BETALAKTAME & BETALAKTAMASEHEMMER IN DER PIPELINE

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HINWEIS

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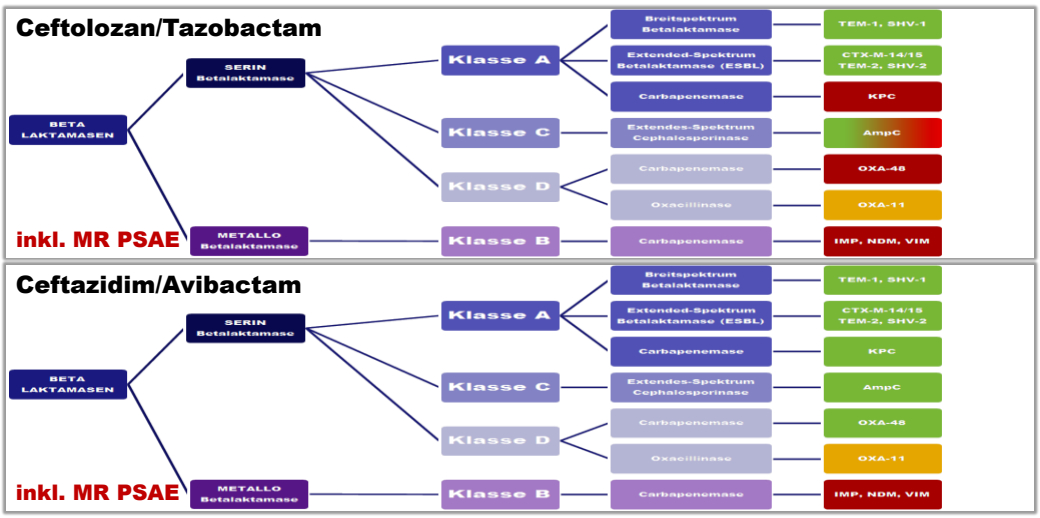
BL & BLI IN DER PIPELINE
Parenterale BLI-Kombinationen

		Dosis
Amoxicillin mit Clavulansäure	Augmentin	3-mal (2 g + 0,2 g)
Ticarcillin mit Clavulansäure**	Timentin	4-mal (3 g + 0,1 g)
Ampicillin mit Sulbactam	Unasyn	3-mal (2 g + 1 g)
Piperacillin mit Tazobactam***	Tazosyn	3-mal (2 g + 0,5 g)
Ceftolozan mit Tazobactam***	Zerbaxa	3-mal (1 g + 0,5 g)
Cefepim mit Tazobactam**	Magnova	3-mal (1 g + 0,125 g)
Cefepim mit Subactam**	Supime	3-mal (1 g + 0,5 g)
Cefoperazon mit Sulbactam**	Sulperazon	3-mal (1 g + 0,5 g)
Cefoperazon mit Tazobactam**	Kephazon	3-mal (1 g + 0,125 g)
Ceftazidim mit Avibactam**	Avycaz	3-mal (2 g + 1 g)
Ceftazidim mit Tazobactam**	Megacid XP	3-mal (1 g + 0,125 g)
Ceftriaxon mit Sulbactam**	Unitrax	4-mal (1 g + 0,5 g)
Ceftriaxon mit Tazobactam**	Xotag	1-mal (1 g + 0,125 g)

* kommerziell erhältlich
** nicht in Mitteleuropa erhältlich
*** bei nachgewiesener oder vermuteter Infektion durch P. aeruginosa:
Pip/Tazo 3–4-mal (4 g + 1 g); Cefto/Tazo 3-mal (2 g + 1 g)

Graninger, Universum Innere Medizin 2016

BL & BLI IN DER PIPELINE
Cefto/Taz & Cefta/Avi



BL & BLI IN DER PIPELINE
Cefto/Taz & Cefta/Avi

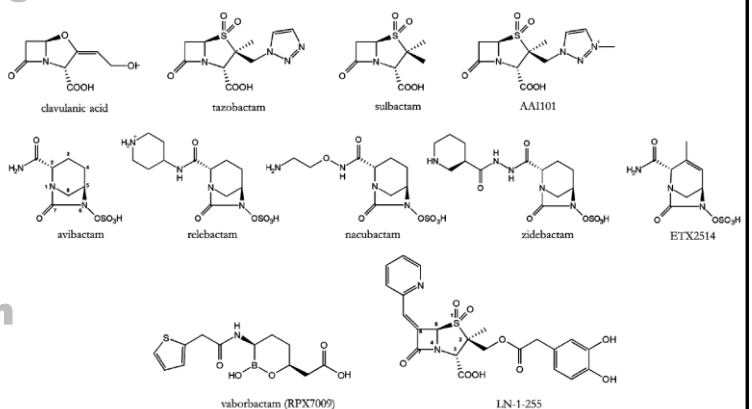
Antibiogramm	Keim 1	Keim 2	Keim 3	Keim 4
Ampicillin	-			
Ampicillin + Sulbactam	-			
Amoxicillin/ Clavulansäure	-			
Piperacillin	-	-	-	+
Piperacillin/ Tazobactam	-	-	-	+
Cefepim	+/-	-	-	+
Cefotaxim	+			
Cefoxitin	-			
Ceftazidim/ Avibactam	+	-	-	+
Ceftazidim	-	-	-	+
Cefuroxim	-			
Ceftolozan/ Tazobactam	-	+	+	+
Ertapenem	+			
Imipenem		+	+	+
Meropenem	+	+	+/-	+
Aztreonam	+			
Ciprofloxacin	-	+	+	+
Amikacin	+	+	+	+
Gentamicin	+	+	+	+
Tobramycin		+	+	+
Teicoplanin				
Vancomycin				
Tigecyclin	+/-			
Colistin	+			
Fosfomycin	+			

1. **Klebsiella pneumoniae 3 MRGN** 10E3 KBE/ml
   Breitspektrum-Betalaktamase (ESBL) nachgewiesen.
   Multiresistente gramnegative Stäbchen (MRGN) mit Resistenzreduzierter Empfindlichkeit gegen 3 von 4 Antibiotikagruppen (Acylureidopenicilline, Cephalosporine der 3./4. Generation, Carbapeneme, Fluorchinolone)
2. **Pseudomonas aeruginosa** 10E3 KBE/ml
3. **Pseudomonas aeruginosa** 10E3 KBE/ml
4. **Pseudomonas aeruginosa** 10E2 KBE/ml

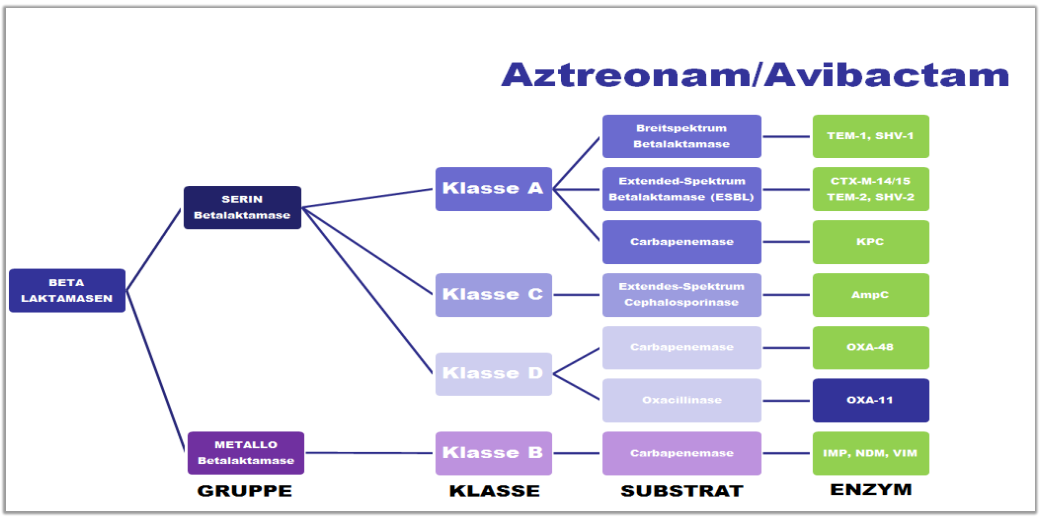
AKH Wien, Mikrobiologie 2017_09

BL & BLI IN DER PIPELINE

- **Avibactam**
- Clavulansäure
- ETX514
- Nacubactam
- Relebactam
- Sulbactam
- Tazobactam
- Vaborbactam
- Zidebactam



BL & BLI IN DER PIPELINE
Aztreonam/Avibactam



BL & BLI IN DER PIPELINE
Aztreonam/Avibactam

Pathogen	Strain	β-Lactamases	MIC (mg/L) ATM	ATM/AVI
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

	MIC (μg/ml) for drug:			
	Aztreonam		Aztreonam-avibactam	
Group (*n*)[a]	MIC_{90}	MIC range	MIC_{90}	MIC range
All MBL producers (90)	>128	≤0.015 to >128	1	≤0.015 to 4
MBL only (9)		≤0.015 to 1		≤0.015 to 0.25
MBL + OSBL (10)	0.25	0.06 to 0.5	0.25	0.03 to 0.25
MBL + ESBL (8)		64 to >128		0.06 to 0.25
MBL + ESBL + OSBL (23)	128	0.5 to >128	0.5	≤0.015 to 2
MBL + AmpC (14)	64	0.03 to 128	2	≤0.015 to 4
MBL + AmpC + OSBL (10)	64	0.12 to 64	2	≤0.015 to 4
MBL + ESBL + AmpC (1)		32		0.03
MBL + ESBL + AmpC + OSBL (8)		16 to >128		0.03 to 0.25
MBL + KPC (1)		>128		0.5
MBL + KPC + AmpC + OSBL (1)		>128		0.5
MBL + KPC + ESBL + AmpC + OSBL (2)		>128		0.5
MBL + OXA-48 (1)		2		1
MBL + OXA-48 + AmpC (1)		16		0.25
MBL + OXA-48 + ESBL + AmpC + OSBL (1)		128		0.25

[a] MBLs include IMP (20 isolates), VIM (40 isolates), and NDM (30 isolates); ESBLs include SHV, TEM, CTX-M, and VEB.

