NEW ANTIBACTERIAL DRUGS

Drug pipeline for Gram-positive bacteria

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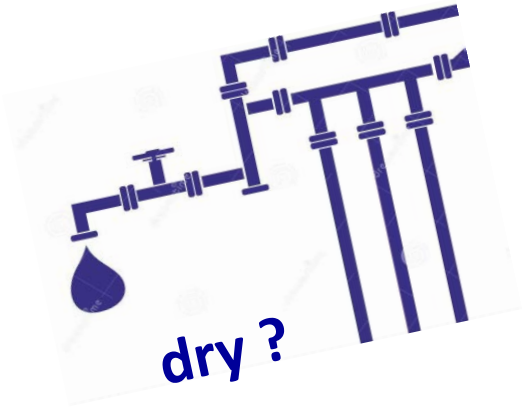
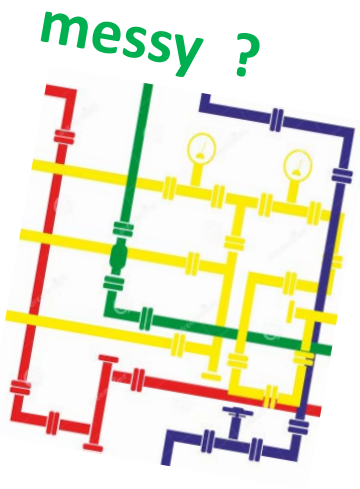
F. Van Bambeke's disclosures

Research grants for work on investigational compounds discussed in this presentation from

- Cempra Pharmaceuticals
- Cerexa
- GSK
- Melinta therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Theravance
- Trius

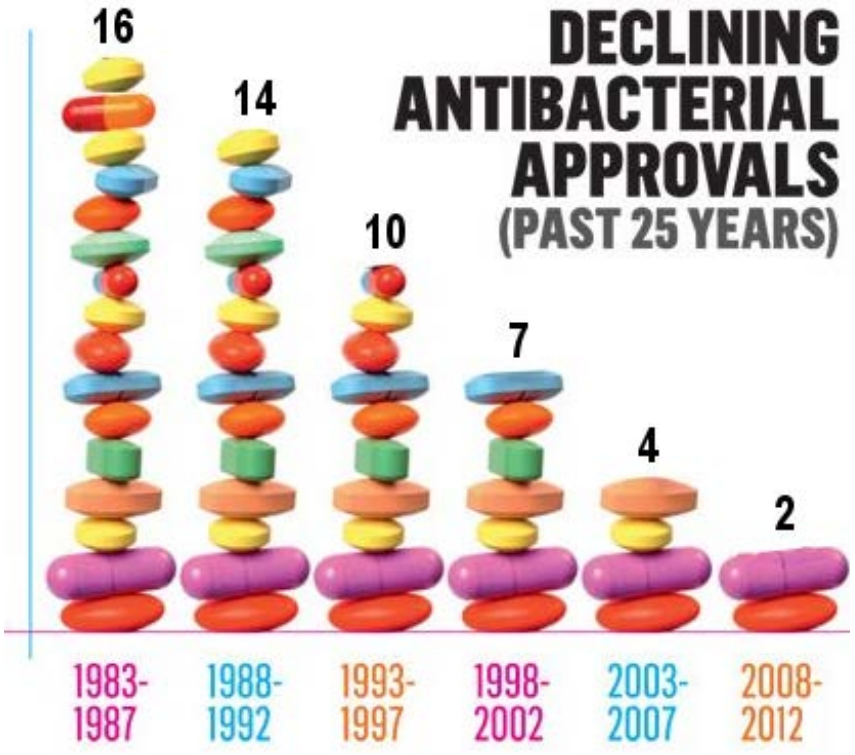
New antibiotics: what is your own view of the pipeline ?





New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



→ telavancin

→ ceftaroline

New antibiotics: where are we ?

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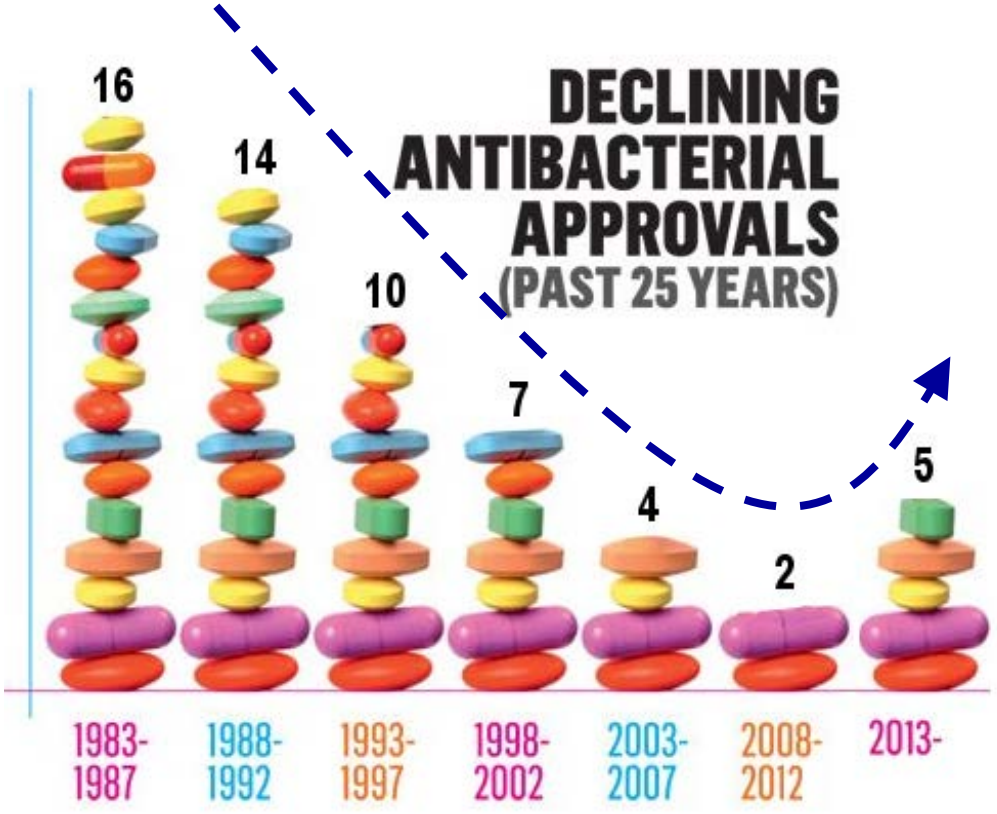


Shall we succeed ?

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam

- telavancin
- ceftaroline

Anti Gram-positive recently approved drugs

company	drug	class	indications	MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglyco-peptide	cSSSI / HABP/VABP	✓	✓	VanB only
Durata Ther.	Dalbavancin	lipoglyco-peptide	ABSSSI	✓	✓	VanB only
The MedCo	Oritavancin	lipoglyco-peptide	ABSSSI	✓	✓	✓
MSD	Tedizolid	oxazolidinone	ABSSSI	✓	✓	✓
Forrest Astra-Zeneca	Ceftaroline	β-lactam	ABSSSI / CABP	✓	✓	✓
Basilea	Ceftobiprole*	β-lactam	CAP / HAP	✓	✓	✓

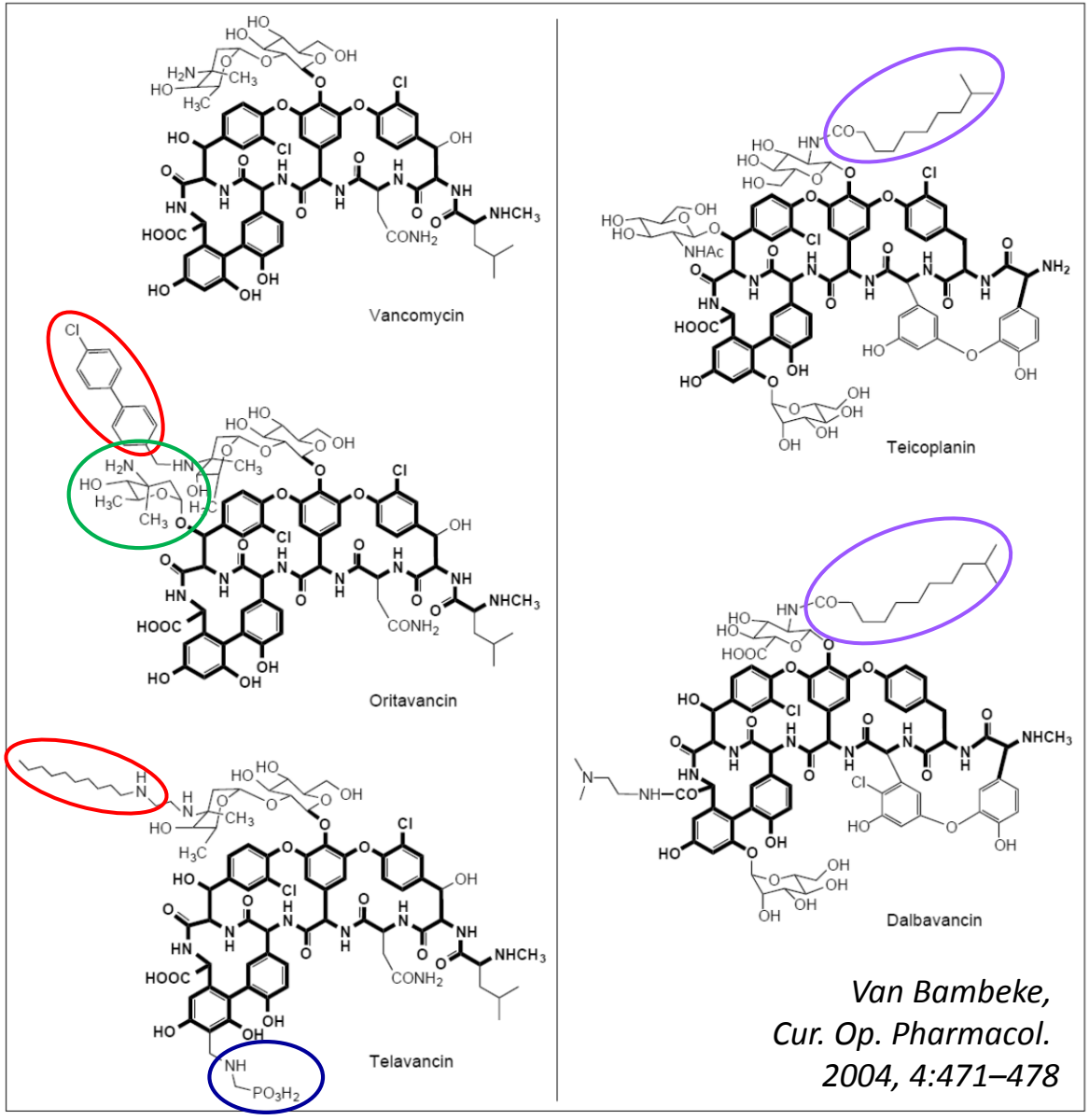
* licensed in 13 countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK; reimbursement and pricing authorization ongoing in most of them

Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

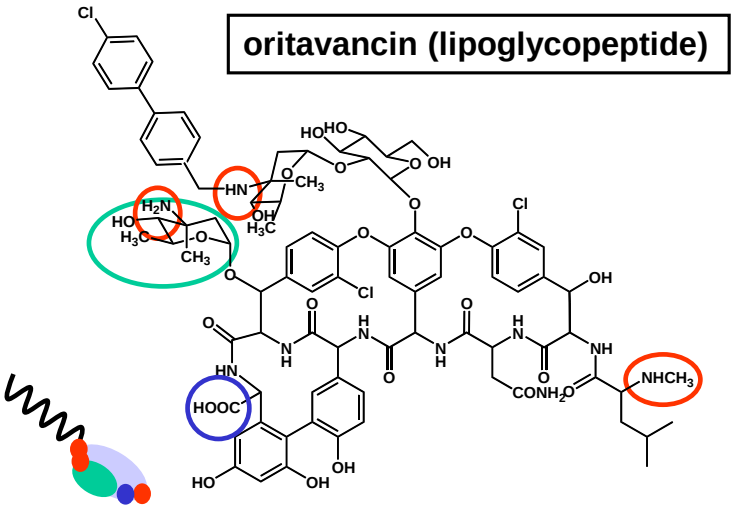
decreased half-life

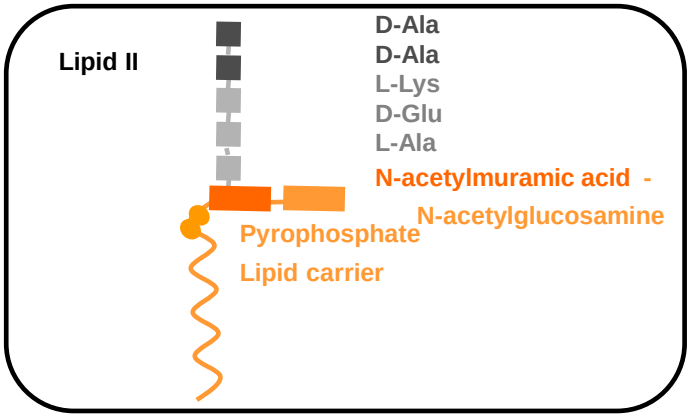


prolonged half-life

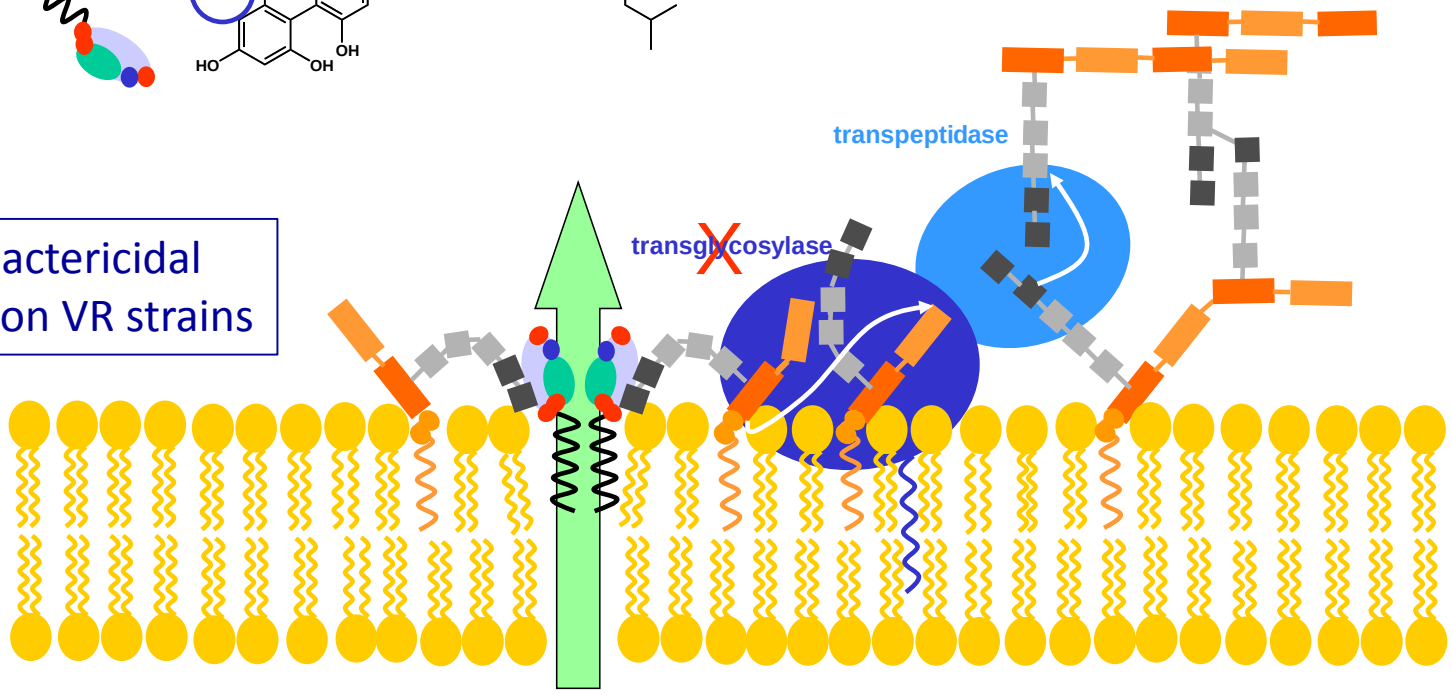
Van Bambeke, Cur. Op. Pharmacol. 2004, 4:471–478

Lipoglycopeptides: dual mode of action





- highly bactericidal
- activity on VR strains



Van Bambeke et al, TIPS 2008, 29:124-134

Lipoglycopeptides: pharmacokinetics

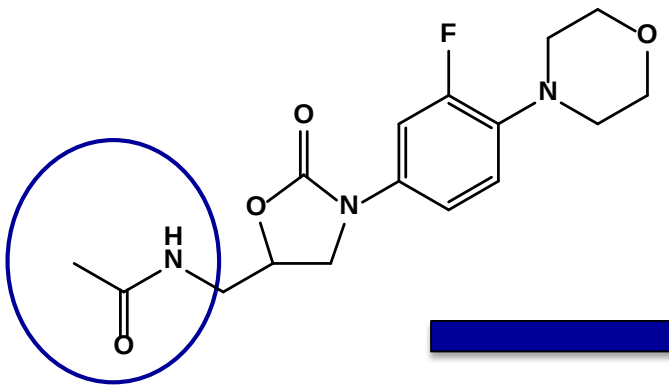
parameter	VAN	ORI	TLV	TEC	DAL
Dosage	15 mg/kg	1200 mg	10 mg/kg	6 mg/kg	1000 mg
Cmax (mg/L)	20-50	138	93	43	287
AUC (mg.h/L)	260	1110 (24h) 2800 (tot)	668	600	3185 (24h) 23443 (tot)
(%) prot. binding	55	85	95	88-94	99
T ½ (h)	1 (β) 3-9 (γ)	14 (β) 245 (γ)	8	10 (β) 168 (γ)	346 (γ)

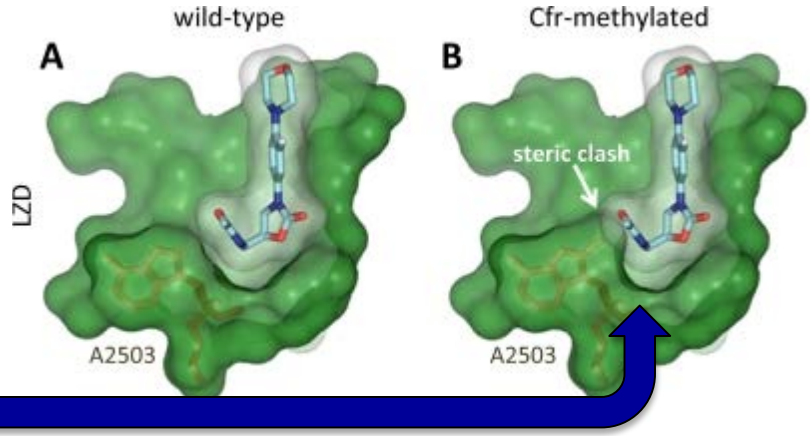
single dose treatment

once-a-week dose treatment (2 doses)

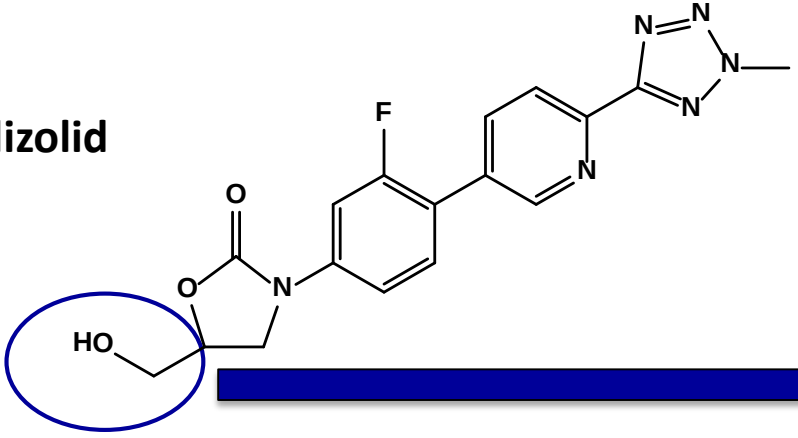
tedizolid vs linezolid

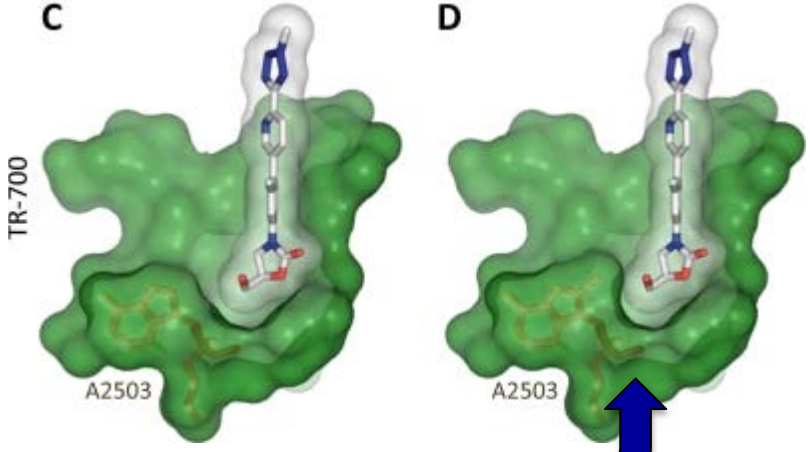
linezolid





tedizolid



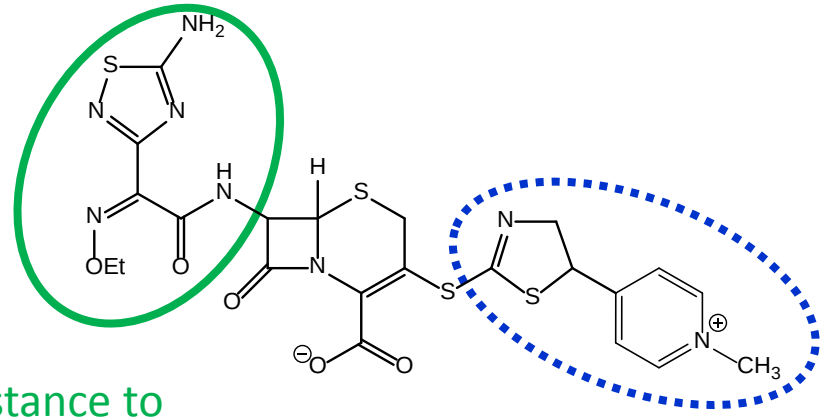


Binding of tedizolid
to methylated ribosomes

Locke et al, AAC (2010) 54: 5337–43

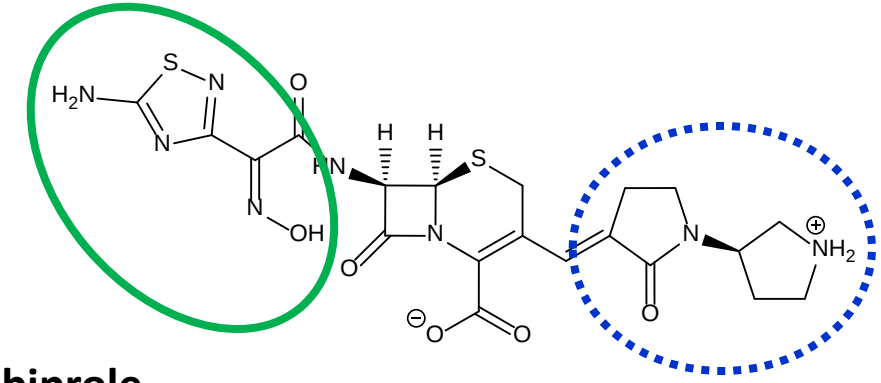
ceftaroline and ceftobiprole

ceftaroline



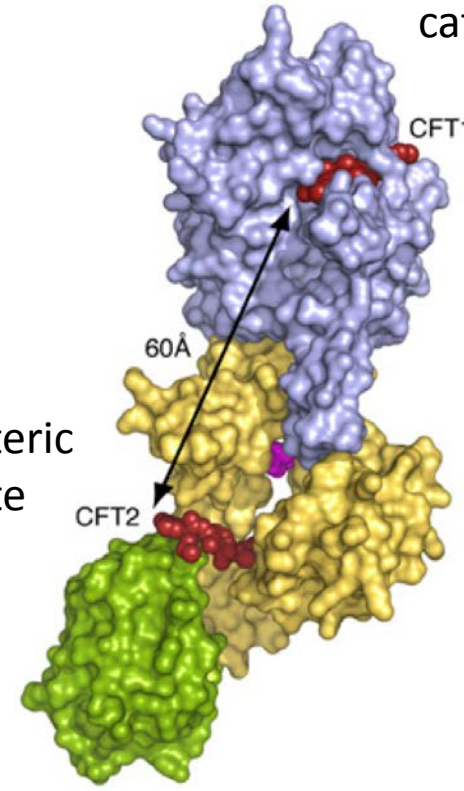
Resistance to β-lactamases

Binding to PBP2a



ceftobiprole

ceftaroline & PBP2a



Otero et al, PNAS (2013) 110:16808–13

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

company	drug	class	status	MRSA	MDRSP	VRE
Cempra	solithromycin	ketolide	Phase III CAPB	✓	✓	
Melinta	delafloxacin	fluoroquinolone	Phase III ABSSSI	✓	✓	
TaiGen	nemonoxacin	fluoroquinolone	Phase III CAPB / ABSSSI	✓	✓	
Dong	zabofloxacin	fluoroquinolone	Phase III CAPB	✓	✓	
Activis	avarofloxacin	fluoroquinolone	Phase II completed CAPB / ABSSSI	✓	✓	
MerLion	finafloxacin	fluoroquinolone	Phase II ABSSSI	✓	✓	
GSK	GSK2140944	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	

