4 Factors independently associated with imipenem, imipenem-relebactam, ceftazidime, and ceftazidime-avibactam MICs against KPC-*K. pneumoniae* isolates by multivariate analysis[a]

Factor	*P* value			
	Imipenem	Imipenem-relebactam	Ceftazidime	Ceftazidime-avibactam
ESBL	0.84	0.44	0.002	0.90
KPC-3 variant	0.21	0.74	0.01	<0.0001
Major OmpK36 mutation	<0.0001	<0.0001	0.001	0.07

[a]Isolates that carried MBL and OXA-carbapenemase were excluded from the analysis.



IMI/REL



CAZ/AVI

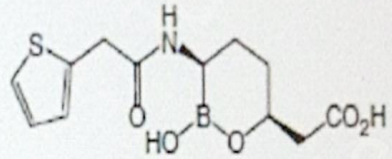
Boronic acid compounds

Lab: Melinta

9

Vaborbactam (+ meropenem) - *Vabomere™*

- First in new class of boronate BLIs
- Approved for cUTI
- Mainly inhibits class A β-lactamases. Restores susceptibility to MEM in KPC-producing Enterobacteriaceae but not in MBL producers



vaborbactam

Bore atome déficient électron= électrophile fort liaison covalente avec sérine ß lactamases

Possède un thiophène comme la céfoxitine

Liaison covalente réversible

Inihibition réversible KPC > 15h *vs* <10 minutes pour ESBL et ampC

D'ou association avec le méropenème

Breakpoints 4/8 mg/L

Pas actif sur Pyo et Acineto (activité = méropénème seul)

Perfusion lente de 3h

TABLE 1 MICs of ceftazidime and aztreonam alone or in combination with BLIs against the panel of engineered *E. coli* strains producing various cloned beta-lactamases[a]

Strain	Beta-lactamase	Class	Antibiotic MIC (μg/ml) in the absence or presence of BLIs									
			CAZ	CAZ + VAB	CAZ + TZB	CAZ + CLA	ATM	ATM + VAB	ATM + TZB	ATM + CLA	MEM	MEM + VAB
ECM6704	None		≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6701	KPC-2	A-CARB	4	≤0.125	4	2	32	≤0.125	16	16	2	≤0.03
ECM6702	KPC-3	A-CARB	16	≤0.125	16	8	32	≤0.125	16	16	2	≤0.03
ECM6706	SME-2	A-CARB	1	≤0.125	≤0.125	0.25	>128	0.25	4	16	16	≤0.03
ECM6696	NMC-A	A-CARB	0.5	≤0.125	0.25	0.25	64	≤0.125	8	8	1	≤0.03
ECM6718	SHV-5	A-ESBL	8	0.5	≤0.125	≤0.125	16	1	≤0.125	≤0.125	≤0.03	≤0.03
ECM6698	SHV-12	A-ESBL	32	2	≤0.125	≤0.125	32	4	≤0.125	≤0.125	≤0.03	≤0.03
ECM6699	SHV-18	A-ESBL	8	0.5	≤0.125	≤0.125	16	1	≤0.125	≤0.125	≤0.03	≤0.03
ECM6713	TEM-10	A-ESBL	128	16	0.25	0.25	16	4	≤0.125	≤0.125	≤0.03	≤0.03
ECM6714	TEM-26	A-ESBL	128	2	≤0.125	0.25	8	2	≤0.125	≤0.125	≤0.03	≤0.03
ECM6695	CTX-M-3	A-ESBL	1	≤0.125	≤0.125	≤0.125	4	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6693	CTX-M-14	A-ESBL	1	≤0.125	≤0.125	≤0.125	4	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6694	CTX-M-15	A-ESBL	4	≤0.125	≤0.125	≤0.125	8	0.25	≤0.125	≤0.125	≤0.03	≤0.03
ECM6692	DHA-1	C	8	0.25	≤0.125	8	2	0.25	≤0.125	2	≤0.03	≤0.03
ECM6691	MIR-1	C	32	0.5	1	32	32	1	16	32	≤0.03	≤0.03
ECM6705	FOX-5	C	32	8	32	32	2	0.5	2	2	≤0.03	≤0.03
ECM6715	AmpC-ECL (P99-like)	C	16	0.25	1	16	16	0.5	2	16	≤0.03	≤0.03
ECM6700	CMY-2	C	16	0.5	0.5	16	8	0.25	1	8	≤0.03	≤0.03
ECM6697	OXA-2	D	1	1	0.25	≤0.125	≤0.125	ND	ND	ND	≤0.03	≤0.03
ECM6712	OXA-10	D	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	ND	ND	ND	≤0.03	≤0.03
ECM6716	OXA-48	D-CARB	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	ND	ND	ND	0.125	0.125
ECM6703	NDM-1	B	>128	>128	>128	>128	≤0.125	≤0.125	≤0.125	≤0.125	16	16
ECM6711	VIM-1	B	128	128	128	128	≤0.125	≤0.125	≤0.125	≤0.125	1	1

[a]All beta-lactamase inhibitors were tested at a fixed concentration of 4 μg/ml. BLIs, beta-lactamase inhibitors; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; VAB, vaborbactam; TZB, tazobactam; CLA, clavulanic acid; ND, not done; A-CARB, class A carbapenemase; D-CARB, class D carbapenemase.

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RPX7009

Meropenem-Vaborbactam Tested against Contemporary Gram-Negative Isolates Collected Worldwide during 2014, Including Carbapenem-Resistant, KPC-Producing, Multidrug-Resistant, and Extensively Drug-Resistant *Enterobacteriaceae*

Mariana Castanheira, Michael D. Huband, Rodrigo E. Mendes, Robert K. Flamm

September 2017 Volume 61 Issue 9 e00567-17 Antimicrobial Agents and Chemotherapy

TABLE 2 Activities of meropenem-vaborbactam (inhibitor at fixed concentration of 8 μg/ml) and comparator antimicrobial agents against Gram-negative isolates collected during 2014

Bacterial group (*n*) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Susceptibility using CLSI breakpoint[a]			Susceptibility using EUCAST breakpoint[a]		
				% S	% I	% R	% S	% I	% R
Enterobacteriaceae (10,426)									
Meropenem-vaborbactam	≤0.015	0.06	≤0.015–>32						
Meropenem	0.03	0.06	≤0.015–>32	97.3	0.3	2.3	97.7	0.8	1.5
CRE (265)									
Meropenem-vaborbactam	0.5	32	≤0.015–>32						
Meropenem	16	>32	0.25–>32	1.9	6.0	92.1	7.9	32.1	60.0
KPC producers (135)									
Meropenem-vaborbactam	0.12	0.5	≤0.015–8						
Meropenem	2	>32	1–>32	0.7	4.4	94.8	5.2	15.6	79.3
Non-KPC-producing CRE (129)									
Meropenem-vaborbactam	4	>32	≤0.015–>32						
Meropenem	8	>32	0.25–>32	3.1	7.0	89.9	10.1	49.6	40.3
P. aeruginosa (264)									
Meropenem-vaborbactam	0.5	8	≤0.015–>32						
Meropenem	0.5	8	≤0.015–>32	78.4	7.0	14.6	78.4	12.9	8.7

Actif sur BLSE, **KPC**
Non actif sur classe B (VIM et NDM)
très peu actif sur classe D
(OXA 48 et OXA 163)

Activité association = activité du méropénème sur *Acinetobacter, Stenotrophomonas, Pseudomonas*

Résistance: ompK 36
Sur-copie des CTXM et efflux
Augmentation des copies du gène BLA_{kpc}
Non affecté par suppression ompK37
Efflux seul

Efflux by the multidrug resistance efflux pump AcrAB-TolC had a minimal impact on vaborbactam activity.

When deletion of the *ompK36* gene, the meropenem MIC (128 µg/ml) was 4-fold higher

Strains of *K. pneumoniae* that carry a **variant of OmpK36** with a duplication of two amino acids, **Gly134 and Asp135** (GD repeat), are frequently reported in clinical settings

TABLE 6 Effects of various concentrations of vaborbactam on meropenem MICs in isogenic KPC-3-producing strains of *K. pneumoniae* with efflux and porin mutations

KPC-3[a]-containing strain	Parent strain	Description	Meropenem MIC (µg/ml) in the presence of the following concn of vaborbactam (µg/ml): 0	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	MPC_{max}[b] (µg/ml)
Isogenic laboratory strains																
KPM1271	KPM1026a	Wild type	16	0.25	0.25	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.25
KPM2601	KPM2600	*ompK35* inactivated	16	2	1	0.5	0.125	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	1
KPM2599	KPM2592	*ompK36* inactivated	32	16	16	8	8	8	0.5	0.25	0.125	0.06	0.06	0.06	0.06	16
KPM2067	KPM2040	*ompK36* inactivated	32	32	16	16	16	4	1	0.5	0.125	0.06	0.06	0.06	0.06	16
KPM2631	KPM2613	*omp35* and *ompK36* inactivated	256	256	256	128	128	64	16	4	1	0.5	0.25	0.25	0.125	128
KPM2965	KPM2966	*acrAB* upregulated, *ompK35* and *ompK36* inactivated	256	256	256	128	128	64	32	8	2	1	0.5	0.5	0.25	128
KPM1272	KPM1027	*acrAB* upregulated, *ompK35* downregulated	16	8	2	2	0.5	0.25	0.06	0.06	0.06	0.06	0.06	0.06	0.06	2
KPM2818	KPM2658	*acrAB* upregulated, *ompK35* downregulated, *ompK36* inactivated	256	256	256	128	64	32	16	8	2	1	1	0.5	0.5	64
Clinical strains and derivatives																
KP1074	NA[c]	*ompK35* inactivated,[d] OmpK36 is the same as in KP1004 but has the GD repeat[e]	128	128	128	64	64	64	8	1	0.5	0.25	0.125	0.125	0.125	32
KPM2644[f]	KP1074	KP1074 Δ*ompK36*, *ompK35* and *ompK36* inactivated	512	512	512	512	256	256	128	8	2	1	0.5	0.5	0.5	32
KP1004	NA	*ompK35* inactivated, full-length *ompK36*	32	4	4	2	0.5	0.125	0.03	0.03	0.03	0.03	0.03	0.03	0.03	2

[a]All strains produced KPC-3 and TEM-1, encoded by genes carried on plasmid pKpQIL. Both KPM1026a derivatives and clinical isolates also produced a chromosomal SHV enzyme, encoded by bla_{SHV-24} and bla_{SHV-11}, respectively.

[b]MPC_{max}, maximum potentiating concentration of the drug required to reduce the meropenem MIC to the level seen in the parent strain that lacks KPC, corresponding to complete inhibition of KPC.

[c]NA, not available.

[d]A frameshift in the OmpK35 sequence at amino acid 42.

[e]The GD repeat is a duplication of two amino acids, Gly134 and Asp135, located within the L3 internal loop and associated with reduced susceptibility to carbapenems due to constriction of the channel (29).

[f]KPM2644 was constructed as follows. First, pKpQIL was cured from KP1074. Second, the resulting strain was used to select for an Sm^r mutant (on 200 µg/ml of streptomycin) to facilitate conjugation experiments. Third, *ompK36* was disrupted in KPM1308, giving rise to KPM2617. Finally, plasmid pKpQIL was conjugated from KP1074 into KPM2617.

IMI/REL compared to MERO/VABOR

- Clinical isolates from 11 Queens and Brooklyn hospitals
- Carbapenems tested at 2-fold dilutions, with 4 ug/ml REL or 8 ug/ml VABOR
- Against KPC *K. pneumoniae* relebactam and vaborbactam restored imipenem or meropenem susceptibility, respectively, to all isolates
- Against resistant *P. aeruginosa*
  - relebactam restored IMI susceptibility to all isolates; IMI MIC $_{50/90}$ 1/2 ug/ml in the presence of REL
  - vaborbactam did not restore MERO susceptibility to MERO resistant *isolates;* MERO MIC $_{50/90}$ 8/32 ug/ml in the presence of VABOR

	MIC 50/90 ug/ml				MIC 50/90 ug/ml	
Organism (n)	**Imipenem**	**Imi + Rel (REL 4ug/ml)**		**Organism (n)**	**Meropenem**	**Mero + Vabor (VABOR 8 ug/ml)**
K. pneumoniae **KPC (111)**	**16 / >16**	**0.25 / 1**		***K. pneumoniae*** KPC (121)	**>16 / >16**	**0.03 / 0.5**
P. aeruginosa IMI-R (144)	**8 / >16**	**1 / 2**		***P. aeruginosa*** MERO-R (98)	**8 / 32**	**8 / 32**

Lapuebla et al AAC 2015 59; 4856; Lapuebla et al AAC 2015 59: 5029

Classe B ?