Singh, J Antimicrob Chemother 2015 – Biedenbach, Antimicrob Agents Chemother 2015

BL & BLI IN DER PIPELINE
Kombination Cef/Avi plus Aztreonam

Synergistic activity of ceftazidime-avibactam and aztreonam against serine and metallo-β-lactamase-producing gram-negative pathogens

	Ceftazidime + Aztreonam		Ceftazidime + Ceftazidime-avibactam		Aztreonam + Ceftazidime-avibactam	
Organism	FIC	Interpretation	FIC	Interpretation	FIC	Interpretation
E. coli NDM	2	I	2	I	0.016	S
P. aeruginosa IMP	0.5	S	2	I	1.5	I
C. freundii VIM	0.5	S	2	I	0.031	S
E. cloacae KPC	0.125	S	0.011	S	0.009	S
K. pneumoniae KPC	0.125	S	0.039	S	0.011	S
A. baumannii OXA	0.094	S	0.063	S	1	A
K. pneumoniae ATCC[a]	0.25	S	0.078	S	0.0094	S

FIC = fractional inhibitory concentration; I = indifferent; S, synergistic; A = additive.
[a] KPC-producing *K. pneumoniae* ATCC® BAA-1705.

Wenzler, Diagn Microbiol Infect Dis 2017

BL & BLI IN DER PIPELINE
Kombination Cef/Avi plus Aztreonam

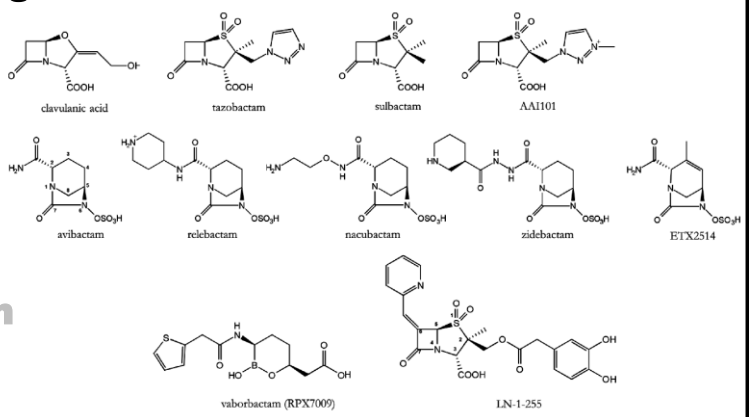
In Vitro Discordance with In Vivo Activity: Humanized Exposures of Ceftazidime-Avibactam, Aztreonam, and Tigecycline Alone and in Combination against New Delhi Metallo-β-Lactamase-Producing Klebsiella pneumoniae in a Murine Lung Infection Model.

The management of infections with New Delhi Metallo-beta-lactamase-1 (NDM) producing bacteria remains clinically challenging given the multi-drug resistant (MDR) phenotype associated with these bacteria. Despite resistance *in vitro*, ceftazidime-avibactam previously demonstrated *in vivo* activity against NDM+ Enterobacteriaceae. Herein, we observed *in vitro* synergy with ceftazidime-avibactam and aztreonam against a MDR *K. pneumoniae* harboring NDM. *In vivo*, humanized doses of ceftazidime-avibactam monotherapy resulted in > 2 $\log_{10}$CFU bacterial reduction, therefore, no *in vivo* synergy was observed.

Monogue, Antimicrob Agents Chemother 2017

BL & BLI IN DER PIPELINE

- Avibactam
- **Clavulansäure**
- ETX514
- Nacubactam
- Relebactam
- Sulbactam
- Tazobactam
- Vaborbactam
- Zidebactam



BL & BLI IN DER PIPELINE
Orale Kombinationen mit Clavulansäure

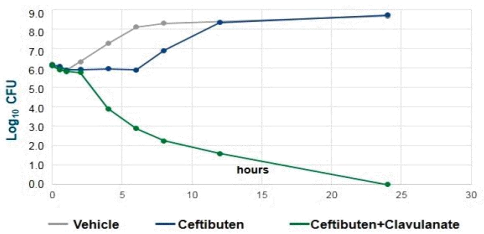
- **Cefixime plus Amoxi/Clav**
  - **Aktivität gegen ESBL (CTX-M-15)**
    - **E. coli**
    - **Klebsiella spp.**
  - **KEINE Aktivität gegen AmpC**
  - **mikrobiolog Testung immer notwendig**
- **Cefalexin plus Amoxi/Clav**
  - **CDI-Risiko geringer, da Cefalexin nicht fäkal ausgeschieden**
- **Cefdinir, Ceftibuten, Cefpodoxim plus Amoxi/Clav**
- **Sulbactam-Kombinationen weniger wirksam**

Livermore, Int J Antimicrob Chemother 2011 – Bingen, Antimicrob Agents Chemother 2013 – Hawkey, J Antimicrob Chemother 2018

BL & BLI IN DER PIPELINE
Ceftibuten/Clavulansäure

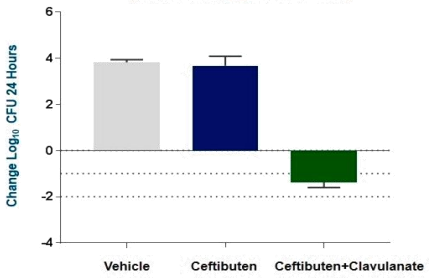
Clavulanate Restores the Efficacy of Ceftibuten Against Target Pathogens

ESBL-Producing *E. coli* (in vitro chemostat)



CFU, colony forming units

ESBL-Producing *E. coli* (mouse thigh infection)



C-Scape, Phase I abgeschlossen

Wise, Achaogen 2018

BL & BLI IN DER PIPELINE
Ceftibuten/Clavulansäure

Organism	ESBL Enzyme	Amoxicillin-Clavulanate MIC (µg/mL)	Ciprofloxacin MIC (µg/mL)	C-Scape MIC (µg/mL)
E. coli	CTX-M-15,TEM-1	16	≤0.03	0.5
E. coli	CTX-M-15,TEM-1	8	>4	0.5
E. coli	CTX-M-14	8	≤0.03	0.5
K. pneumoniae	SHV-5,TEM-1	8	0.25	0.12
K. pneumoniae	SHV WT,CTX-M-15, OXA-1/30-like	16	1	0.5
K. pneumoniae	SHV-11,SHV-12,TEM-1	8	>4	0.25
K. pneumoniae	SHV-30	8	0.12	0.25
P. mirabilis	CTX-M-15-like,TEM WT	2	≤0.03	0.03
P. mirabilis	CTX-M-14-like,TEM WT	8	4	0.03
P. mirabilis	None	0.5	>4	<0.015
P. mirabilis	None	1	≤0.03	<0.015
E. coli	None	8	>4	0.25
K. pneumoniae	None	2	>4	0.06

MIC >2 | MIC 1-2 | MIC <1

JMI Laboratories, Inc. – Achaogen Data on File

Jubb, Achaogen 2017

BL & BLI IN DER PIPELINE

- Avibactam
- Clavulansäure
- **ETX514**
- Nacubactam
- Relebactam
- Sulbactam
- Tazobactam
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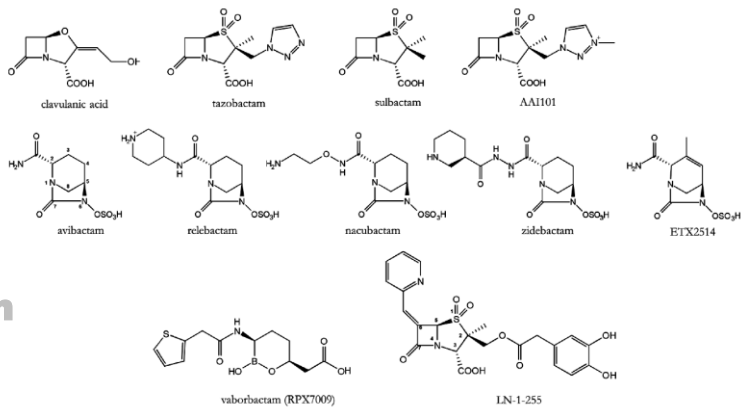
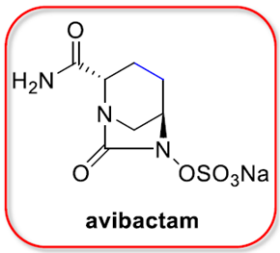
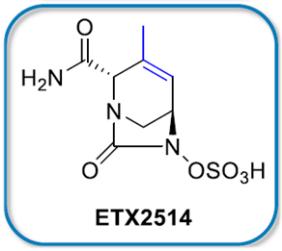
- Zidebactam



BL & BLI IN DER PIPELINE
Diazabicylooctanon ETX2514





Betalaktamasehemmung Avibactam vs ETX2514

		Class A				Class C		Class D			
Compound	Structure	TEM-1	CTX-M-15	KPC-2	SHV-5	*E. cloacae* P99	*P. aer.* AmpC	OXA-10	OXA-23	OXA-24	OXA-48
Avibactam		4×10^6	8×10^5	6×10^3	1×10^6	8×10^3	3×10^3	7×10^1	1×10^2	8×10^1	5×10^3
ETX2514		1×10^7	7×10^6	9×10^6	6×10^6	2×10^6	9×10^5	9×10^3	5×10^3	9×10^3	8×10^5
	Fold increase in potency	25X	9X	150X	60X	250X	300X	130X	50X	110X	160X