Constructed based on www.pewtrusts.org

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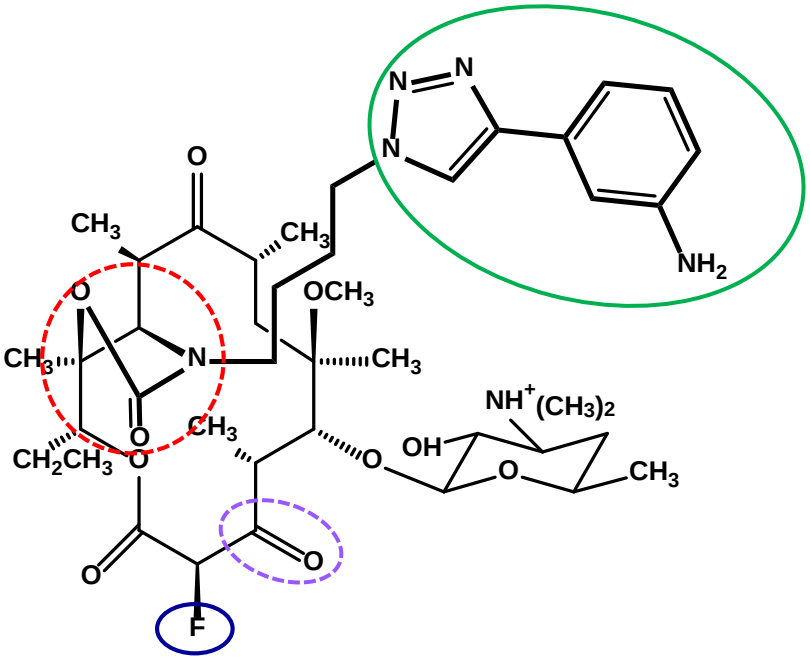
GSK	GSK2140944	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	

Constructed based on www.pewtrusts.org

solithromycin vs telithromycin

lower interaction
with nicotinic receptor

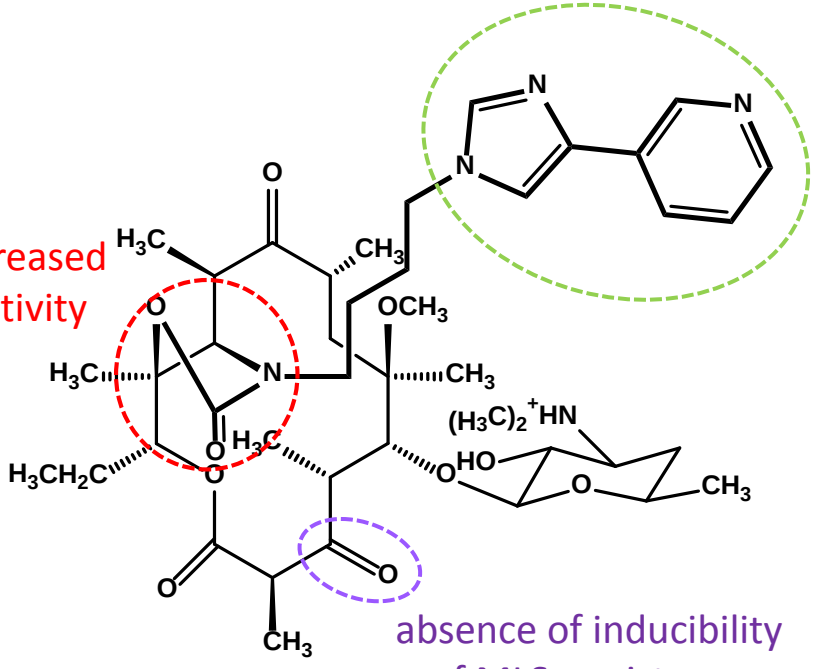


increased
activity

solithromycin

- binding to ribosomal domain II
- poor recognition by pneumococci efflux pumps

increased
activity



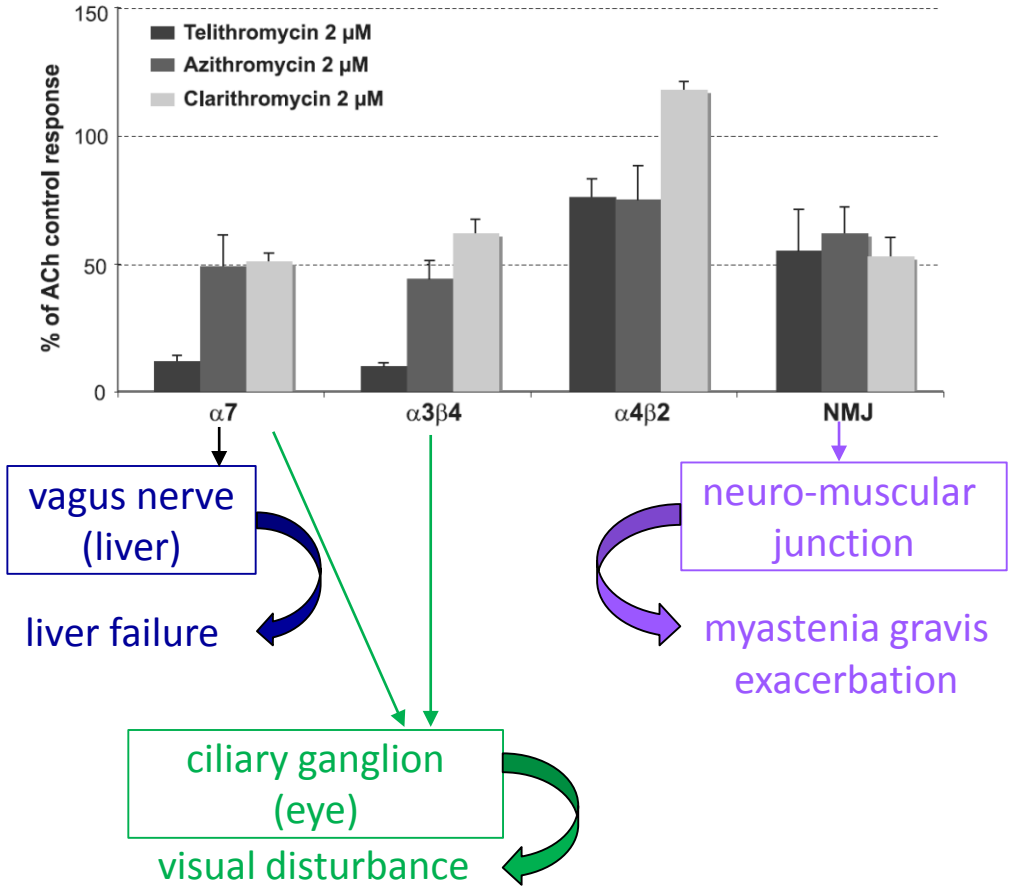
absence of inducibility
of MLS_B resistance

telithromycin

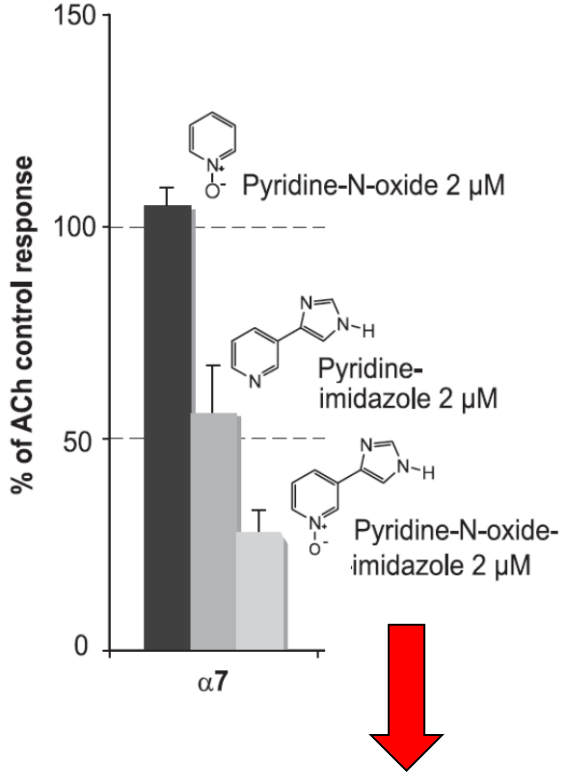
Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

telithromycin : structure-toxicity relationship

Inhibition of acetycholine nicotinic receptors



Role of telithromycin metabolites



Metabolites
NOT present for solithromycin

Adapted from Bertrand et al, AAC (2010) 54:5399-42

solithromycin: ongoing clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
NCT01966055; Phase I	Solithromycin; dose not specified	Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents	Recruiting
NCT01168713; Phase II	Oral solithromycin (800 mg QD day 1; 400 mg QD days 2-5) ; comparator: oral levofloxacin (750 mg QD days 1-5)	Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia	Completed (2011)
NCT01591447; Phase II	Single dose solithromycin 1000 mg by oral route	Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea	Completed (2013)
NCT01968733; Phase III	Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified	Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV)	Recruiting
NCT01756339; Phase III	Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7)	Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL)	Recruiting

Van Bambeke, Ann. Med (2014) 46:512-29

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NCT01756339; Phase III	Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7)	Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL)	Recruiting

Van Bambeke, Ann. Med (2014) 46:512-29

solithromycin : CABP Phase II data

Efficacy summary: clinical success at TOC

Population	Solithromycin 800/400 mg *n/N* (%)[a]	95% CI	Levofloxacin 750 mg *n/N* (%)	95% CI
Co-primary efficacy variable				
ITT	55/65 (84.6)	73.5–92.4	58/67 (86.6)	76.0–93.7
CE	46/55 (83.6)	71.2–92.2	54/58 (93.1)	83.3–98.1
Micro-ITT	14/18 (77.8)	52.4–93.6	10/14 (71.4)	41.9–91.6
ME	12/15 (80.0)	51.9–95.7	10/13 (76.9)	46.2–95.0
Day 3, ITT (according to Biomarkers Consortium criteria)	47/65 (72.3)	59.8–82.7	48/67 (71.6)	59.3–82.0