Ambler-Klasse	Wichtige Enzyme	Ceftazidim/ Avibactam	Ceftolozan/ Tazobactam	Imipenem/Cilastatin + Relebactam	Meropenem + Vaborbactam	Aztreonam/ Avibactam	Cefiderocol
A	ESBL (TEM, SHV, CTX-M)						
	KPC						
B	MBL (NDM, VIM, IMP)						
C	AmpC (MOX, CMY, FOX)						
D	OXA (OXA-48, OXA-23)						

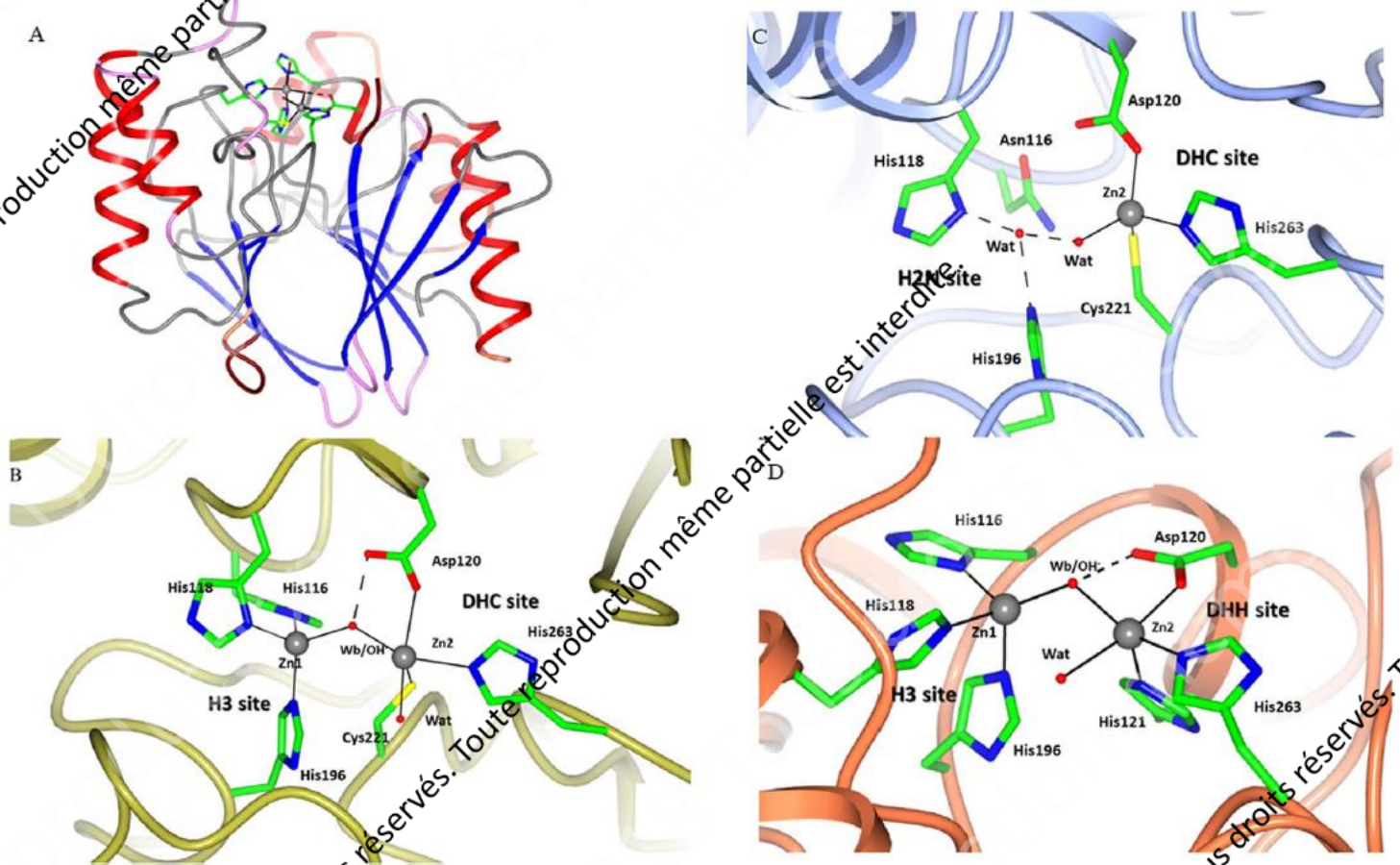
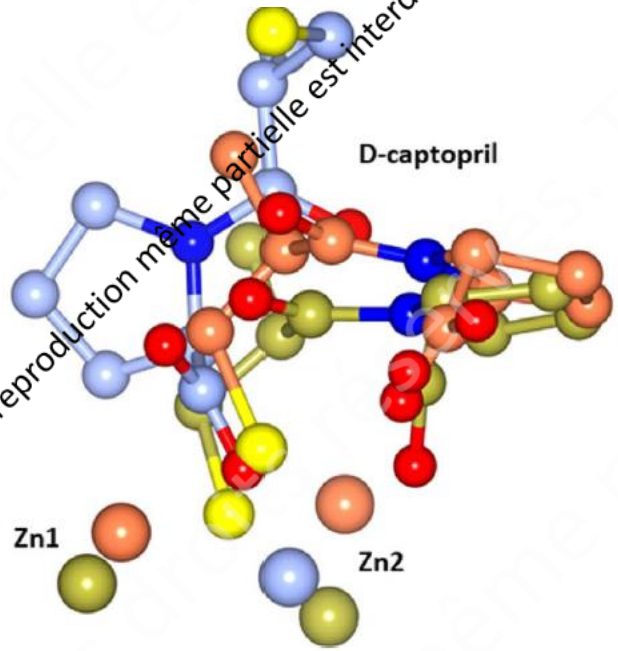


Fig. 4. (A) The MBL fold. The active site location is shown by representing active site residues as sticks. (B) Subclass B1 active site and zinc coordination sphere. (C) Subclass B2 active site and zinc coordination sphere. (D) Subclass B3 active site and zinc coordination sphere. The coordination bonds to the Zn^{2+} ions (grey spheres) are represented as thin black lines.



In addition, the work of Brem et al. (Brem et al., 2016b) shows the ability of D-captopril to potentiate the effects of meropenem against pathogens expressing different MBLs.

Inhibiteurs de MDL

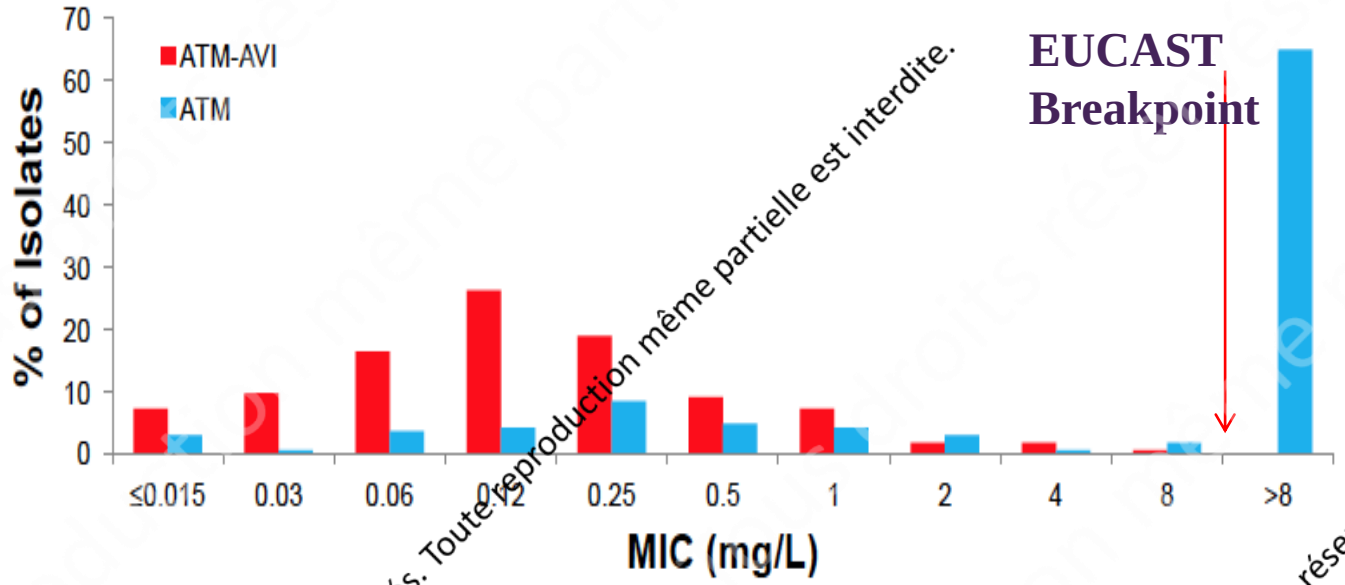
Zinc binding inihibitors:
Dérives du captopril
Thiazolidines
Dérivés de l'acide dipicolinique
Triazole –thiones

Zn chelator inhibitors: EDTA
phytotoxin aspergillomarasmine A (AMA)
spiro-indoline-thiadiazole

Microbiological Activity

MBL-Producing *Enterobacteriaceae*

MIC Distribution of ATM and ATM-AVI (at constant 4 mg/L AVI) for MBL-producing *Enterobacteriaceae* (n=163), collected from global surveillance studies (2012-2014)



- Avibactam potentiates the activity of aztreonam against MBL-producing *Enterobacteriaceae* (MIC_{90} decreases from >128 to 1 mg/L; 8 mg/L highest MIC observed)

May The A+A Force Be With You!

Loading dose of 500 mg aztreonam/137 mg avibactam infused over 30 minutes, followed by 1500 mg aztreonam/410 mg avibactam every 6 hours infused over 3 hours

Table 1. Susceptibility and β-lactamase content of clinical isolates

Pathogen	Strain	β-Lactamases	MIC (mg/L)	
			ATM	ATM/AVI[a]
K. pneumoniae	ARC3803	NDM-1, CTX-M-15, OXA-1, SHV-1, TEM-1	256	0.25
	ARC3602	NDM-1, TEM-1, CTX-M-15, SHV-11, CMY-6	256	0.5
	ARC3802	NDM-1, TEM-1, CTX-M-15, SHV-2a, SHV-11	128	0.125
E. coli	ARC3805	NDM-1, TEM-208, OXA-1, OXA-2, CTX-M-15, CMY-4	>256	4
	ARC3807	NDM-1, TEM-1, SHV-12, OXA-9, CMY-42	>256	8
	ARC3600	NDM-1, OXA-1, CMY-6	16	0.125

ATM, aztreonam; AVI, avibactam.
[a]Avibactam at 4 mg/L.

JAntimicrob Chemother 2015; **70**: 2618–2626

The Zone of Hope

Informs therapy options for CPE co-producing metallo- and serine-β-lactamases

E. coli
NDM-1, OXA-1, -2, -9
CMY-6, CTX-M-15, TEM-1B

K. pneumoniae
VIM-1, OXA-9
SHV-12, TEM-1A

K. pneumoniae
IMP-4, OXA-1
SFO-1, TEM-1B, OKP-B-2

Avery LM, Nicolau DP. *International Journal of Antimicrobial Agents* (2018), doi: 10.1016/j.ijantimicag.2018.07.011 [In press].

A number of clinical observations have now been published evaluating aztreonam combined with ceftazidime/avibactam

These have shown successful outcomes in small numbers of patients with infections due to NDM-producing Enterobacteriaceae, carbapenem-resistant *P. aerug*inosa and *Stenotrophomonas malto*philia.

However, no randomized controlled trials are underway with this combination, nor have analyses been published evaluating the optimal time of administration of aztreonam relative to the ceftazidime/avibactam.

These are important considerations that need investigation.

Nacubactam is a DBO inhibitor with in vitro activity against class A, class C, and some class D β-lactamases. Lab :Roche

Nacubactam (NAC, RG6080, OP0595) is a novel dual action diazabicyclooctane having both a ß- lactamase inhibitor activity and a direct antibacterial activity that can additionally translate to an "enhancer" effect when partnered with beta-lactams.

Activité > DBO sur MDL, also inhibit enterobacterial PBP2, achieving antibacterial activity and potentiating PBP3- targeted β-lactams; this can allow activity against strains with enzymes not inhibited by DBOs, including MBLs.