Tommasi, ECCMID 2017

BL & BLI IN DER PIPELINE

- Avibactam
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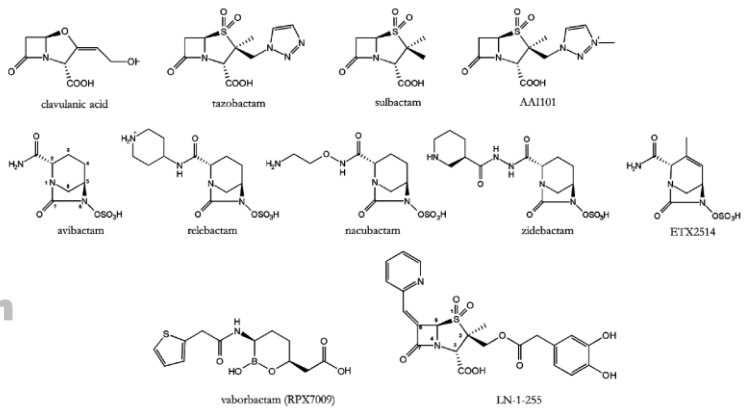
- ETX514
- **Nacubactam**
- Relebactam
- Sulbactam
- Tazobactam
- Vaborbactam
- Zidebactam



BL & BLI IN DER PIPELINE
Nacubactam

Infectious diseases development programs

Roche pRED

Molecule	Nacubactam (DBO beta lactamase inhibitor, RG6080, OP0595)	
Indication	Infectious diseases	
Phase/study	Phase I	Phase I
# of patients	N=56	N=32
Design	• Randomized, double-blind, placebo-controlled, multiple-ascending dose (MAD) study in healthy volunteers with nacubactam monotherapy and in combination with meropenem	Open-label, two-part study: • **Part 1:** Adults with stable mild, moderate or severe renal impairment and a control group of participants with normal renal function • **Part 2:** Adults with stable end-stage renal disease undergoing hemodialysis
Primary endpoint	• Safety, PK	• Safety, PK
Status	• FPI Q4 2016 • Study completed	• FPI Q4 2016
Collaborator	Meiji and Fedora	

DBO=diazabicyclooctane

Infectious Diseases

www.roche.com

BL & BLI IN DER PIPELINE

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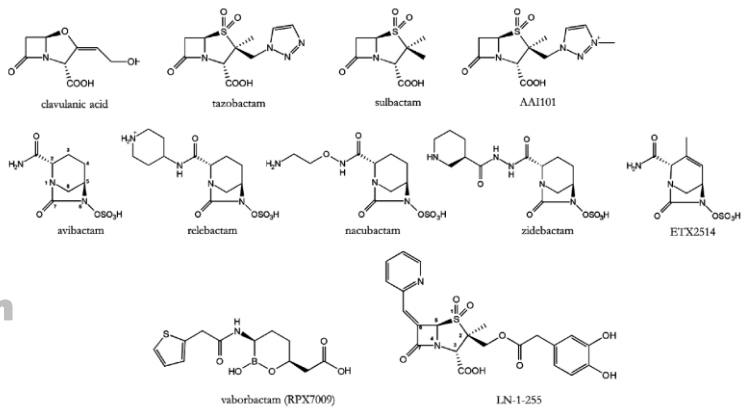
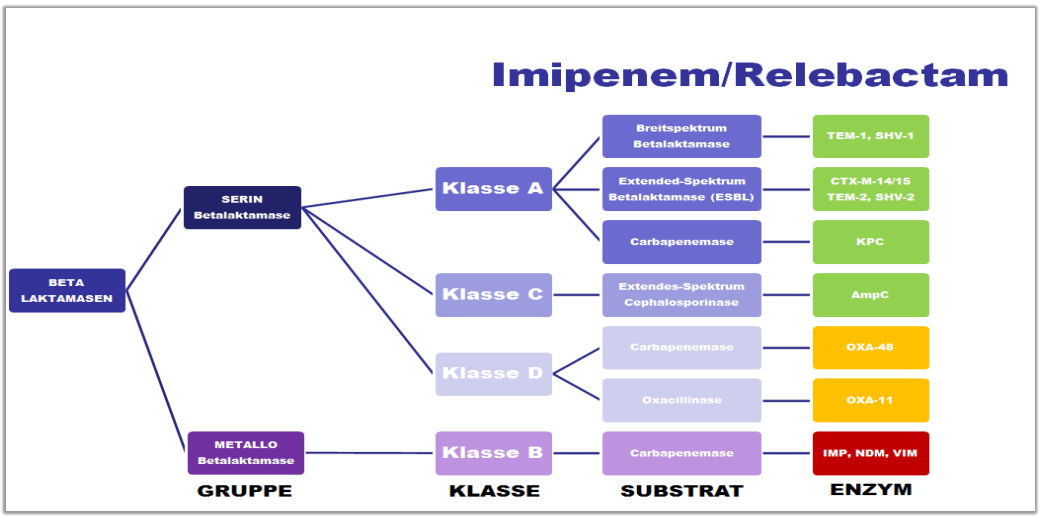


BL & BLI IN DER PIPELINE
Imipenem/Relebactam



BL & BLI IN DER PIPELINE
Imipenem/Relebactam

organism	strain	enzyme	biapenem		meropenem		ertapenem		imipenem	
			alone	with 9f	alone	with 9f	alone	with 9f	alone	with 9f
Escherichia coli	EC1007	KPC-3	8	≤0.06	4	≤0.06	8	≤0.06	8	0.13
Enterobacter cloacae	ECL1058	KPC-3, SHV-11, TEM-1	8	≤0.06	8	≤0.06	32	0.25	8	0.25
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	8	0.25	4	≤0.06	16	0.25	4	0.13
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	4	≤0.06	4	≤0.06	16	0.25	8	0.13
Klebsiella pneumoniae	KP1004	KPC-2, TEM-1, SHV-11	8	≤0.06	8	≤0.06	32	≤0.06	8	≤0.06
Klebsiella pneumoniae	KP1008	KPC-2	8	≤0.06	4	≤0.06	8	≤0.06	4	≤0.06
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	4	≤0.06	4	≤0.06	4	≤0.06	4	0.13
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	16	0.25	64	1	>64	2	16	0.25
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	16	≤0.06	16	≤0.06	32	≤0.06	16	0.13
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	64	0.25	>64	0.5	>64	4	64	0.25
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	32	≤0.06	8	≤0.06	16	≤0.06	32	≤0.06

enzyme	class	9f	clavulanic acid	tazobactam
KPC-2	A	0.069	41.2	1.6
CTX-M-15	A	0.044	0.027	0.001
SHV-12	A	0.029	≤0.039	0.0004
TEM-10	A	0.110	0.020	0.005
P99	C	0.053	1106	1.10
CMY-2	C	0.099	845	0.71

Hecker, J Med Chem 2015

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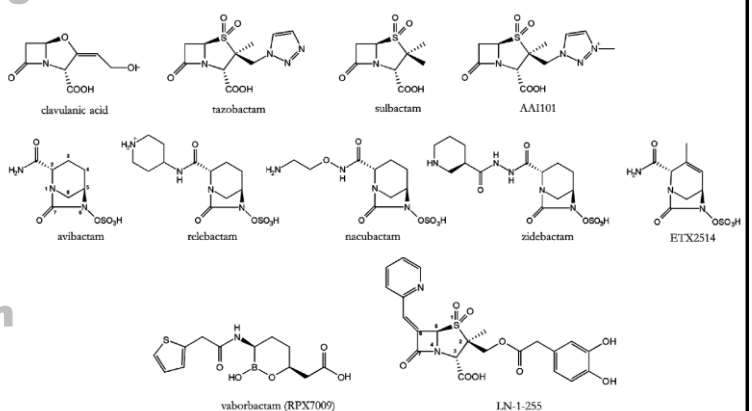

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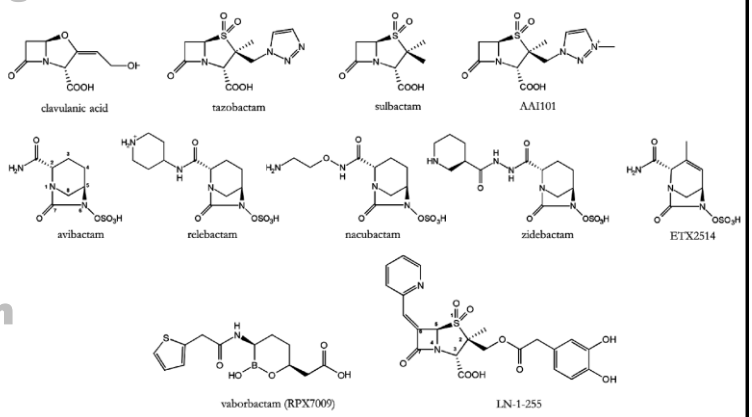
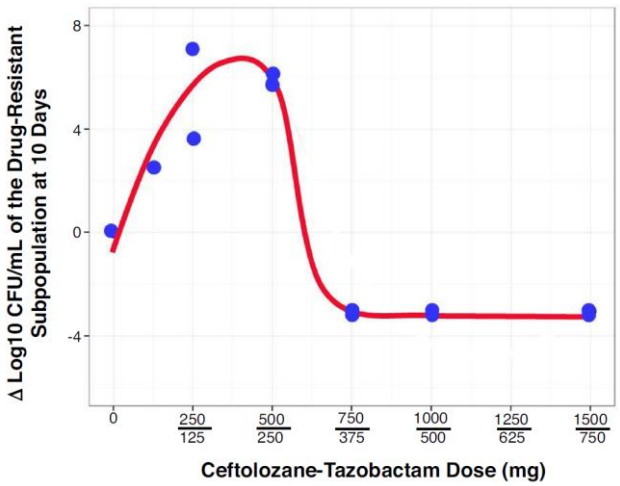


BL & BLI IN DER PIPELINE
Ceftolozan/Tazobactam



Beziehung zwischen Medikamenten-exposition und Unterdrückung resistenter Populationen

Ambrose, Curr Opin Pharmacol 2017

BL & BLI IN DER PIPELINE
Cefepim/Tazobactam

Potential of high-dose cefepime/tazobactam against multiresistant Gram-negative pathogens

Background: Early β-lactamase inhibitors were combined with established penicillins, but different combinations may be more appropriate to counter current β-lactamase threats, with development facilitated by the US Generating Antibiotic Incentives Now (GAIN) Act. Cefepime/tazobactam is especially attractive, combining an AmpC-stable cephalosporin with a clinically established inhibitor, active against ESBLs and suitable for high-dose administration.

