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Antibiotics and non-antibiotics to treat MDR microorganisms

New antibiotics in the pipeline against multidrug resistant Gram-negatives

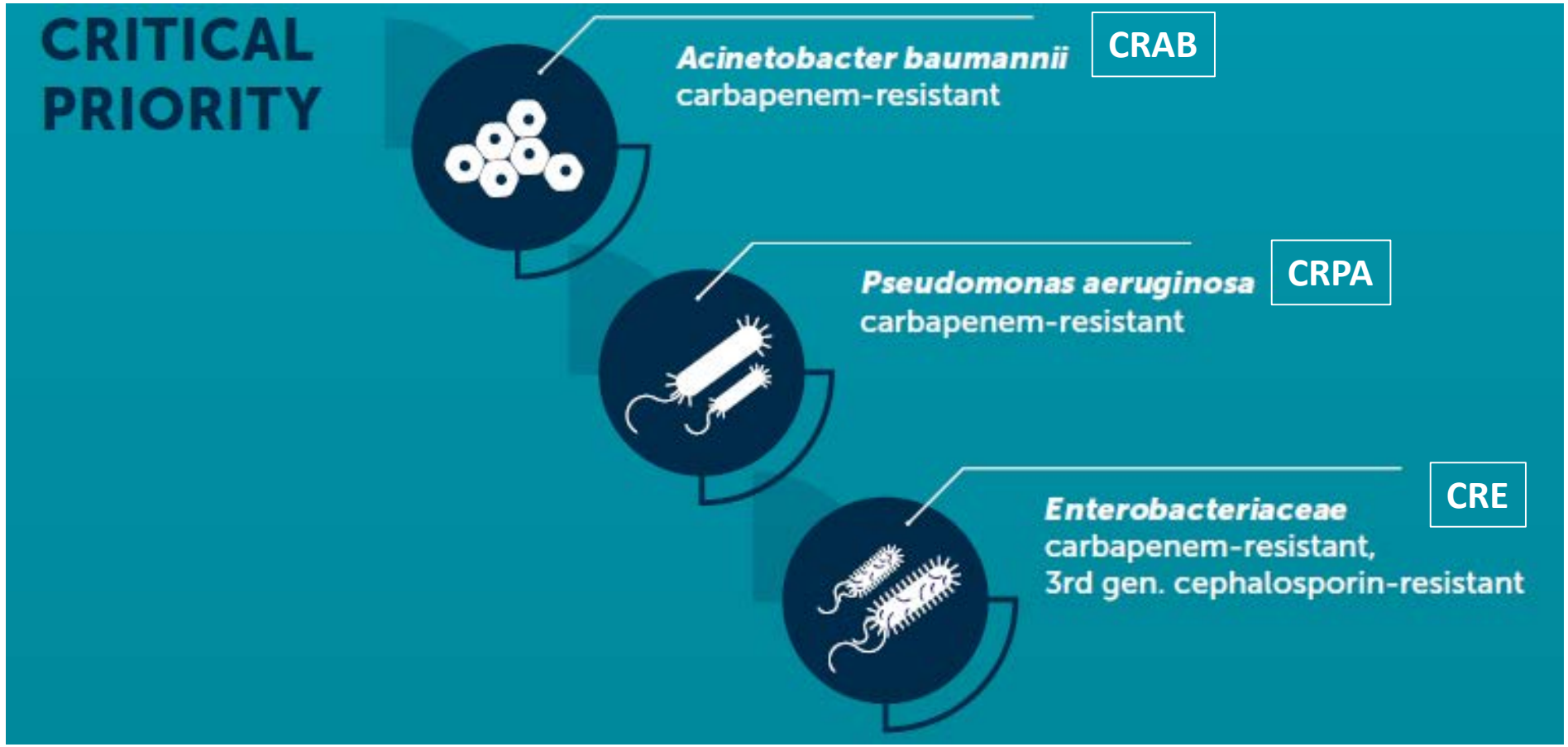
Disclosures

Ongoing research projects financed by the *Region Wallonne* with Eumedica as industrial partner

Collaborations with industrial partners over the last 5 years but for molecules active against Gram-positive organisms

The WHO database…..

Products against critical priority pathogens



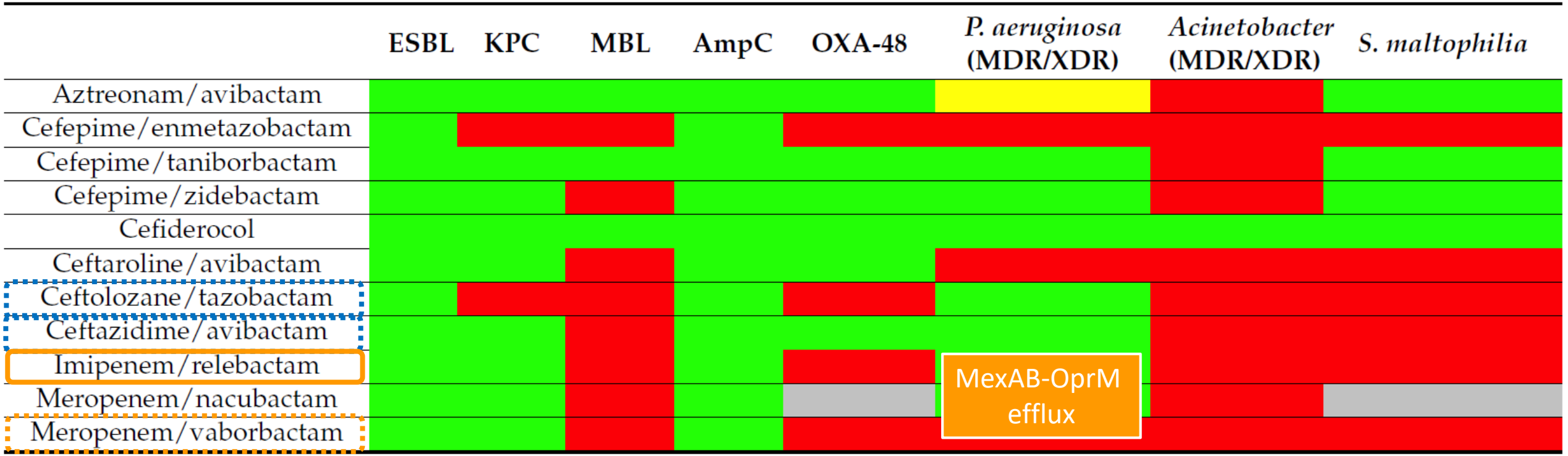
Registered / marketed drugs

Antibacterial agents that gained market authorization between 1 July 2017 and 1 November 2021

Name (trade name USA/ EU)	Market authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Indication/s	WHO EML & AWaRe classification	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Vaborbactam + meropenem (Vabomere / Vaborem)	Melinta Therapeutics (USA) (Menarini, EU)	US FDA (8/2017) EMA (11/2018)	Boronate BLI + β-lactam (carbapenem)	iv	cUTI, (cUTI, cIAI, HAP/VAP in EU)	WHO EML: yes AWaRe: Reserve	○	○	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen (Cipla USA/ QiLu Antibiotics, China)	US FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML: yes AWaRe: Reserve	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	US FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	WHO EML: no AWaRe: Reserve	?	○	●	/	-	-	-	-
Relebactam + imipenem / cilastatin (Recarbrio)	Merck Sharp & Dohme	US FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP) EMA (2/2020 G-ve)	O-BLI + β-lactam (carbapenem) / degradation inhibitor	iv	cUTI, cIAI, HAP/VAP	WHO EML: no AWaRe: Reserve	○	?	●[1]	/	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	US FDA (11/2019 cUTI, 9/21 HAP/ VAP) EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HAP/VAP, aerobic G-ve[5]	WHO EML: yes AWaRe: Reserve	●	●	●	/	?	-	-	-

https://www.who.int/publications/i/item/9789240047655

Beta-lactams + BLIs



Green = antimicrobial activity, red = no antimicrobial activity, yellow = partial antimicrobial activity, grey = not available. ESBL = extended-spectrum β-lactamase, Ambler Class A β-lactamases; KPC = *Klebsiella pneumoniae* carbapenemase, Ambler Class A β-lactamases; MBL = metallo-β-lactamases, Ambler Class B β-lactamases; AmpC = cephalosporinase, Ambler Class C β-lactamases; OXA-48 = oxicillinase-48, Ambler Class D β-lactamases; MDR = multidrug resistant; XDR = extended drug resistant.

Small differences for specific beta-lactamases → selection based on lab recommendations

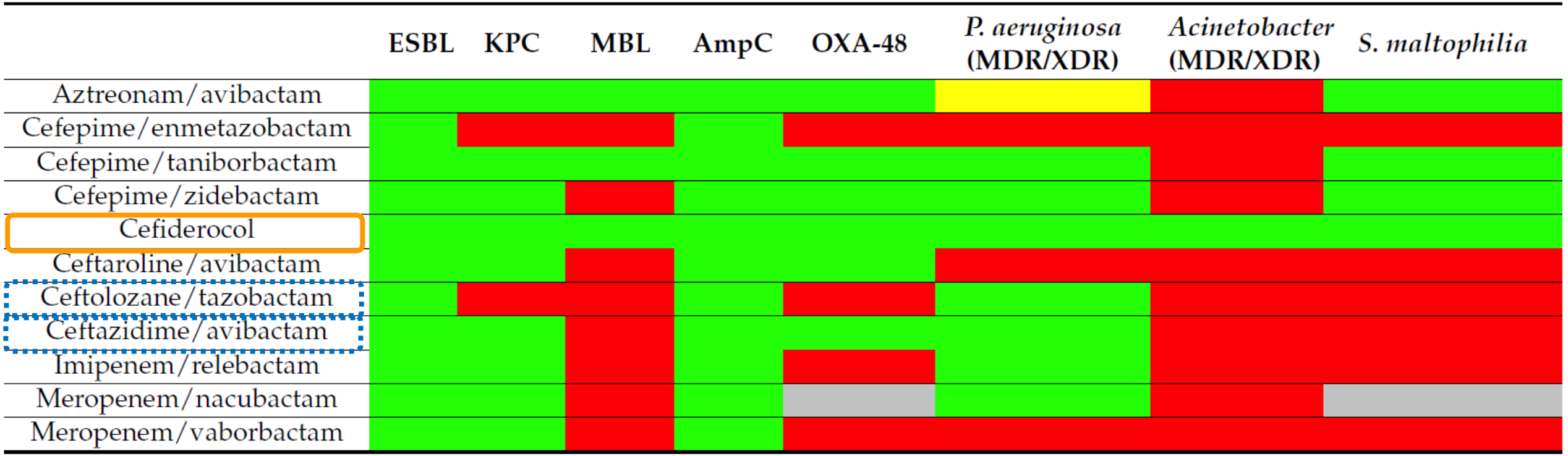
Principe et al., Pharmaceuticals 2022; 15:463

Beta-lactams + BLIs: indications

	cIAI	cUTI	HAP	VAP	Dosing regimen
Ceftazidime/ avibactam	■	■	■	■	2g+0.5g q8h over 2h
Ceftolozane/ tazobactam	■	■	■	■	1g+0.5g q8h over 1h
Meropenem/ vaborbactam		■			2g+28 q8h over 3h
Imipenem-cilas./ relebactam			■	■	0.5g+0.5g+0.25g q6h over 30min

SmPC data

Beta-lactams + BLIs



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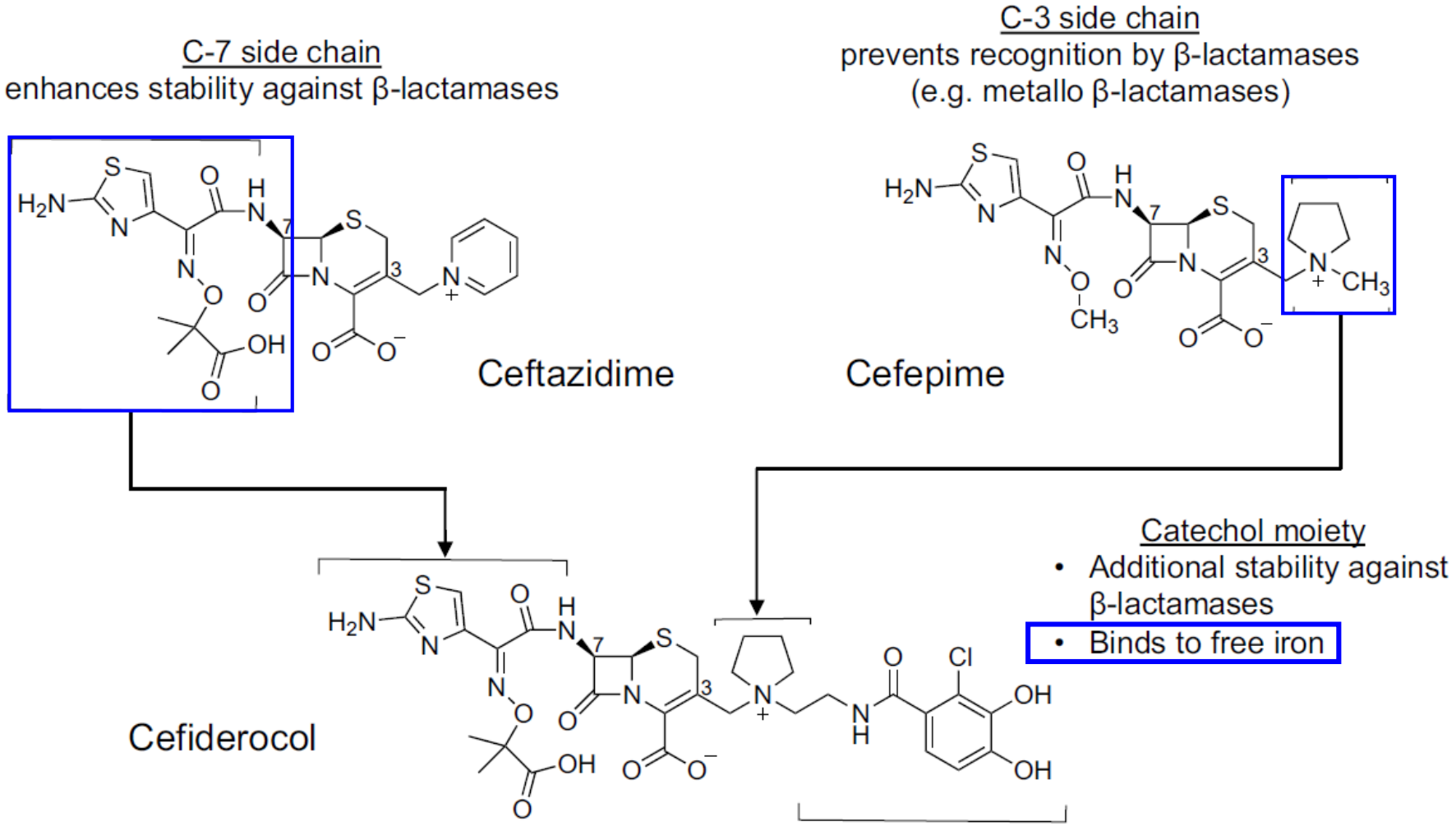
Principe et al., Pharmaceuticals 2022; 15:463

Cefiderocol

First siderophore cephalosporine



Zhanel et al., Drugs. 2019;79(3):271-289.

Cefiderocol

First siderophore cephalosporine

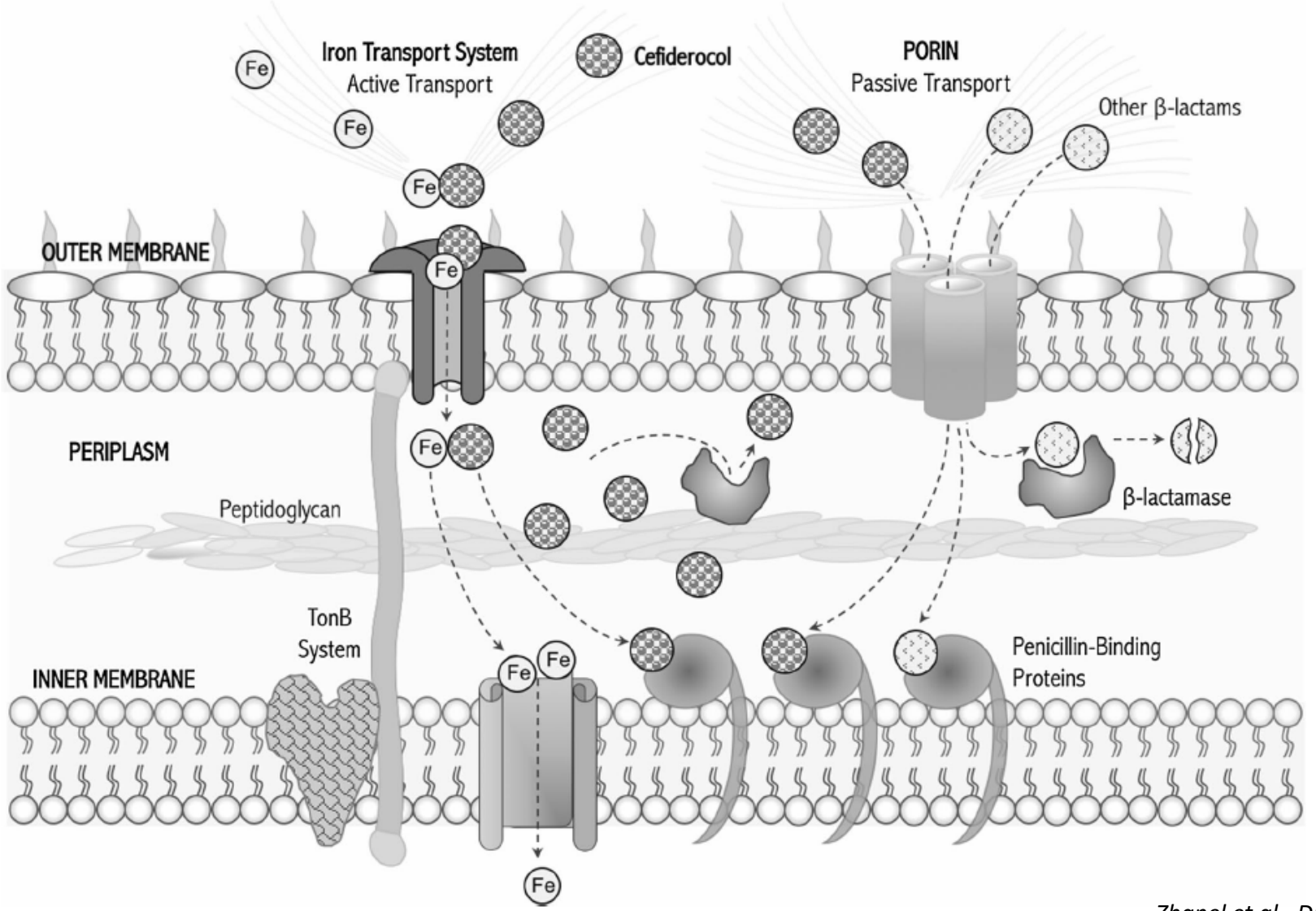


Fig. 3 Mechanism of action of cefiderocol against Gram-negative bacilli

Zhanel et al., Drugs. 2019;79(3):271-289.