Isolate group:		NAC	MEM:NAC [1:1][1]	MEM:NAC [2:1][1]	MEM:NAC [2][2]	MEM:NAC [4][2]	MEM
All (n=1553)	MIC_{50}	2	0.12	0.25	≤ 0.004	≤ 0.004	0.5
	MIC_{90}	> 32	2	4	0.5	0.25	128
Class A (n= 577)	MIC_{50}	2	0.03	0.03	≤ 0.004	≤ 0.004	0.03
	MIC_{90}	> 32	0.06	0.06	0.015	0.015	0.12
Class B (n= 123)	MIC_{50}	4	2	4	0.008	≤ 0.004	32
	MIC_{90}	> 32	32	32	64	64	> 256
Class C (n= 254)	MIC_{50}	2	0.06	0.06	≤ 0.004	≤ 0.004	0.12
	MIC_{90}	> 32	0.25	0.25	0.06	0.015	0.5
Class D (n= 212)	MIC_{50}	32	1	2	0.25	0.12	4
	MIC_{90}	> 32	4	8	8	4	64
KPC (n= 381)	MIC_{50}	4	0.5	1	0.008	≤ 0.004	64
	MIC_{90}	> 32	2	4	0.5	0.25	256
GES (n=6)[3]	MIC range	1 - > 32	0.12 - 4	0.12 - 8	≤ 0.004 - 8	≤ 0.004 - 1	0.12 - 256

NAC, nacubactam; MEM; meropenem

[1]Fixed MEM:NAC ratio; [2]Fixed NAC concentration (mg/L); [3]GES-6 or GES-20 carbapenemase-positive

Nacubactam (RG6080) alone and in combination against metallo-beta-lactamase (MBL)-producing Enterobacteriaceae

D. Livermore

Activité > DBO sur MDL

2 populations MIC 1-8 mg/L (85%) ou >32mg/L (Proteae)

ACTIVITY ON MBLs

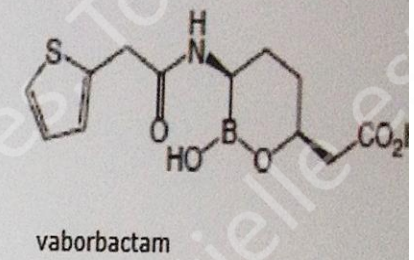
309 Enterobacteriaceae: 158 NDM,52 VIM,99 MBL

8+4 mg/L aztreonam-nacubactam inhibited	308
8+4 mg/l aztreonam + avibactam	303
8+4 mg/l cefepime + nacubactam	278
8+4 mg/l Cefepime+ avibactam	68
4+4 mg/l meropenem +nacubactam	262
8+4 mg/l meropenem + avibactam	85

Boronic acid compounds

Vaborbactam (+ meropenem) - *Vabomere™*

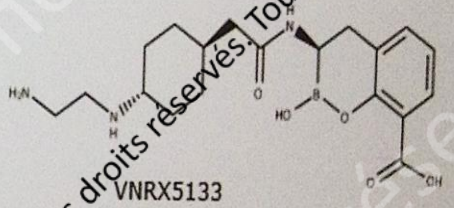
- First in new class of boronate BLIs
- Approved for cUTI
- Mainly inhibits class A β-lactamases. Restores susceptibility to MEM in KPC-producing Enterobacteriaceae but not in MBL producers



vaborbactam

VNRX-5133 (+cefepime)

- Dual inhibitor of SBLs and MBLs
- Potent activity against Enterobacteriaceae, including most MBLs (not IMP)
- Improved activity vs PA compared to cefepime alone or meropenem



VNRX5133

Lab: venatox

Ria Donnelly, Wendy Kloezen, Mark Goldman, Anita C. Van Mil, Claudia M. Lagarde, Joseph Meletiadis,2, Johan Mouton P1539

VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D).

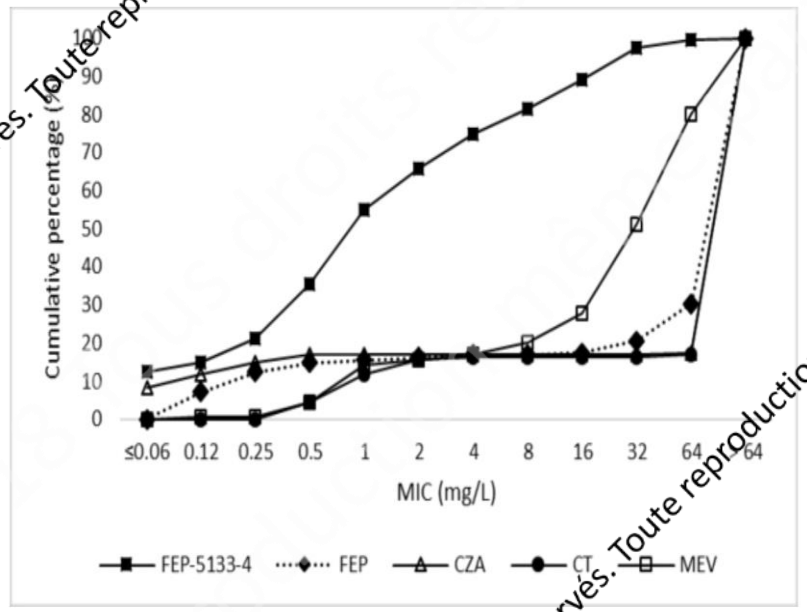
At a fixed concentration of 1 mg/L VNRX-5133, the MIC50 and MIC90 were reduced to **0.25 and 2** mg/L, respectively, for Enterobacteriaceae isolates, and to **16 and 64** mg/L, respectively, for *P. aeruginosa* isolates.

To obtain a breakpoint MIC of ≤16 mg/L cefepime for 90% of the P. aeruginosa isolates, including strains with reduced permeability, 4 mg/L VNRX-5133 was required.

Shazad Mushtaq1, Anna Vickers1, Neil Woodford1, David Livermore :
by VNRX 5133 at 8 mg/L
With KPC carbapenemases (GM MIC cefepime reduced from 24.8 mg/L to **0.16** mg/L),
VIM carbapenemases (15.2 mg/L to **0.23** mg/L),
NDM carbapenemases (104 mg/L mg/L to **2.9** mg/L),
Combinations of ESBL plus impermeability (93.8 to **1** mg/L)
and AmpC plus impermeability (2.7 mg/L to **0.38** mg/L)

Actif sur VIM, NDM et pas IMP
Pas actif sur Acinetobacter et variable Pseudomonas
Faible sur Stenotrophomonas

155 **Enterobacteriaceae** (130 NDM-producers, 25 OXA-producers), and 50 VIM-producing **P. aeruginosa** from 2013-2015 were included in this analysis. MICs of cefepime with VNRX-5133 at a fixed concentration of 4 mg/L (FEP/VNRX-5133)



N=155 Enterobacteriaceae (130 NDM, 25 OXA-48); FEP-5133-4, cefepime tested in combination with VNRX-5133 at 4 mg/l; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam

The combination of cefepime and VNRX-5133 demonstrated potent in vitro activity against these highly resistant Enterobacteriaceae, and was the most active antimicrobial tested.

81% of isolates were inhibited at the susceptible breakpoint of 8 mg/L, and a total of 89% were inhibited at 16 mg/L. In comparison, susceptibility was 17% for ceftazidime-avibactam, 16% for ceftolozane-tazobactam, 17% for meropenemvaborbactam

P1542 In Vitro activity of cefepime in combination with VNRX-5133 against meropenem and/or cefepime resistant clinical isolates of **Pseudomonas aeruginosa**

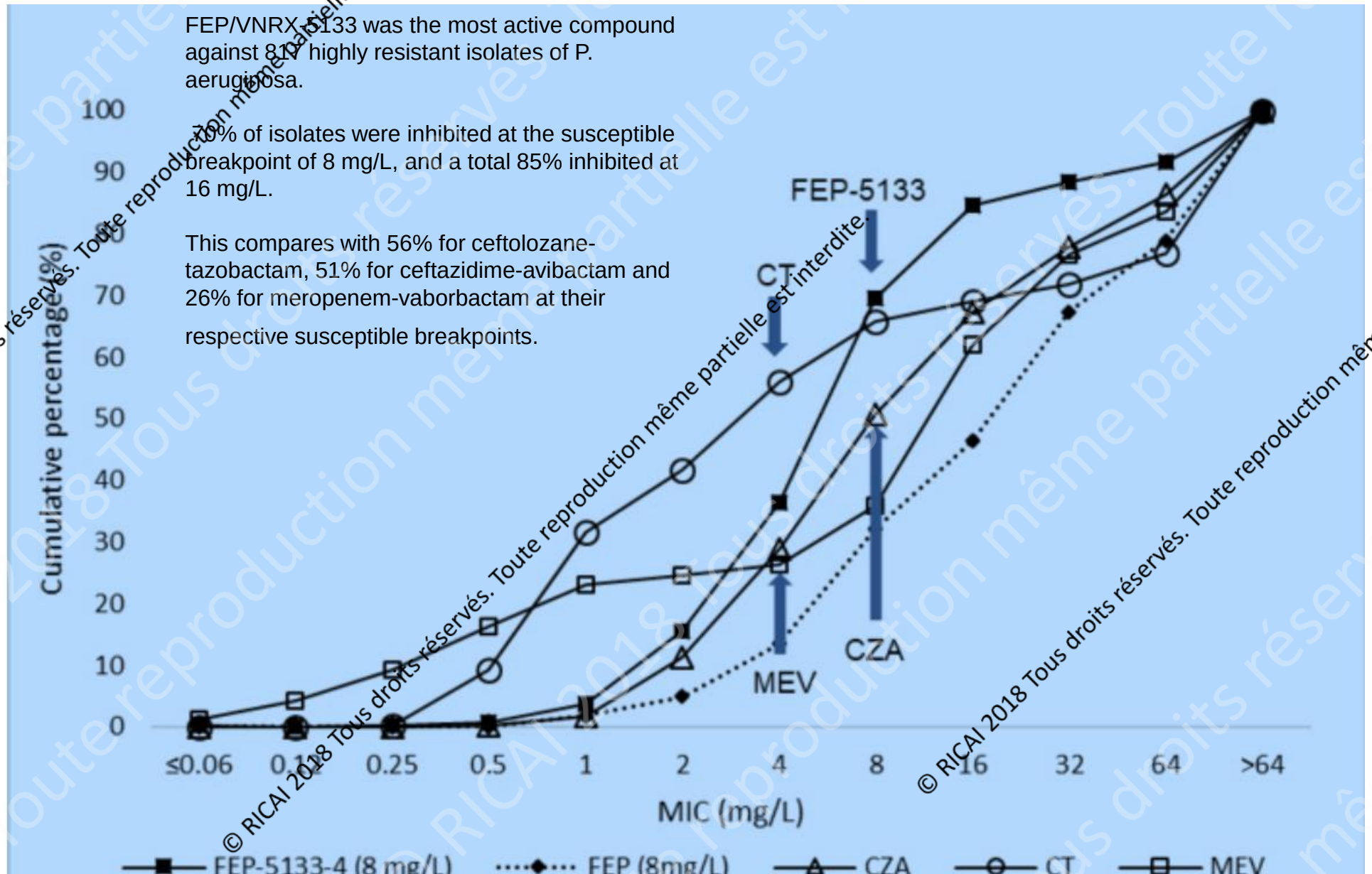
Mark Estabrook*1, Meredith Hackel1, Dan Sahm1

817 P. aeruginosa

FEP/VNRX-5133 was the most active compound against 817 highly resistant isolates of P. aeruginosa.

70% of isolates were inhibited at the susceptible breakpoint of 8 mg/L, and a total 85% inhibited at 16 mg/L.

This compares with 56% for ceftolozane-tazobactam, 51% for ceftazidime-avibactam and 26% for meropenem-vaborbactam at their respective susceptible breakpoints.



Zidebactam Lab: Wockhardt

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

WCK 5107 (Zidebactam) and WCK 5153 Are Novel Inhibitors of PBP2 Showing Potent "β-Lactam Enhancer" Activity against *Pseudomonas aeruginosa*, Including Multidrug-Resistant Metallo-β-Lactamase-Producing High-Risk Clones

Bartolome Moya,[a]* Isabel M. Barcelo,[a] Sachin Bhagwat,[b] Mahesh Patel,[b] German Bou,[c] Krisztina M. Papp-Wallace,[d,e] Robert A. Bonomo,[d,e,f] Antonio Oliver[a]

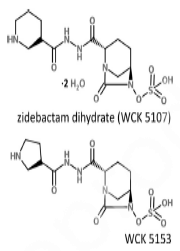


FIG 1 Chemical structures of ZID (zidebactam; WCK 5107) and WCK 5153.

Zidebactam (ZID) and WCK 5153 (Fig. 1) are the first described Gram-negative ß-lactam enhancers belonging to the bicyclo-acyl hydrazide (BCH) series.

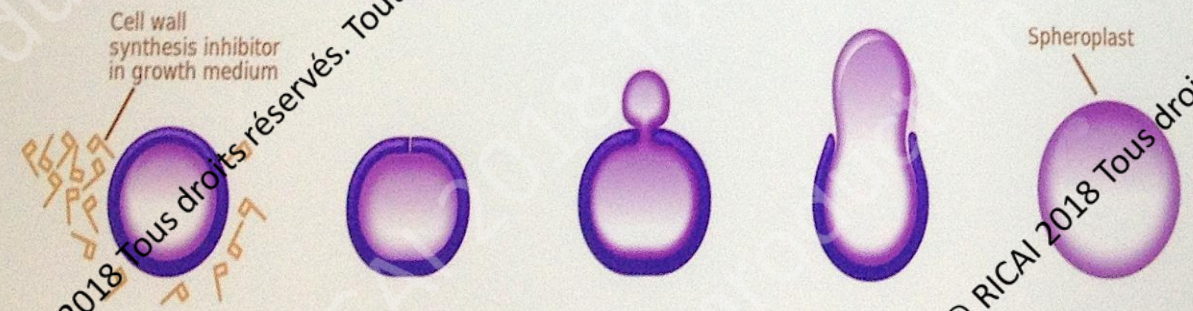
ZID in combination with cefepime (FEP) is currently under clinical development for infections caused by MDR Gram-negative organisms, including P. aeruginosa and Acinetobacter baumannii.

Although derived from a diazabicyclooctane (DBO) scaffold, BCHs were designed with the objective of augmenting PBP2 binding in P. aeruginosa and A. baumannii rather than the conventional approach of optimizing the ß-lactamase inhibitory activity of the compound.

Avibactam, the first example of a DBO,in contrast possessed weak PBP2 affinity in Enterobacteriaceae

Cefepime-zidebactam

- Zidebactam is a **β-lactam "enhancer"** reduces the level of cefepime exposure required for efficacy. Both together act against PBP-1, 2 & 3:
  - **High-affinity PBP2** engagement by zidebactam causes the cells to convert into **spheroplasts**
  - Perturbation in the outer membrane, leading to **modulation of membrane-bound resistance mechanisms** such as efflux, porin, and expression of **β**–lactamases
  - Then cefepime engages to other essential PBPs, leading to pronounced **bacterial lysis**.