Methods: Organisms ($n = 563$) were clinical isolates submitted to the UK national reference laboratory. MICs were determined by CLSI agar dilution with tazobactam at 4 mg/L and, for a subset, at 8 mg/L.

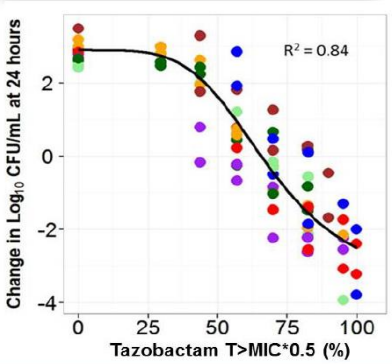
Results: Cefepime/tazobactam 8+4 mg/L achieved coverage of 96%–100% of Enterobacteriaceae with penicillinases, AmpC, ESBL, K1 or OXA-48 β-lactamases. Even at 1+4 mg/L, the combination inhibited >94% of isolates with penicillinases, AmpC enzymes or ESBLs. Most Enterobacteriaceae with KPC and NDM carbapenemase were resistant at current cefepime breakpoints but 80% of those with VIM types were susceptible at 8+4 mg/L. Tazobactam did little to potentiate cefepime against non-fermenter groups, though gains were seen against AmpC-producing *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. Increasing the tazobactam concentration to 8 mg/L gave further small increases in activity against Enterobacteriaceae groups.

Conclusions: High-dose cefepime/tazobactam, justifying an 8+4 or 8+8 mg/L breakpoint, can achieve a carbapenem-like spectrum, with some additional coverage of OXA-48 (and maybe VIM) Enterobacteriaceae. Clinical evaluation is warranted.

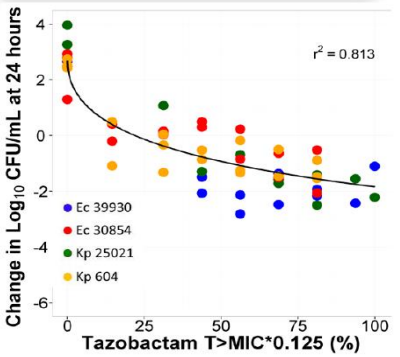
Livermore, J Antimicrob Chemother 2018

BL & BLI IN DER PIPELINE
Cephalosporin plus Tazobactam

Ceftolozane-Tazobactam



Cefepime-Tazobactam

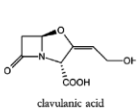


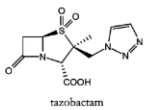
The translational relationship is not the same across β-lactam partners

VanScoy, Antimicrob Agents Chemother 2013 – VanScoy, ICAAC 2015 Poster A-499

BL & BLI IN DER PIPELINE

BLI in der Pipeline


clavulanic acid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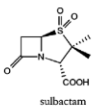
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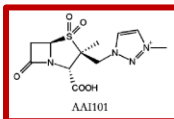
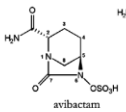

AAI101

besserer KPC-Inhibitor
als Tazobactam
Klasse D BL
Kombination mit Cefepim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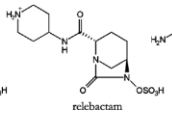
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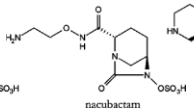
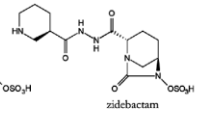
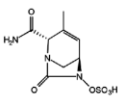
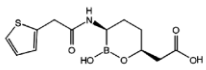
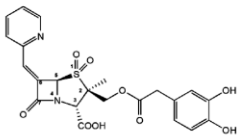

nacubactam


zidebactam


ETX2514

Ceftolozane-tazobactam (2:1)
Ceftazidime-avibactam (4:1)
Ceftaroline-avibactam
Aztreonam-avibactam
Meropenem-Vaborbactam
Imipenem-cliastatin-relebactam (2:2:1)
Nacubactam
Cefepime-zidebactam
Cefepime-AAI101
Sulbactam-ETX2514
VNRX – 5133

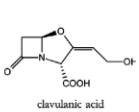

vaborbactam (RPX7009)

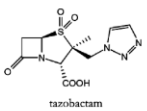

LN-1-255

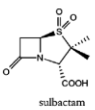
Docquier, Drug Res Update 2018

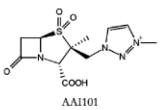
BL & BLI IN DER PIPELINE

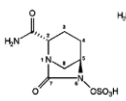
- Avibactam
- Clavulansäure
- ETX514
- Nacubactam
- Relebactam
- Sulbactam
- Tazobactam
- **Vaborbactam**
- Zidebactam

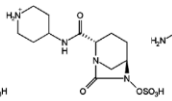

clavulanic acid


tazobactam


sulbactam


AAI101


avibactam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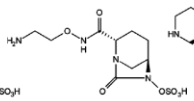
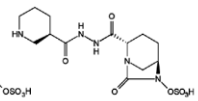

nacubactam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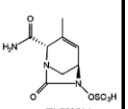
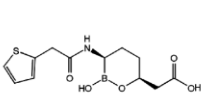
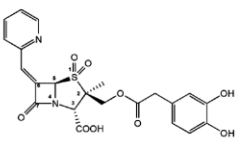
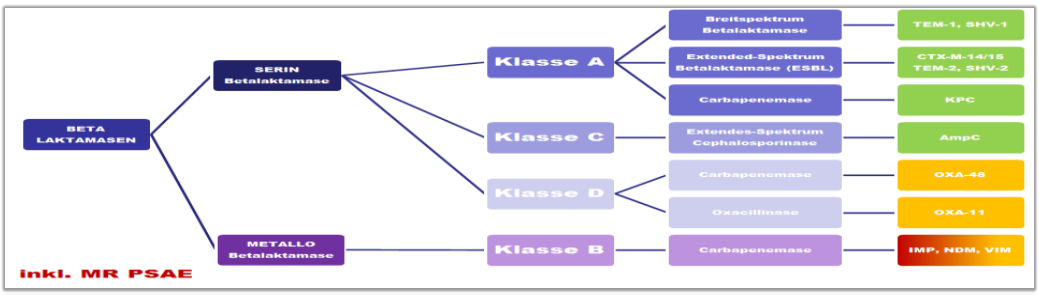

ETX2514


vaborbactam (RPX7009)


LN-1-255

BL & BLI IN DER PIPELINE
Meropenem/Vaborbactam



MPR 30.08.2017

BL & BLI IN DER PIPELINE
Meropenem/Vaborbactam

- Betalaktamaseinhibitor
  - RPX7009
- wirkungsvolle Serinproteaseinhibitoren
- Bildung reversibler kovalenten Bindung zwischen Serin und Boronsäuregruppe
- cyclische Boronsäureester als Inhibitoren
- Kombination mit Meropenem

Compound	Activity	All 2,029 isolates	*E. coli* ESBL (27)	*K. pneumoniae* ESBL (71)	*K. pneumoniae* KPC (26)
GSK2251052	Range (µg/mL)	0.25-4	0.5-2	0.5-2	0.25-2
	MIC_{50} (µg/mL)	1	1	1	2
	% Susceptible	-	-	-	-
Levofloxacin	Range (µg/mL)	≤0.5->16	≤0.5->16	≤0.5->16	≤0.5->16
	MIC_{50} (µg/mL)	16	>16	>16	>16
	% Susceptible	81.4	3.7	28.2	15.4
Gentamicin	Range (µg/mL)	≤0.5->16	≤0.5->16	≤0.5->16	≤0.5->16
	MIC_{50} (µg/mL)	16	>16	>16	16
	% Susceptible	87.2	63.0	43.7	76.9
Tigecycline	Range (µg/mL)	0.06-8	0.12-1	0.12-4	0.25-4
	MIC_{50} (µg/mL)	2	0.5	2	2
	% Susceptible	92.2	100	95.8	92.3
Polymyxin B	Range (µg/mL)	≤0.25->8	0.5-4	0.5->8	0.5->8
	MIC_{50} (µg/mL)	>8	2	2	>8
	% Susceptible	58.7	96.3	93.0	88.5
Imipenem	Range (µg/mL)	≤0.03 ->64	0.12-16	0.06-1	8->64
	MIC_{50} (µg/mL)	2	0.5	0.5	64
	% Susceptible	73.5	96.3	100	0

MIC_{50}: Susceptible; Intermediate; Resistant (CLSI Breakpoints M100-S21 & FDA)

P. Aeruginosa (n-98)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	% Susceptible
Piperacillin-tazobactam	16/4	>128/4	16/4 to > 128/4	52
Ceftazidime	8	>16	1 to > 16	37
Amikacin	4	16	≤0.5 to > 64	94
Ciprofloxacin	>4	>4	≤0.125 to > 4	35
Meropenem	8	32	4 to >64	0
Meropenem-RPX7009 (4µg/ml)	8/4	32/4	0.125/4 to >64/4	NA
Meropenem-RPX7009 (8µg/ml)	8/8	32/8	0.25/8 to 64/8	NA