Cefiderocol – in vitro activity

Table 1 In vitro activity (MIC, mg/L) of cefiderocol, ceftazidime-avibactam and meropenem against Gram-negative aerobes Adapted from references [7, 8, 11, 32–44]

Gram-negative aerobes	Cefiderocol			Ceftazidime-avibactam		Meropenem	
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Acinetobacter baumannii (all)	0.12	1	≤ 0.002 to 64	16	> 64	32	> 64
Meropenem non-susceptible[a]	0.25	1	≤ 0.002 to 64	32	> 64	64	> 64
Multidrug-resistant[b]	0.25	8	0.015 to > 256	32	> 64	64	> 64
Burkholderia cepacia	0.008	0.016	0.002 to 0.016	NA	NA	4	8
Citrobacter freundii	0.06	0.25	≤ 0.002 to 1	0.12	0.5	≤ 0.06	≤ 0.06
Citrobacter koseri	0.25	0.5	0.06 to 2	0.12	0.12	≤ 0.06	≤ 0.06
Enterobacter asburiae	0.25	1	≤ 0.06 to 0.5	0.25	0.5	≤ 0.06	0.12
Enterobacter cloacae	0.25	1	≤ 0.03 to 64	0.25	1	≤ 0.06	0.125
Enterobacteriales (all)	0.12	1	≤ 0.002 to 8	0.12	0.5	≤ 0.06	0.12
Meropenem non-susceptible[c]	1	4	0.008 to 32	1	> 64	16	> 64
KPC-producers	1	4	0.004 to 32	1	4	32	> 64
Escherichia coli	0.06	0.5	≤ 0.002 to 4	0.12	0.25	≤ 0.06	≤ 0.06
Klebsiella aerogenes	0.12	0.5	≤ 0.004 to 8	0.25	0.5	≤ 0.06	0.12
Klebsiella oxytoca	0.06	0.25	≤ 0.002 to 2	0.12	0.25	≤ 0.06	≤ 0.06
Klebsiella pneumoniae (all)	0.12	2	≤ 0.06 to 8	0.25	1	≤ 0.06	8
Ceftazidime-avibactam non-susceptible[d]	2	4	0.25 to 16	64	64	32	64
Meropenem non-susceptible[a]	1	4	≤ 0.03 to 8	8	64	8	32
KPC-producers	1	2	0.03 to 64	2	4	> 16	> 16
Pseudomonas aeruginosa (all)	0.06	0.5	≤ 0.002 to 8	2	8	0.5	8
Multidrug-resistant	0.25	1	≤ 0.002 to 32	32	> 64	32	> 64
Ceftazidime-avibactam non-susceptible[e]	0.12	1	≤ 0.002 to 4	16	64	16	64
Ceftolozane-tazobactam non-susceptible[f]	0.25	4	0.004 to 8	8	64	16	32
Meropenem non-susceptible[a]	0.25	1	0.008 to 4	8	64	8	16
Serratia liquefaciens	0.06	0.12	0.015 to 0.25	0.25	0.5	≤ 0.06	0.12
Serratia marcescens	≤ 0.06	0.5	≤ 0.002 to > 64	0.12	0.5	≤ 0.06	0.12
Stenotrophomonas maltophilia	0.06	0.5	≤ 0.002 to 4	16	64	> 64	> 64
Ciprofloxacin non-susceptible[g]	0.06	0.5	0.002 to 2	NA	NA	NA	NA
Colistin non-susceptible[h]	0.12	0.5	0.002 to 2	NA	NA	NA	NA

Very broad spectrum, but still some bugs do escape !

Zhanel et al., Drugs. 2019;79(3):271-289.

Cefiderocol – clinical indications

EU SmPC: treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options

WARNINGS:

Limitations of the clinical data

In clinical trials, cefiderocol has only been used to treat patients with the following types of infection: complicated urinary tract infections (**cUTI**); hospital-acquired pneumonia (**HAP**), ventilator-associated pneumonia (**VAP**), healthcare-associated pneumonia (**HCAP**); sepsis and patients with **bacteraemia**.

The use of cefiderocol to treat patients with infections due to Gram-negative aerobic pathogens who have limited treatment options is based on PK/PD analyses and on limited clinical data (randomized clinical trial with 80 patients treated with cefiderocol and 38 patients treated with best available therapy for infections caused by carbapenem-R organisms.

All-cause mortality in patients with infections due to **carbapenem-resistant Gram-negative bacteria**

A higher all-cause mortality rate was observed in patients treated with cefiderocol as compared to best available therapy (BAT) in a randomised, open-label trial in critically-ill patients with infections known or suspected to be due to carbapenem-resistant Gram-negative bacteria. The **higher day 28 all-cause mortality rate** with cefiderocol occurred in patients treated for nosocomial pneumonia, bacteraemia and/or sepsis [25/101 (24.8%) vs. 9/49 (18.4%) with BAT]. The cause of the increase in mortality has not been established.

Cefiderocol – reasons for failures in the CREDIBLE-CR trial

Table 5. 4-Fold MIC Increases in the Cefiderocol Group, CREDIBLE-CR Trial

Subject ID/Diagnosis	Pathogen	MIC (mcg/mL) at Baseline	MIC (mcg/mL)/Study Day	Outcome by TOC	Day of Death
1/VABP	*A. baumannii*	0.25	1.0 (day 3)	Death	9
2/VABP	*A. baumannii*[a]	1.0	8 (day 10)	Death	13
3/VABP	*S. maltophilia*[a]	0.06	0.25 (day 8)	Death	8
4/HABP	*A. baumannii*[a]	1.0	4.0 (day 11)	Death	13
	P. aeruginosa	0.25	2.0 (day 11)[c]		
5/VABP	*S. maltophilia*	0.06	0.25 (day 14)	Death	15
6/Sepsis	*A. baumannii*	2	>64 (day 16)	Cure	27
7/VABP	*A. baumannii*	0.25	4.0 (day 14)	Failure[b]	39
8/VABP	*A. baumannii*[a]	1.0	8.0 (day 15)	Failure[b]	45
9/HABP	*K. pneumoniae*[a]	0.25	2 (day 23)	Failure[b]	31
10/VABP	*P. aeruginosa*[a]	0.5	2.0 (day 16)[c]	Failure[b]	Survived
11/BSI	*E. coli*[a]	0.5	2 (day 11)	Failure[b]	Survived
12/cUTI	*K. pneumoniae*	0.12	0.5 (day 17)	Cure	Survived
13/cUTI	*P. aeruginosa*	0.12	2.0 (day 22)[c]	Cure	Survived
14/VABP	*A. baumannii*	0.06	1.0 (day 3)	Cure	Survived
15/VABP	*K. pneumoniae*[a]	0.06	0.5 (day 8)	Cure	Survived

Table 4. Characteristics of Patients Who Died due to Treatment Failure, CREDIBLE-CR Trial

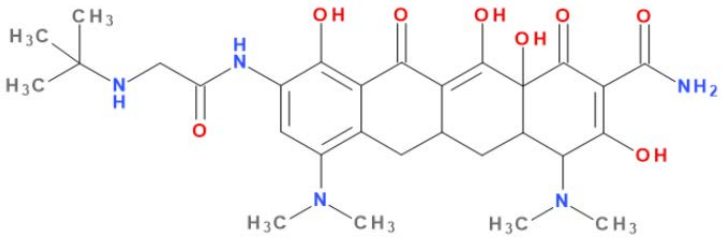
Parameter	Cefiderocol (N = 101) n (%)	BAT (N = 49) n (%)
Failure of study drug treatment	16 (15.8)	4 (8.2)
Timing of death		
<Day 15	11 (10.9)	1 (2.1)
Day 15–30	3 (3.0)	3 (6.1)
≥Day 30	2 (2.0)	0
Baseline pathogen		
A. baumannii or A. nosocomialis	9 (8.9)	1 (2.1)
Mixed (≥2 pathogens)	4 (4.0)[a]	0
P. aeruginosa	0	1 (2.1)
S. maltophilia	1 (1.0)	0
Enterobacteriaceae (K. pneumoniae or E. cloacae)	2 (2.0)	2 (4.1)
APACHE II score group		
≥16	11 (10.9)	3 (6.1)
≤15	5 (5.0)	1 (2.1)
Mean	19	19
Baseline clinical diagnosis group		
HABP/VABP	13 (12.9)	2 (4.1)
BSI	2 (2.0)	2 (4.1)
cUTI	1 (1.0)	0

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BAT, best available therapy; BSI, bloodstream infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

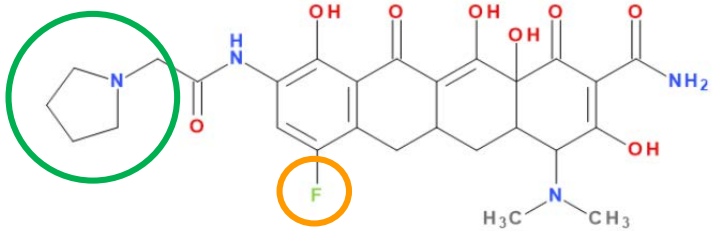
[a]Mixed: (1) *A. baumannii* and *S. maltophilia*; (2) *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*; (3) *A. baumannii*, *E. coli*, *K. pneumoniae*; (4) *A. baumannii*, *P. aeruginosa*.

Naseer et al., Clin Infect Dis. 2021;72(12):e1103-e1111

Eravacycline

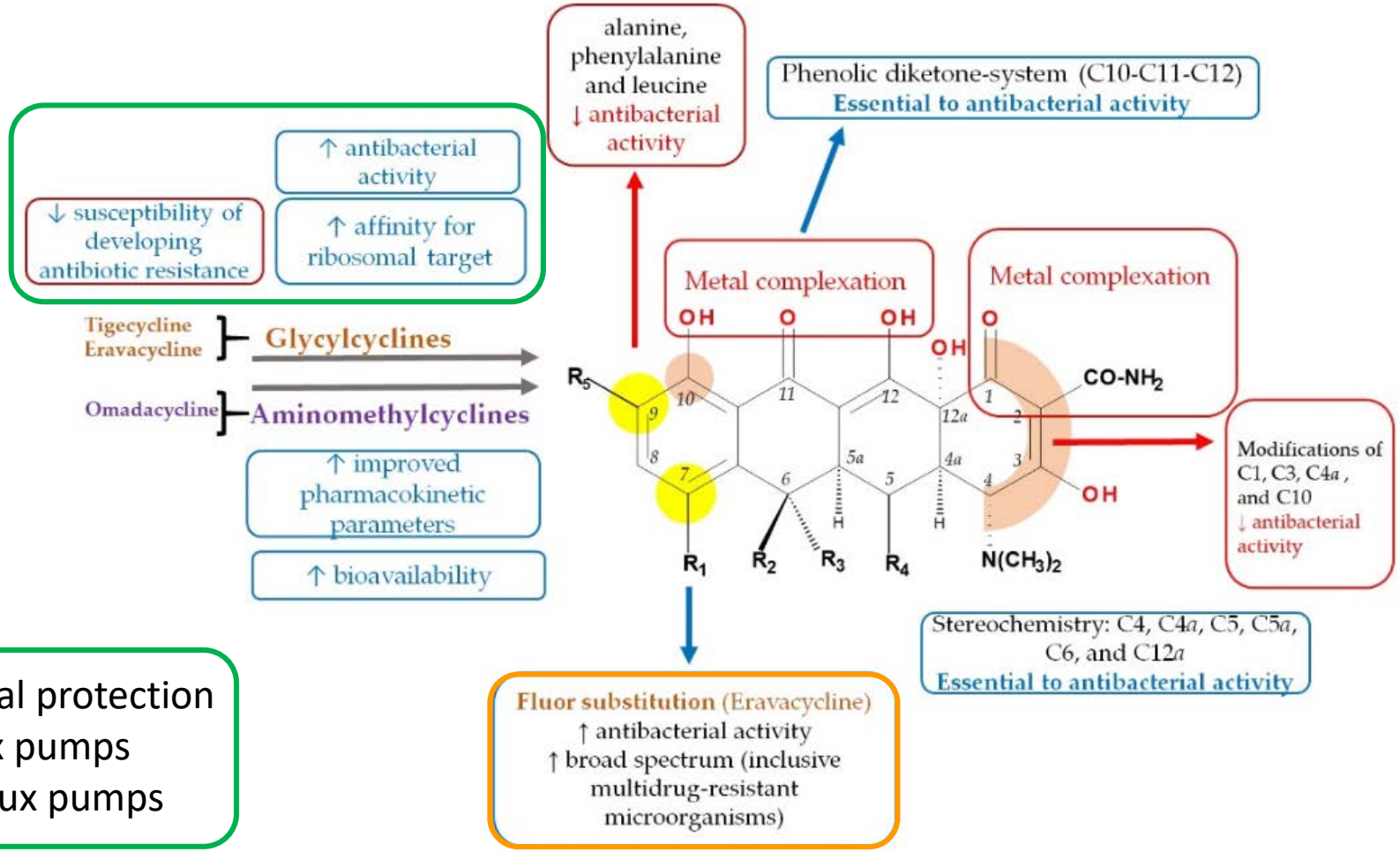


Tigecycline



Eravacycline

- ✓ Ribosomal protection
- ✓ Tet efflux pumps
- ✗ MDR efflux pumps



Rusu & Buta, Pharmaceutics 2021; 13:2085

Eravacycline - in vitro activity

In vitro activity of eravacycline and comparator agents against MDR *Enterobacteriaceae*, individual genera/species of *Enterobacterales*, and *A. baumannii*, cumulative 2013 to 2017 data

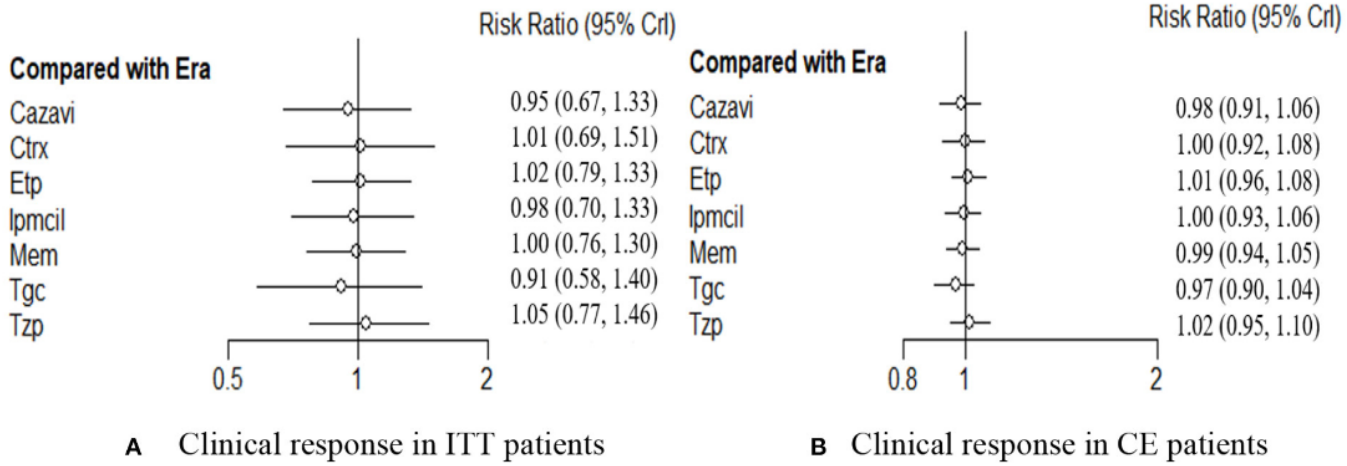
		CLSI criteria					EUCAST criteria				
			MIC (μg/ml)					MIC (μg/ml)			
Organism	Antimicrobial agent	No. of Isolates	50%	90%	Range	% susceptible	No. of Isolates	50%	90%	Range	% susceptible
All *Enterobacteriaceae*	Eravacycline	2,051	0.25	1	0.03 to 16	80.5[a]	2,186	0.25	1	0.06 to 16	82.0[b]
	Amikacin	1,656	2	8	≤0.25 to >64	96.0	1,614	2	8	≤0.25 to >64	92.5
	Aztreonam	2,051	>16	>16	≤0.5 to >16	18.4	2,186	>16	>16	≤0.03 to >16	6.2
	Cefepime	2,051	4	>16	≤0.25 to >16	42.1	2,186	4	>16	0.015 to >16	35.3
	Cefotaxime	1,656	>64	>64	≤0.015 to >64	17.5	1,614	>64	>64	≤0.015 to >64	8.1
	Ceftazidime	2,051	>16	>16	≤0.5 to >16	24.3	2,186	32	>16	≤0.03 to >16	9.0
	Ceftriaxone	2,051	>4	>4	≤0.5 to >4	14.7	2,186	>4	>4	≤0.015 to >4	6.0
	Colistin	2,051	0.5	1	≤0.12 to >4	NA[c]	2,186	0.5	1	≤0.12 to >4	98.7
	Ertapenem	1,656	0.12	>2	0.004 to >2	75.7	1,614	0.25	>2	0.004 to >2	73.9
	Gentamicin	2,051	1	>8	≤0.25 to >8	58.6	2,186	1	>8	≤0.12 to >8	62.1
	Imipenem	395	0.5	8	≤0.25 to >8	76.0	572	0.5	2	≤0.25 to >8	90.4
	Levofloxacin	2,051	4	>4	≤0.25 to >4	34.8	2,186	2	>8	0.008 to >4	43.4
	Meropenem	1,656	0.06	1	≤0.004 to >4	90.7	1,614	0.06	1	≤0.004 to >4	91.6
	Minocycline	1,112	4	>16	≤0.12 to >16	58.0	1,166	4	>16	≤0.12 to >16	NA
	Piperacillin-tazobactam	2,051	32	>64	≤0.5 to >64	44.2	2,186	64	>64	≤0.25 to >64	25.2
	Tetracycline	2,051	>8	>8	≤0.25 to >8	40.1	2,186	4	>8	≤0.25 to >8	NA
	Tigecycline	2,051	1	2	0.06 to 16	92.0[a]	2,186	0.5	2	0.06 to 16	51.7[b]
	Trimethoprim-sulfamethoxazole	1,656	>4	>4	≤0.06 to >4	37.6	1,614	>4	>4	≤0.06 to >4	45.9

FDA breakpoints for eravacycline (S ≤ 0.5 μg/mL) and tigecycline (S ≤ 2 μg/mL)
EUCAST breakpoints eravacycline (S ≤ 0.5 μg/mL) and tigecycline (S ≤ 0.5 μg/mL)

Morissey et al., Antimicrob Agents Chemother 2020; 64:e01699-19

Eravacycline in the clinics

Meta-analysis - cIAI



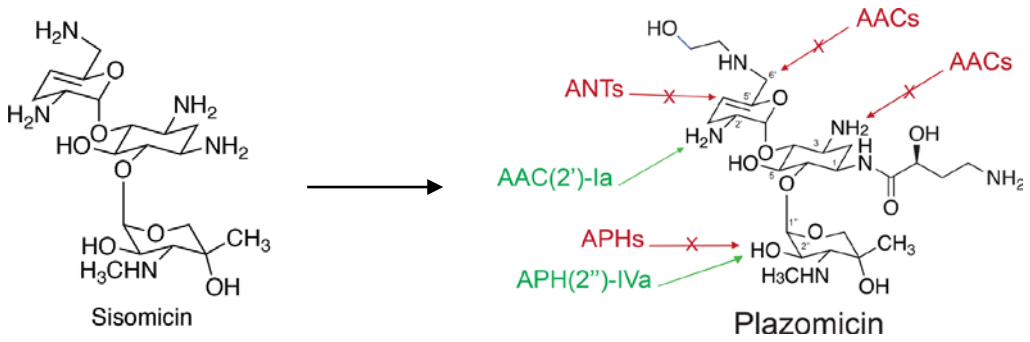
Current indications (iv/po):
complicated intra-abdominal infections (cIAI) in adults

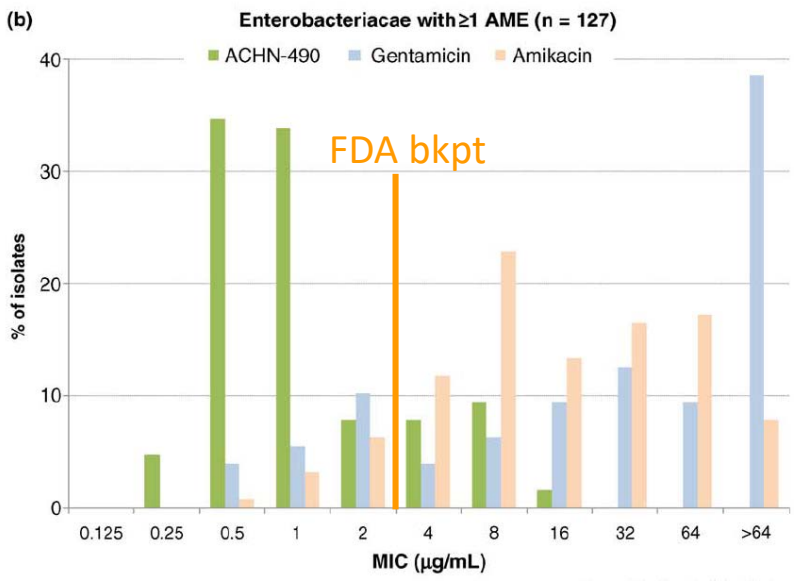
In clinical trials, there were no immunocompromised patients, and the majority of patients (80%) had APACHE II scores <10 at baseline; 5.4% of the patients had concurrent bacteraemia at baseline; 34% of the patients had complicated appendicitis