Moya et al. Antimicrob Agents Chemother 2016; 61:e02529-16.

Zidebactam

- Activité intrinsèque 60% des Entérobactérales à 4 mg/L
- E. coli *Enterobacter* 0,06-0,25
- *Klebsiella* 0,12 >128
- *Proteae, Serratia* >> 128mg/L

- + céfépime actif sur 75% à 2 mg/L et 90% à 8 mg/L
- Peu actif sur OXA
- Pyo actif sur MBL 91% à 8 mg/L

IDWeek 2018
Poster #1370

Cefepime/VNRX-5133 Broad-Spectrum Activity is maintained against Emerging KPC- and PDC-Variants in Multidrug Resistant *K. pneumoniae* and *P. aeruginosa.*

Daigle, D.M.[1], Hamrick, J.C.[1], Chatwin, C.[1], Lou, D.[1], Schuster, M.[1], Kurepina, N.[2], Kreiswirth, B.N.[2], Shields, R.K.[3], Oliver, A.[4], Nguyen, M.H.[3], Clancy, C.J.[3], Pevear, D.C.[1] and Burns, C.J.[1]
[1]VenatoRx Pharmaceuticals, Inc. Malvern, PA 19355 USA, [2]Rutgers University, Newark NJ; [3]University of Pittsburgh, Pittsburgh PA, [4]Palma de Mallorca hospital, Spain.

Results:

Table 1: Susceptibility of parent and clinically-evolved KPC variant producing *K. pneumoniae* isolates.

K. pneumoniae producing KPC-3 relative to clinically evolved KPC-variant producing isolates	Minimal Inhibitory Concentration (µg/mL)					
	ceftazidime	ceftazidime/ avibactam	ceftolozane	ceftolozane/ tazobactam	cefepime	cefepime/ VNRX-5133
Kp 47621 (WT parent)	>128	2	>64	>64	>128	1
Kp 47623 (D179D, T243M)	>128	64	>64	>64	8	0.5
Kp 47769 (WT parent)	>128	2	64	64	16	0.125
Kp 47771 V240G	>128	64	>64	>64	16	4
Kp 47772 D179Y	128	8	64	64	8	2
Kp 47953 (WT parent)	128	8	64	64	8	2
Kp 48152 (T243A)	128	16	64	32	8	2
Kp 48823 (WT parent)	128	2	64	64	8	2
Kp 48824 (A177E, D179Y)	>128	>128	>64	>64	4	1
Kp 48825 (L7P, A177E, D179Y)	>128	>128	>64	>64	1	0.5

Microbiological activity of cefepime/VNRX-5133 was also evaluated against ceftolozane/tazobactam-sensitive pre-treatment isolates relative to post-treatment clinical isolates of ceftolozane/tazobactam-resistant *P. aeruginosa*, resulting from mutations in β-lactamases (OXA and PDC) that evolved during clinical therapy (**Table 2**).[7] Cefepime/VNRX-5133 MIC among these clinical isolates varied from 4-8 µg/mL in all but one case (16 µg/mL) however, this elevated MIC was not due to the PDC-221 variant, as an engineered strain of *P. aeruginosa* producing PDC-221 had a cefepime/VNRX-5133 MIC of 1 µg/mL, unchanged relative to WT PDC-1.

P. aeruginosa

TABLE 1 MICs and MBCs of β-lactams and zidebactam and WCK 5153 in the studied strains

Strain[a]	MIC/MBC (μg/ml)[b,c,d]								
	FEP	MEM	MEC	ZID	WCK 5153	FEP + ZID (2 μg/ml)	FEP + WCK 5153 (1 μg/ml)	FEP + ZID (1 μg/ml)	FEP + WCK 5153 (0.5 μg/ml)
PAO1	1/2	0.25/0.5	>32/ND	4/8	2/4	0.03/0.12	0.03/0.06	0.06/0.12	0.06/0.06
PAdB	16/32	2/2	>32/ND	8/8	4/8	4/4	2/2	4/8	4/4
PAΔDDh2Dh3	16/16	1/2	>32/ND	4/16	2/8	1/2	1/4	2/8	2/4
PAOD	1/2	2/2	>32/ND	4/8	2/4	0.06/0.12	0.03/0.06	0.25/0.5	0.06/0.12
PAOM	0.12/0.12	0.06/0.12	2/ND	2/2	2/2	0.03/0.03	0.03/0.06	0.06/0.06	0.03/0.6
PAOMxR	2/4	1/2	>32/ND	8/16	4/4	2/4	2/2	4/4	2/2

[a]PAO1, wild-type reference strain; PAdB, *dacB* knockout mutant of PAO1; PAΔDDh2Dh3, *ampD* triple (*ampD-ampDh2-ampDh3*) knockout mutant of PAO1; PAOD, PAO1 *oprD*-defective mutant of the porin OprD; PAOM, *oprM* knockout mutant of PAO1; PAOMxR, *mexR* knockout mutant of PAO1.

[b]FEP, cefepime; MEM, meropenem; MEC, amdinocillin; ZID, zidebactam; WCK 5153, bicyclo-acyl hydraziide.

[c]Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints: FEP, ≤8 μg/ml; MEM, ≤2 μg/ml; MEC, ZID, and WCK 5153, not determined (ND).

[d]Range of concentrations tested, 0.0156 to 32 μg/ml.

Zidebactam and WCK 5153 MICs for the AmpC ß-lactamase-hyperproducing derivatives remained within 1 doubling dilution, suggestive of low-level to no class C -lactamase hydrolysis.

Likewise, neitheroverexpression nor lack of the intrinsic efflux pump MexAB-OprM caused a MIC change of more than 1 doubling dilution.

On the other hand, cefepime showed potent PBP1a and PBP3 inhibition, while meropenem inhibited PBP2, PBP3, and PBP4.
Nevertheless, none of the compounds demonstrated significant class D enzyme inhibition

Zidebactam alone exhibited potent in vitro activity against some Enterobacteriaceae and *P. aeruginosa*, including ß-lactamase-producing strains.

Cefepime/zidebactam MIC values were lower than those of each agent tested alone for many ß-lactamase-producing strains, indicating synergy.

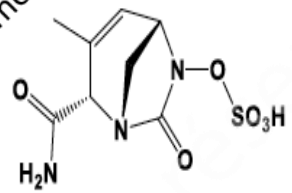
Cefepime/zidebactam (1:1) was very active against Enterobacteriaceae producing CTX-M-15 (MIC50/90 0.25/1 mg/L), SHV (MIC50/90 0.12/0.25 mg/L), other ESBLs (20, including GES-18, OXA-1/30 andOXY-, PER-, TEM- and VEB-like; MIC50/90 0.25/1 mg/L), plasmidic AmpC (MIC50/90 **0.06/0.06** mg/L), derepressed AmpC (MIC50/90 **0.12/0.5** mg/L), KPC (MIC50/90 **0.25/1** mg/L) and metallo-ß-lactamases (MBLs including VIM, IMP and NDM; MIC50/90 **0.5/8** mg/L).

Cefepime/zidebactam (1:1) was also active against Pseudomonas aeruginosa with overexpression of AmpC (MIC50/90 **4/8** mg/L) and MBLs (VIM and IMP); MIC50/90 **4/8** mg/L].

Cefepime/zidebactam showed moderate activity against OXA-23/24/58-producing Acinetobacter baumannii [MIC50/90 32 mg/L (1:1)].

Helio S. Sader* J Antimicrob Chemother 2017; 72: 1696–170

Extended spectrum DABCO BLI

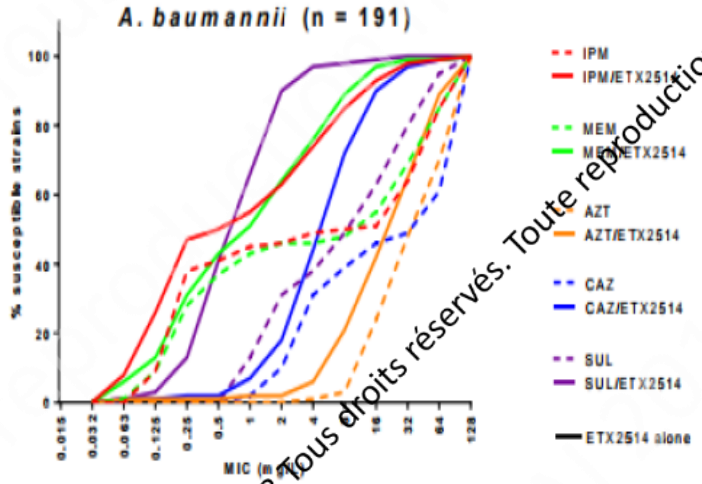


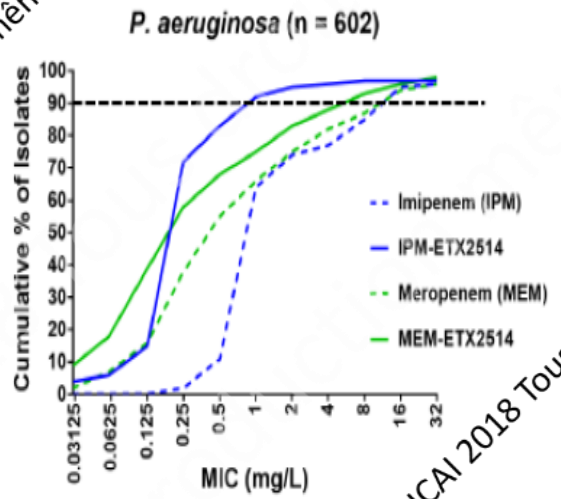
Designed Acinetobacter

Lab: Entasis

ETX2514 – Class A √
Class C √
Class D √

- Covalent reactivity increased due to strain
- Combination w/ sulbactam against *A. baumannii*
- Phase 1 (Entasis Therapeutics from AstraZeneca)





Durant-Reville et al. *Nat. Microbiol.* 2(9), 2017, 17104

β-lactamase inhibitors

β-lactamase with PBPIs			
	Phase	Indications/ Target Pathogens	Mode of Administration
Vabormere: vaborbactam (boronate) + meropenem	NDA	cUTI, HABP/VABP	IV
Relebactam (DABCO) + imipenem + cilastatin	3	HABP/VABP	IV
Zidebactam (DABCO) + cefepime	1	CRE (ESBLs & KPCs)	IV
Nacubactam (DABCO) + meropenem?	1	CRE	IV
AAI-101 (β-lactam) + cefepime or piperacillin	1	CRE (ESBLs & KPCs)	IV
VNRX-5133 (boronate) + unknown antibiotic	1	MBL producers	IV
ETX2514 + sulbactam (DABCO)	1	Aba	IV

Novel β-lactam / β-lactamase Inhibitors for Carbapenemase-Producing Enterobacteriaceae

- **β-lactam plus Novel Inhibitor**
  - Ceftazidime - Avibactam [KPC, OXA]
  - Meropenem - Vaborbactam [KPC]
  - Imipenem - Relebactam [KPC]
  - Aztreonam - Avibactam [MBL]
  - Cefepime - VNRX-5113 [KPC, OXA, MBL]
  - Cefepime - Zidebactam [KPC, OXA, MBL]
  - Meropenem - Nacubactam [KPC, MBL]

KPC: *K. pneumoniae* carbapenemase; OXA: oxacillinase; MBL: metallo-β-lactamase
Except Ceftazidime-Avibactam, referenced combinations are not licensed by EMA [status: Phase II or III, preregistration]

Novel β-lactam / β-lactamase Inhibitors for CPE and *P. aeruginosa*

- **β-lactam plus Novel Inhibitor**
  - Ceftazidime - Avibactam [CPE, PSA]
  - Imipenem – Relebactam [CPE, PSA]
  - Cefepime - VNRX-5113 [CPE, PSA]*
  - Cefepime - Zidebactam [CPE, PSA]*