Stintzi, PNAS 2000 – Mendes, ICAAC 2010 – Page, Ann NY Acad Sci 2013 – Lapuebla, Antimicrob Agents Chemother 2015
Chellat, Angew Chemie 2016

BL & BLI IN DER PIPELINE
Meropenem/Vaborbactam

Parent and mutant	Meropenem MIC (μg/ml) in presence of VAB (μg/ml) at: Alone	2	4	8	16	Porin gene mutation(s)[a] *ompK35*	*ompK36*
KPM1275	32	≤0.06	≤0.06	≤0.06	≤0.06	Same as ATCC 43816 sequence	Same as ATCC 43816 sequence
KPM1852	>64	2	0.5	0.25	0.125	Same as ATCC 43816 sequence	Same as ATCC 43816 sequence
KPM1853	>64	16	4	1	1	Same as ATCC 43816 sequence	FS_aa324
KP1008	4	≤0.06	≤0.06	≤0.06	≤0.06	Same as ATCC 43816 sequence	Same as ATCC 43816 sequence
KPM1837	64	4	1	0.5	0.25	Same as ATCC 43816 sequence	No PCR product
KPM1838	128	4	2	0.5	0.5	Same as ATCC 43816 sequence	TAG_aa298
KPM1839	512	2	4	0.5	0.5	Same as ATCC 43816 sequence	V317D
KP1008-12	>64	8	ND	0.5	ND	Same as ATCC 43816 sequence	FS_aa55

No mutations in the coding region of bla_{KPC} were identified. These data indicate that the selection of mutants with reduced sensitivity to meropenem-vaborbactam from KPC-producing *Klebsiella pneumoniae* strains is associated with previously described mechanisms involving porin mutations and the increase in the bla_{KPC} gene copy number and not changes in the KPC enzyme and can be prevented by the drug concentrations achieved with optimal dosing of the combination.

Sun, Antimicrob Agents Chemother 2017

BL & BLI IN DER PIPELINE
Meropenem/Vaborbactam

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	8	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	0.25	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.

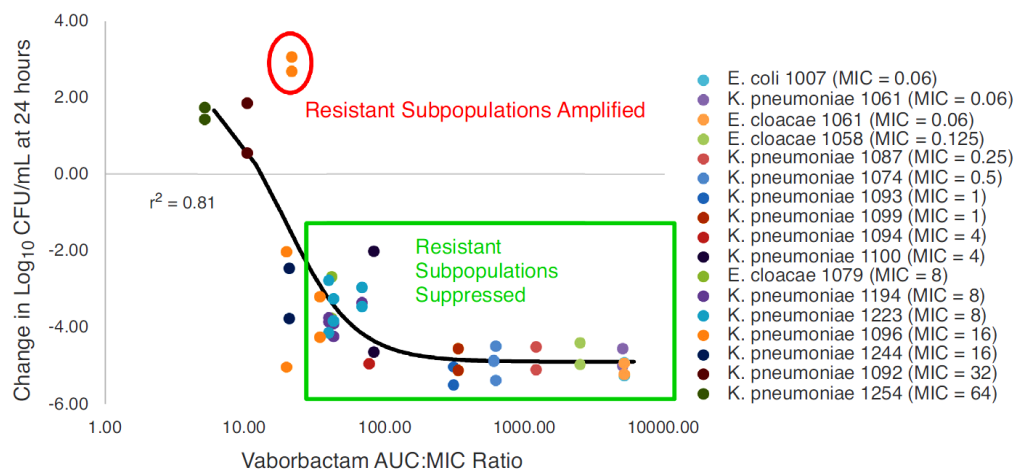
Lomovskaya, Antimicrob Agents Chemother 2017

BL & BLI IN DER PIPELINE
Cyclische Borsäurederivate

Bacterial species and isolate	β-Lactamase(s) produced (Ambler class)	Cyclic boronate 2 (10 mg/liter) supplementation	MIC (mg/liter) for β-lactam[a]: AMP	AMP/SUL	PIP	PIP/TAZ	TIM/CLAV	AZT	FAZ	CRO	CAZ	FEP	ERT	IMI	MEM	DOR
E. coli																
EC107, ST 131	CTX-M-15 (A), OXA-1 (D)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>16	>16	>32	≤0.25	≤0.5	≤0.5	≤0.5
		+	>16	>16/8	>64	>128/4	64/2	≤1	8	<0.5	≤1	8	≤0.25	≤0.5	≤0.5	≤0.5
EC114, ST 131	TEM-1 (A), CTX-M-15 (A), OXA-1 (D)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	≤0.25	≤0.5	≤0.5	≤0.5
		+	>16	>16/8	>64	>128/4	>64/2	≤1	8	<0.5	≤1	8	≤0.25	≤0.5	≤0.5	≤0.5
EC86	CTX-M-15 (A), CMY-4 (C), OXA-181 (D)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>16	>16	>32	>8	>8	4	>4
		+	>16	>16/8	>64	>128/4	>64/2	8	>16	8	8	≤4	4	4	1	2
EC113, ST 131	CTX-M-27 (A)	–	>16	8/4	>64	≤8/4	16/2	>16	>16	>32	8	>32	≤0.25	≤0.5	≤0.5	≤0.5
		+	≤8	≤4/2	≤16	≤8/4	≤8/2	≤1	4	<0.5	≤1	≤4	≤0.25	≤0.5	≤0.5	≤0.5
K. pneumoniae																
KP15	TEM-1 (A), SHV-11 (A), KPC-2 (A)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	>8	>4
		+	>16	16/8	>64	>128/4	>64/2	>16	>16	1	4	≤4	≤0.25	≤0.5	1	≤0.5
KP41	TEM-1 (A), SHV-1 (A), SHV-5 (A), SHV-11 (A), CTX-M-15 (A), OXA-232 (D)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	>8	>4
		+	>16	>16/8	>64	>128/4	64/2	>16	>16	>32	>16	32	>8	>8	>8	>4
KP58	SHV-11 (A), VIM-4 (B)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	>8	>4
		+	>16	>16/8	>64	>128/4	>64/2	2	>16	1	2	>32	≤0.25	2	≤0.5	≤0.5
P. stuartii PS71	TEM-1 (A), SHV-5 (A), VEB-1 (A), VIM-1 (B)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	>8	>8
		+	>16	>16/8	>64	>128/4	>64/2	>16	4	16	>16	8	≤0.25	>8	1	2
P. aeruginosa PA12, ST 111	VIM-2 (B)	–	>16	>16/8	>64	128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	>8	>4
		+	>16	>16/8	64	128/4	>64/2	16	>16	>32	>16	>32	>8	>8	>8	>4
A. baumannii AB14	OXA-23 (D), OXA-51 (D)	–	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	>32	>8	>8	4	>4
		+	>16	>16/8	>64	>128/4	>64/2	>16	>16	>32	>16	32	>8	>8	4	>4

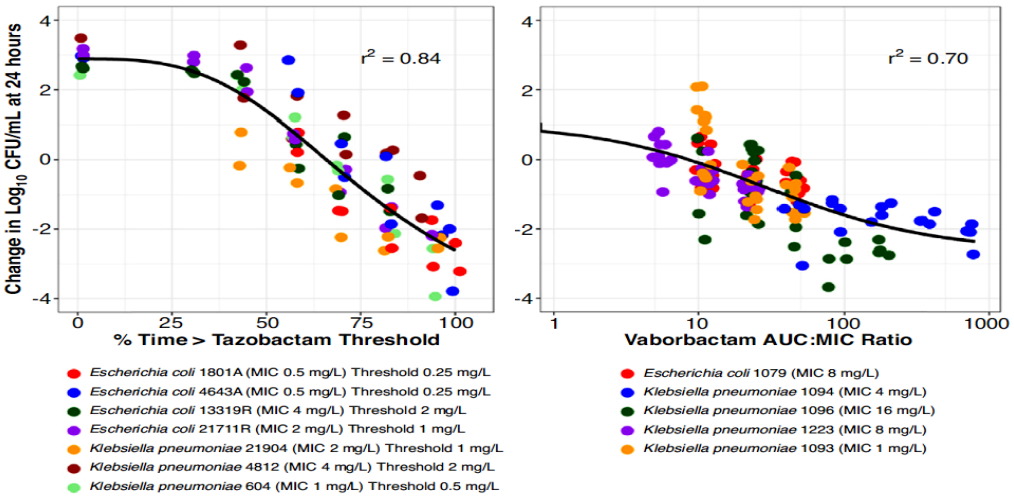
Cahill, Antimicrob Agents Chemother 2018