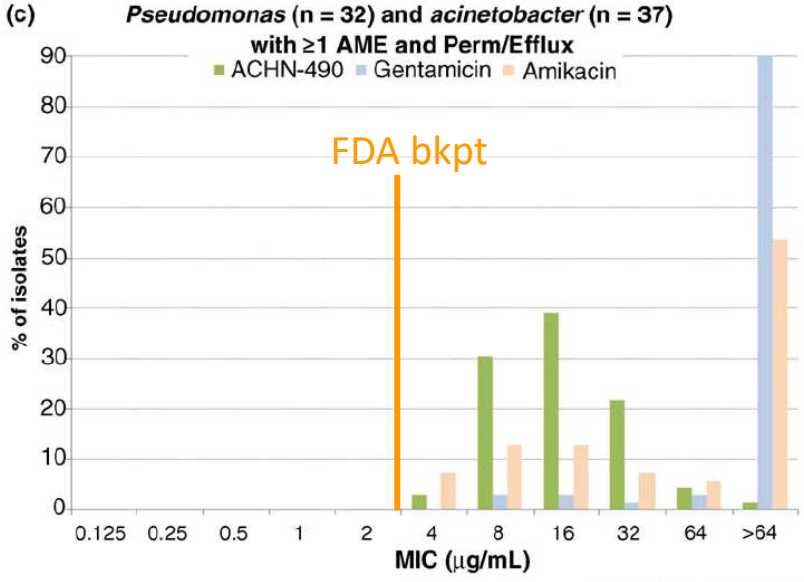
Meng et al., Front Med. 2022; 9:935343

Plazomicin

Aminoglycoside protected against most inactivating enzymes, but still inactive if
- ribosome methylation
- efflux (*Pseudomonas, Acinetobacter*)





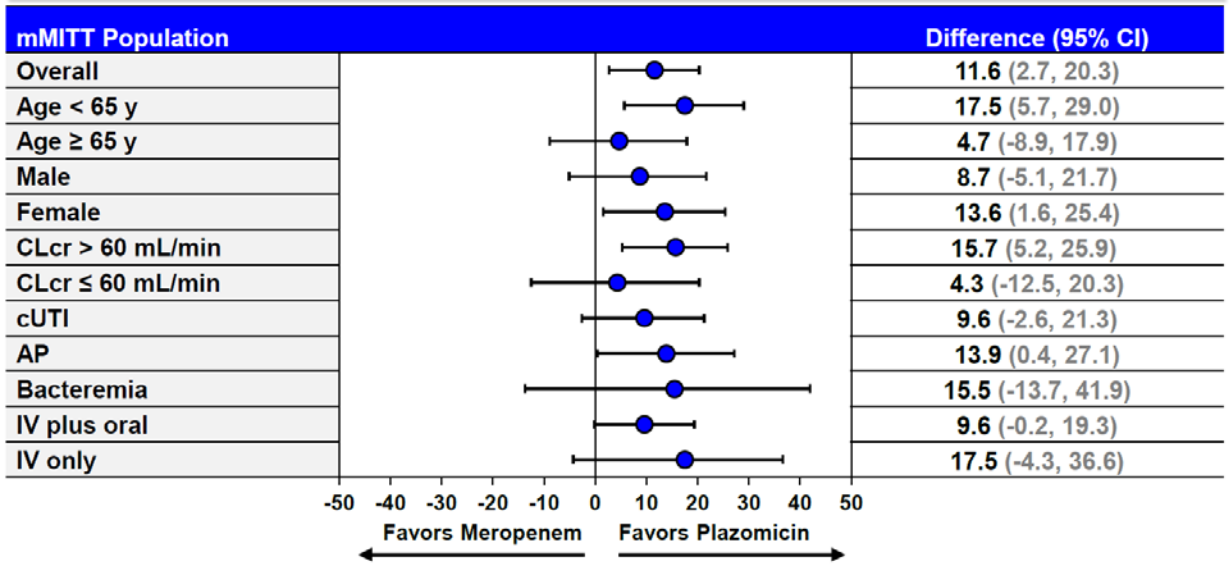


Cox et al., ACS Infect. Dis. 2018; 4:980−987;

Armstrong & Miller, Curr Op Microbiol 2010;13:565–573

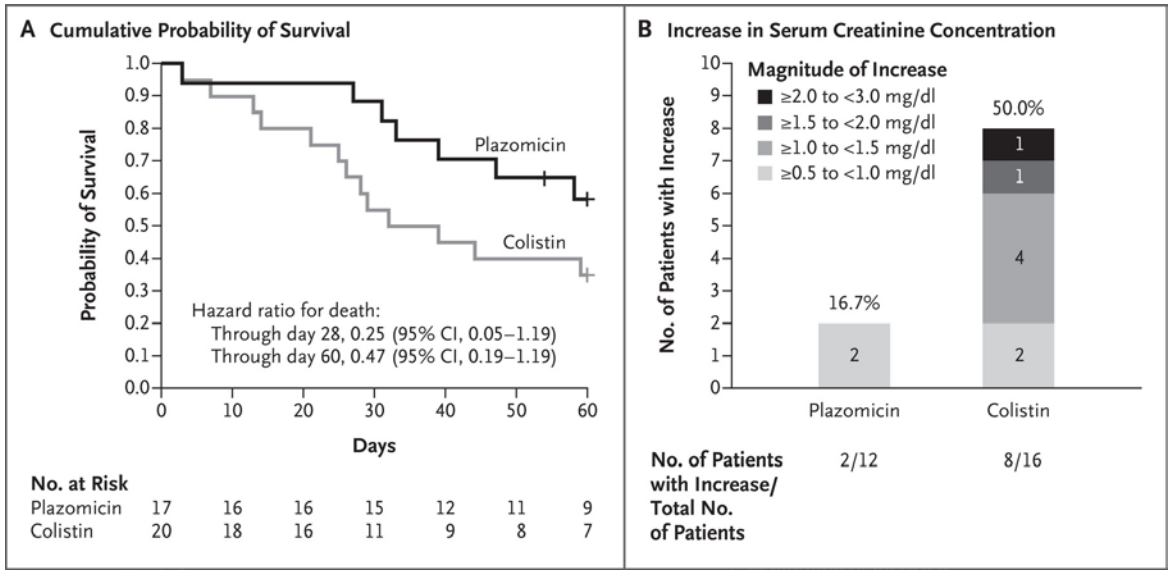
Plazomicin in the clinics

Complicated UTIs



Baseline Pathogen	Plazomicin N=191 n/N1	Plazomicin N=191 %	Meropenem N=197 n/N1	Meropenem N=197 %	Difference Plazomicin – Meropenem (95% CI)
Enterobacteriaceae	177/198	89%	157/208	76%	**13.9** (6.2, 21.5)
ESBL-producing	42/51	82%	45/60	75%	**7.4** (-9.6, 23.1)
Aminoglycoside-nonsusceptible	41/52	79%	35/51	69%	**10.2** (-8.1, 27.8)
Escherichia coli	120/128	94%	106/142	75%	**19.1** (10.0, 27.9)
Klebsiella pneumoniae	27/33	82%	32/43	74%	**7.4** (-13.9, 26.5)
Proteus mirabilis	9/11	82%	4/7	57%	**24.7** (-21.4, 64.5)
Enterobacter cloacae	13/16	81%	3/3	100%	**-18.8** (-46.3, 51.6)

A pathogen-focused trial (CRE)



Current indications:
patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s):
Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and *Enterobacter cloacae.*

Achaogen; FDA slides 2018 – Wagenlehner et al., N Engl J Med. 2019;380(8):729-740.

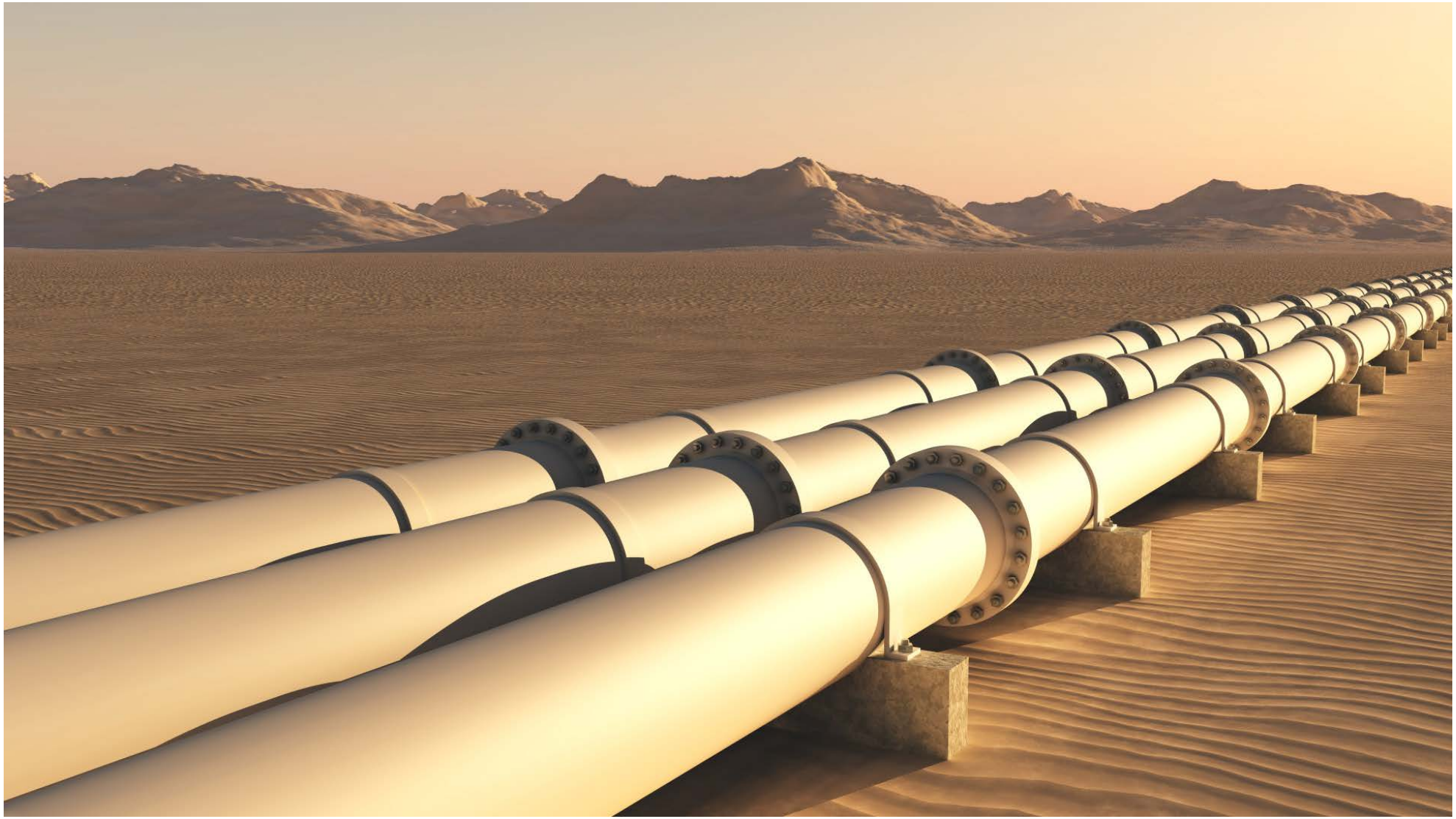
Pipeline of products in clinical development

Expected activity against priority pathogens

Active?	Critical priority pathogens					Other priority pathogens								
	Acinetobac baumannii	Pseudomor aeruginosa	Enteroba..	All critical priority pathogens	Subtotal	Gram-positive priority p..	Neisseria gonnorhoe	Helicobact pylori	Staphyloco aureus	Enterococc faecium	Streptococ pneumonia	Campyloba spp.	Subtotal	Total
Yes	9	13	18	6	30	18	4	3	17	4	7	2	23	46
Possibly	14	14	9	3	17	1	1	2	1	1		1	3	20
No	3	5	3	15	16	3	6	7	3	7	6	7	9	18

https://www.who.int/publications/i/item/9789240047655

The streamline: β-lactams (+β-lactamase inhibitors)



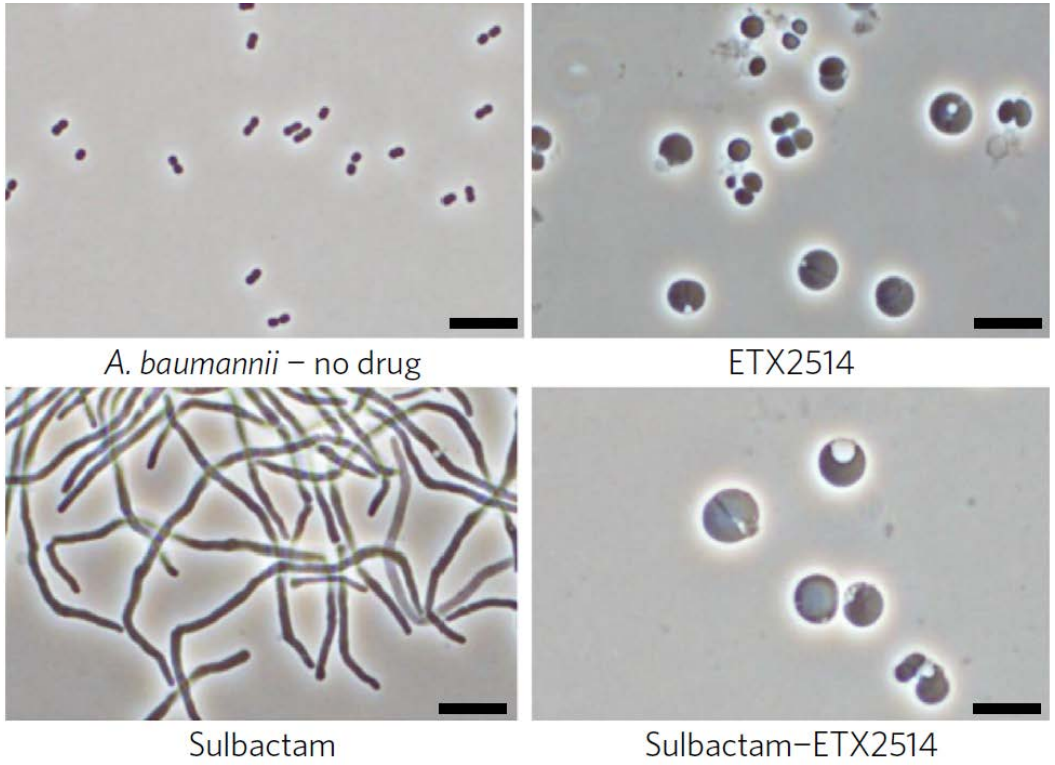
Pipeline of products in clinical development (phase III)

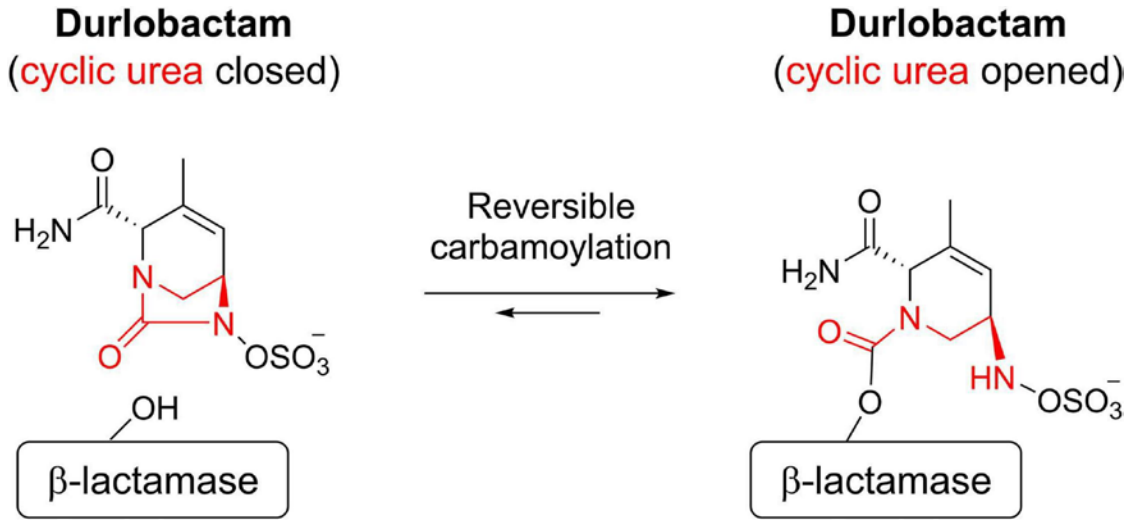
INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/ PBP1,3 binder	iv	Entasis Therapeutics	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate BLI + β-lactam (cephalosporin)	iv	VenatoRx Pharmaceuticals / GARDP	○	●	●	/	?	✓	-	-

DBO: Diazabicyclooctane β-lactamase Inhibitor
CRAB: carbapenem-resistant *A. baumannii*; CRPA: carbapenem resistant *P. aeruginosa*; CRE: carbapenem-resistant Enterobacterales
NCR: no cross-resistance; CC: chemical class; T: new target; MOA: new mode of action

DBO-BLI + PBP binders

Durlobactam=
Diazabicyclooctane (DBO) β-lactamase Inhibitor (BLI) also binds to PBP2 → rod-like shape
Sulbactam:
Intrinsic activity on CRAB by binding to PBP1-3 → elongated shape





Shapiro et al., Front Microbiol 2021;12:709974
Durand-Réville et al., Nat Microbiol 2017;2:17104

ETX-2514 (durlobactam)+sulbactam – clinical trials

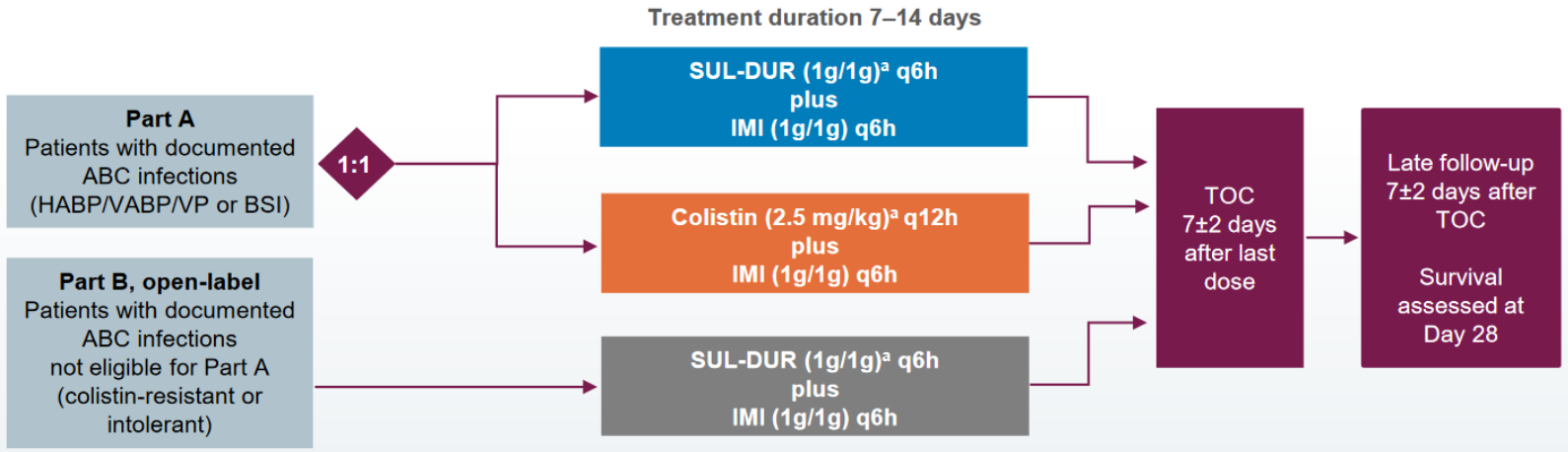
NIH U.S. National Library of Medicine
ClinicalTrials.gov