*MBL: metallo-β-lactamase

Novel β-lactam / β-lactamase Inhibitors for CPE, *P. aeruginosa*, Acinetobacter

- **β-lactam plus Novel Inhibitor**

ETX 2514 sulbactam

- **Cefepime - Zidebactam [CPE, PSA, ACB]**

Activités comparées des inhibiteurs de ß-lactamases

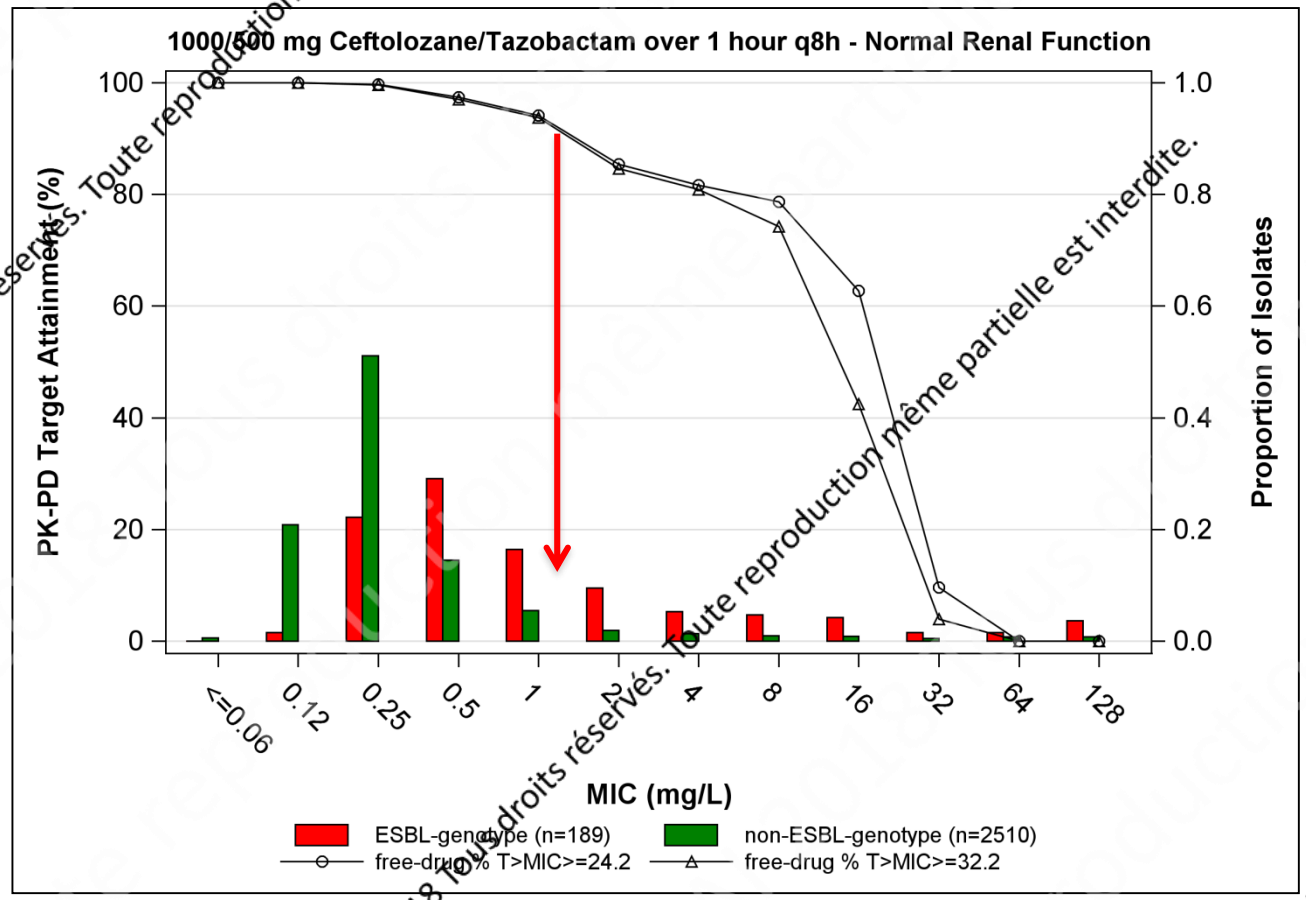
Agent	KPC A	MDL B	ampC C	Oxa D	Pseudomonas aeruginosa MDR	Acinetobacter baumannii MDR
Avibactam-ceftazidime	X	N	X	v	X	N
Aztreonam-Avibactam	X	X*	X		N	N
Relebactam-imipenem	X		X		X	N
Vaborbactam-Meropenem	X	N	X	N	N	N
VNRX 5133 -Céfépime	X	X	X	X	X	X
Zidebactam--Céfépime	X	X	X	Xf	X	Xf
Nacubactam-Méropenem	X	X	X	v	f	X
ETX 2514- Sulbactam	X		X	X	N	X

* Entérobactérales

L. Dubreuil 2018

Probability of Target Attainment Against Enterobacteriaceae

1.5-g CEFTOLOZANE/TAZOBACTAM dose



- PTA is ≥ 80.9% for the 1 $\log_{10}$ kill target against Enterobacteriaceae with an MIC value up to 4 mg/L in plasma for the 1.5 g ceftolozane/tazobactam dose

%T>MIC, percentage of time that the drug concentration exceeds minimum inhibitory concentration. Rubino et al. ICAAC 2014. Poster A-1347.

Probability of Target Attainment Against Enterobacteriaceae

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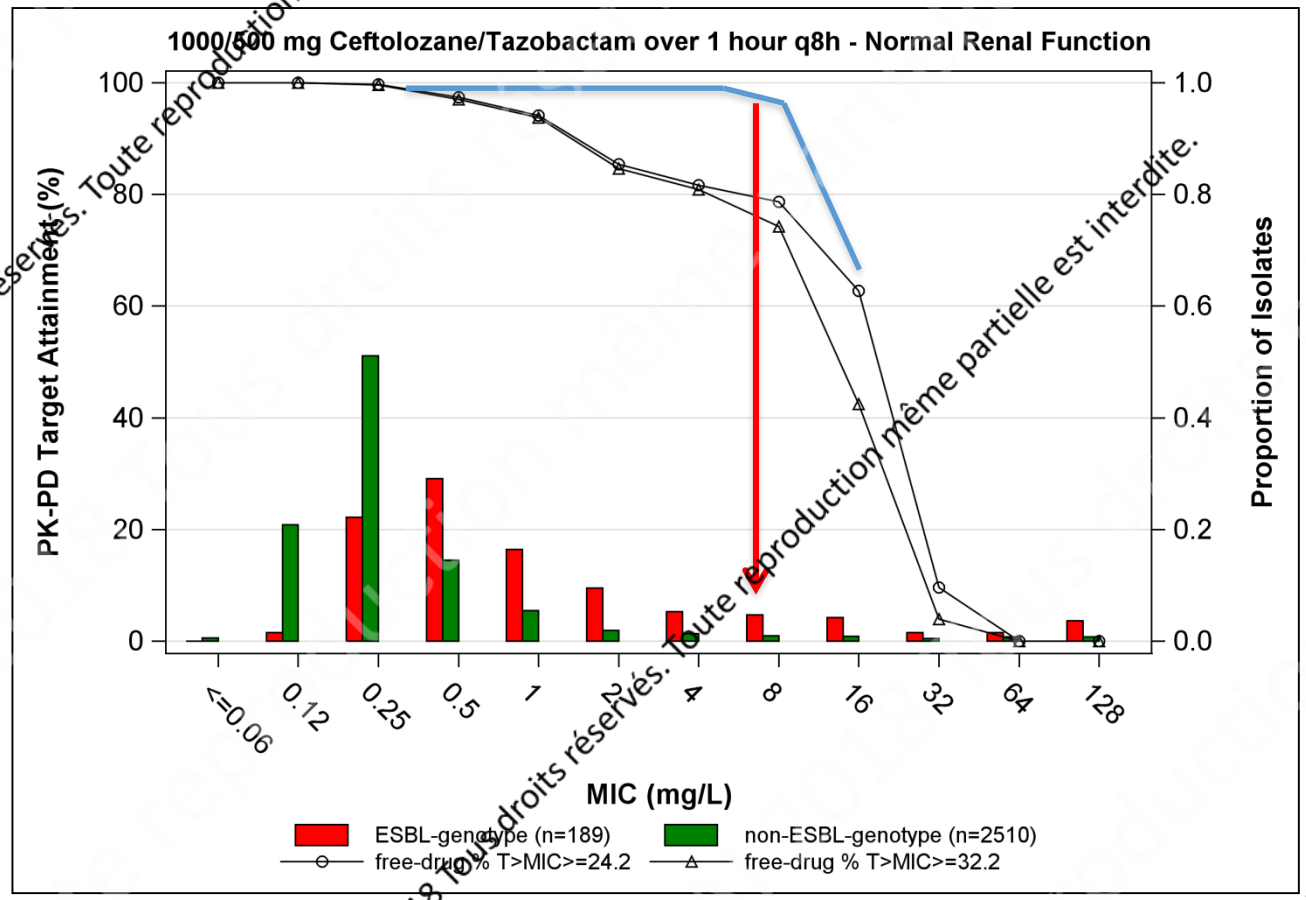

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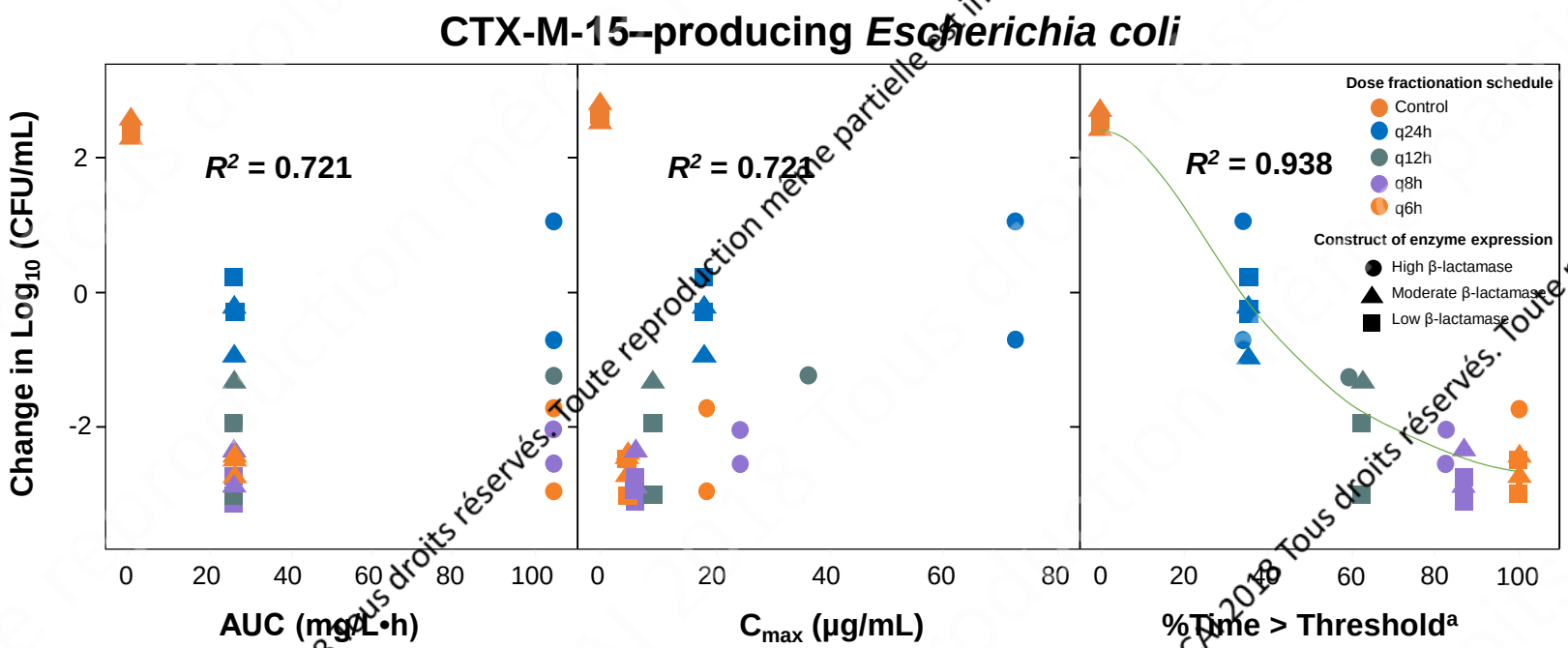
%T>MIC, percentage of time that the drug concentration exceeds minimum inhibitory concentration. Rubino et al. ICAAC 2014. Poster A-1347.

In Vitro Efficacy of Tazobactam Correlates Best With %Time > Threshold

- Dose fractionation studies used to establish pharmacokinetic/pharmacodynamic (PK/PD) parameters of tazobactam in combination with ceftolozane
- The %Time > threshold concentration was the exposure measure most associated with tazobactam efficacy, regardless of enzyme expression



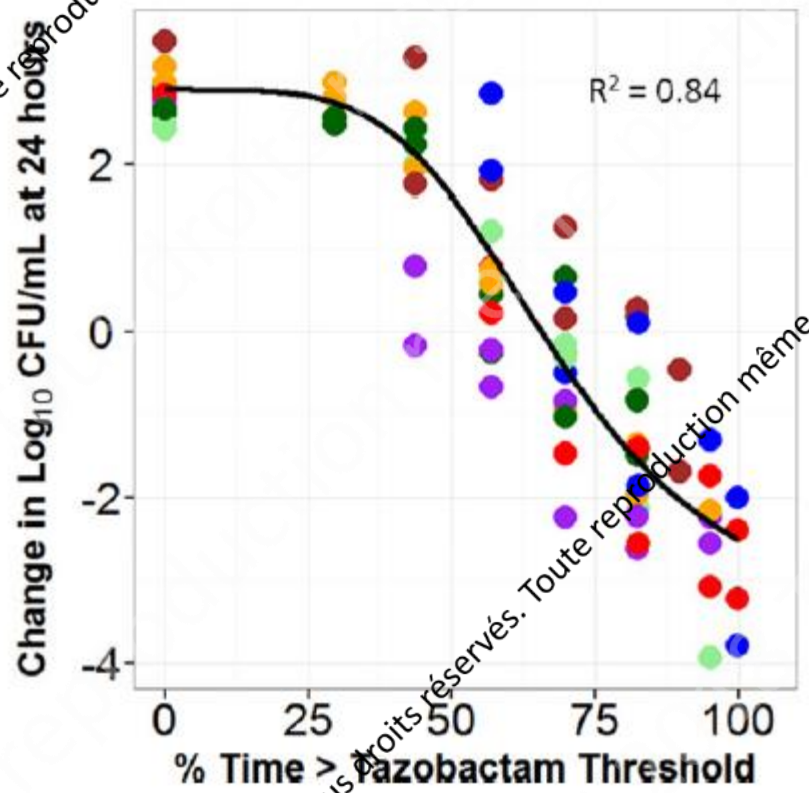
[a]The threshold concentration was 0.05 mg/L for the low- and moderate-β-lactamase genetic constructs and 0.25 mg/L for the high-β-lactamase genetic constructs

AUC, area under the plasma concentration-time curve; C_{max}, maximum (peak) plasma drug concentration.