BL & BLI IN DER PIPELINE
Dosierung & Resistenzverhinderung



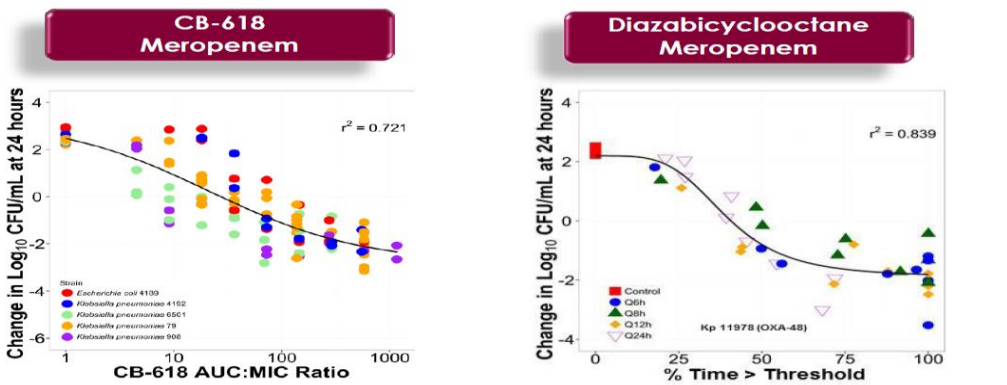
Ambrose, Curr Opin Pharmacol 2017

BL & BLI IN DER PIPELINE
Meropenem/Vaborbactam



Ambrose, Curr Opin Pharmacol 2017

BL & BLI IN DER PIPELINE
BLI PK-PD-mäßig nicht vergleichbar

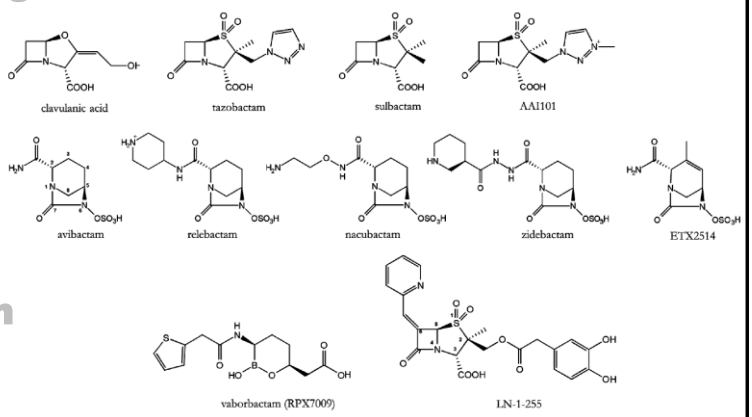


No, the PK-PD determinant of β-lactamase inhibitor efficacy is not the same across β-lactamase inhibitors

VanScoy, ICAAC 2015 Poster A-044

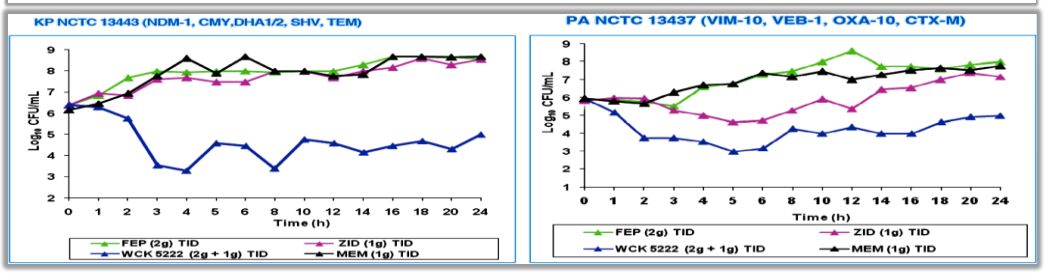
BL & BLI IN DER PIPELINE

- Avibactam
- Clavulansäure
- ETX514
- Nacubactam
- Relebactam
- Sulbactam
- Tazobactam
- Vaborbactam
- **Zidebactam**



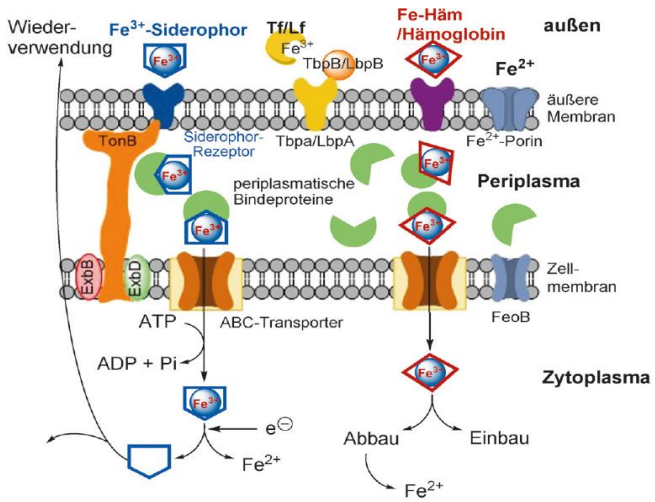
BL & BLI IN DER PIPELINE
Cefepim/Zidebactam

- ESBL Gram-negative Enterobakterien
  - inkl Piperacillin–Tazobactam resistente Stämme
- Cefepim-res Enterobacter mit CMY β-Laktamase
- KPC und andere CRE mit OXA 48/181 β-Laktamase
- MBL/NDM Enterobakterien und Pseudomonaden
- Ceftazidim und Meropenem res Pseudomonaden
- Imipenem resistenter Acinetobacter
- Staphylokkken, Pneumokokken & Streptokokken



Moya, ID week 2016

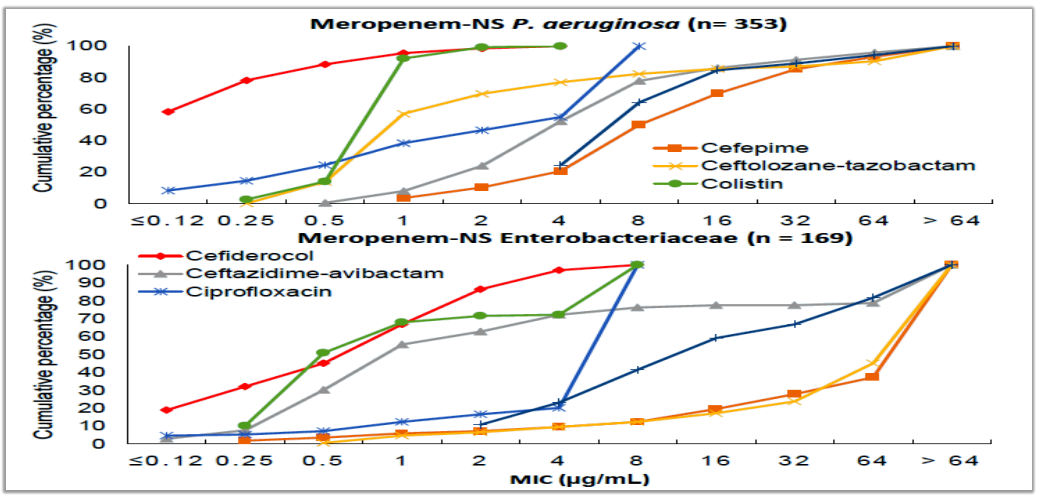
BL & BLI IN DER PIPELINE
Cefiderocol



- Siderophor-Ceph
- Bindung von 3-wertigem Eisen
- aktiver Transport über das Eisen-transportsystem in die Zelle

Ito, Antimicrob Agents Chemother 2016 – Portsmouth, ECCMID 2017 – Bilitewski, Angew Chem 2017

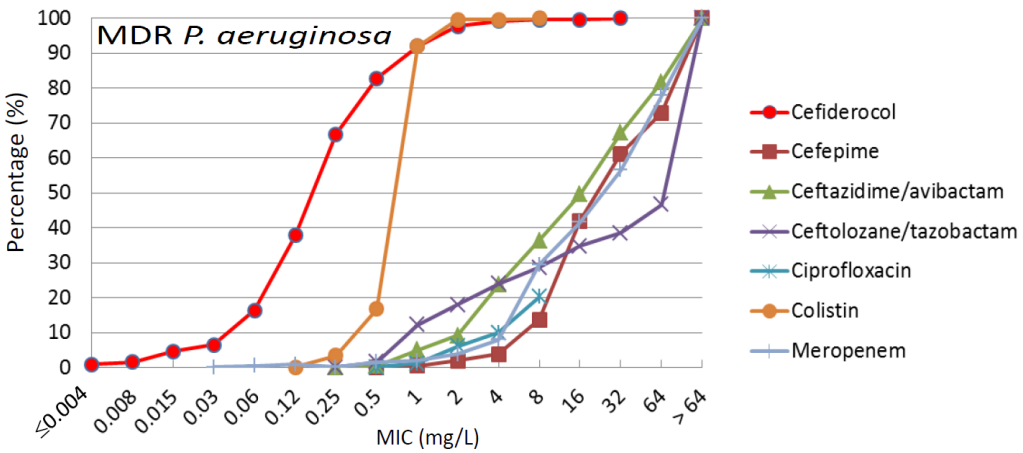
BL & BLI IN DER PIPELINE
Cefiderocol



Stintzi, PNAS 2000 – Page, Ann NY Acad Sci 2013 – Chellat, Angew Chemie 2016
Fallagas, ECCMID 2017 P064 – Portsmouth, ECCMID 2017 – Hackel, IDSA 2017 PO1828