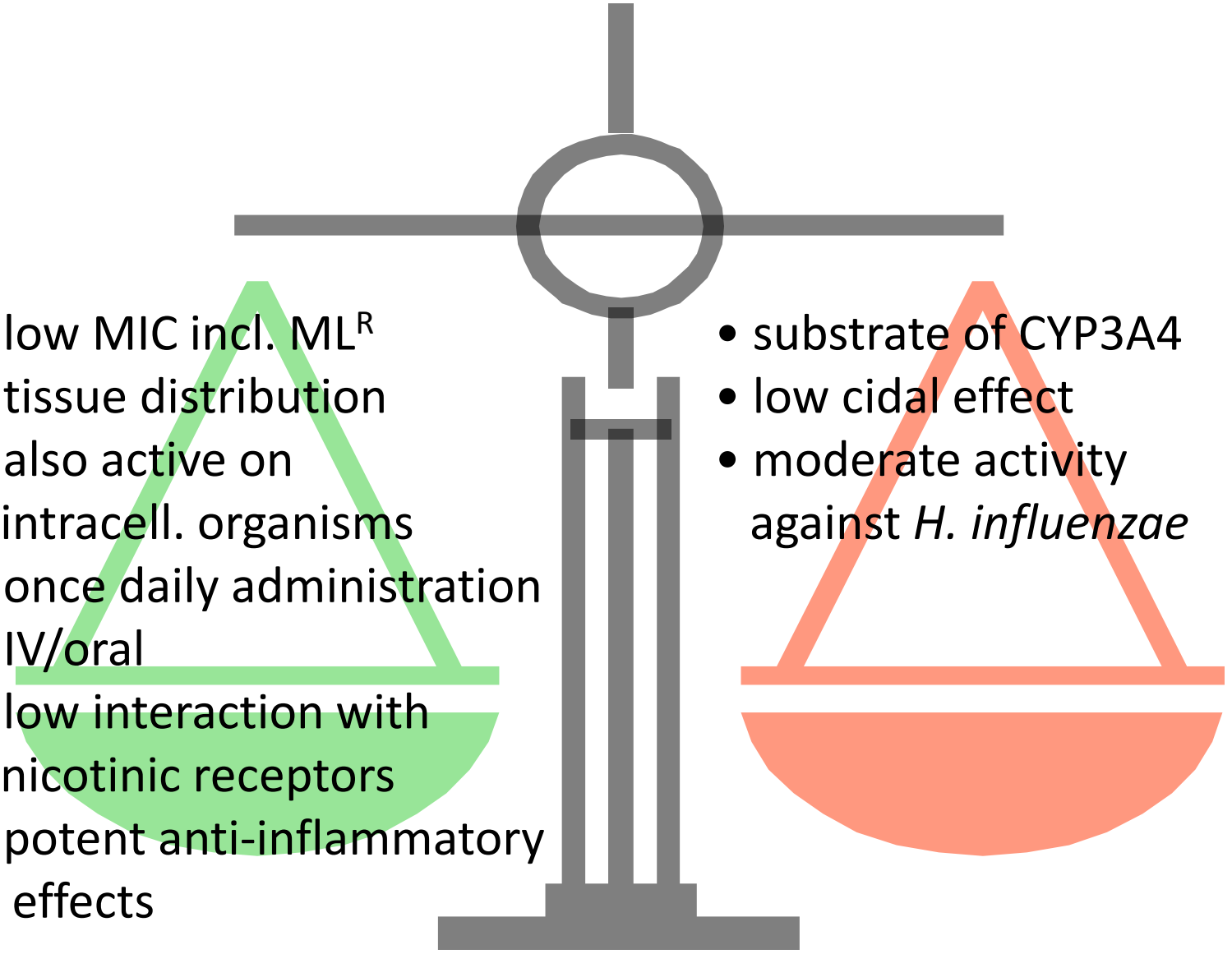
[a] *n*, number of patients with clinical success; *N*, number of patients in the specified population; %, 100 × (*n*/*N*).

Summary of treatment-related AEs

System organ class preferred term	Safety population [*n* (%)] Solithromycin 800/400 mg (*N* = 64)	Levofloxacin 750 mg (*N* = 68)
Patients with at least 1 TEAE considered related to study drug	7 (10.9)	13 (19.1)
Cardiac disorders	0 (0.0)	2 (2.9)
Gastrointestinal disorders	5 (7.8)	7 (10.3)
Investigations	1 (1.6)	1 (1.5)
ALT increased	0 (0.0)	1 (1.5)
AST increased	0 (0.0)	1 (1.5)
Blood CPK increased	1 (1.6)	0 (0.0)
GGT increased	0 (0.0)	1 (1.5)

Oldach et al, AAC (2013) 57:2526-34

Solithromycin : pros and cons



- low MIC incl. ML^R
- tissue distribution
- also active on intracell. organisms
- once daily administration
- IV/oral
- low interaction with nicotinic receptors
- potent anti-inflammatory effects

- substrate of CYP3A4
- low cidal effect
- moderate activity against *H. influenzae*

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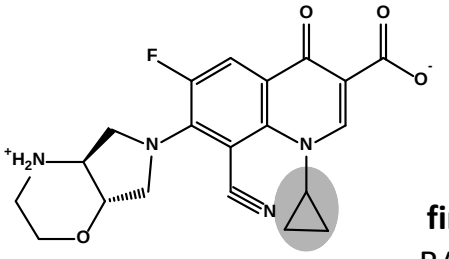
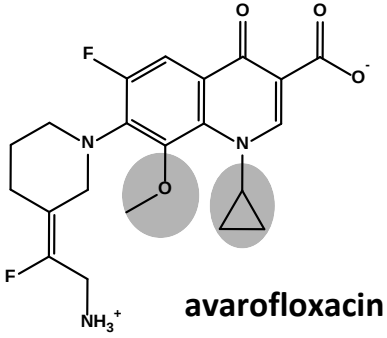
Constructed based on www.pewtrusts.org

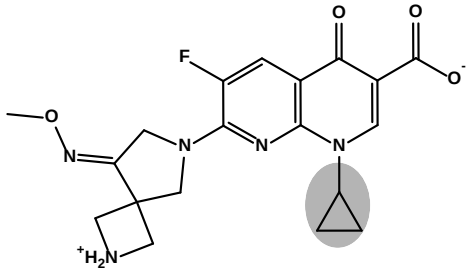
new (fluoro)quinolones



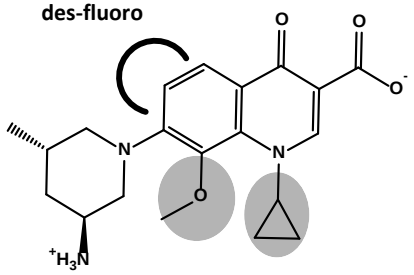
finafloxacin
BAY35-3377



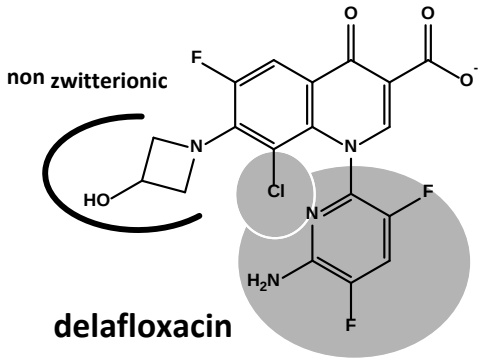
avarofloxacin
JNJ-Q2



zabofloxacin
DW-224a



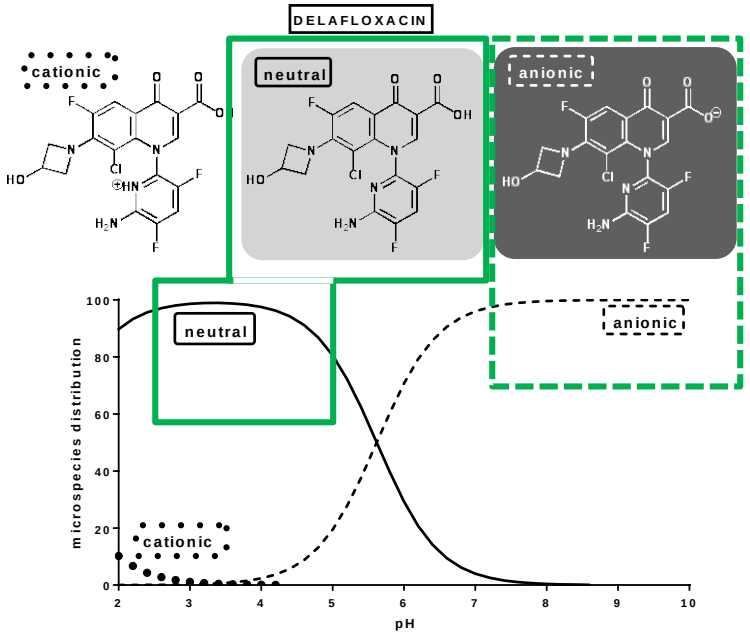
nemonoxacin
TG-873870

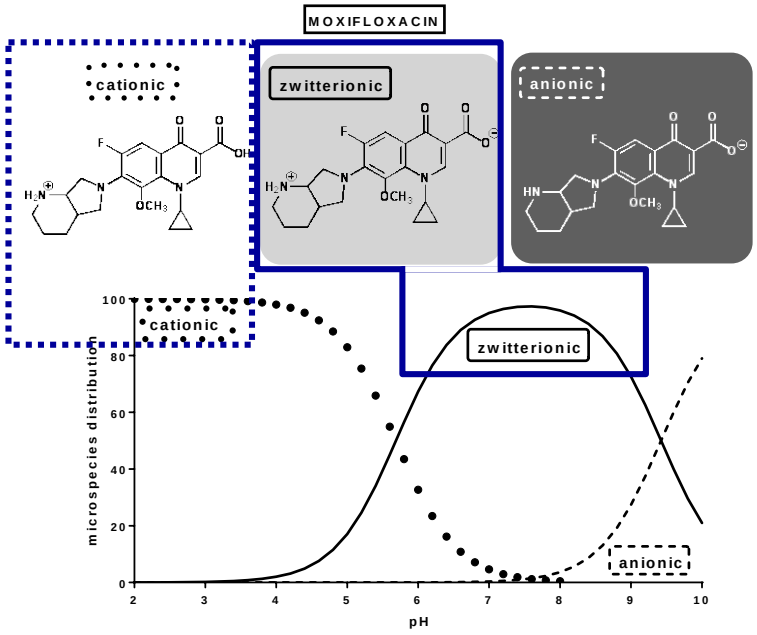


delafloxacin
WQ-3034; ABT-492; RX-3341

Van Bambeke, Ann. Med (2014) 46:512-29

Delafloxacin, the first “non-zwitterionic” quinolone





Van Bambeke, Future Microbiol. (in press)