VanScoy et al. *Antimicrob Agents Chemother.* 2013;57:2809-14.

The Relationship Between Tazobactam %T>Threshold and Change in Log_{10} CFU

PK/PD In Vitro Infection Model



Ceftolozane-tazobactam

Seuil de tazobactam

Escherichia coli

1501A	MIC 0.5 mg/L	Threshold 0.25mg/L
4643E	MIC 0.5 mg/L	Threshold 0.25mg/L
21711R	MIC 2mg/L	Threshold 1mg/L
13319R	MIC 4mg/L	Threshold 2mg/L

Klebsiella pneumoniae

604C	MIC 1 mg/L	Threshold 0.5mg/L
21904E	MIC 2 mg/L	Threshold 1mg/L
4812E	MIC 4mg/L	Threshold 2mg/L

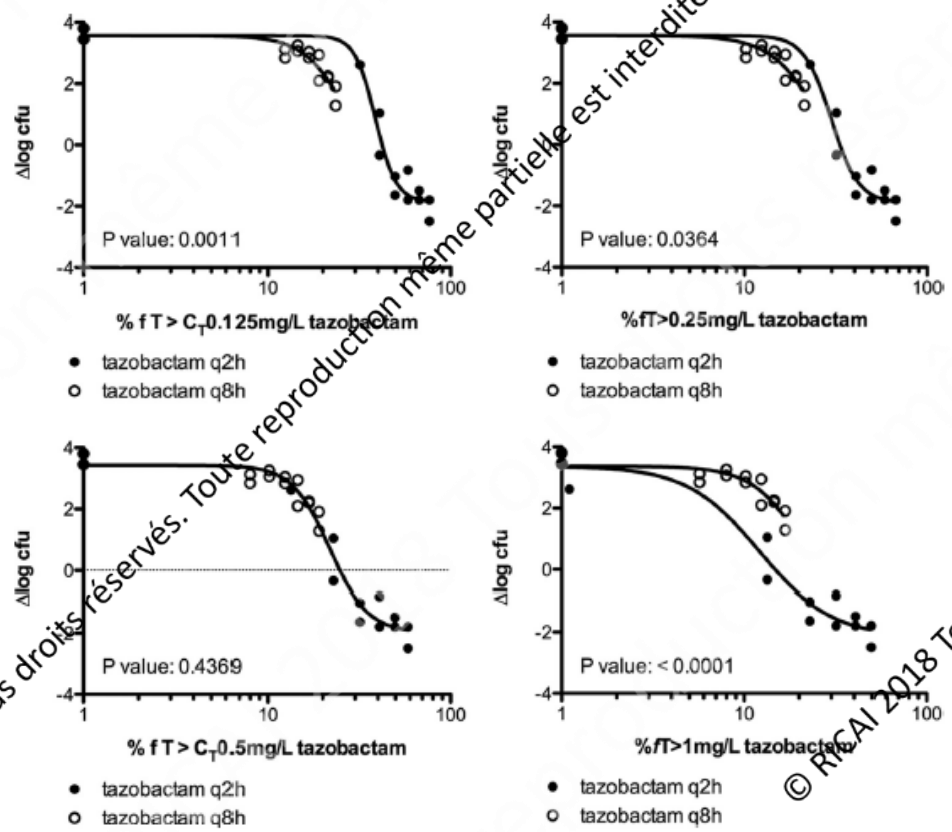
The threshold concentration identified for each isolate ranged from 0.5 to 4 mg/liter.

Vanscoy B, Mendes RE, McCauley J, Bhavnani SM, Bulik CC, Okusanya OO, Forrest A, Jones RN, Friedrich LV, Steenbergen JN, Ambrose PG. Pharmacological basis of β-lactamase inhibitor therapeutics: tazobactam in combination with Ceftolozane. Antimicrob Agents Chemother. 2013 Dec;57(12):5924-30.

M. J. Melchers, E. et al.
AAC 2016 60 (12)

Ceftolozane-tazobactam

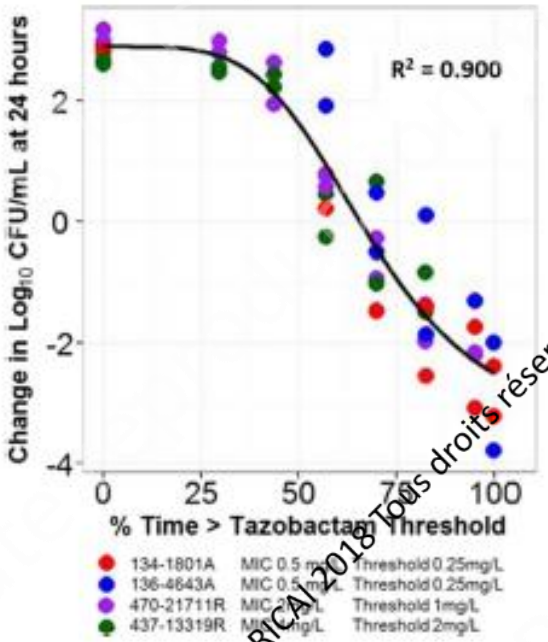
The main PDI (pharmacokinetic/PD index (PDI)-response) that correlated with the effect of tazobactam was the fTCT achieved with a CT of 0.5 mg/liter tazobactam.



CT = ½ CMI

The enabling translational relationship for the tazobactam threshold that allowed comodeling of all four clinical isolates was the product of the individual isolate's ceftolozane-tazobactam MIC value (determined with a tazobactam concentration of 4 mg/liter) and 0.5.

The tazobactam %Timethresholds associated with net bacterial stasis and 1- and 2-log10 CFU reductions in bacteria at 24h were 65.9, 77.3, and 90.2% of the dosing interval

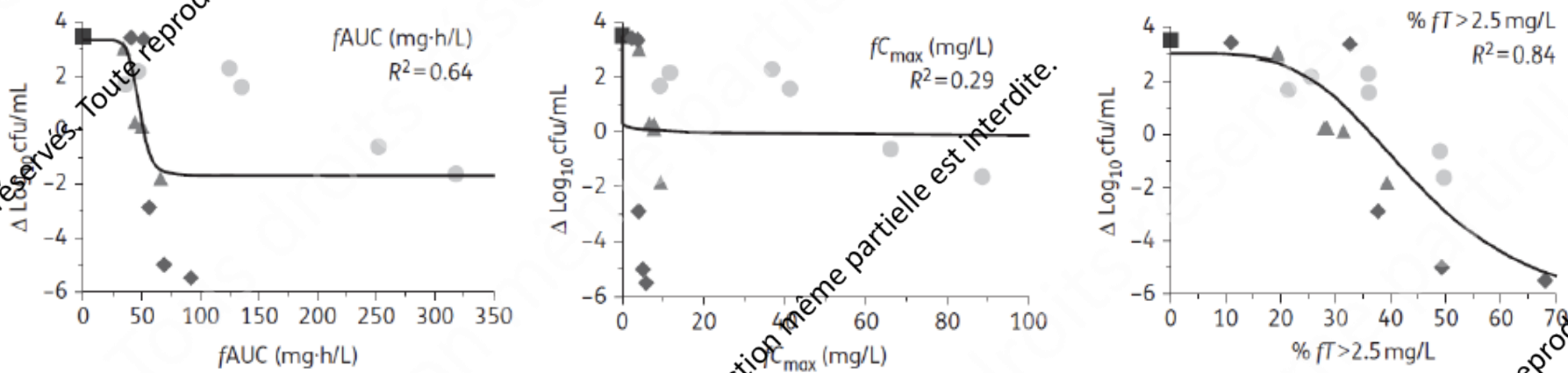


Aztréonam-Avibactam

Activity in Hollow Fiber System

%*f*T>2.5 mg/L PD Driver for Avibactam

Correlation of AVI exposure parameters to ATM-dependent efficacy against *E. coli* ARC3600 in the HFS (MIC = 0.125 mg/L) while keeping ATM at 50% *f*T>MIC



- **ATM-dependent efficacy of AVI correlated best with %*f*T>2.5 mg/L, when compared to *f*AUC and *f*C_{max}**
  - Same driver as for CAZ-AVI, but magnitude differs
  - %*f*T>2.5 mg/L was confirmed with five additional MBL-producing strains
    - Geometric mean to achieve 1-log-unit kill in HFS is 45 (range: 38-58)

Dose fixe de céfépime **on fait varier:**

les concentrations de Tazobactam

les rythmes d'administration du tazobactam

Abaissement logarithmique de la charge bactérienne [Δlog10 CFU] dans la cuisse de souris

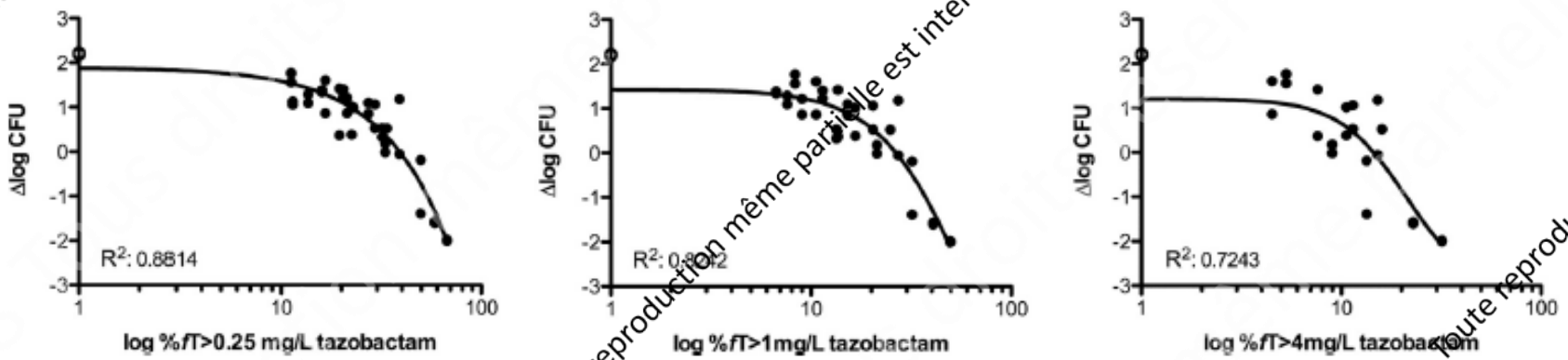


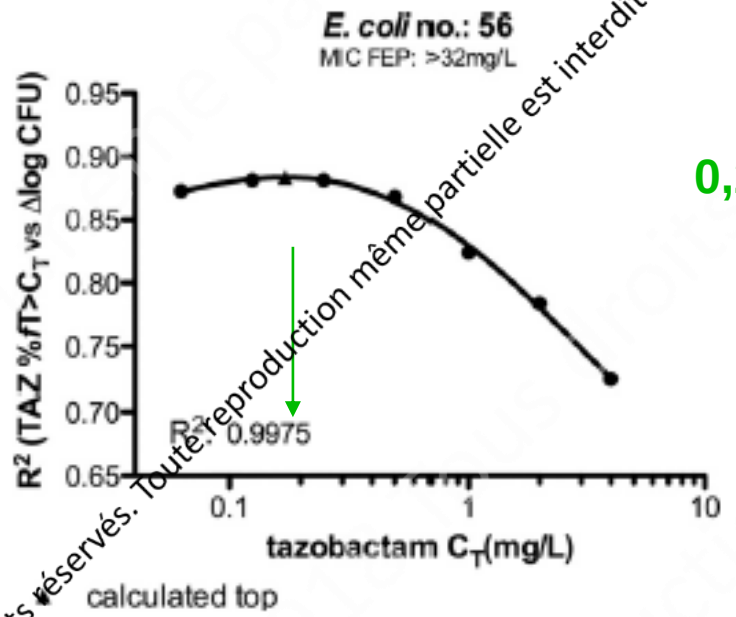
FIG 3 Dose-response relationships for tazobactam, as determined by dose fractionation experiments, in mice infected in the thighs with *E. coli* isolate 56. Fixed doses of cefepime were coadministered q2h. The logarithmic scale of the *x* axis starts at 1. R^2 is noted in the left bottom corner of each graph where a curve could be fitted. Open circles represent data for controls without tazobactam.

The first approach was to determine the relationship between exposure and efficacy for a range of threshold levels and by visual inspection to decide which looked best.

To quantify these relationships, the R^2 for each of the plots was plotted against the concentration threshold value, and a fourth-order polynomial was fitted to the data points to allow calculation of the optimum value.

$$ax^4 + bx^3 + cx^2 + dx + e = 0$$ Ferrari (1522 - 1565)

The calculated CT with the highest R^2 was subsequently used as the tazobactam threshold for each strain.