BL & BLI IN DER PIPELINE
Cefiderocol

Comparison of MIC Distribution with other comparators



Yamano, Shionogi 2017

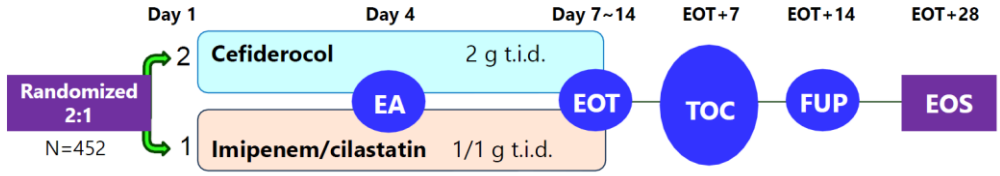
BL & BLI IN DER PIPELINE
Cefiderocol

Species/antibiotic	MIC (mg/L) MIC range	MIC_{50}	MIC_{90}	Resistance (%) S	I	R
A. baumannii (*n*=107)						
cefiderocol	≤0.03–2	0.06	0.5	NA	NA	NA
meropenem	8–>64	64	>64	0	0	100
ceftazidime	8–>64	>64	>64	0.9	5.6	93.5
cefepime	8–>16	>16	>16	5.6	7.5	86.9
ceftazidime/avibactam	0.25–>64	32	64	NA	NA	NA
ceftolozane/tazobactam	2–>64	32	>64	NA	NA	NA
aztreonam	8–>32	>32	>32	NA	NA	NA
amikacin	8–>64	>64	>64	6.5	5.6	87.9
ciprofloxacin	≤0.25–>4	>4	>4	2.8	0	97.2
colistin	≤0.5–>8	1	8	57.9	0	42.1
tigecycline	≤0.25–4	1	2	NA	NA	NA
P. aeruginosa (*n*=82)						
cefiderocol	≤0.03–1	0.12	0.5	NA	NA	NA
meropenem	4–>64	32	>64	0	14.6	85.4
ceftazidime	4–>64	32	>64	13.4	26.8	59.8
cefepime	1–>16	16	>16	25.6	43.9	30.5
ceftazidime/avibactam	1–>64	16	>64	NA	NA	NA
ceftolozane/tazobactam	0.5–>64	>64	>64	NA	NA	NA
aztreonam	≤0.5–>32	16	>32	48.8	19.5	31.7
amikacin	≤4–>64	64	>64	40.2	8.5	51.2
ciprofloxacin	≤0.25–>4	>4	>4	19.5	1.2	79.3
colistin	≤0.5–>8	≤0.5	1	97.6	1.2	1.2
tigecycline	≤0.25–>4	>4	>4	NA	NA	NA
K. pneumoniae (*n*=244)						
cefiderocol	≤0.03–4	0.5	1	NA	NA	NA
meropenem	2–>64	32	>64	0	3.3	96.7
ceftazidime	0.5– >64	>64	>64	1.6	1.6	96.7
cefepime	1–>16	>16	>16	0.4	1.2	98.3
ceftazidime/avibactam	0.12–>64	1	>64	NA	NA	NA
ceftolozane/tazobactam	1–>64	>64	>64	NA	NA	NA
aztreonam	≤0.5–>32	>32	>32	5.7	0.4	93.9
amikacin	≤4–>64	16	>64	61.5	14.8	23.8
ciprofloxacin	≤0.25–>4	>4	>4	4.9	0.8	94.3
colistin	≤0.5–>8	≤0.5	>8	62.7	0	37.3
tigecycline	≤0.25–4	0.5	2	90.2	7.4	2.5

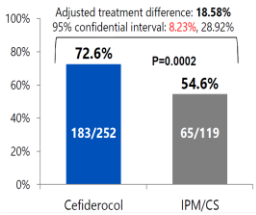
Falagas, J Antimicrob Chemother 2017

BL & BLI IN DER PIPELINE
Cefiderocol

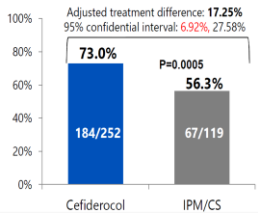
APEKS-cUTI Study Design



Primary Endpoint
Composite Outcome at TOC
(Clinical Response and Microbiological Response)



Secondary Endpoint
Microbiological Response at TOC



Safety Population	Cefiderocol (N = 300)	Imipenem/cilastatin (N = 148)	Total (N=448)
Subject with AEs	120 (40.0%)	74 (50.0%)	194 (43.3%)
Subjects with Drug-related AEs	26 (8.7%)	17 (11.5%)	43 (9.6%)
Subjects Discontinuing due to AEs	5 (1.7%)**	3 (2.0%)	8 (1.8%)
Subject with SAEs	14 (4.7%)	12 (8.1%)	26 (5.8%)
Subjects who died	1 (0.3%)*	0 (0%)	1 (0.2%)

*Death was not considered drug related by investigator
**(Cefiderocol) *C. diff*, Hypersensitivity (itching), Increased hepatic enzymes, diarrhea

Portsmouth, ECCMID 2017

BL & BLI IN DER PIPELINE
Cefiderocol

Pharmakokinetik bei gesunden Probanden

	1,000 mg 1st (n = 8)		2,000 mg (n = 8)	
PK parameter	Day 1	Day 10	Day 1	Day 10
C_{max} (μg/ml)	72.2 (12.0)	69.8 (13.3)	141 (22.7)	153 (12.9)
T_{max} (h)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.00 (1.00–1.25)	1.00 (1.00–1.25)
AUC_{0-8} (μg · h/ml)	165.5 (10.7)	NE	314.8 (14.9)	NE
AUC_{0-last} (μg · h/ml)	176.4 (11.0)	NE	337.2 (15.6)	NE
AUC_{0-inf} (μg · h/ml)	177.4 (10.9)	NE	338.5 (15.5)	NE
$AUC_{0-\tau}$ (μg · h/ml)	NE	160.5 (13.5)	NE	366.5 (14.0)
$t_{1/2,z}$ (h)	2.37 (11.4)	2.35 (18.5)	2.40 (13.2)	2.72 (21.6)
CL (liters/h)	5.64 (10.9)	6.23 (13.5)	5.91 (15.5)	5.46 (14.0)
MRT (h)	2.49 (12.1)	NE	2.53 (13.5)	NE
Feu[c] (%)	70.9 (6.7)	70.0 (6.1)	67.7 (4.7)	71.4 (5.3)
CL_R (liters/h)	4.02 (14.8)	4.36 (12.8)	4.02 (17.2)	3.89 (15.1)

- **primär renale Ausscheidung**

Salsho, Antimicrob Agents Chemother 2018

BL & BLI IN DER PIPELINE
BL/BLI-Kombinationen im Vergleich

		Ceftazidim/ Avibactam	Ceftolozan/ Tazobactam	Imipenem/ Relebactam	Meropenem/ Vaborbactam	Colistin	Cefiderocol (S-649266)
Pseudomonas aeruginosa	Pseudomonas aeruginosa, **Wildtyp**						
	Pseudomonas aeruginosa, **AmpC+**						
	Pseudomonas aeruginosa **Porinverlust** (oprD-loss)						
	Pseudomonas aeruginosa **Effluxpumpen**						
	Pseudomonas aeruginosa **Carbapenem-R (Carbapenemase-negativ)**						
	Pseudomonas aeruginosa, **MDR**						
	Pseudomonas aeruginosa, **XDR**						
	Pseudomonas aeruginosa, **MBL+**						
Enterobacteriaceae spp.	Enterobacteriaceae spp., **Wildtyp**						
	Enterobacteriaceae spp., **ESBL+**						
	Enterobacteriaceae spp., **OXA-48-like+**						
	Enterobacteriaceae spp., **KPC+**						
	Enterobacteriaceae spp., **Carbapenem-R (Carbapenemase-negativ)**						
	Enterobacteriaceae spp. **MBL+ (VIM, IMP, NDM)**						
Acinetobacter	Acinetobacter baumannii, **Wildtyp**						
	Acinetobacter baumannii, **Carbapenem-R**						
Stenotrophomonas	Stenotrophomonas maltophilia, **Wildtyp**						
	Stenotrophomonas maltophilia **Carbapenem-R**						

In-vitro-Aktivität >80% In-vitro-Aktivität 50–80% In-vitro-Aktivität <50% Keine Daten verfügbar

* Proteus spp., Neisseria spp., Serratia spp., Providencia spp., Burkholderia pseudomallei, Morganella morganii besitzen gegenüber Colistin eine natürliche Resistenz


Neue Kombinationen und was sie können

Thalhammer
Jatros Infektiologie 2017

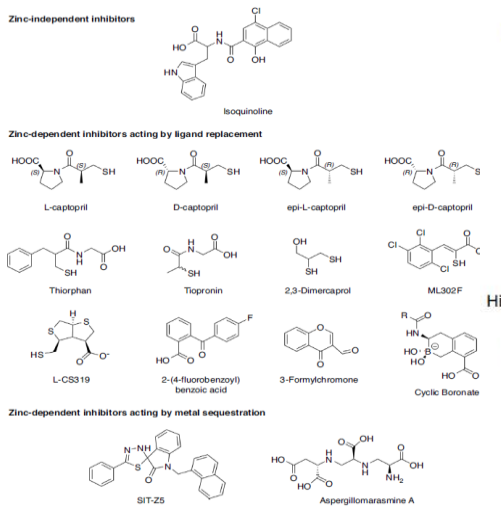
BL & BLI IN DER PIPELINE
Metallobetalaktamasehemmer

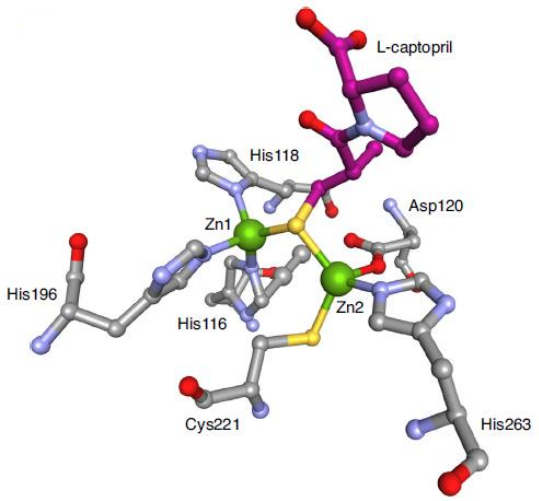
- **MBL hydrolysieren alle Betalaktame**
- **Monobactame werden nicht inaktiviert**

  ABER: Inaktivierung durch Serinbetalaktamasen, die mit MBL koproduziert werden
- **MBL sind Zink-abhängig**
  - **Zink-bindende MBL-Hemmer**
    - **D-Captopril**
  - **Hemmer der Zink-Chelatbildung**
    - **Aspergillomarasmin A (AMA)**
    - **NOTA & DOTA**