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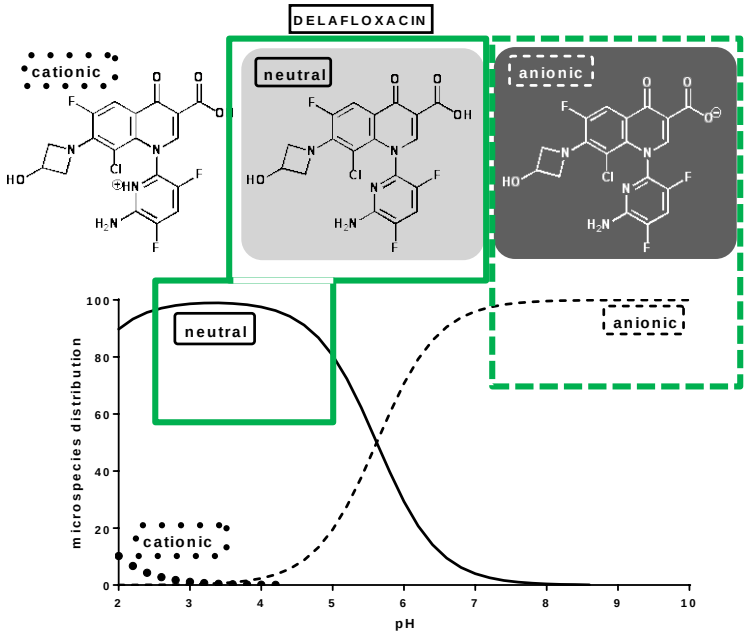
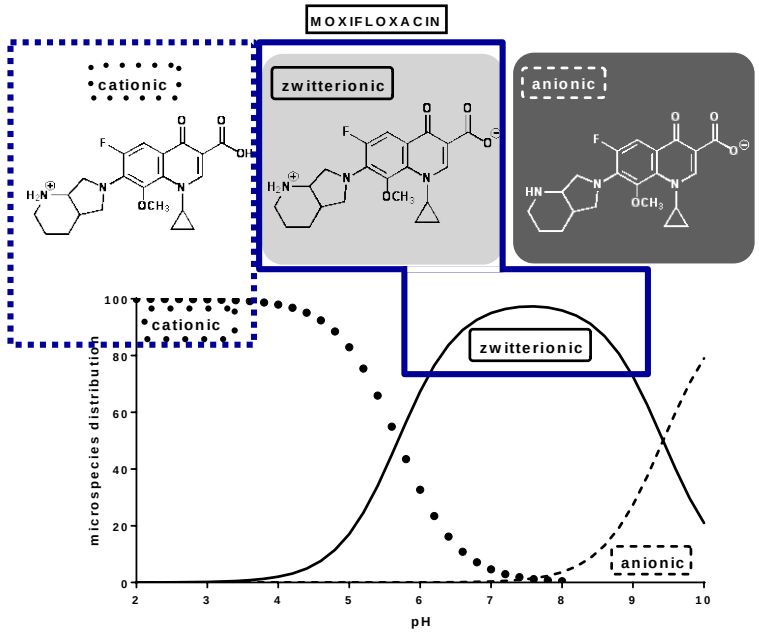
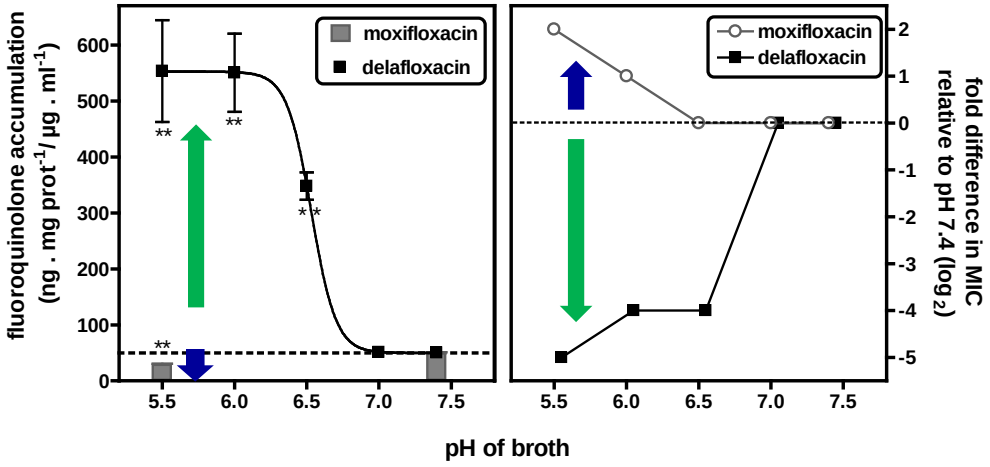




Increased

- uptake by bacteria
- activity at acidic pH



Van Bambeke, Future Microbiol. (in press); Lemaire et al, AAC (2011) 55:649-58

new (fluoro)quinolones: *in vitro* activity

Susceptibility of relevant pathogens to antibiotics in development and their comparators.

Species	Phenotype	Antibiotic	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)
S. aureus	MRSA FQ-S	moxifloxacin	0.06	0.12	0.06–0.25
		finafloxacin	0.125	0.25	0.125–0.25
		zabofloxacin	0.031	0.125	0.016–1
		avarofloxacin	≤0.008	≤0.008	≤0.008–0.015
		nemonoxacin	0.03	0.06	≤0.008–0.12
		delafloxacin			0.008–0.03
	MRSA FQ-R	moxifloxacin	4	8	0.25–>16
		finafloxacin	2	16	0.25–32
		zabofloxacin	2	32	0.016–64
		avarofloxacin	0.25	0.25	0.015–2
		nemonoxacin	4	16	0.25–64
		delafloxacin			0.5–2
S. pneumoniae	all	moxifloxacin	0.12	0.25	0.008–>8
		zabofloxacin	0.063	1	0.008–4
		avarofloxacin	0.008	0.015	≤0.004–1
	S	moxifloxacin	0.12	0.25	0.03–0.25
		zabofloxacin	0.016	0.03	≤0.001–0.06
		nemonoxacin	0.12	0.12	0.06–0.25

⇨as or more active ~ moxifloxacin, but cross resistance

Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

new (fluoro)quinolones: ongoing clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
ZABOFLOXACIN			
NCT01081964; Phase II	Zabofloxacin (400 mg orally QD for 3 or 5 days); comparator: levofloxacin (500 mg orally QD for 7 days)	Safety and Efficacy Study of Oral Zabofloxacin in Community Acquired Pneumonia	Completed (2012)
NCT01658020; Phase III	Zabofloxacin (400 mg orally QD); comparator: moxifloxacin (400 mg orally QD)	A Study to Evaluate Efficacy and Safety Profile of Zabofloxacin Tablet 400mg and Moxifloxacin Tablet 400mg (DW224-III-3) after Multi-dose Oral Administration in Patients With Acute Bacterial Exacerbation of Chronic Obstructive Pulmonary Disease.	Ongoing, not recruiting

Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

new (fluoro)quinolones: ongoing clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
NEMONOXACIN			
NCT00434291; Phase II	Not provided	Safety and Efficacy Comparison of TG-873870 (Nemonoxacin) to Levofloxacin in Community-Acquired Pneumonia	Not provided
NCT00685698; Phase II	Nemonoxacin 750 mg, oral administration, once daily for 7±1 and 14±1 days	Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections	Completed (2009)
NCT01537250; Phase II	Nemonoxacin (750 mg orally 2 tablets or 500 mg orally 3 tablets) ; comparator: levofloxacin (500 mg orally QD + placebo) for 7 days	Study to Assess the Efficacy and Safety of Nemonoxacin Malate in Treating Adult Patients With Community-acquired Pneumonia (CAP)	Completed (2010)
NCT01944774; Phase II	Nemonoxacin (500 mg or 650 mg QD IV for 7~14 days) ; comparator: moxifloxacin (400 mg QD IV for 7~14 days)	Study to Evaluate the Efficacy and Safety of Intravenous Infusion With TG-873870 (nemonoxacin) Versus Moxifloxacin in Treating Adult Patients With Community Acquired Pneumonia (CAP)	Recruiting
NCT01529476; Phase III	Nemonoxacin (500 mg orally) ; comparator levofloxacin (500 mg orally) for 7~14 days	Study to Evaluate the Efficacy and Safety of Oral Administration With Nemonoxacin and Levofloxacin in Patients With Community-acquired Pneumonia (CAP)	Completed (2012)

Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

new (fluoro)quinolones: ongoing clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
NEMONOXACIN			
NCT00434291; Phase II	Not provided	Safety and Efficacy Comparison of TG-873870 (Nemonoxacin) to Levofloxacin in Community-Acquired Pneumonia	Not provided
NCT00685698; Phase II	Nemonoxacin 750 mg, oral administration, once daily for 7±1 and 14±1 days	Safety and Efficacy Study of TG-873870 (Nemonoxacin) in Diabetic Foot Infections	Completed (2009)
NCT01537250; Phase II	Nemonoxacin (750 mg orally 2 tablets or 500 mg orally 3 tablets) ; comparator: levofloxacin (500 mg orally QD + placebo) for 7 days	Study to Assess the Efficacy and Safety of Nemonoxacin Malate in Treating Adult Patients With Community-acquired Pneumonia (CAP)	Completed (2010)
NCT01944774; Phase II	Nemonoxacin (500 mg or 650 mg QD IV for 7~14 days) ; comparator: moxifloxacin (400 mg QD IV for 7~14 days)	Study to Evaluate the Efficacy and Safety of Intravenous Infusion With TG-873870 (nemonoxacin) Versus Moxifloxacin in Treating Adult Patients With Community Acquired Pneumonia (CAP)	Recruiting
NCT01529476; Phase III	Nemonoxacin (500 mg orally) ; comparator levofloxacin (500 mg orally) for 7~14 days	Study to Evaluate the Efficacy and Safety of Oral Administration With Nemonoxacin and Levofloxacin in Patients With Community-acquired Pneumonia (CAP)	Completed (2012)

Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

Nemonoxacin – CABP phase III data

Clinical response at TOC or ET visit

Population	Clinical response	No. of patients (%)		
		Nemonoxacin		Levofloxacin 500 mg
		750 mg	500 mg	
Eval-ITT	*n*	79	77	79
	Clinical cure	71 (89.9)	67 (87.0)	72 (91.1)
	Clinical failure[a]	8 (10.1)	10 (13.0)	7 (8.9)
Eval-PPc	*n*	72	73	72
	Clinical cure	66 (91.7)	64 (87.7)	65 (90.3)
	Clinical failure[a]	6 (8.3)	9 (12.3)	7 (9.7)
ITT	*n*	86	89	90
	Clinical cure	71 (82.6)	67 (75.3)	72 (80.0)
	Clinical failure	15 (17.4)	22 (24.7)	18 (20.0)
PPc	*n*	79	82	79
	Clinical cure	66 (83.5)	64 (78.0)	65 (82.
	Clinical failure	13 (16.5)	18 (22.0)	14 (17.

Summary of drug-related TEAEs (>2%)

System organ class (preferred term)[a]	No. of subjects (%)		
	Nemonoxacin		Levofloxacin 500 mg (n = 90)
	750 mg (n = 86)	500 mg (n = 89)	
Subjects with any drug-related TEAE	27 (31.4)	27 (30.3)	27 (30.0)
Neutropenia	8 (9.3)	8 (9.0)	10 (11.1)
Dizziness	3 (3.5)	4 (4.5)	2 (2.2)
Nausea	5 (5.8)	1 (1.1)	3 (3.3)
Diarrhea	1 (1.2)	5 (5.6)	1 (1.1)
Thrombocythemia	4 (4.7)	2 (2.2)	1 (1.1)
ECG QTc interval prolonged	2 (2.3)	0	3 (3.3)
Blood amylase increased	1 (1.2)	1 (1.1)	2 (2.2)
Headache	1 (1.2)	2 (2.2)	0
ALT/SGPT	0	2 (2.2)	1 (1.1)
AST/SGOT	0	2 (2.2)	0

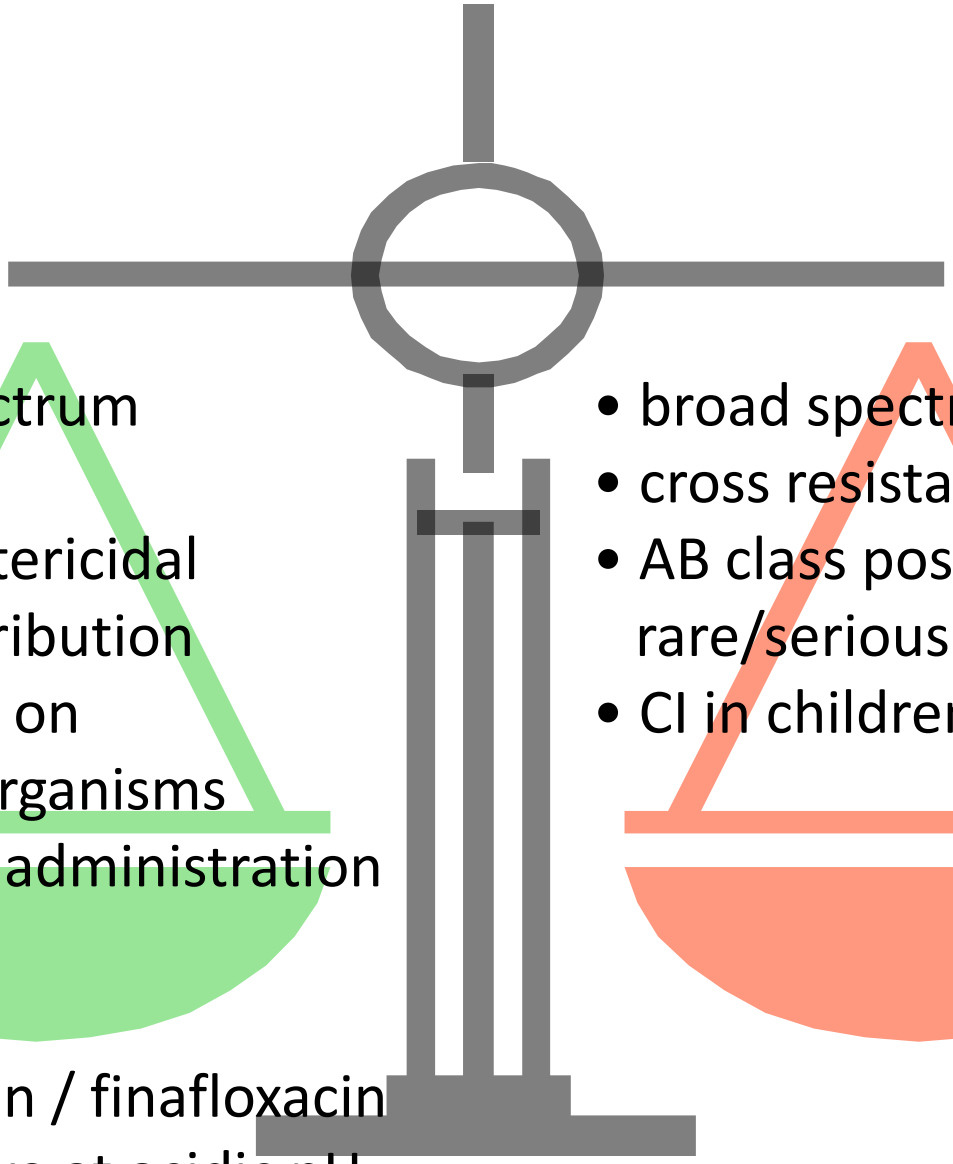
Van Rensburg et al, AAC (2010) 54:4098-106