0,25mg/L

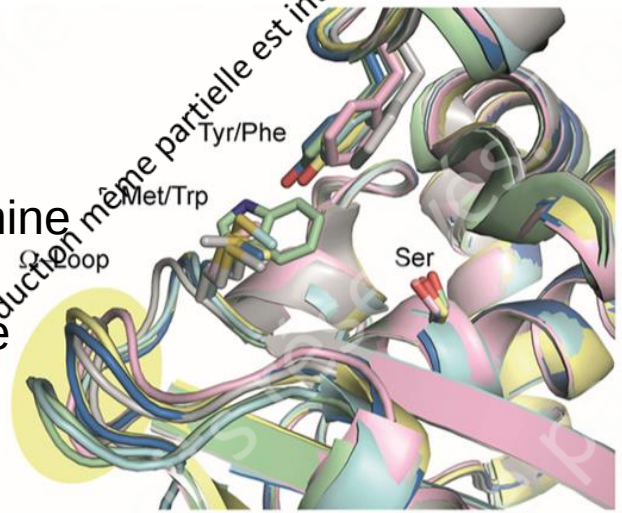
FIG 5 Relationship between R^2 of graphs, tazobactam (TAZ) $\%fT>C_T$ against Δlog CFU, and tazobactam threshold (concentration thresholds of 0.0625, 0.125, 0.25, 0.5, 1, 2, and 4) for *E. coli* 56. The filled triangle marks the top of the curve.

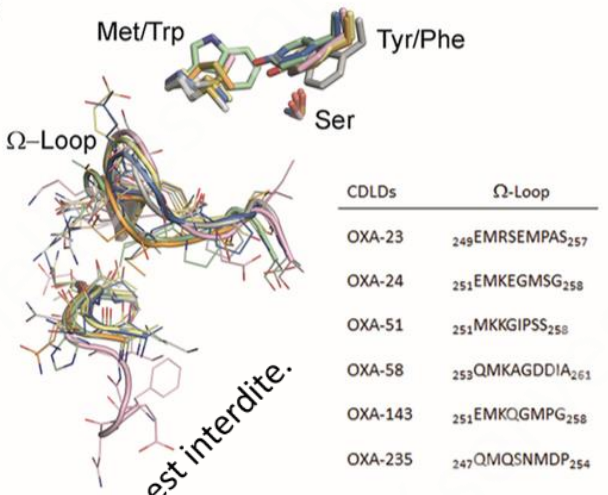
PK/PD

Agent	Inhibiteur		Antibiotique associé	
	fT > CT	%	T > CMI	
Ceftolozane-Tazobactam	0,5 (½ CMI)		35-50%	
Ceftazidime-avibactam	1	50	50%	
Aztréonam-avibactam	2,5		50%	
Céfépime-tazo	0,25	25% bactériostase		
Mero-vaborbactam	AUC vabor free / CMI association		40-60%	
Nacubactam	¼ CMI			
CB 618	AUIC ≥ 136			

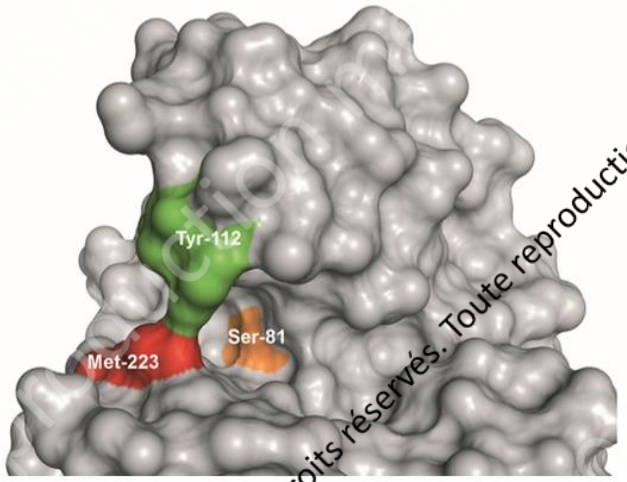
L. Dubreuil 2018

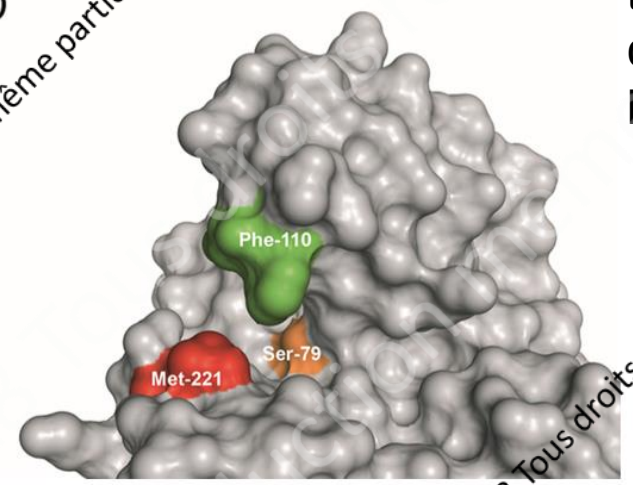
tyrosine or phenylalanine and a methionine





CDLDs	Ω-Loop
OXA-23	$_{249}$EMRSEMPAS$_{257}$
OXA-24	$_{251}$EMKEGMSG$_{258}$
OXA-51	$_{251}$MKKGIPSS$_{258}$
OXA-58	$_{253}$QMKAGDDIA$_{261}$
OXA-143	$_{251}$EMKΩGMPG$_{258}$
OXA-235	$_{247}$QMQSNMDP$_{254}$





Oxa 24
Oxa 135

OXA 23

FIG 4 (A) Comparison of the OXA-type carbapenemases employed in this study, OXA-23 (gray), OXA-24 (yellow), OXA-51 (green), OXA-58 (pink), OXA-143 (blue), and OXA-235 (cyan), highlighting the side chain residues responsible of the major structural differences. The side chain of the catalytic serine is also shown. (B) Detailed view of the Ω-loop and neighbor turn involving β1-strand and α1-helix. Note the relevant differences in the arrangement and sequence of the Ω-loop among the enzymes studied. (C and D) Selected views of the tunnel-like entrance to the active site of OXA-24 (C) and OXA-23 (D) enzymes. The position of the Tyr/Phe and Met residues that are involved in this entrance are highlighted in green and red, respectively. The catalytic serine is shown in orange. Note how the active site of OXA-24 containing a Try residue is more closed than the OXA-23 one having a Phe residue.

The differences in the Ω-loop might cause significant variations in the plasticity of these loops and therefore in the efficacy of the ligands.

TABLE 1 β-Lactam MIC values with *A. baumannii* ATCC 17978 and clinical isolates producing CHDLs in the presence and absence of β-lactamase inhibitors

A. baumannii strain	MICs (mg/liter) for[a]:																				
	Inhibitors at 16 mg/liter				Inhibitors at 4 mg/liter				Inhibitors at 16 mg/liter			Inhibitors at 4 mg/liter				Inhibitors at 16 mg/liter			Inhibitors at 4 mg/liter		
	IP	IP + TZ	IP + AV	IP + LN	IP + TZ	IP + AV	IP + LN	MP	MP + TZ	MP + AV	MP + LN	MP + TZ	MP + AV	MP + LN	AP	AP + TZ	AP + AV	AP + LN	AP + TZ	AP + AV	AP + LN
ATCC 17978 (OXA-23)	16	8	8	0.5	16	8	2	8	8	4	0.5	8	8	1	8,192	8,192	512	32	8,192	2,048	128
Clinical isolate (OXA-23)	32	16	8	1	16	16	4	16	8	8	1	16	16	4	16,384	16,384	1,024	128	16,384	4,096	1,024
ATCC 17978 (OXA-24)	64	64	32	0.5	64	32	2	64	64	16	0.25	64	64	2	16,384	8,192	1,024	32	8,192	4,096	128
Clinical isolate (OXA-24)	256	256	128	8	256	256	128	256	256	128	8	256	256	128	>16,384	>16,384	8,192	2,048	>16,384	>16,384	16,384
ATCC 17978 (OXA-58)	32	16	4	0.5	16	16	2	8	4	2	0.5	4	4	1	8,192	8,192	1,024	32	8,192	4,096	256
Clinical isolate (OXA-58)	8	8	4	1	8	4	2	4	4	1	0.5	4	4	1	8,192	4,096	1,024	128	8,192	4,096	256
ATCC 17978 (OXA-51 like)	4	4	2	1	4	4	2	4	2	2	0.5	4	2	1	8,192	4,096	1,024	32	8,192	4,096	256
ATCC 17978 (OXA-143)	64	32	8	1	64	32	4	128	128	16	1	128	64	16	16,384	8,192	512	32	16,384	2,048	256
Clinical isolate (OXA-143)	32	16	4	2	32	16	8	128	128	32	4	128	64	32	16,384	16,384	1,024	256	16,384	4,096	512
ATCC 17978 (OXA-235)	2	2	2	0.5	2	2	1	2	1	1	0.5	1	1	0.5	2,048	512	128	32	2,048	256	64
Clinical isolate (OXA-235)	8	4	2	1	8	2	2	4	2	0.5	0.5	2	2	1	16,384	8,192	128	128	16,384	1,024	1,024
ATCC 17978 pET-RA	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	64	32	32	32	64	32	32

[a]IP, imipenem; MP, meropenem; AM, ampicillin; TZ, tazobactam; AV, avibactam; LN, LN-1-255. Data represent the means from three independent experiments.

The hydrophobic bridge of OXA-24/40 (composed of Tyr-112 and Met-223) was shown to be important in conferring inhibition by LN-1-255.

However, this bridge is not a universal feature of CHDLs; for example, OXA-48 does not possess it.

Conclusions

Inhibiteurs à

- **Spectres différents Entérobactérales ou/et Pseudomonas ou/et Acinetobacter**

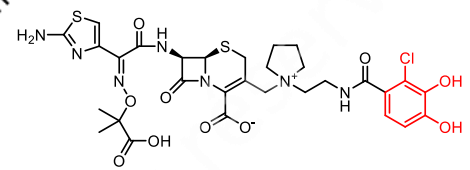
- **profils d'inhibition des ß lactamases différents en fonction des classes ABCD**

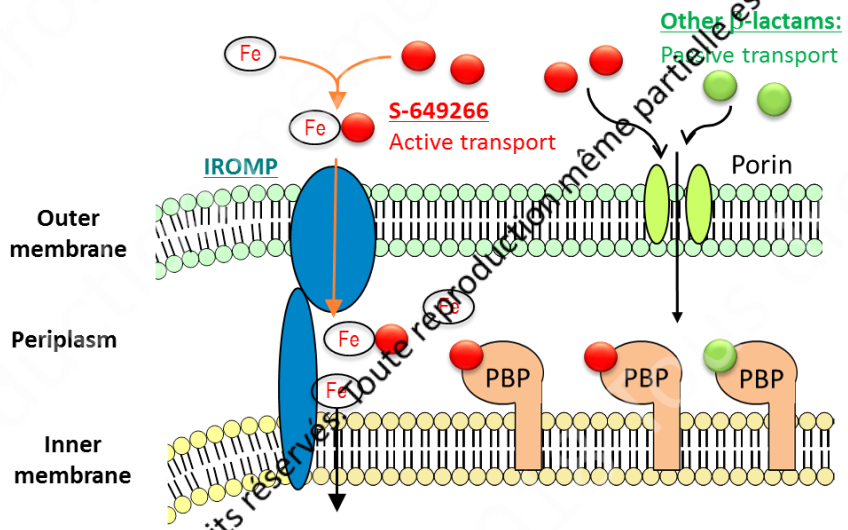
PK/PD différents

Sur une même classe (Oxacillinases D):