Docquier, Drug Res Update 2018

BL & BLI IN DER PIPELINE
Zink-abhängige MBL-Hemmer





Rotond, Curr Op Microbiol 2017

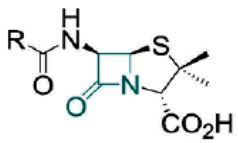
BL & BLI IN DER PIPELINE
Zinkchelator

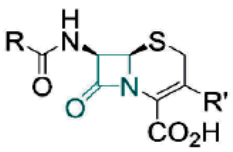
Antibiotic	EDDS (32 mg/L)	MIC (mg/L)
Piperacillin	–	>128
	+	2
Cefuroxime	–	>128
	+	4
Ceftazidime	–	>128
	+	2
Imipenem	–	128
	+	0.25
Meropenem	–	>128
	+	0.015
Gentamicin	–	0.5
	+	0.5

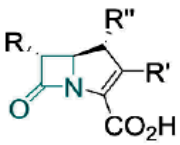
Clinical isolate	Imipenem MIC (mg/L) (fold change in MIC)	+EDDS
Serratia marcescens T2352 (NDM-1)	256	0.5 (**512**)
K. pneumoniae T2301 (NDM-1)	16	0.125 (**128**)
Enterobacter cloacae T2311 (NDM-1)	16	0.5 (**32**)
A. baumannii T2304 (NDM-1)	128	16 (**8**)
E. coli T2351 (NDM-5)	32	0.5 (**64**)
E. coli T2239 (NDM-7)	32	0.5 (**64**)
P. aeruginosa T2325 (IMP-1)	16	1 (**16**)
P. aeruginosa T1098 (IMP-7)	128	32 (**4**)
Acinetobacter genospecies 3 T2236 (SIM-1)	32	0.125 (**256**)
Citrobacter freundii T2354 (VIM-4)	4	1 (**4**)
E. cloacae T2353 (VIM-1)	8	1 (**8**)
P. aeruginosa T2357 (VIM-1)	256	8 (**32**)
E. coli T2228 (VIM-1)	8	0.5 (**16**)
K. pneumoniae T2216 (VIM-1)	8	0.125 (**64**)
P. aeruginosa T2217 (VIM-2)	128	16 (**8**)
P. aeruginosa T2282 (VIM-2)	512	8 (**64**)
P. aeruginosa T2283 (VIM-2)	16	0.5 (**32**)
P. aeruginosa T2229 (SPM-1)	512	16 (**32**)
E. cloacae T2218 (GIM-1)	2	0.5 (**4**)
E. coli T3261 (KPC-2)	8	8 (1)
C. freundii T2482 (KPC-3)	8	8 (1)
K. pneumoniae T2743 (KPC-9)	64	64 (1)
A. baumannii T3161 (OXA-23)	64	64 (1)
E. coli T3124 (OXA-48)	2	2 (1)

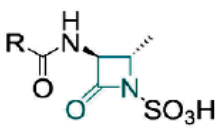
Proschak, J Antimicrob Chemother 2017

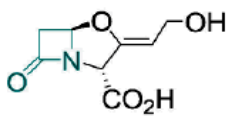
BL & BLI IN DER PIPELINE
Cyclobutanone

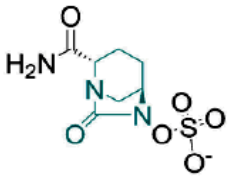

penicillin

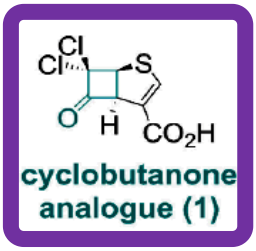

cephalosporin


carbapenem


monobactam


clavulanic acid

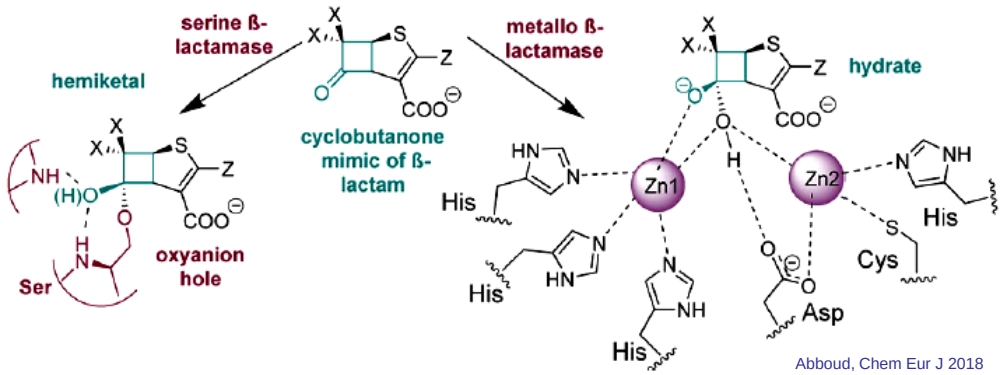

avibactam


cyclobutanone analogue (1)

Abboud, Chem Eur J 2018

BL & BLI IN DER PIPELINE
Cyclobutanone

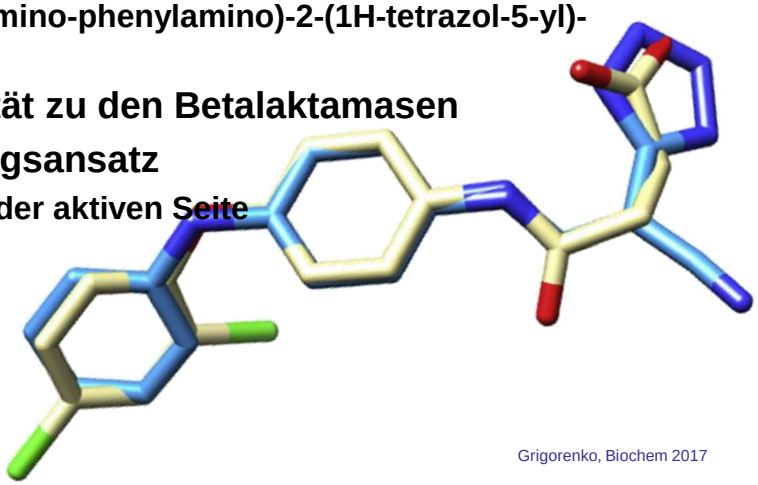
- Betalaktamanaloga
- Hemmung von SBLs und MBLs



Abboud, Chem Eur J 2018

BL & BLI IN DER PIPELINE
Phenoxyanilin

- nicht-BL-Betalaktamasehemmer
  - 3-(4-Phenylamino-phenylamino)-2-(1H-tetrazol-5-yl)-acrylonitrile
- höhere Affinität zu den Betalaktamasen
- neuer Bindungsansatz
  - Blockierung der aktiven Seite



Grigorenko, Biochem 2017

BL & BLI IN DER PIPELINE
Aktivität neuer Substanzen im Überblick

Klasse	Kategorie	relevante Enzyme	produzierende Spezies	BLA-Substrat, inaktive/aktive Substanzen
A	Serin-BLA, ESBL	TEM-3 ff, CTX-M-1 bis 165, SHV	Enterobacteriaceae, H. influenzae, N. gonorrhoeae	▪ Hydrolyse von Penizillinen, 1.–3.-(4.)-Generation-Cephalosporinen, Monobactame ▪ Inhibition durch Clavulanat, Avibactam, Relebactam, Vaborbactam, Zidebactam ▪ aktiv sind Carbapeneme, Temocillin, Cefiderocol
A	Serin-BLA, Carbapenemase	KPC, IMI, SME	insbesondere E. coli, K. pneumoniae	▪ mäßige Carbapenem-Hydrolyse ▪ Hemmung durch Boronsäure, Clavulanate ▪ aktiv sind Avibactam, Relebactam, Vaborbactam, Zidebactam, Cefiderocol
B	Metallo-β-Laktamase	NDM, VIM, IMP, GIM, SPM-1	A. baumannii, P. aeruginosa, Enterobacteriaceae	▪ starke Carbapenem-Hydrolyse ▪ aktiv sind Aztreonam und Cefiderocol ▪ Hemmung durch EDTA, Avibactam, Zidebactam ▪ keine Hemmung durch Clavulanate, Relebactam, Vaborbactam, Boronsäure,
C	Serin-BLA,	AmpC, ACC, FOX, LAT, MOX	variabel durch Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter (SPACE-bugs), E. cloacae	▪ Hydrolyse von 1.–3.-(4.)-Generation-Cephalosporinen inkl. Cephamycinen (Cefoxitin), Penizilline, Monobactame ▪ keine Hemmung durch Clavulanate, Tazobactam ▪ aktiv sind Boronsäure, Carbapeneme, Temocillin, Cefiderocol ▪ Hemmung durch Avibactam, Relebactam, Vaborbactam, Zidebactam, Nacubactam
D	Serin-BLA	OXA	Enterobacteriaceae, P. aeruginosa, A. baumannii	▪ Hydrolyse von Penizillinen, 1.–3.-Generation-Cephalosporinen ▪ aktiv sind Carbapeneme, Cephalosporine der Klasse III (falls keine Koproduktion von ESBLs), Aztreonam, Cefiderocol ▪ keine Hemmung durch Clavulanate, EDTA, Boronsäure, Vaborbactam; Hemmung durch Tazobactam, Zidebactam ▪ mäßige Hemmung durch Avibactam, (Relebactam?)

Dalhoff, KHHyg up2date 2017

BL & BLI IN DER PIPELINE
Zusammenfassung

- **PK-PD-Effizienzdeterminante**
  - T>MHK oder AUC:MHK
  - Unterschiede bei ein und demselben BLI
- **BL/BLI-Expositionsdosierung**
  - Hemmung der Resistenzentwicklung
- **PK-PD-Limitationen**
  - $KPC3_{bla}$: Ceftazidim/Avibactam und Ceftarolin/Avibactam

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

	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	–	–	–
Class B						
MBL	–	–	–	–	–	–
Class C						
AmpC	+	+	+	–	±	–
Class D						
OXA	±	–	±	–	–	–

Ambrose, Curr Opin Pharmacol 2017 – Basarab, 7th FIDSSA Conference 2017

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