Status	Study Title	Conditions	Interventions	Locations
Completed	Study to Determine and Compare Plasma and Intrapulmonary Concentrations of **ETX2514** and Sulbactam in Healthy Subjects	• Healthy	• Drug: **ETX2514** and sulbactam	• Pulmonary Associates, PA Phoenix, Arizona, United States
Completed	Study to Determine the Excretion and Metabolism of 14C-**ETX2514** Administered Intravenously in Healthy Male Subjects	• Acinetobacter Baumannii-calcoaceticus Complex Infections	• Drug: **ETX2514** • Drug: 14C-**ETX2514**	• Pharmaron Clinical Pharmacology Center Baltimore, Maryland, United States
Completed Has Results	Evaluation of Safety and Efficacy of Intravenous Sulbactam-**ETX2514** in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections	• Complicated Urinary Tract Infection • Acute Pyelonephritis	• Drug: Sulbactam-**ETX2514** • Drug: Placebo • Drug: Imipenem-cilastatin	• Universeity Multiprofile Hospital for Active Teatment Sofia, Bulgaria • University Multiprofile Hospital for Active Teatment-Clinic of Nephrology Sofia, Bulgaria • Multiprofile Hospital for Active Teatment (MHAT) and Emergency Medicine - Pirogov Sofia, Bulgaria • Multiprofile Hospital for Active Teatment (MHAT) and Emergency Medicine - Doverie Sofia, Bulgaria
Completed	Evaluation of the Pharmacokinetics, Safety, and Tolerability of Intravenous **ETX2514** and Sulbactam Administered Concurrently to Subjects With Various Degrees of Renal Impairment and Healthy Matched Control Subjects	• Acinetobacter Baumannii Infection	• Drug: **ETX2514**SUL	• DaVita Clinical Research Lakewood, Colorado, United States • University of Miami, Division of Clinical Pharmacology Miami, Florida, United States • Davita Clinical Research Minneapolis, Minnesota, United States
Completed	Study Evaluating the Effect of **ETX2514** on Cardiac Repolarization in Healthy Male or Female Volunteers	• Acinetobacter Baumannii-calcoaceticus Complex Infections	• Drug: **ETX2514** • Drug: Placebo • Drug: moxifloxacin	• Pharmaron Clinical Pharmacology Center Baltimore, Maryland, United States
Completed	Evaluation of the Safety, Tolerability and Pharmacokinetics of Intravenous **ETX2514** Administered in Healthy Subjects	• Acinetobacter Baumannii Infection	• Drug: **ETX2514** • Drug: Placebo • Drug: Sulbactam • Drug: Imipenem/Cilastatin	• Melbourne, Victoria, Australia
Completed	Study to Evaluate the Efficacy and Safety of Intravenous Sulbactam-**ETX2514** in the Treatment of Patients With Infections Caused by Acinetobacter Baumannii-calcoaceticus Complex	• Acinetobacter Baumannii-calcoaceticus Complex • Hospital-acquired Bacterial Pneumonia • Ventilator-associated Bacterial Pneumonia • (and 2 more...)	• Drug: **ETX2514**/Sulbactam + Imipenem/Cilastin • Drug: Colistin + Imipenem/Cilastin	• Entasis Research Site Chicago, Illinois, United States • Entasis Research Site Shreveport, Louisiana, United States • Entasis Research Site Cincinnati, Ohio, United States • (and 89 more...)

ETX-2514 (durlobactam)+sulbactam

ATTACK Study Design

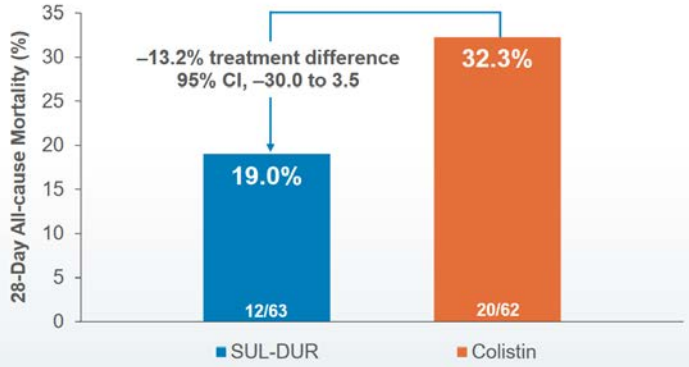
- ATTACK is a Phase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including CRABC strains



This trial is registered at ClinicalTrials.gov: NCT03894046. Please see ECCMID abstract #02093 for Part B.
[a]SUL-DUR dosing was adjusted for renal function. Colistin dosing was adjusted to ideal body weight and renal function. A single colistin loading dose of 2.5 to 5 mg/kg given intravenously over 3 to 6 minutes (or according to standard of care) was administered on Day 1 for patients who had not received prior colistin therapy.
BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; q×h, every × hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

Primary Efficacy Endpoint Achieved

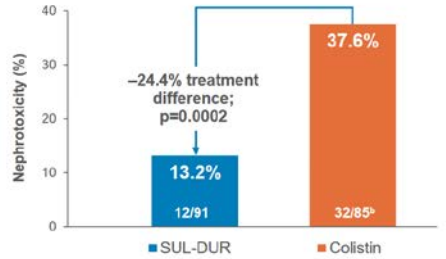
SUL-DUR noninferior on 28-day all-cause mortality vs colistin in the CRABC m-MITT population



Participants with missing survival status were treated as a death.
Noninferiority was concluded if the upper limit of the 2-sided 95% confidence interval (CI) was less than +20%.

Statistically Significant Reduction in Nephrotoxicity, Consistent With Lower Incidence of Renal/Urinary AEs

SUL-DUR vs colistin as measured by the RIFLE criteria[a] at any post-baseline visit

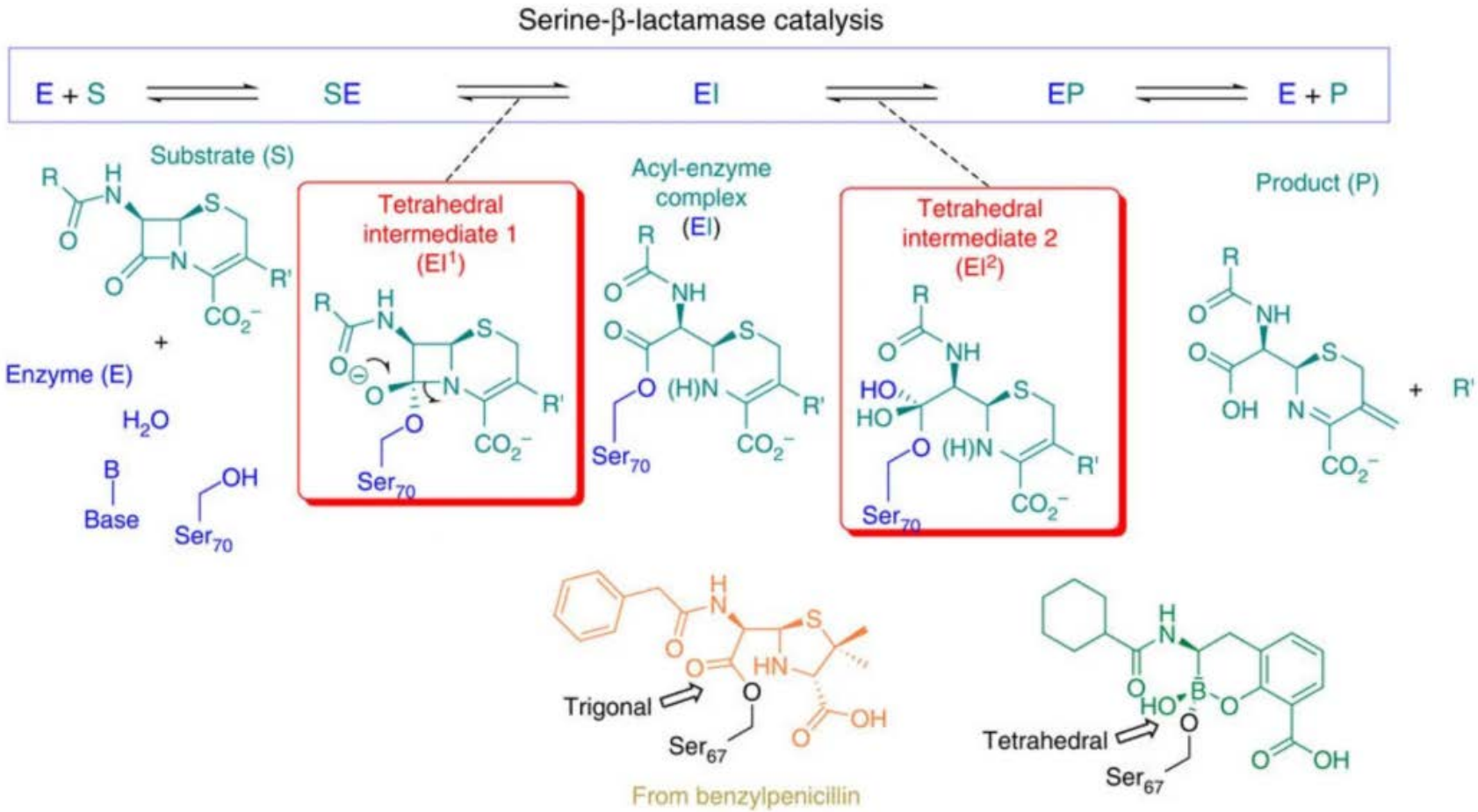


Please see ECCMID abstract 02145 for additional safety data.
[a]RIFLE (risk, injury, failure, loss, or end-stage renal disease) measured by creatinine level or glomerular filtration rate, but not urinary output, per Hartzell JD, et al. *Clin Infect Dis*. 2009;48:1724–1728. Nephrotoxicity defined as meeting any of the RIFLE criteria at any post-baseline visit; if patients had multiple RIFLE events, the patient was counted only once at the highest severity. No patients in this study experienced end-stage renal disease.
[b]Nephrotoxicity analysis excluded 1 patient in the colistin group with chronic haemodialysis at baseline.

Entasis, ECCMID 2022

Boronate BLI + β-lactam

Boronate BLIs:
Inhibition of serine β-lactamases by mimicking the tetrahedral adduct and covalently binding to the serine

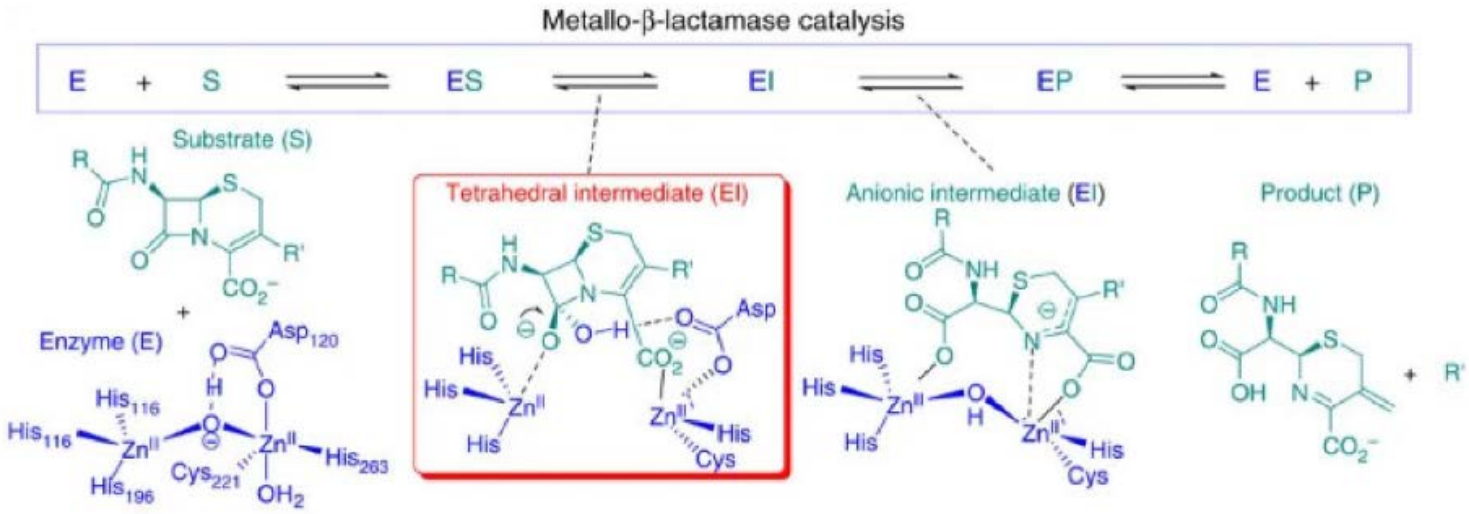


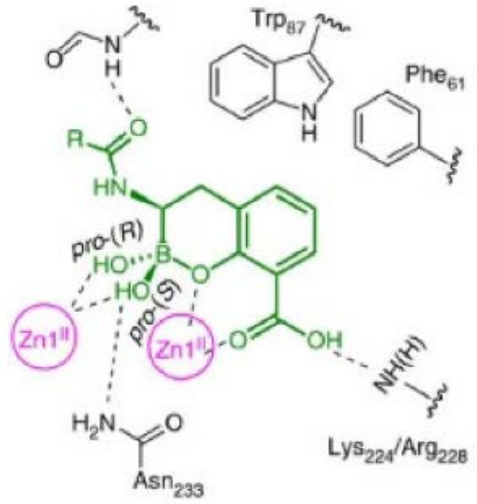
Iqbal et al., Molecules 2022;27:3832

Boronate BLI + β-lactam

Boronate BLIs:
Inhibition of serine β-lactamases
by mimicking the tetrahedral adduct
and covalently binding to the serine

Inhibition of metallo β-lactamases
by reversible 'fast on–fast off' non covalent
complexation and ability to adopt multiple forms
when interacting with different enzymes.





Iqbal et al., Molecules 2022;27:3832

VNRX-5133 (taniborbactam)+cefepime – clinical trials

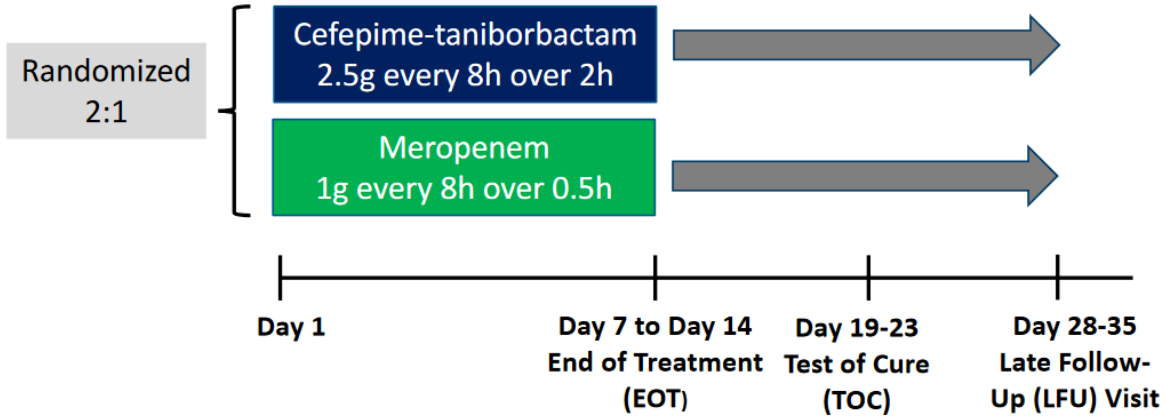
NIH U.S. National Library of Medicine
ClinicalTrials.gov

Status	Study Title	Conditions	Interventions
Completed	Safety and Efficacy Study of Cefepime/**VNRX-5133** in Patients With Complicated Urinary Tract Infections	• Urinary Tract Infections • Acute Pyelonephritis	• Drug: Cefepime/**VNRX-5133** (taniborbactam) • Drug: Meropenem
Completed	Safety and Pharmacokinetics of **VNRX-5133** in the Epithelial Lining Fluid of Healthy Adult Subjects	• Healthy Subjects	• Drug: **VNRX-5133** + cefepime
Completed	**VNRX-5133** With VNRX-5022 in Subjects With Varying Degrees of Renal Impairment	• Pharmacokinetics	• Drug: **VNRX-5133** and VNRX-5022
Completed	**VNRX-5133** SAD/MAD Safety and PK in Healthy Adult Volunteers	• Bacterial Infections	• Drug: **VNRX-5133** • Drug: Placebo
Completed	**VNRX-5133** Drug-Drug Interaction in Healthy Adult Volunteers	• Bacterial Infections	• Drug: **VNRX-5133** • Drug: VNRX-5022 • Drug: Metronidazole • Drug: Placebo
Completed	Safety and Intrapulmonary Pharmacokinetics of Cefepime and Taniborbactam in Healthy Subjects	• Healthy Subjects	• Drug: cefepime-taniborbactam
Completed	Safety and Efficacy Study of Cefepime/VNRX-5133 in Patients With Complicated Urinary Tract Infections	• Urinary Tract Infections • Acute Pyelonephritis	• Drug: Cefepime/VNRX-5133 (**taniborbactam**) • Drug: Meropenem

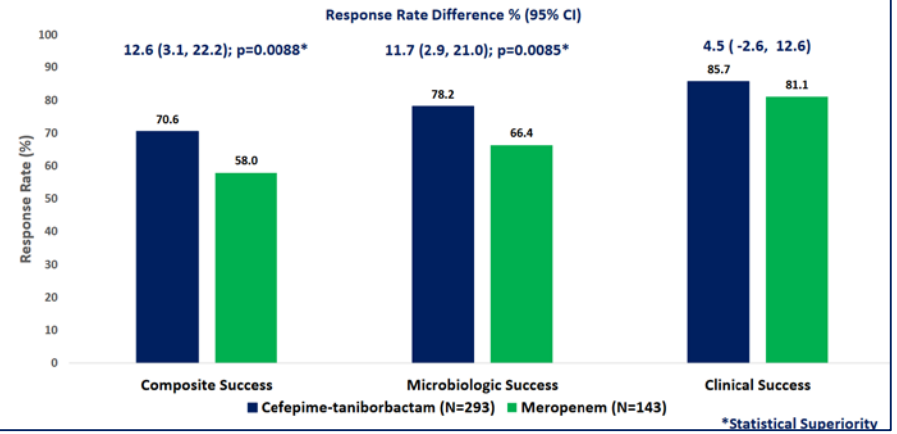
VNRX-5133 (taniborbactam)+cefepime

CERTAIN-1 (Cefepime Rescue with Taniborbactam in cUTI) Study Design

- Randomized, multicenter, double blind, double dummy, active controlled, non-inferiority study
  - Hospitalized patients with cUTI or AP
- MicroITT Population (Primary Efficacy Population):
  - Entry urine culture with Gram-negative pathogen(s) at ≥10^5 CFU/mL against which both cefepime-taniborbactam and meropenem have antibacterial activity; no more than 2 microorganisms identified in the entry urine culture
- Primary Endpoint: Composite microbiologic and clinical response at TOC in the microITT population
  - Non-inferiority margin set at 15%; prespecified superiority test if non-inferiority concluded



Cefepime-Taniborbactam Superior to Meropenem for the Primary Efficacy Endpoint
(Test of Cure Visit, MicroITT Population)



Summary of Adverse Events (Safety Population)