new (fluoro)quinolones: ongoing clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
DELAFLOXACIN			
NCT00719810; Phase II	Delafloxacin (300 mg or 450 mg IV BID) ; comparator: tigecycline (100 mg on day 1 then 50 mg IV BID)	Safety and Efficacy Study of a Fluoroquinolone to Treat Complicated Skin Infections	Completed (2008)
NCT01283581; Phase II	Delafloxacin (300mg IV BID) for 5-14 days; comparators: linezolid (600mg IV BID) and vancomycin (15mg/kg, up to 1250 mg, IV BID) for 5-14 days	A Study to Assess Objective Endpoint Measurements of Response in Bacterial Skin Infections	Completed (2011)
NCT01811732; Phase III	Delafloxacin (300 mg IV BID) for up 5-14 days; comparator: vancomycin (15mg/kg IV) + aztreonam (2g) BID	Delafloxacin Versus Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections	Recruiting
NCT01984684; Phase III	Delafloxacin (300 mg IV BID 300mg iv BID for 3 days) followed by 450mg oral BID for up 5-14 days total; comparator: vancomycin (15mg/kg IV) + aztreonam (2g) BID	Delafloxacin vs Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections	Not yet recruiting

Adapted from Van Bambeke, Ann. Med (2014) 46:512-29

new (fluoro)quinolones : pros and cons



- broad spectrum
- low MICs
- highly bactericidal
- tissue distribution
- also active on intracell. organisms
- once daily administration
- oral or IV

- broad spectrum
- cross resistance with other FQ
- AB class possibly showing rare/serious side effects
- CI in children/pregnancy

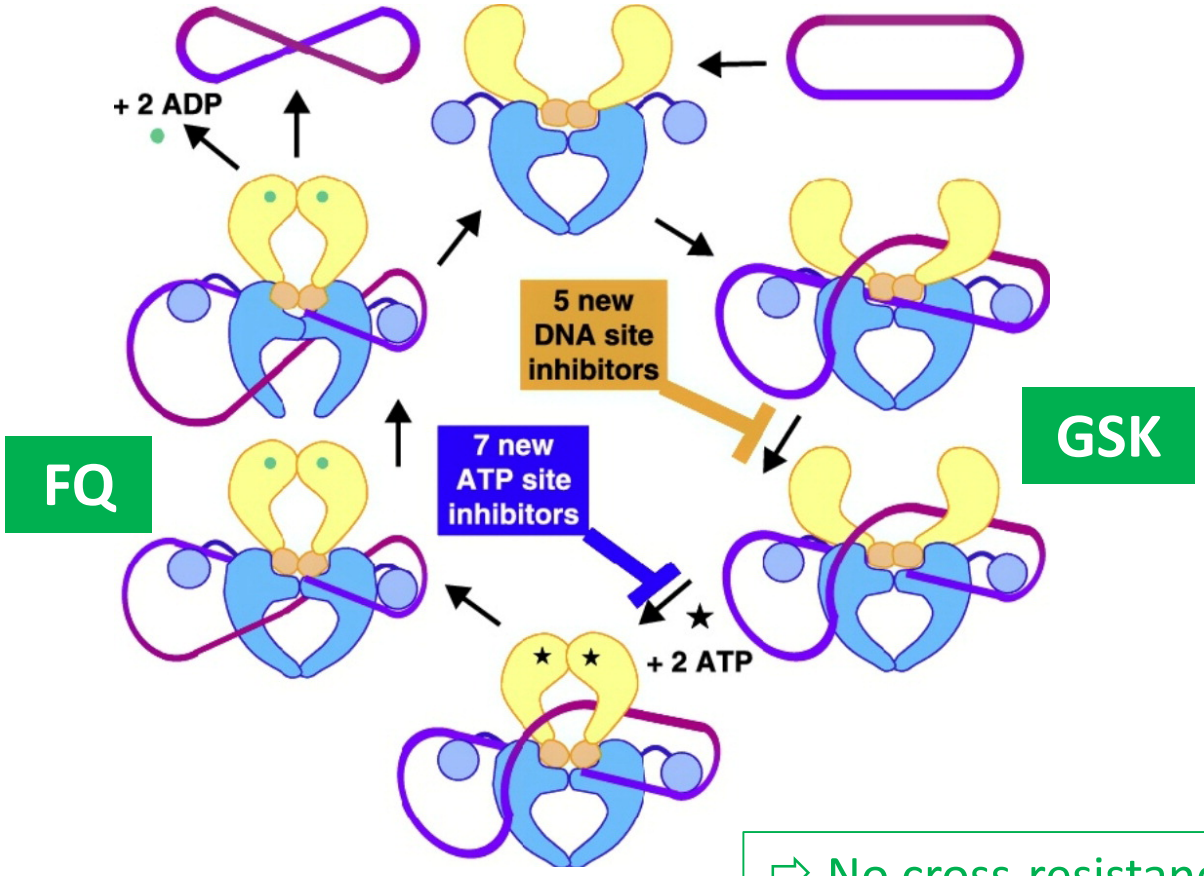
- delafloxacin / finafloxacin highly active at acidic pH

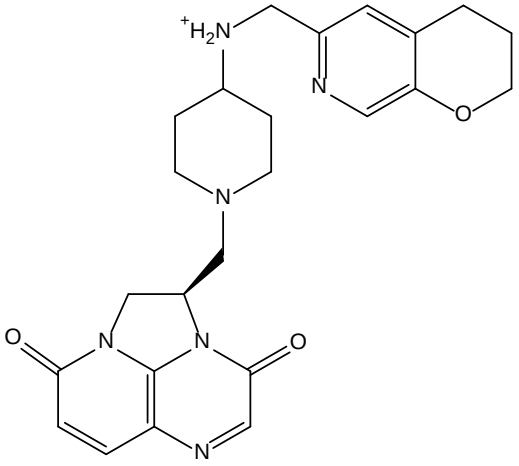
Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

company	drug	class	status	MRSA	MDRSP	VRE
Cempra	solithromycin	ketolide	Phase III CAPB	✓	✓	
Melinta	delafloxacin	fluoroquinolone	Phase III	✓	✓	
TaiGen	nemonoxacin	fluoroquinolone	Phase III CAPB / ABSSSI	✓	✓	
Dong	zabofloxacin	fluoroquinolone	Phase III CAPB	✓	✓	
Activis	avarofloxacin	fluoroquinolone	Phase II completed CAPB / ABSSSI	✓	✓	
MerLion	finafloxacin	fluoroquinolone	Phase II ABSSSI	✓	✓	
GSK	GSK2140944	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	

Constructed based on www.pewtrusts.org

GSK2140944 – topoisomerase inhibitor





⇨ No cross-resistance with fluoroquinolones

Ehmann & Lahiri, Cur. Op. Pharmacol. (2014) 18:76–83

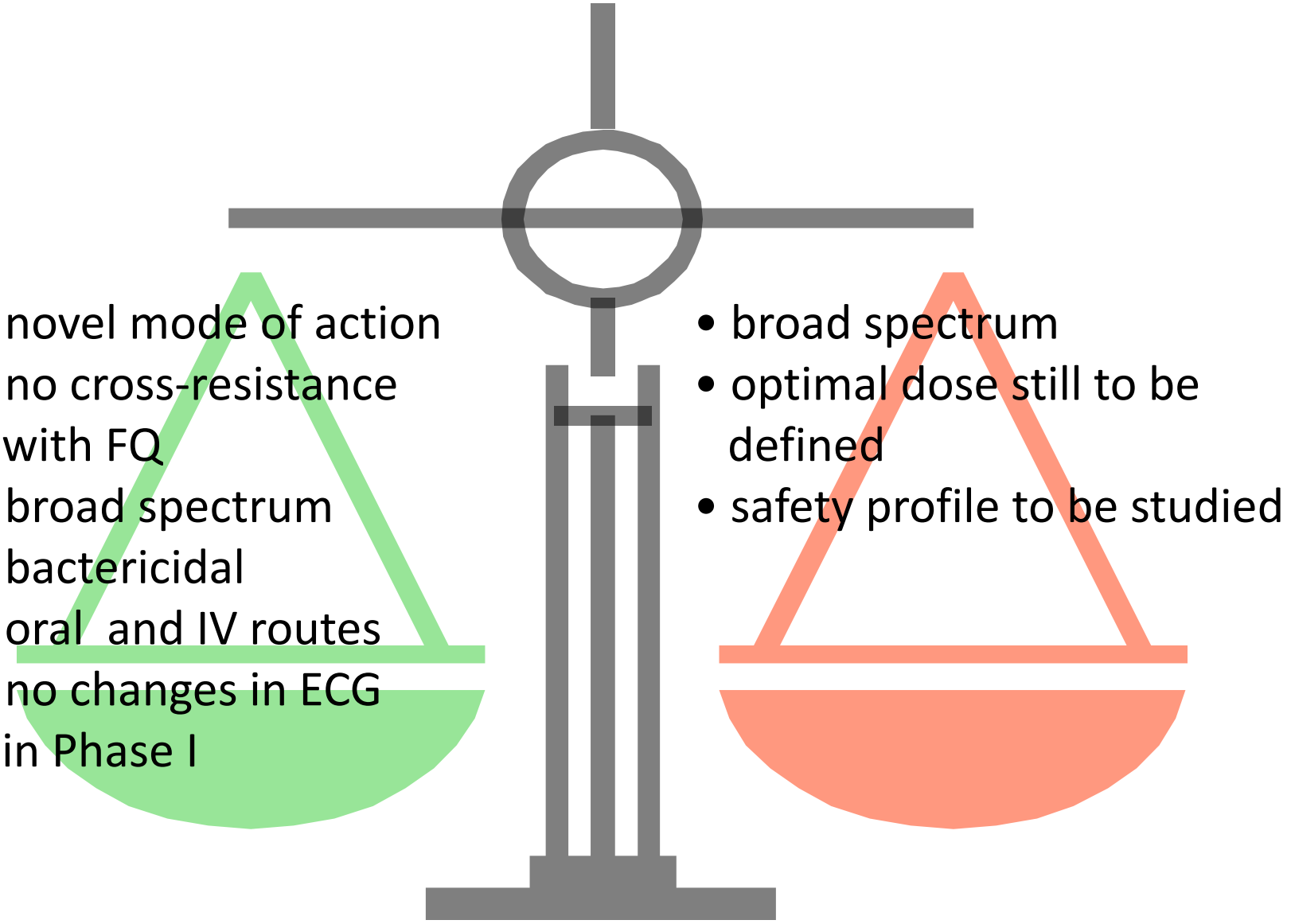
GSK2140944 – *In vitro* activity

Isolates Associated with Lower Respiratory Tract and Skin Infections

Organism (N)	MIC Range	MIC_{50}	MIC_{90}
SA (1,008)	≤0.06 - 2	0.25	0.5
Methicillin-resistant SA (490)	≤0.06-1	0.5	0.5
Levofloxacin-resistant MRSA (375)	≤0.06-1	0.25	0.5
Spy (201)	0.03-0.5	0.25	0.25
Spn (549)	0.03-1	0.12	0.25
Levofloxacin-resistant Spn (22)	0.06-0.5	0.25	0.5
HI (n=981)	≤0.015-8	0.5	1
MC (n=158)	≤0.06 - 0.12	≤0.06	≤0.06