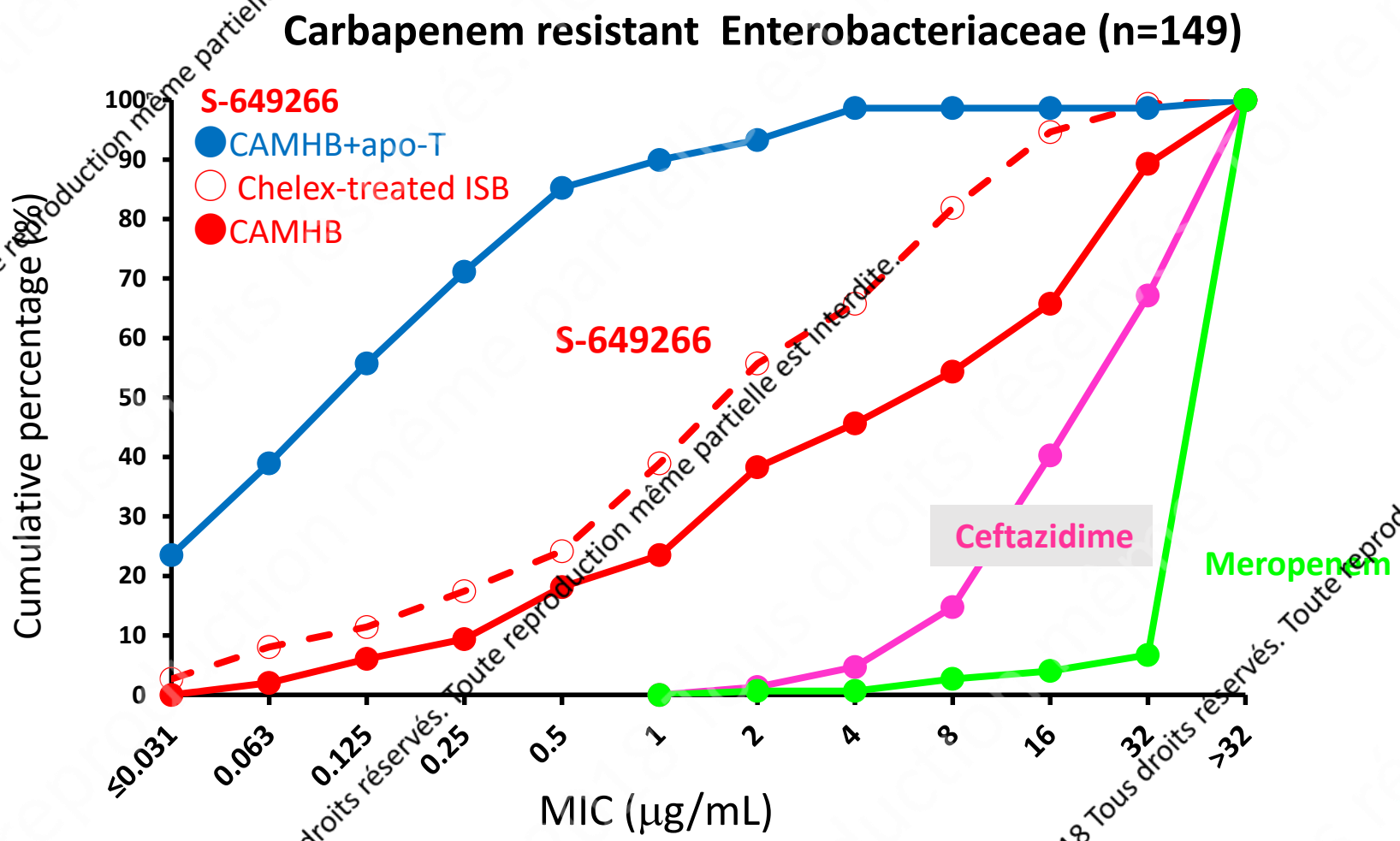
Variation d'activité selon la structure 3D ou les mutations sur boucle Ω rendant fragiles ces molécules au long court

Cefiderocol (S-649266), A Siderophore Cephalosporin,





Antibacterial activity against CRE



The test strains include both KPC- and NDM-producers
Ceftazidime, Meropenem: MIC was determined in CAMHB

Influence du chélateur sur les valeurs de CMI de la sidérophore-céphalosporine S 649266

Relationships between $\%T_{f>MIC}$ and Efficacy in Rat RTI Models

Efficacy against MDR *P. aeruginosa* and *A. baumannii*

Test strains	Results of rat infusion study†		Chelex treated ISB	
			MIC (μg/mL)	$\%T_{f>MIC}$
***P. aeruginosa* ATCC27853**	1-hour infusion	-2.9	0.5	100
	3-hour infusion	-2.9		100
***P. aeruginosa* SR27001 (IMP-1 producer, MDRP)**	1-hour infusion	-2.8	8	50
	3-hour infusion	-3.1		100
***A. baumannii* 1484911**	1-hour infusion	-2.6	0.125	100
	3-hour infusion	-2.0		100
***A. baumannii* 1485176 (MDRA, CC92)**	1-hour infusion	-3.6	0.25	100
	3-hour infusion	-3.8		100
***A. baumannii* 1515988**	1-hour infusion	-4.3	0.25	100
	3-hour infusion	-4.7		100
A. baumannii 1485247 (MDRA)	1-hour infusion	-0.7	2	100
	3-hour infusion	-3.1		100

†:Change from baseline control $\log_{10}$CFU/lung

: ≥-ca 2 $\log_{10}$ reduction

Conclusion:

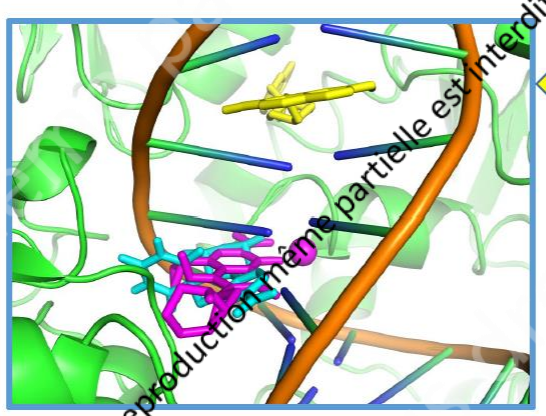
The probability of achieving a PK/PD exposure based on 75% of $T_{f>MIC}$ in plasma is recommended to be the appropriate target to demonstrate the clinical efficacy of S-649266

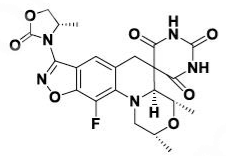
Type-II Topoisomerase Inhibitors

Fluoroquinolines, Quinolines, Spiropyrimidinetriones			
	Phase	Indications	Mode of Administration
Delafloxacin (FQ)	NDA	cSSTI; CAP	PO &IV
Lascufloxacin (FQ)	3	RTI; CAP	PO &IV
Finafloxacin (FQ)	2	aEI	PO &IV
Gepotidacin (quinoline)	2	cSSTI; STD	PO &IV
Zoliflodacin (SPT)	2	STD	PO
Alalevonadifloxacin (FQ)	1	cSSTI	PO
TNP-2092 (FQ/Rif hybrid)	1	PJI	PO

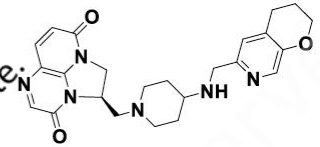
Topoisomerase Target

DNA Gyrase – creates negative supercoils in dsDNA
Topoisomerase IV – decantenates intertwined dsDNA

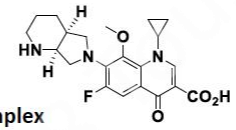




Zoliflodacin
- Binds to Gyrase/cleaved DNA complex
- Independent of Mg^{2+}



Gepotidacin
Binds to Gyrase/DNA complex

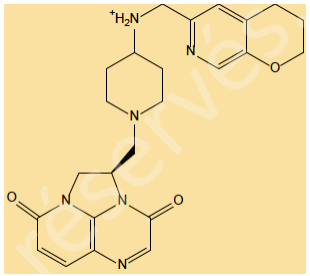


Moxifloxacin
Binds to Gyrase/cleaved DNA complex
Dependent on Mg^{2+}

Basarab, G. *Top. Med. Chem.*.**2017**.

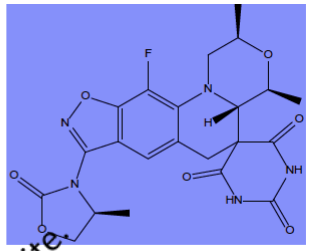
Triazaacénaphthylène

Gepotidacin



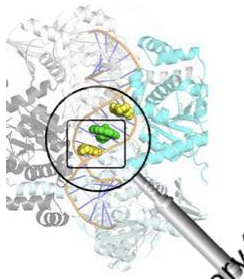
Spiropyrimidénétrione

Zoliflodacin

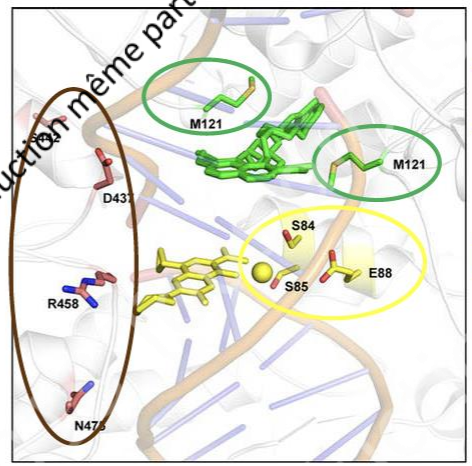


Ehmann & Lahiri, Curr Op. Pharmacol. 2014; 18:76–83

Drugs acting on new binding sites of known targets: the example of topoisomerase II inhibitors



zoliflodacin mutable sites



Resistance to DNA site inhibitors

Resistance to FQ

No cross-resistance has been described

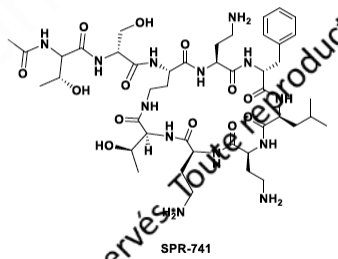
Basarab et al. SpringerPlus 2015; 5:11827

Protein biosynthesis inhibitors

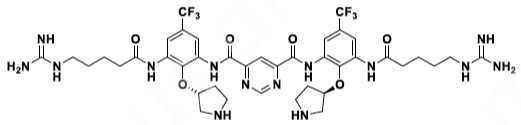
Ribosome inhibitors			
	Phase	Indications	Mode of Administration
Plazomicin (aminoglycoside)	3	cUTI, HAP/VAP	IV
Eravacycline (tetracycline)	3	cIAI, cUTI	PO & IV
Omadacycline (tetracycline)	3	CAP, cSSTI	PO & IV
Solithromycin (macrolide)	3	CAP	PO & IV
Nafithromycin (macrolide)	2	CAP	PO
TP-271 (tetracycline)	1	CAP	PO & IV
TP-6076 (tetracycline)	1	CRE	PO & IV
KBP-7072 (tetracycline)	1	CAP	PO & IV

Membrane Disrupters

Colistins & Defensins			
	Phase	Indications	Mode of Administration
Murepavidin (POL-7080) Cyclic peptide binds to lpt1	2	VAP, RTI (Pseudomonas only)	IV
Brilacidin	2	SSTI	IV
SPR-741 (cyclic peptide potentiator) + unknown	1	TBD	IV

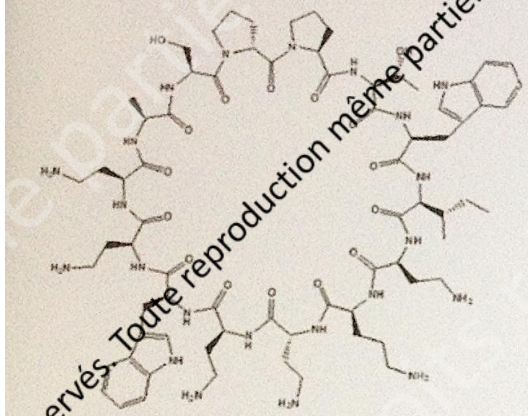


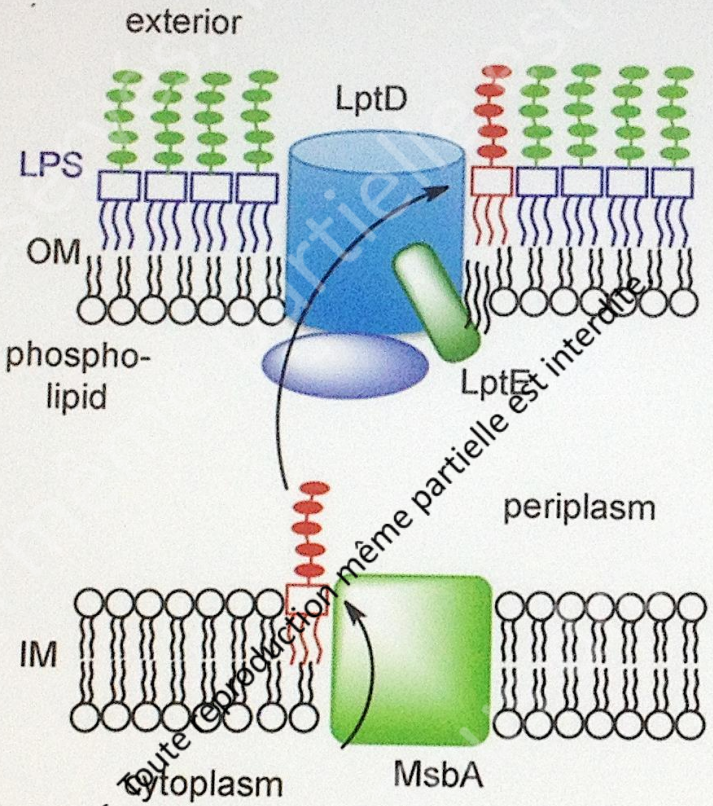
SPR-741



Brilacidin

Murepavadine: a specific antipseudomonal peptidomimetic





MDR isolates (300)

Murepavadin	0.12	0.25
Colistin	1	1
Amikacin	8	>64
Cefepime	16	>32
Ceftazidime	32	>32
Ciprofloxacin	8	>8
Meropenem	8	>16
Piperacillin-tazobactam	64	>128

Strong activity against *P. aeruginosa* among over 1500 worldwide isolates (MIC90 ≤0.25 µg/mL)

Proven efficacy in animal models with good penetration into lung epithelial lining fluid (ELF)

Clinical cure rate at test-of-cure was 91% in 12 patients with VAP caused by *P. aeruginosa*

Inhibition of LPS transport to the cell surface
Inhibition of Outer membrane LPS synthesis

Werneburg M, et al. Chembiochem 2012;13:1767–1775
Andolina G, et al. ACS Chem Biol. 2018 Mar 16;13:666
Murepavadin (POL7080) [Internet]. Polyphor Ltd. [cited 2017 Nov 7]. https://www.polyphor.com/pol7080/