	Cefepime-taniborbactam (N = 440) n (%)	Meropenem (N = 217) n (%)
Patients with At Least one TEAE	**156 (35.5)**	**63 (29.0)**
TEAEs Occurring at > 2% of Patients in Either Treatment Group		
Headache	27 (6.1)	8 (3.7)
Diarrhoea	18 (4.1)	5 (2.3)
Constipation	14 (3.2)	3 (1.4)
Hypertension	10 (2.3)	2 (0.9)
Nausea	9 (2.0)	2 (0.9)
Alanine aminotransferase increased	4 (0.9)	5 (2.3)
Patients with At Least One Serious TEAE	**9 (2.0)**	**4 (1.8)**
Patients with At Least One TEAE with Action of Drug Withdrawn	**13 (3.0)**	**2 (0.9)**
Patients with At Least One Fatal TEAE	**1 (0.2)**	**0**

Venatorx, IDweek 2022

Pipeline of products in clinical development (phase I) – β-lactams + BLIs

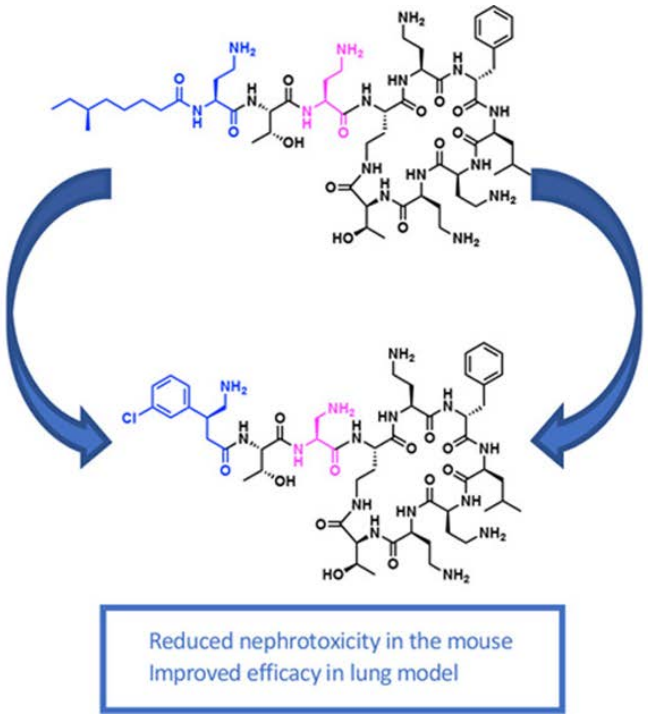
INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
Zidebactam + cefepime	1[8]	DBO-BLI/ PBP2 binder[9] + cephalosporin	iv	Wockhardt	●	●	●	/	-	-	-	-
OP0595 (nacubactam) + meropenem	1	DBO-BLI/PBP2 binder[9] + β-lactam (carbapenem)	iv	Meiji Seika	○	○[10]	●	/	-	-	-	-
ETX0282 + cefpodoxime proxetil	1	DBO-BLI/PBP2 binder[9] + β-lactam (cephalosporin)	oral	Entasis Therapeutics	○	○	●	/	-	-	-	-
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + β-lactam (undisclosed)	oral	Arixa Pharmaceuticals / Pfizer[11]	○	○	●[12]	/	-	-	-	-
QPX7728 + QPX2014	1	Boronate-BLI + undisclosed	iv	Qpex Biopharma	●	●	●	/	?	-	-	-
QPX7728 + QPX2015	1	Boronate-BLI + undisclosed oral β-lactam	oral and iv	Qpex Biopharma	○	○	●	/	?	-	-	-
VNRX-7145 + ceftibuten	1	Boronate-BLI + β-lactam (cephalosporin)	oral	VenatoRx Pharmaceuticals	○	○	●	/	?	✓	-	-

Other drug classes ….

Pipeline of products in clinical development (phase I) – polymyxins

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
SPR-206	1	Polymyxin	iv	Spero Therapeutics	●	●	●	/	-	-	-	-
MRX-8	1	Polymyxin	iv	MicuRx	●	●	●	/	-	-	-	-

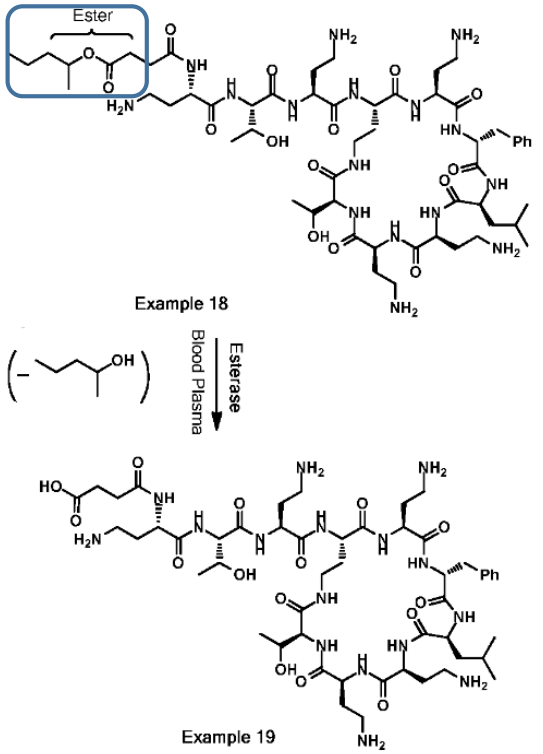
SPR-206



Brown et al. ACS Infect. Dis. 2019;5:1645–1656

MRX-8

ester bond facilitates the breakdown of the parent compound in plasma into a des-fatty acyl less toxic nonapeptide form



Gordeev et al., Patent WO2016100578

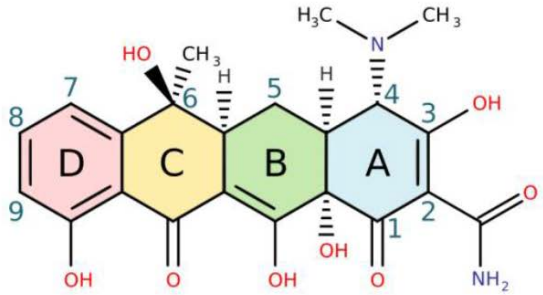
Pipeline of products in clinical development (phase I) – others

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens				Innovation			
					CRAB	CRPA	CRE	OPP1	NCR	CC	T	MoA
KBP-7072	1	Tetracycline	oral	KBP BioSciences	●	○	○	●	-	-	-	-
EBL-1003 (apramycin)	1	Aminoglycoside	iv	Juvabis	●	?	●	/	-	-	-	-

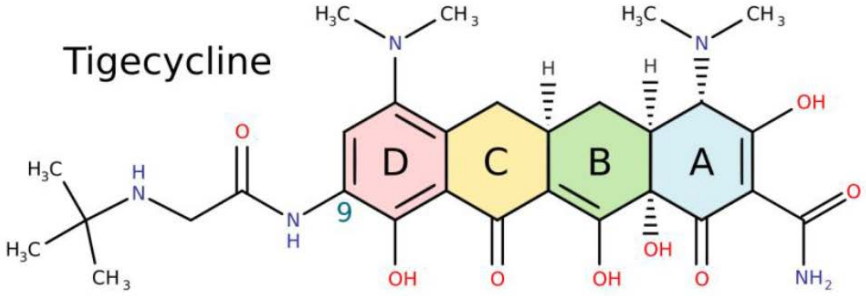
Pipeline of products in clinical development (phase I) – others

Zifanocycline (KBP-7072)

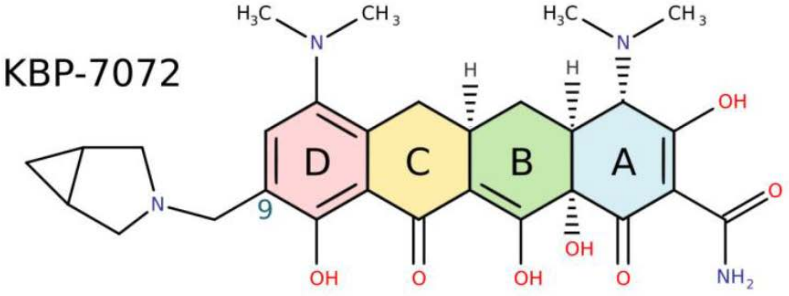
Tetracycline

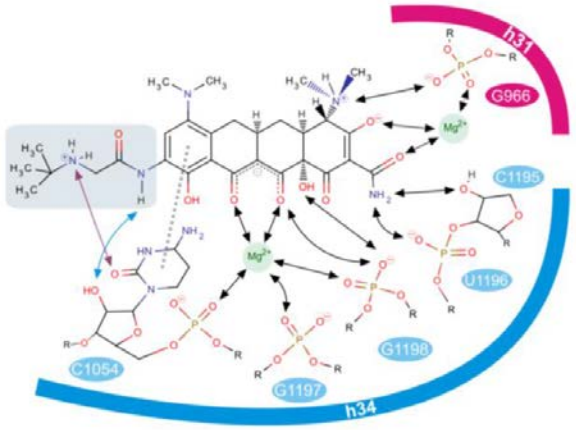


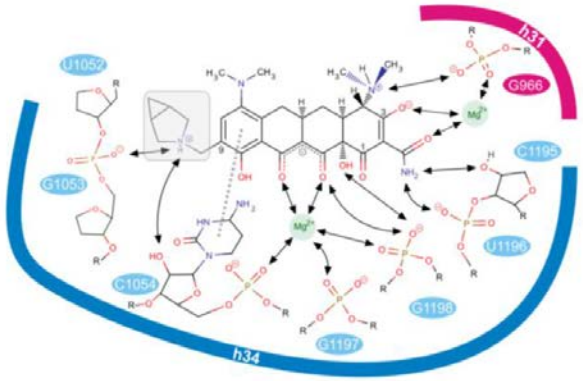
Tigecycline

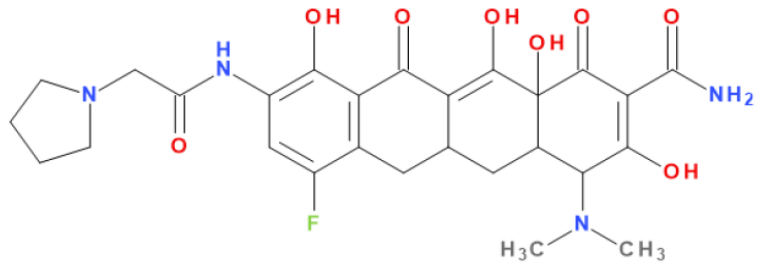


KBP-7072









Eravacycline

Kaminishi et al., BioRxiv 2018; doi 10.1101/508218

Zifanocycline – in vitro data

In vitro activity of old and new generation tetracycline agents

	MIC_{50}/MIC_{90}, mg/L (% susceptible by CLSI/EUCAST[a])					
Organism (*n*)	KBP-7072	doxycycline	minocycline	omadacycline	tetracycline	tigecycline
E. coli						
TET-S (51)	0.12/0.25	1/2 (100.0/–)	1/1 (100.0/–)	0.5/1 (–/–)	1/2 (100.0/–)	0.12/0.25 (100.0/100.0)
TET-R[d] (52)	0.25/1	32/>32 (5.8/–)	8/32 (42.3/–)	1/4 (–/–)	>64/>64 (0.0/–)	0.25/0.5 (100.0/98.1)
K. pneumoniae						
TET-S (54)	0.25/0.5	1/2 (100.0/–)	1/2 (100.0/–)	1/2 (100.0/–)	1/2 (100.0/–)	0.5/0.5 (100.0/–)
TET-R[e] (51)	1/4	16/>32 (0.0/–)	4/>32 (52.9/–)	4/16 (54.9/–)	>64/>64 (0.0/–)	1/2 (92.2/–)

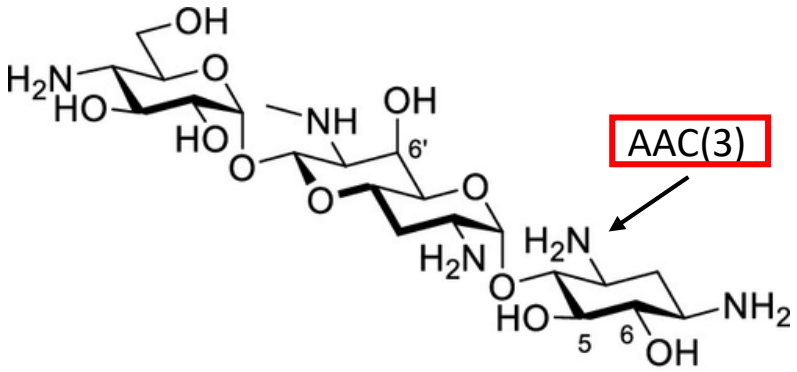
TET, tetracycline; S, susceptible; R, resistant.
[a]CLSI and EUCAST breakpoints were applied. FDA breakpoint interpretive criteria were used for tigecycline and omadacycline, with susceptibility shown in place of CLSI.
[d]Contains 20 *tet*(A), 8 *tet*(A)/*tet*(B), 21 *tet*(B) and 3 *tet*(D).
[e]Contains 40 *tet*(A), 2 *tet*(A)/*tet*(B), 2 *tet*(A)/*tet*(G), 5 *tet*(D) and 2 *tet*(G).

Pfaller et al., JAC Antimicrob Resist. 2021;3(4):dlab177

Pipeline of products in clinical development (phase I) – others

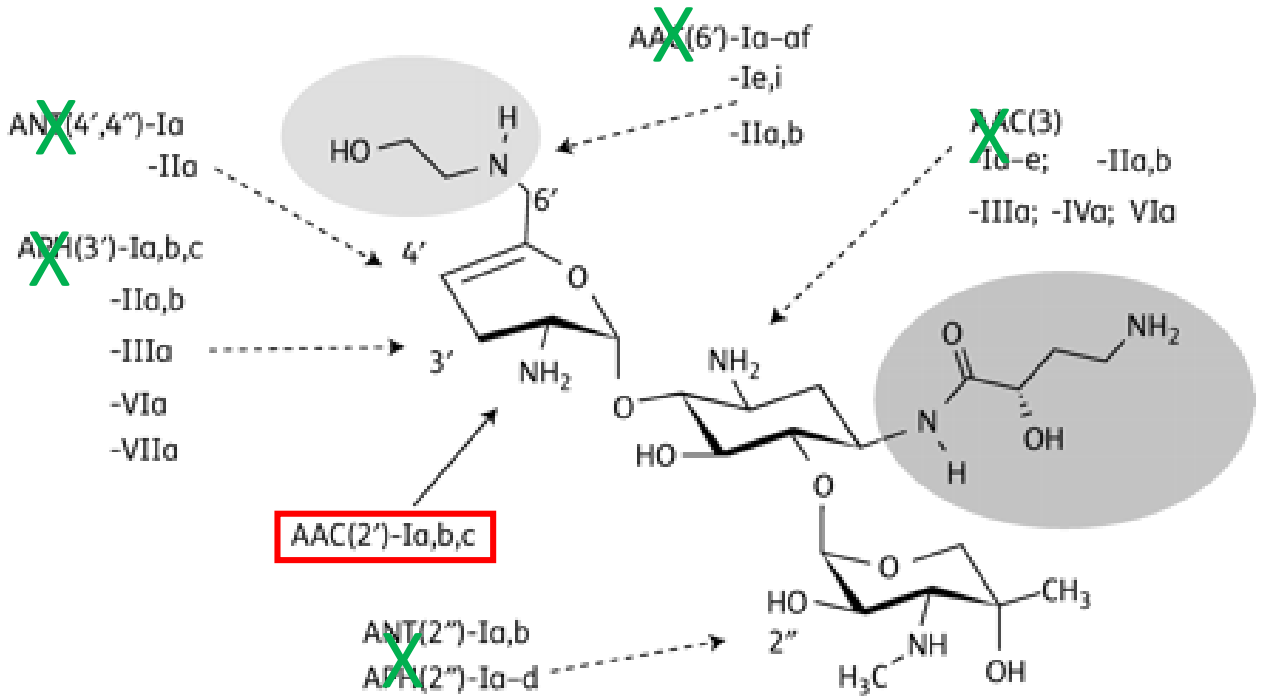
Apramycin (EBL-1003)

Used since a long time (‘80s)
in veterinary medicine !



active on methylated ribosomes (*arm* mechanisms)

plazomicin



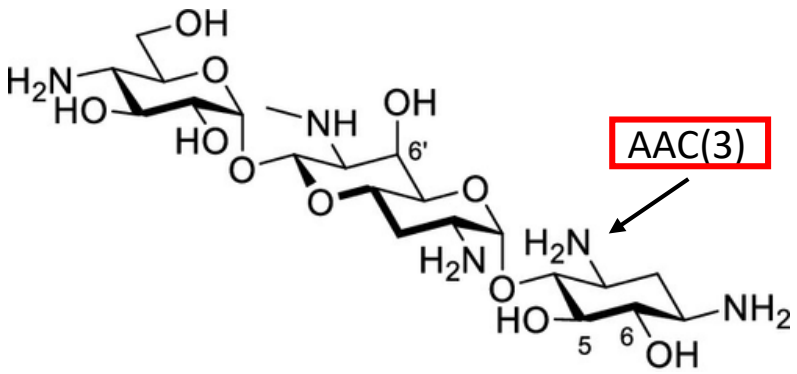
inactive on methylated ribosomes (*arm* mechanisms)

Livermore et al., J Antimicrob Chemother 2011; 6(1):48–53

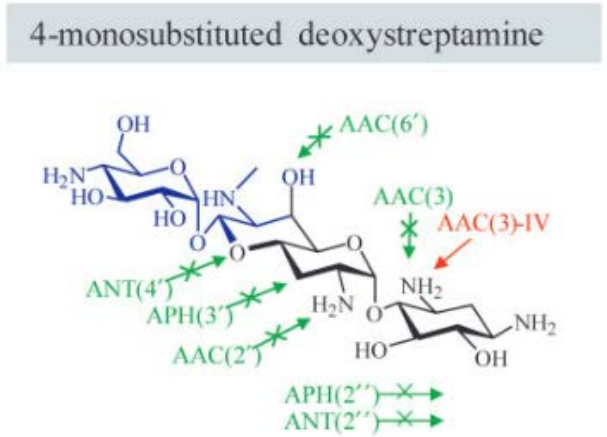
Pipeline of products in clinical development (phase I) – others

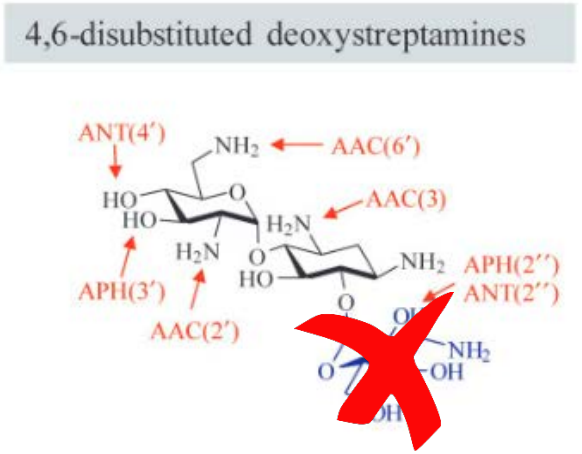
Apramycin (EBL-1003)

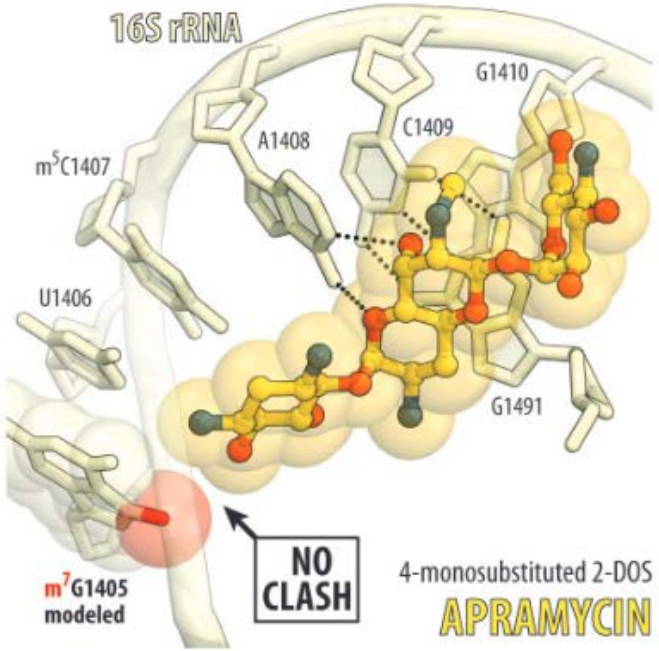
Used since a long time (‘80s)
in veterinary medicine !