ICAAC (2013) F1216

GSK2140944 : pros and cons



- novel mode of action
- no cross-resistance with FQ
- broad spectrum
- bactericidal
- oral and IV routes
- no changes in ECG in Phase I

- broad spectrum
- optimal dose still to be defined
- safety profile to be studied

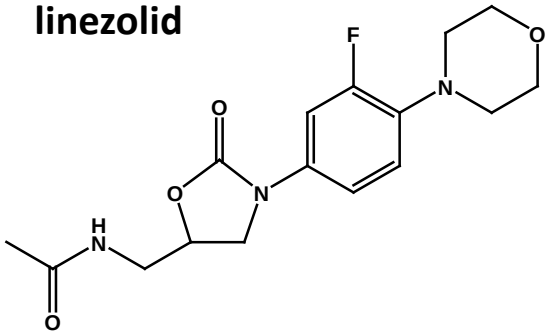
Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

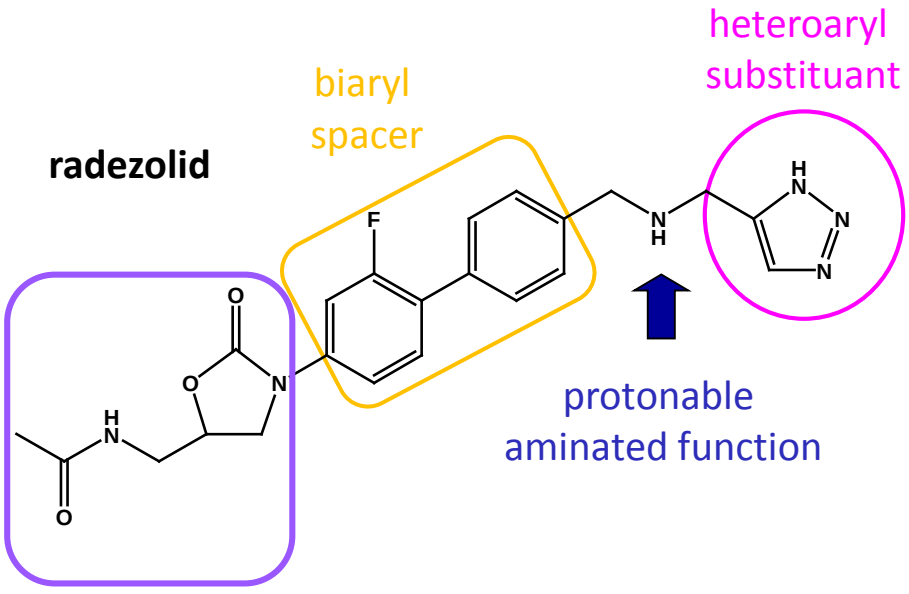
Constructed based on www.pewtrusts.org

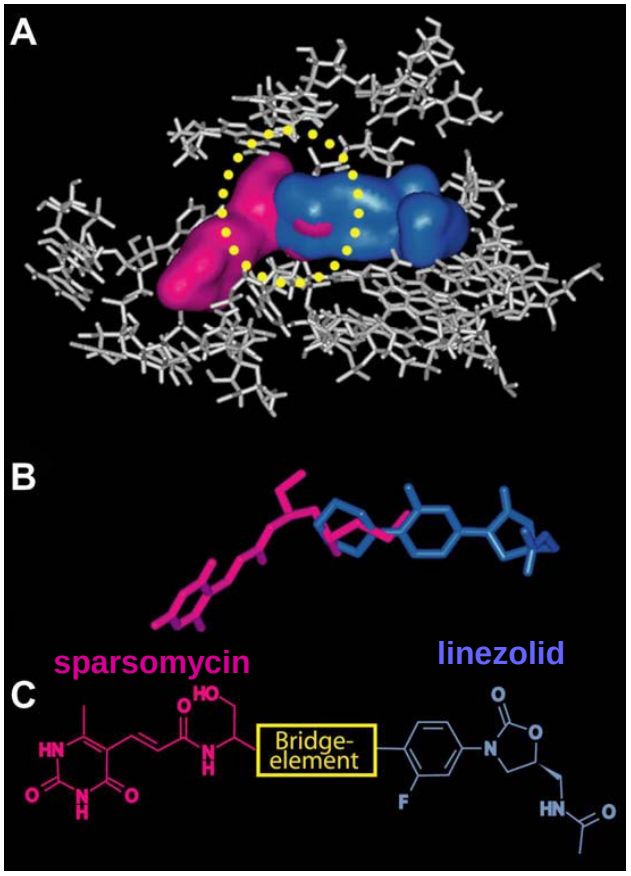
radezolid vs linezolid

linezolid



radezolid





Zhou et al., J. Bioorg. Med. Chem. Lett. (2008) 18:6179-83

Radezolid vs linezolid

Oxazolidinone MICs for *S. aureus* ribosomal mutants

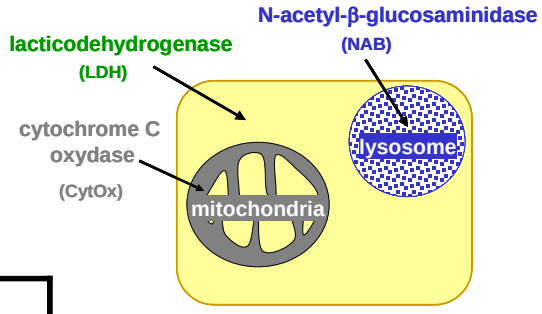
Strain[a]	Source or reference	Resistance mechanism[b]	MIC (μg/ml)[c]		
			LZD	TR-700	RZD
29213	ATCC		2	0.5	1
29213-1	43	23S (G2447T ×3)	32	4	4
29213-2	43	23S (T2500A ×2)	8	2	4
29213-3	43	L3 (ΔPhe127-His146)	8	2	2
33591	ATCC		1	0.25	0.5
33591-1	43	23S (G2576T ×3)	16	2	2
33591-2	43	23S (G2576T/T2571C ×3)	16	2	2
33591-3	43	L4 (Lys68Gln)	2	0.5	1
NRS127	NARSA[d]	L3 (ΔSer145)	8	1	4

Oxazolidinone MICs for *S. aureus cfr* strains

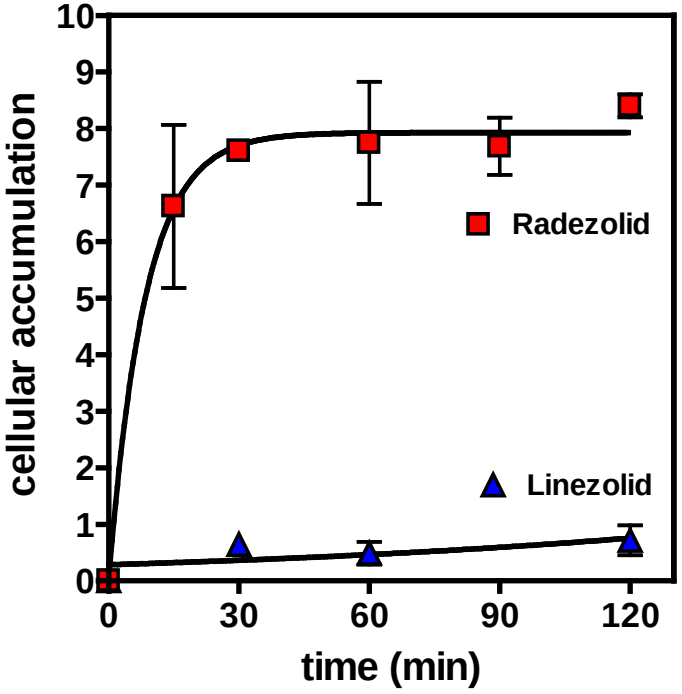
Strain	Reference	Presence of *cfr*	MIC (μg/ml)[a]		
			LZD	TR-700	RZD
RN4220(pLI50)	68	–	2	0.5	0.5
RN4220(pLXM1)[b]	68	+	8	0.5	1
CM05Δ[c]	44	–	2	0.5	1
CM05[c]	68	+	8	0.5	2
29213	ATCC	–	2	0.5	1
29213(p42262)[d]	45	+	16	0.5	2
42262[e]	51	+	16	0.5	4

Locke et al, AAC (2010) 54: 5337–43

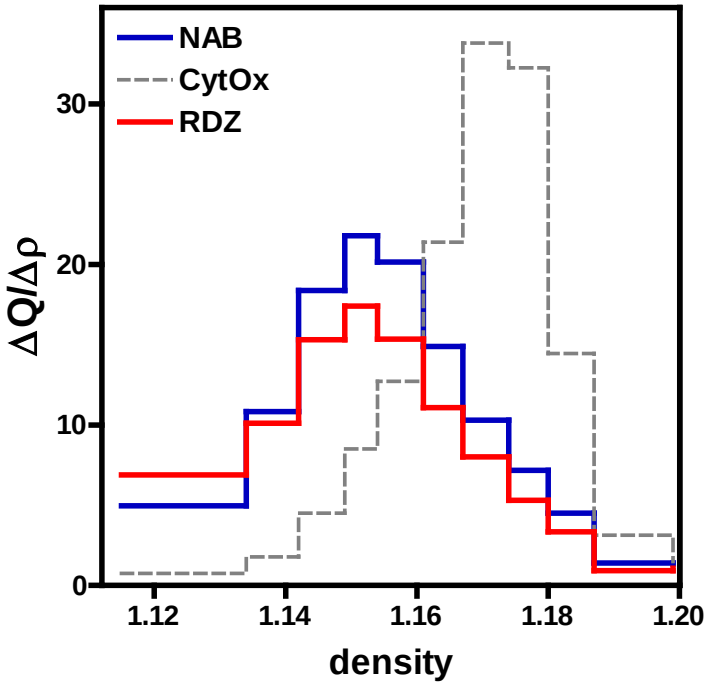
Radezolid cellular pharmacokinetics in macrophages