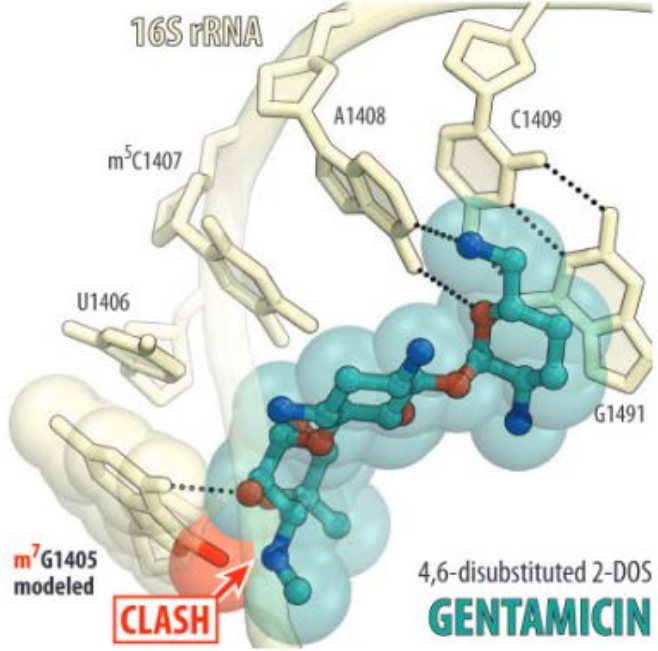


active on methylated ribosomes (*arm* mechanisms)









Juhas et al., J Antimicrob Chemother 2019; 74(4):944-952

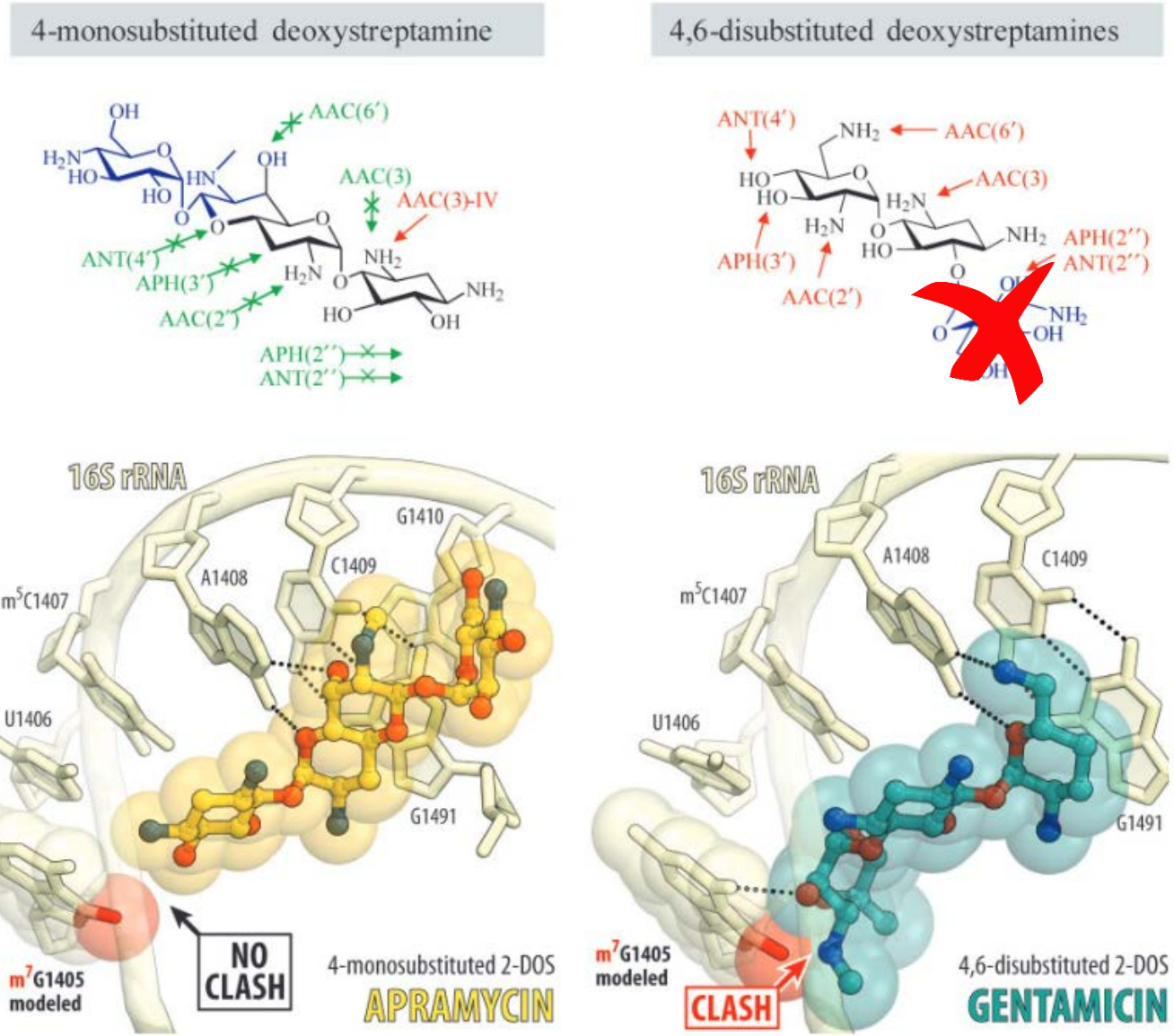
Pipeline of products in clinical development (phase I) – others

Apramycin (EBL-1003)

Table 4. Apramycin activity in comparison with gentamicin, amikacin, tobramycin and plazomicin against engineered *E. coli* strains expressing individual aminoglycoside resistance mechanisms

	MIC (mg/L)				
Resistance mechanism	APR	GEN	AMK	TOB	PLZ
None	4	0.5	1–2	0.5	0.5
AAC(6′)-I	4	2	64	32–64	0.5
AAC(6′)-II	4	64	8	32–64	1
AAC(3)-I	8	>64	1–2	1	0.5–1
AAC(3)-II	8	>64	1	32	4
AAC(3)-III	4	>64	0.5–1	>64	0.5
AAC(3)-IV	>64	2	1–2	2	0.5
AAC(3)-VI	4	>64	1–2	4	1
AAC(2′)-I	2–4	4	1–2	8–16	8–16
APH(3′)-I	2	1–2	1–2	8	0.5
APH(3′)-II	4	0.5	8	0.5	0.5
APH(3′)-III	4	0.5	32	4–8	0.5
APH(3′)-VI	4	0.5	64	0.5	0.5–1
APH(2″)-II	2–4	>64	2–4	64	8
APH(2″)-IV	4	>64	1–2	32–64	8
ANT(4′)-II	2–4	0.5	1–2	0.5	0.5–1
ANT(2″)-I	4	16–32	1	16–32	0.5
armA	2–4	>64	>64	>64	>64
rmtB	4	>64	>64	>64	>64
rmtC	2–4	>64	>64	>64	>64
rmtF	2–4	>64	>64	>64	>64

APR, apramycin; GEN, gentamicin; AMK, amikacin; TOB, tobramycin; PLZ, plazomicin.



Juhas et al., J Antimicrob Chemother 2019; 74(4):944-952

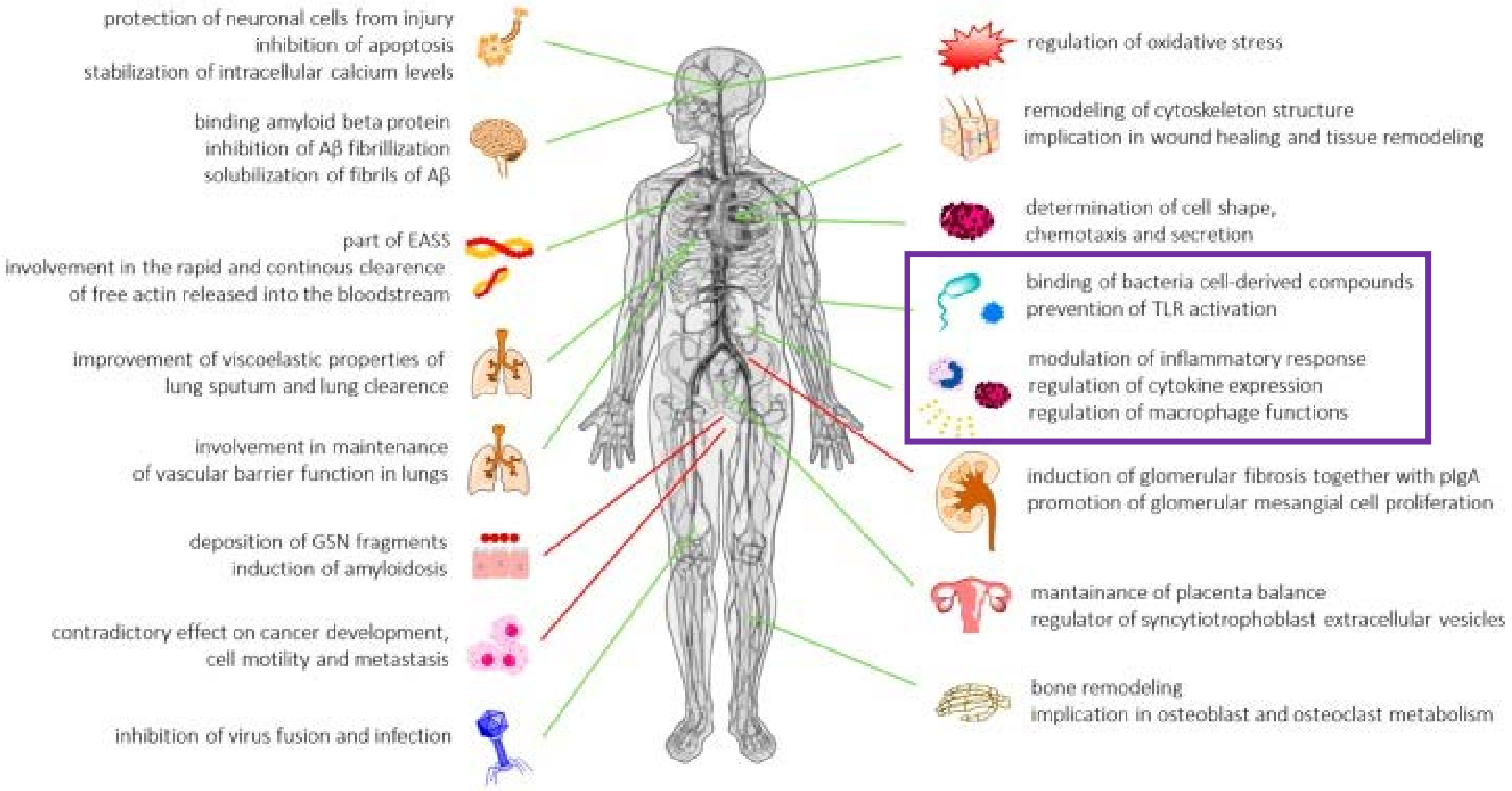
Pipeline of products in clinical development – innovative compounds

Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Expected activity against priority pathogens
Rhu-pGSN (rhu-plasma gelsolin)	1b/2a	Recombinant human plasma gelsolin protein	iv	BioAegis Therapeutics	Non-specific Gram-positive and Gram-negative
TRL1068	1	mAb	iv	Trellis Bioscience	Gram-positive and Gram-negative biofilms
OligoG (CF-5/20)	2b	Alginate oligosaccharide (G-block) fragment	inhalation	AlgiPharma	*P. aeruginosa*
Ftortiazinon (fluorothyazinone) + cefepime	2	Thyazinone (type III secretion system inhibitor) + cephalosporin	oral	Gamaleya Research Institute of Epidemiology and Microbiology	*P. aeruginosa*
GSK3882347	1	Undisclosed (FimH antagonist)	oral	GSK	*E. coli*

Legend

: antibodies; : immunomodulating agents; : miscellaneous (e.g. virulence, adhesion, biofilm and quorum sensing).

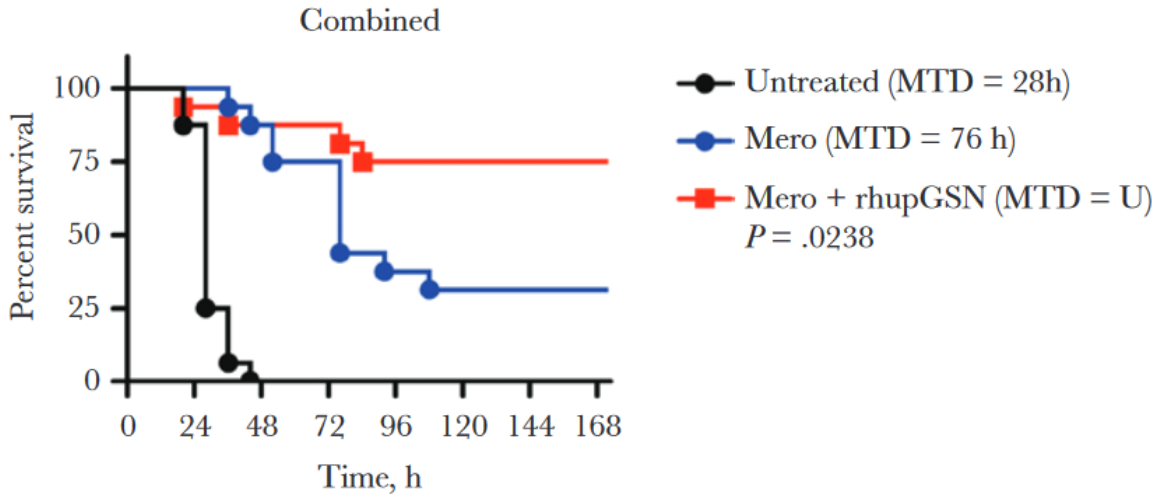
Plasma gelsolin (rhuP-GSN)

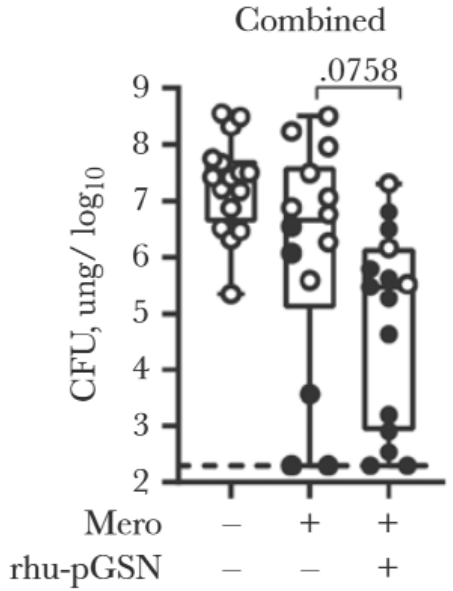


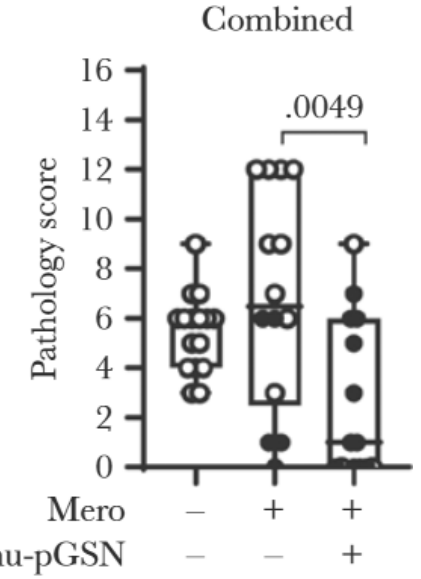
Piktel et al., Int J Mol Sci. 2018;19:2516.

Plasma gelsolin (rhuP-GSN)- demonstration of activity in vivo

Recombinant Human Plasma Gelsolin Improves Survival and Attenuates Lung Injury in a Murine Model of Multidrug-Resistant *Pseudomonas aeruginosa* Pneumonia

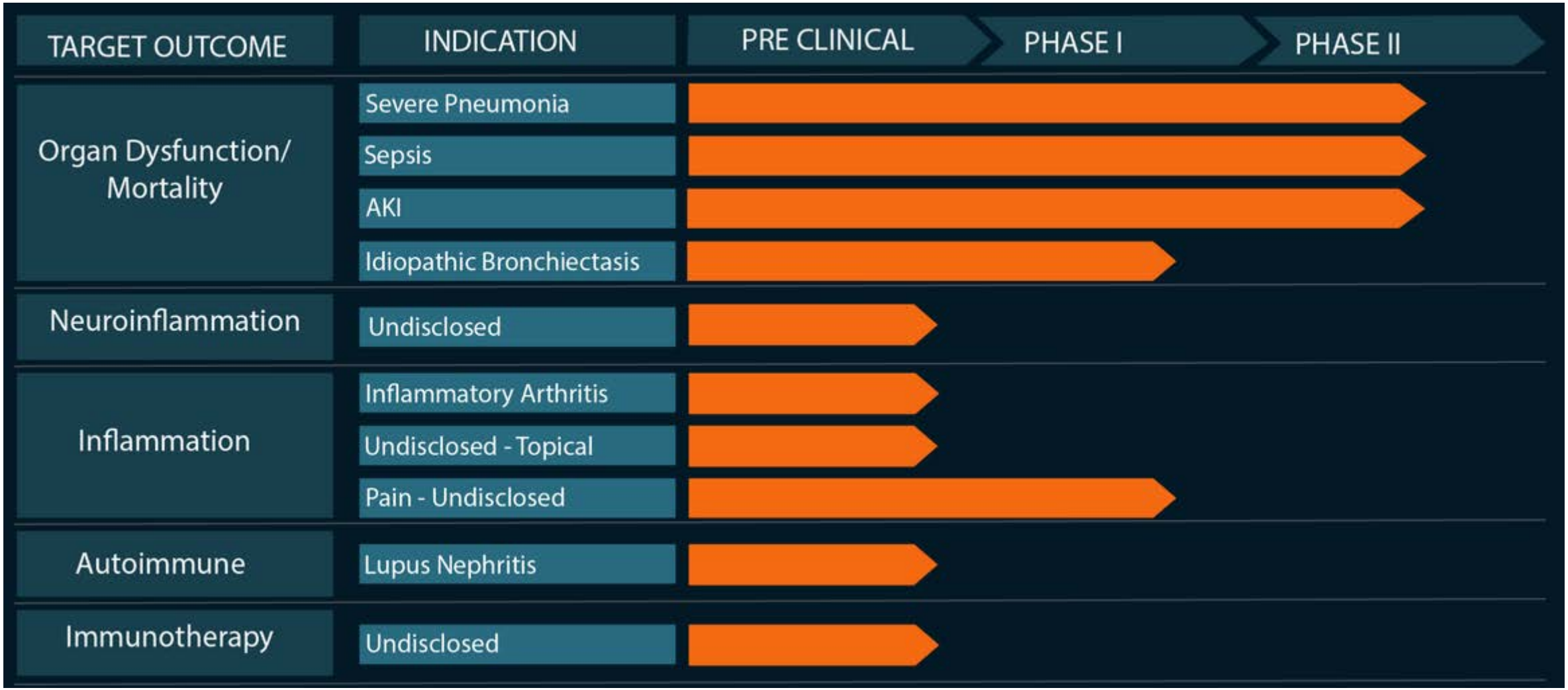






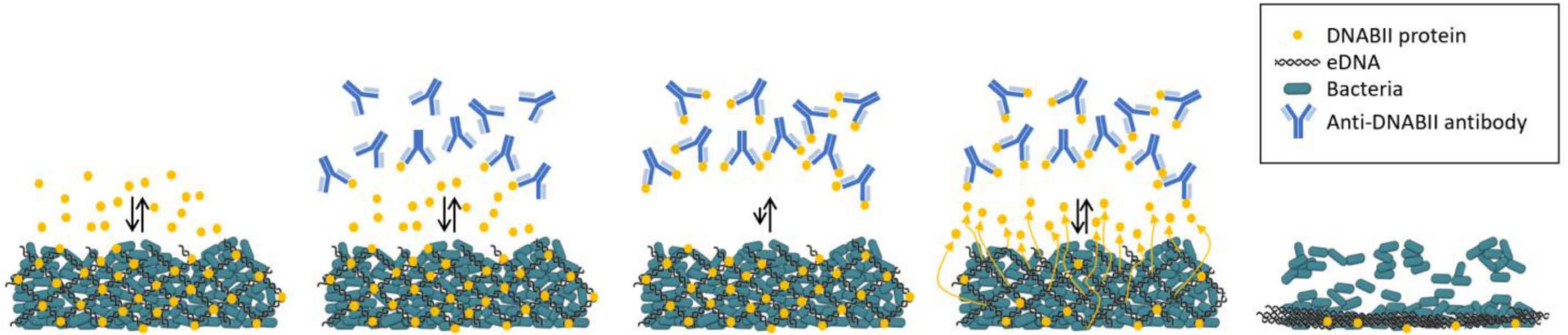
DiNubile et al., Open Forum Infect Dis. 2020;7(8):ofaa236

Plasma gelsolin (rhuP-GSN)



https://www.bioaegistherapeutics.com/plasma-gelsolin-protein/

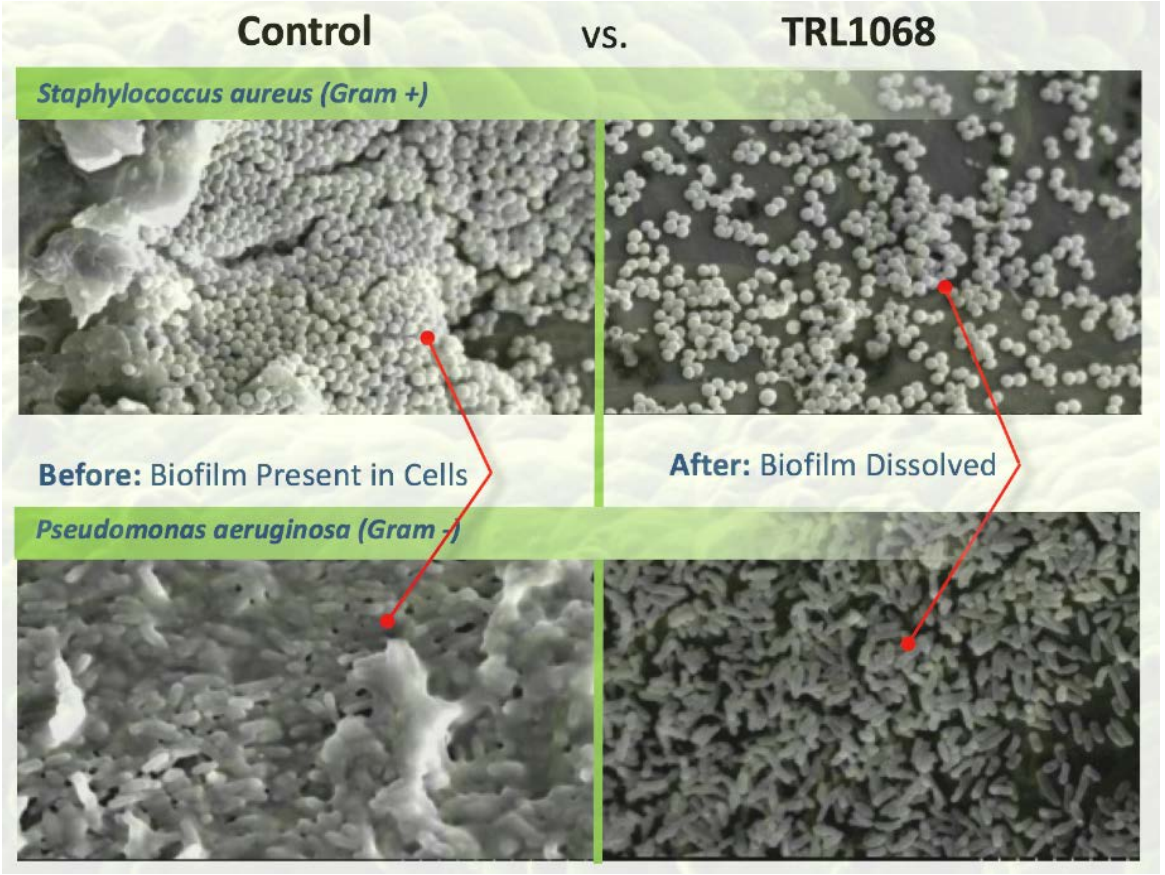
TRL-1068 Antibody against DNABII protein



Rogers et al., Antibiotics 2022;11:104

TRL-1068 Antibody against DNABII protein

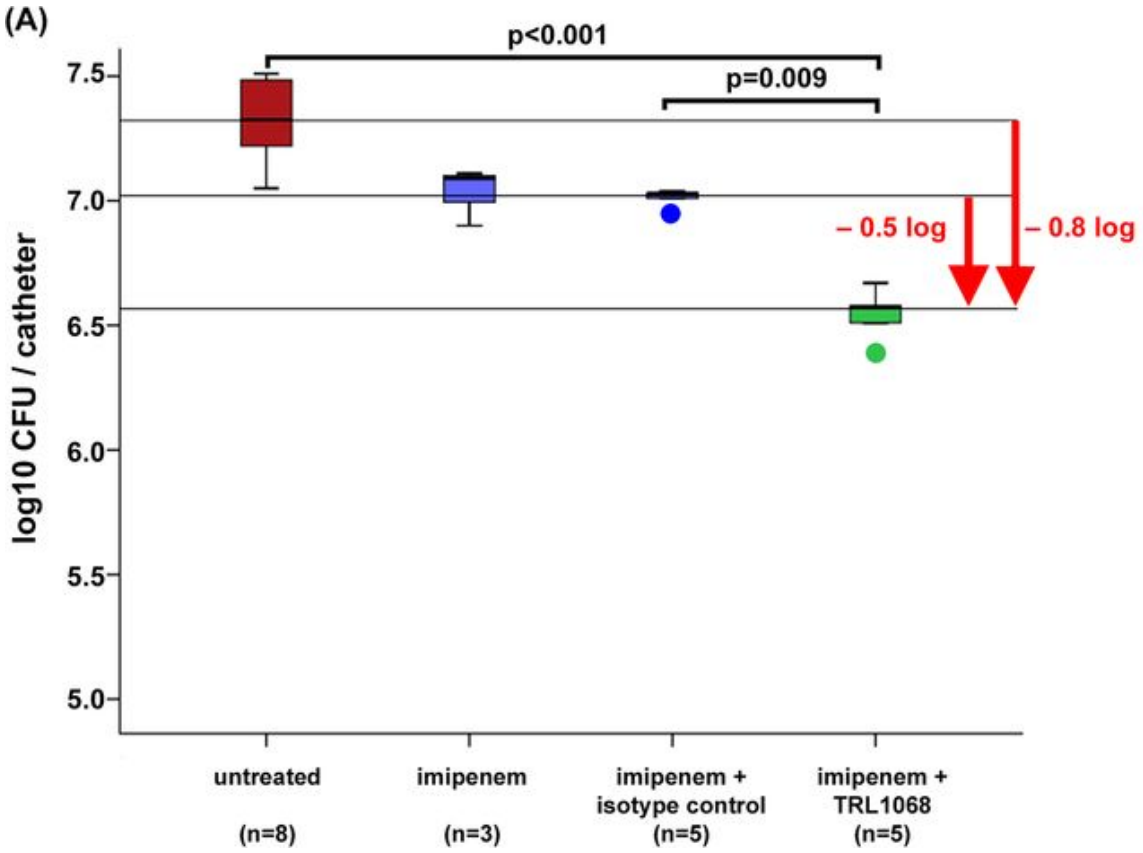
Species Targeted by TRL1068 (by epitope sequence)	**Gram**
Carbapenem-resistant Enterobacteriaceae (CRE)	-
Drug-Resistant *Neisseria gonorrhoeae*	-
Multidrug-resistant *Acinetobacter*	-
Extended Spectrum β-lactamase Enterobacteriaceae (ESBLs)	-
Multi-drug resistant *Pseudomonas aeruginosa*	-
Drug-resistant non-typhoidal *Salmonella*	-
Drug-resistant *Salmonella* Typhi	-
Drug-resistant *Shigella*	-
Methicillin Resistant *Staphylococcus aureus (MRSA)*	+
Drug-resistant *Streptococcus pneumoniae*	+
Vancomycin-resistant Enterococcus (VRE)	+
Vancomycin-resistant *Staphylococcus aureus (VRSA)*	+
Erythromycin-resistant Group A *Streptococcus*	+
Clindamycin-resistant Group A *Streptococcus*	+
Drug-resistant *Borrelia burgdorferi*	N/A
Drug-resistant *Treponema denticola*	N/A

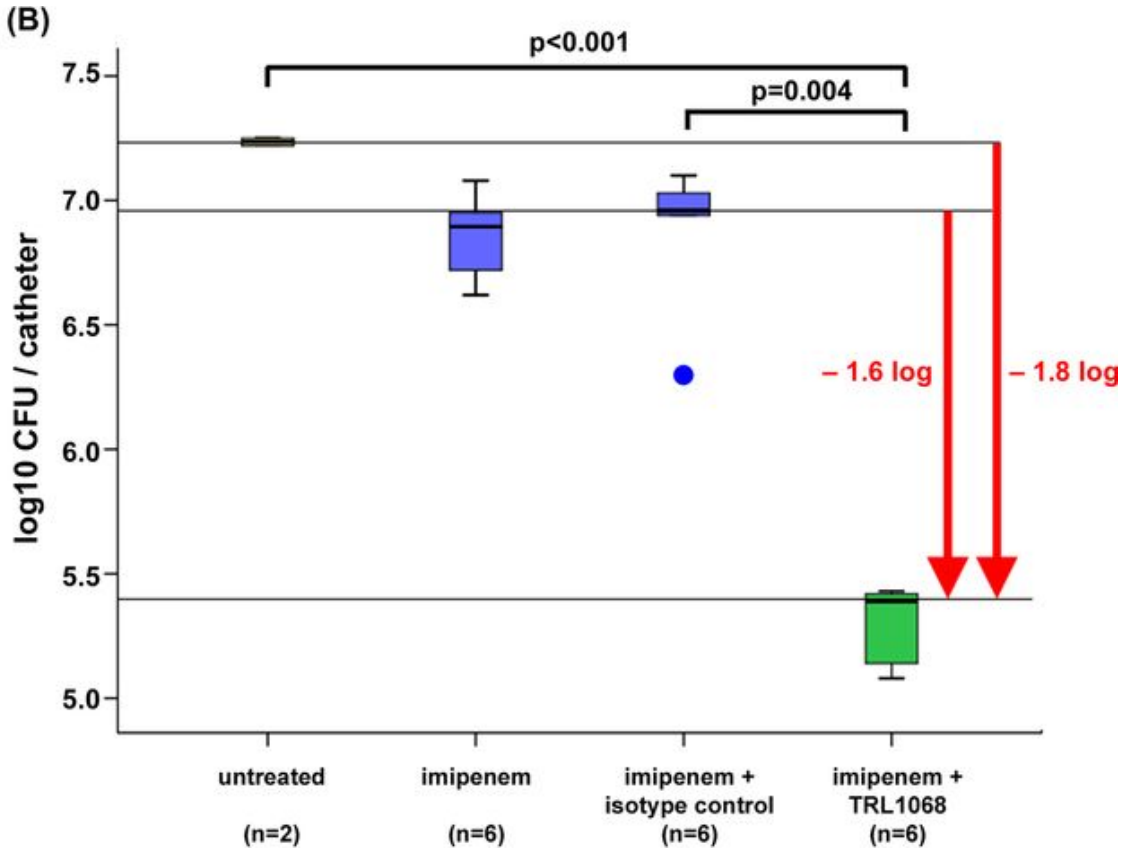


http://www.trellisbio.com/pipeline/bacteria.html

TRL-1068 Antibody against DNABII protein

A Human Biofilm-Disrupting Monoclonal Antibody Potentiates Antibiotic Efficacy in Rodent Models of both Staphylococcus aureus and Acinetobacter baumannii Infections

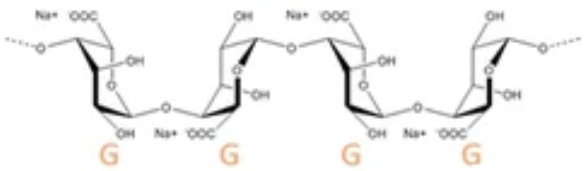




Xiong et al., Antimicrob Agents Chemother. 2017;61:e00904-17

OligoG

Alginate Oligomers



G-block alginate

Mucins	Bacteria	Fungi	Biofilms
• Mucin binding	• Cell surface binding	• ↓ Growth	• ↓ Biofilm growth
• Alter sputum viscoelasticity	• ↓ Growth & Motility	• ↓ Hyphal formation	• ↓ Biofilm stability
• Potentiates rhDNase I	• Potentiates antibiotics	• Potentiates antifungals	• ↓ EPS production
• Facilitates mucus release	• ↓ Virulence factors	• ↓ Virulence factors	• ↓ eDNA production
• ↓ Intestinal transit time			• ↓ Quorum Sensing

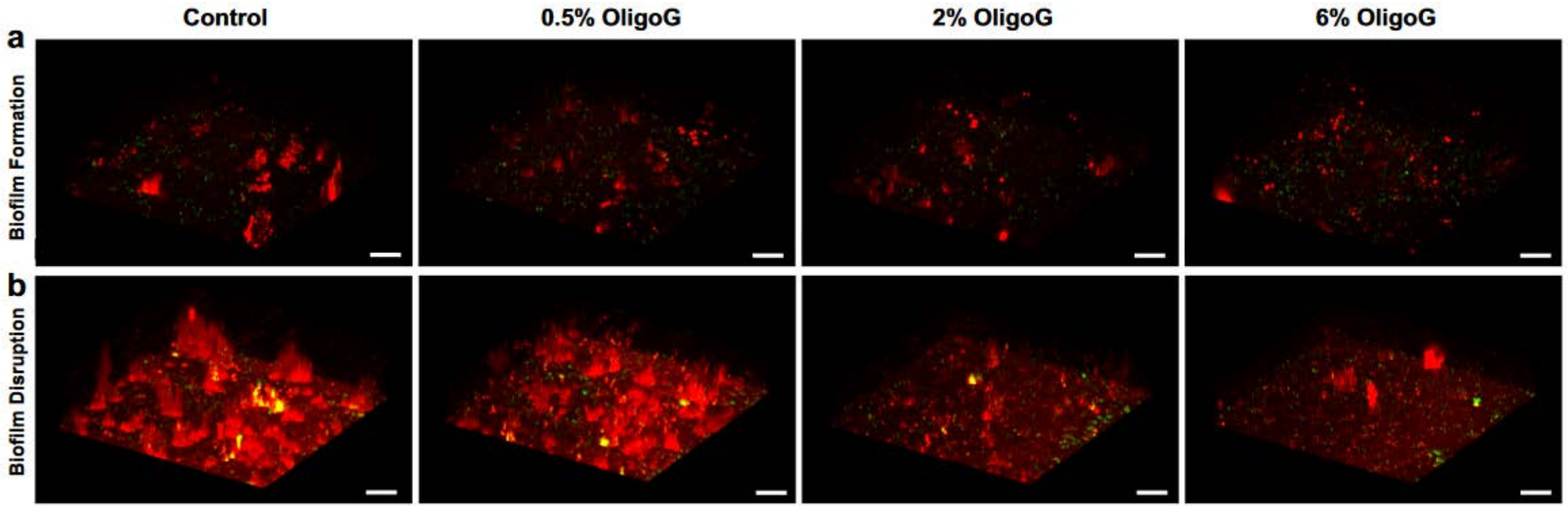
Medical Indications

- CF / COPD
- Bronchiectasis
- MDR infections
- Chronic wounds
- Biofilm related disease
- Surface coatings

Rye et al., 2018; https://doi.org/10.1007/978-981-10-6910-9_10

OligoG

Targeted disruption of the extracellular polymeric network of *Pseudomonas aeruginosa* biofilms by alginate oligosaccharides

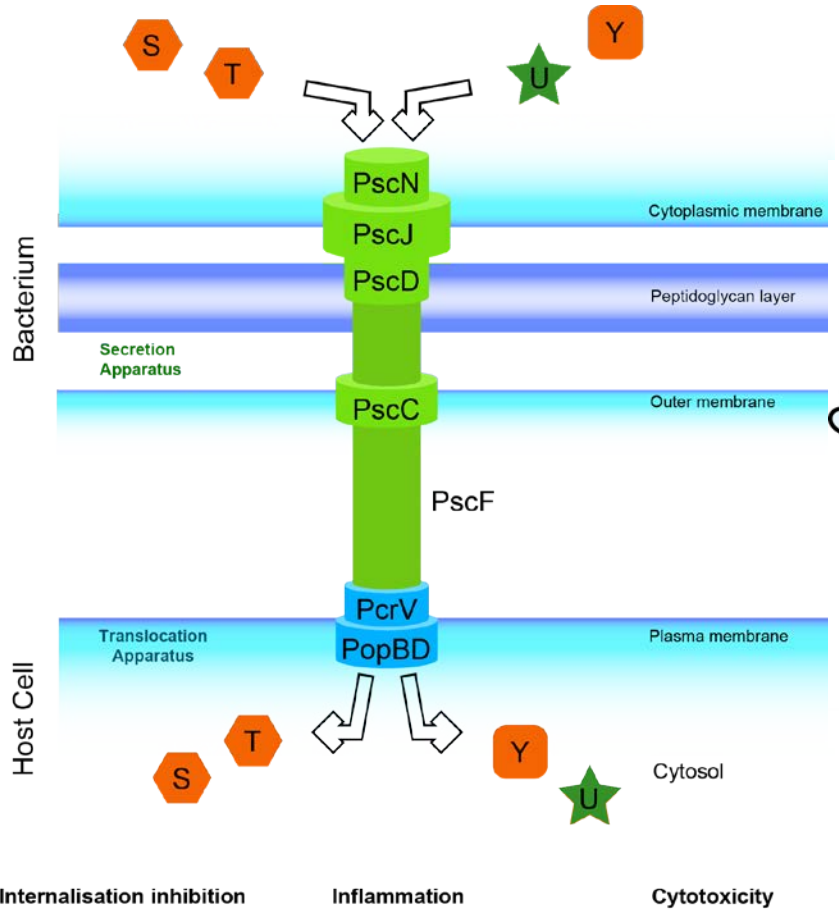


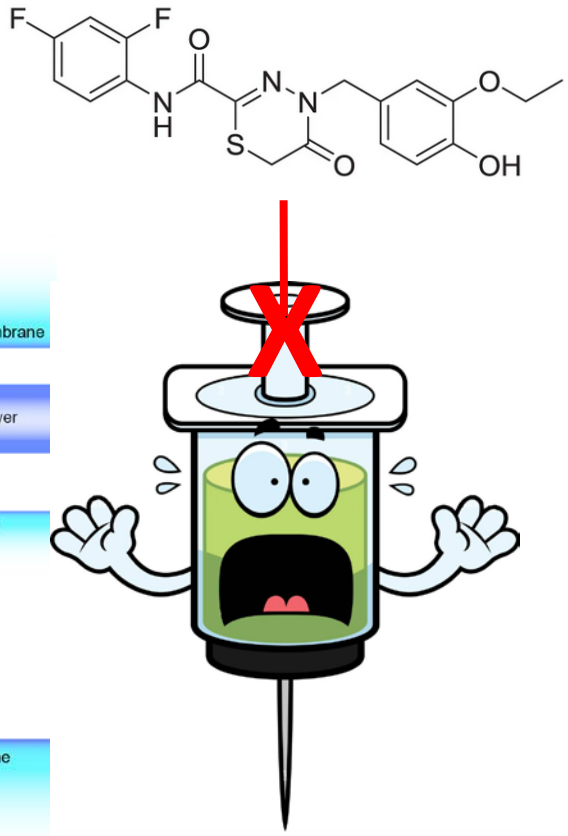
EPS labelling

Powel et al., NPJ Biofilms Microbiomes 2018;4:13

Ftortiazinon (fluorothyazinon + cefepime)

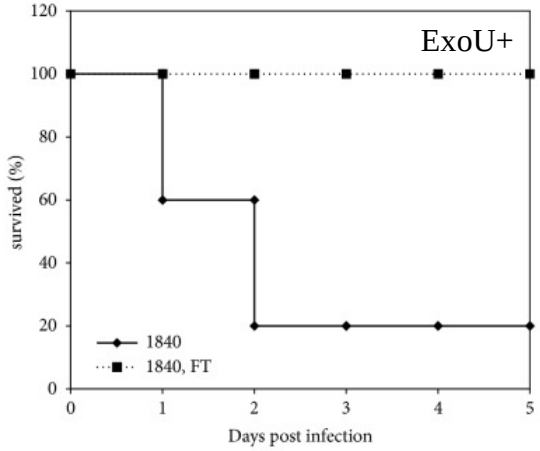
Type III Secretion System

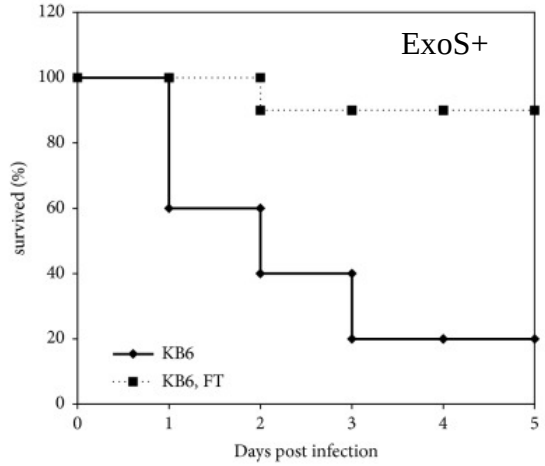




Courtesy of A. Anantharajah

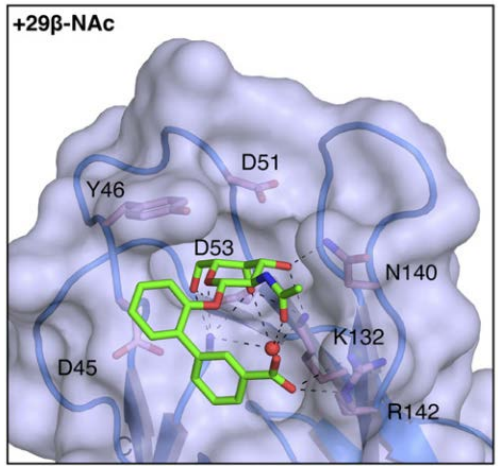
Small Molecule Inhibitor of Type Three Secretion System Belonging to a Class 2,4-disubstituted-4H-[1,3,4]-thiadiazine-5-ones Improves Survival and Decreases Bacterial Loads in an Airway *Pseudomonas aeruginosa* Infection in Mice

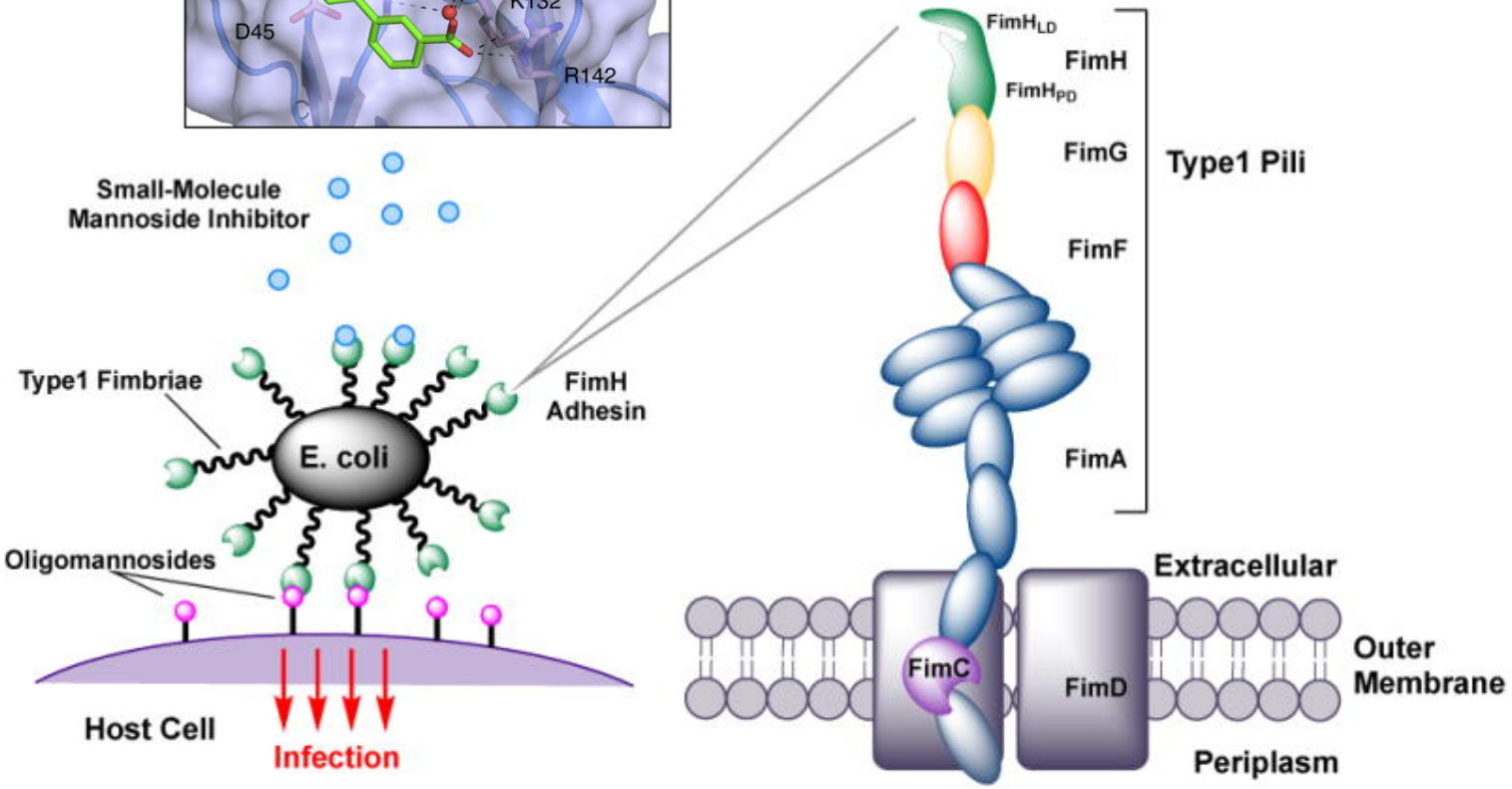




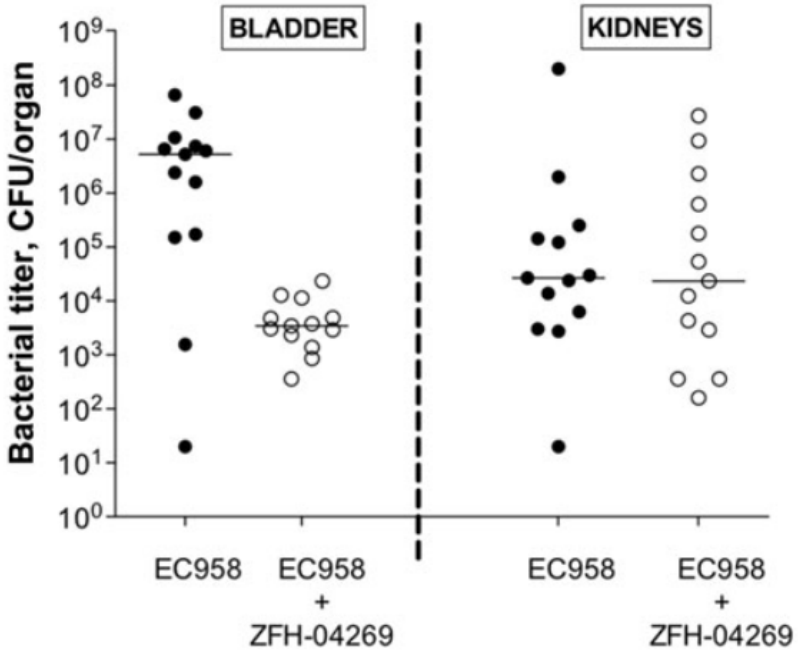
Sheremet et al., Biomed Res Int. 2018;2018:5810767

GSK3882347 (inhibitor of FimH)





A FimH Inhibitor Prevents Acute Bladder Infection and Treats Chronic Cystitis Caused by Multidrug-Resistant Uropathogenic *Escherichia coli* ST131



Mydock-McGrane et al., Expert Opin Drug Discov. 2017;12:711–731

Totsika et al., J Infect Dis 2013;208(6):921-8

GSK3882347 (inhibitor of FimH) – clinical trials

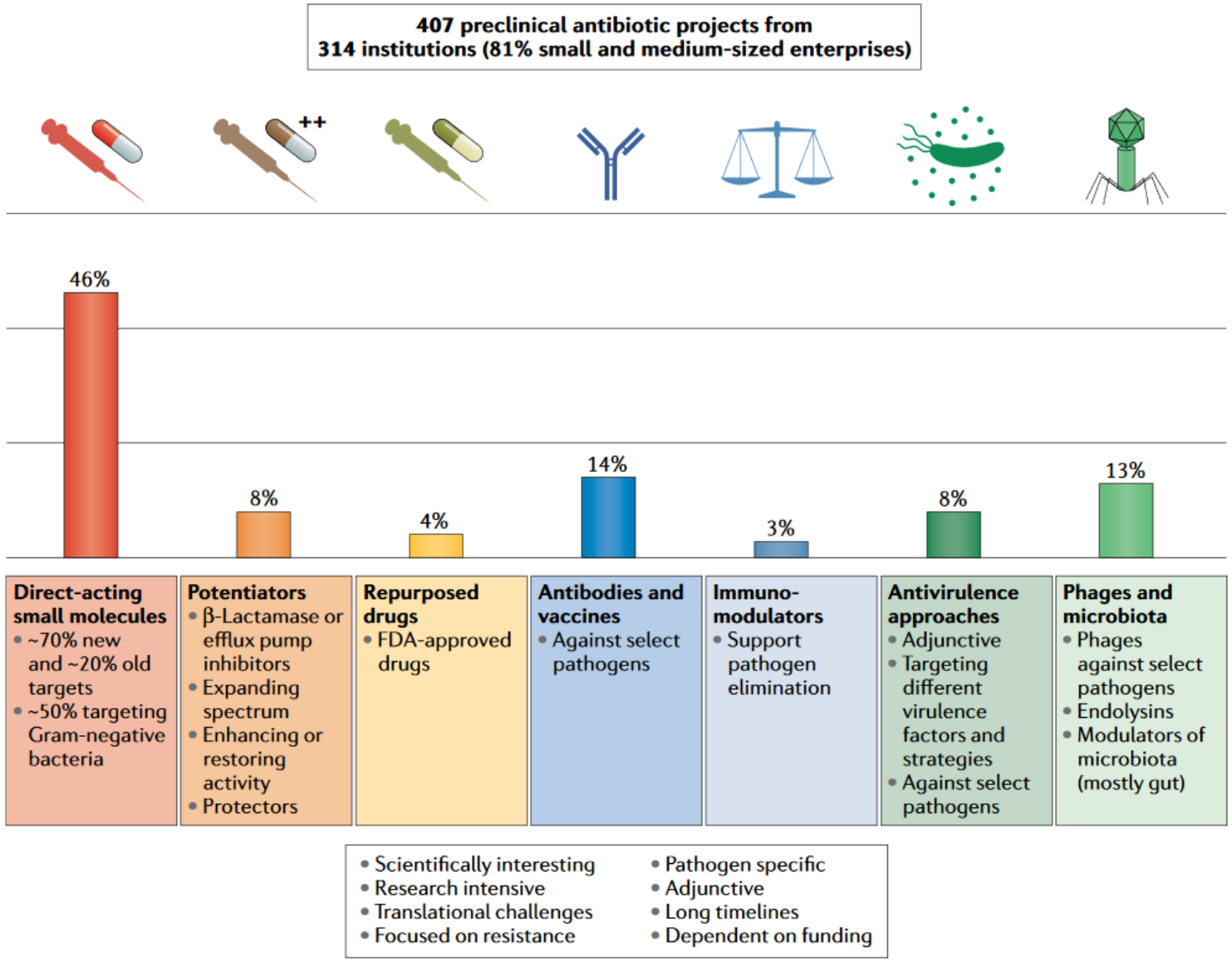
NIH U.S. National Library of Medicine
ClinicalTrials.gov

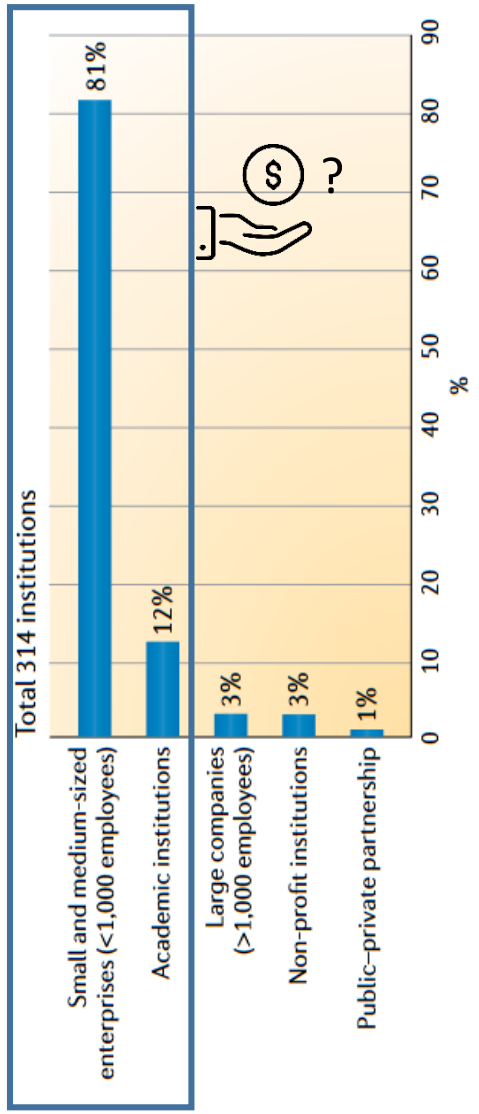
Status	Study Title	Conditions	Interventions
Recruiting	Safety, Tolerability, Pharmacokinetic and Microbiological Investigation of **GSK3882347** in Female Participants With Urinary Tract Infections	• Uncomplicated Urinary Tract Infections	• Drug: **GSK3882347** • Drug: Nitrofurantoin • Drug: Placebo
Completed	Safety, Tolerability and Pharmacokinetic Investigation of **GSK3882347** in Healthy Participants.	• Urinary Tract Infections	• Drug: **GSK3882347** • Drug: Placebo

Mydock-McGrane et al., Expert Opin Drug Discov. 2017;12:711–731

And the preclinical pipeline ….

And the preclinical pipeline ….



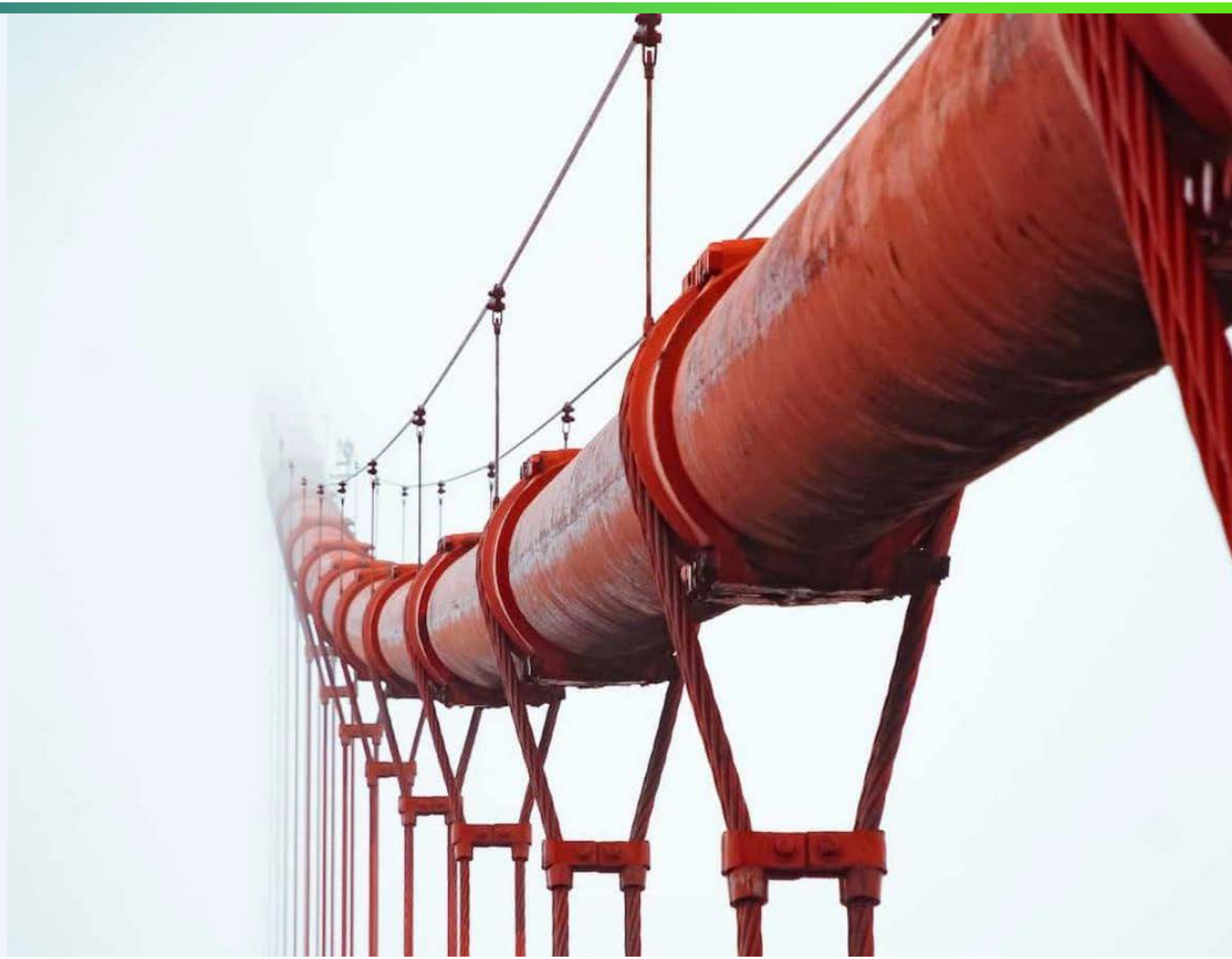


Theuretzbacher et al., Nat Rev Microbiol. 2020;18(5):275-285

What will be our future ?

- Nothing completely new in the short-term pipeline ….
- Alternative strategies explored in the long-term pipeline (>< virulence)

- Will they come on time and be able to save lives for « untreatable » infections ?



Thank you for your attention !