Cellular accumulation



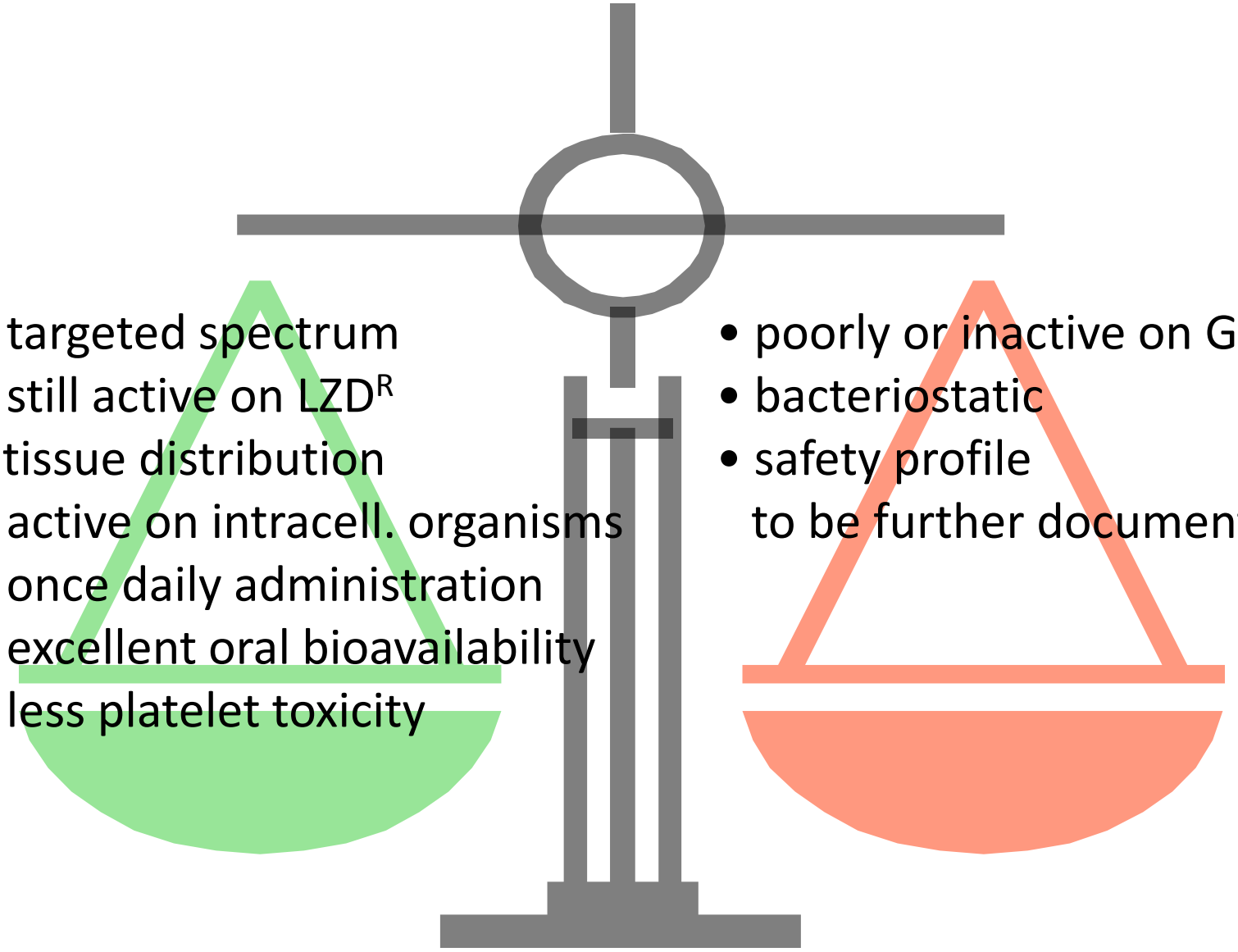
Subcellular distribution



⇨accumulation in acidic vacuoles

Lemaire et al., AAC (2010) 54:2540-48

new oxazolidinones : pros and cons



- targeted spectrum
- still active on LZD^R
- tissue distribution
- active on intracell. organisms
- once daily administration
- excellent oral bioavailability
- less platelet toxicity

- poorly or inactive on Gram(-)
- bacteriostatic
- safety profile
  to be further documented

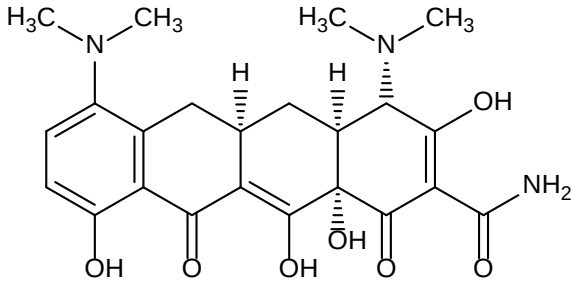
Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

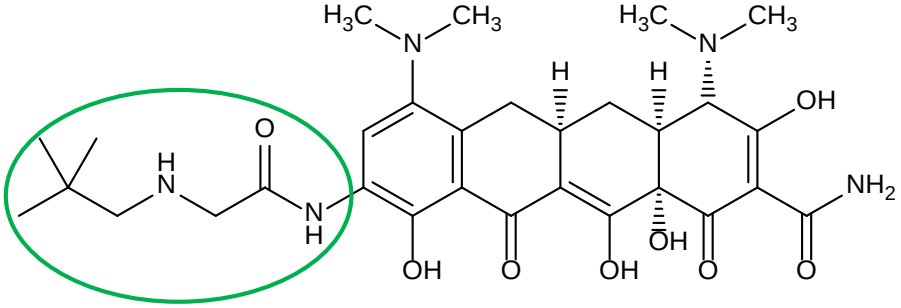
Constructed based on www.pewtrusts.org

Omadacycline (PTK-0796) vs tigecycline

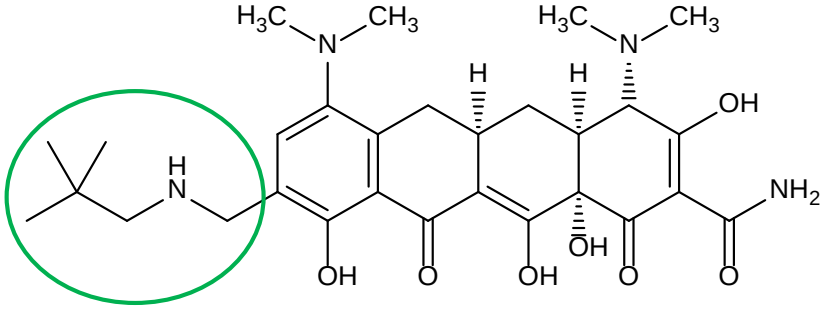
minocycline

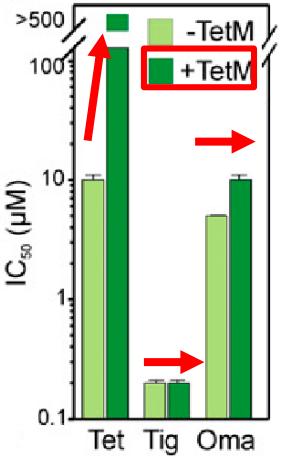


tigecycline



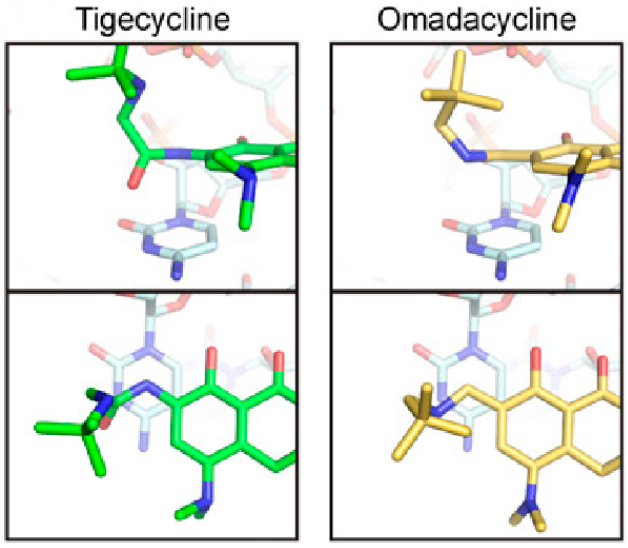
omadacycline





Active if
- ribosomal protection
- Tet-mediated efflux

Inactive if broad spectrum efflux (*P. aeruginosa*)



Jenner et al., PNAS (2013) 110:3812-16

Omadacycline : CSSSI Phase II data

Omadacycline 100 mg [i.v.] QD; possible transition to 200 mg [p.o.] QD
linezolid 600 mg [i.v.] BID; possible transition to 600 mg [p.o.]y BID

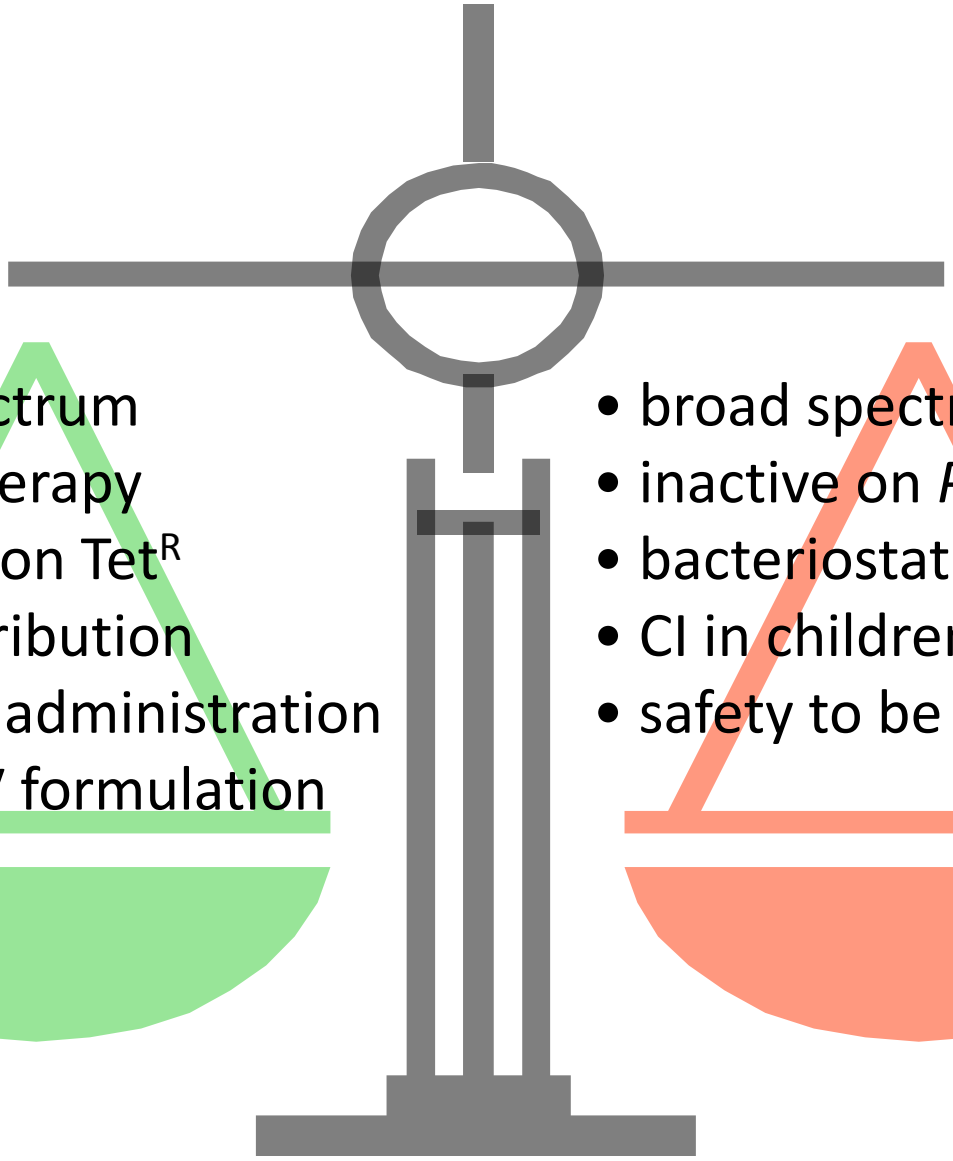
TABLE 4 Rates of successful clinical response at test of cure by analysis population

Population	Rate of clinical response (% [no. successful/total no.]) in patients given:	
	Omadacycline	Linezolid
Intent to treat	88.3 (98/111)	75.9 (82/108)
Modified intent to treat	89.3 (75/84)	75.6 (59/78)
Clinically evaluable	98.0 (98/100)	93.2 (82/88)
Subjects with no prior antibiotics[a]	96.3 (53/55)	95.2 (40/42)
Microbiologically evaluable	97.4 (75/77)	93.7 (59/63)
S. aureus	97.2 (70/72)	92.7 (51/55)
MRSA	97.7 (43/44)	93.8 (30/32)
Gram-positive bacterium other than *S. aureus*	100 (3/3)	100 (7/7)
Gram-negative bacterium	100 (2/2)	100 (1/1)

[a] No prior antibiotic exposure 72 h before enrollment.

Noel et al., AAC (2012) 56:5650-546

Omadacycline: pros and cons



- broad spectrum
  -> monotherapy
- still active on Tet^{R}
- tissue distribution
- once daily administration
- oral and IV formulation

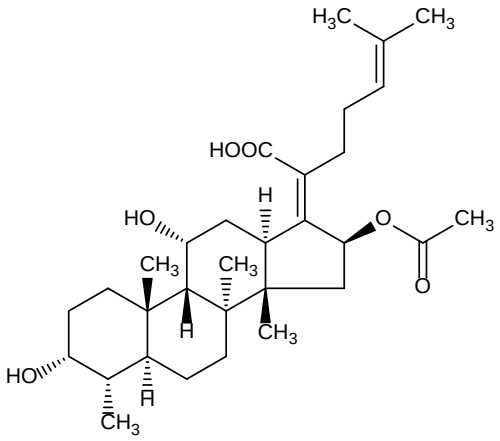
- broad spectrum
- inactive on *P. aeruginosa*
- bacteriostatic
- CI in children/pregnancy
- safety to be documented

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

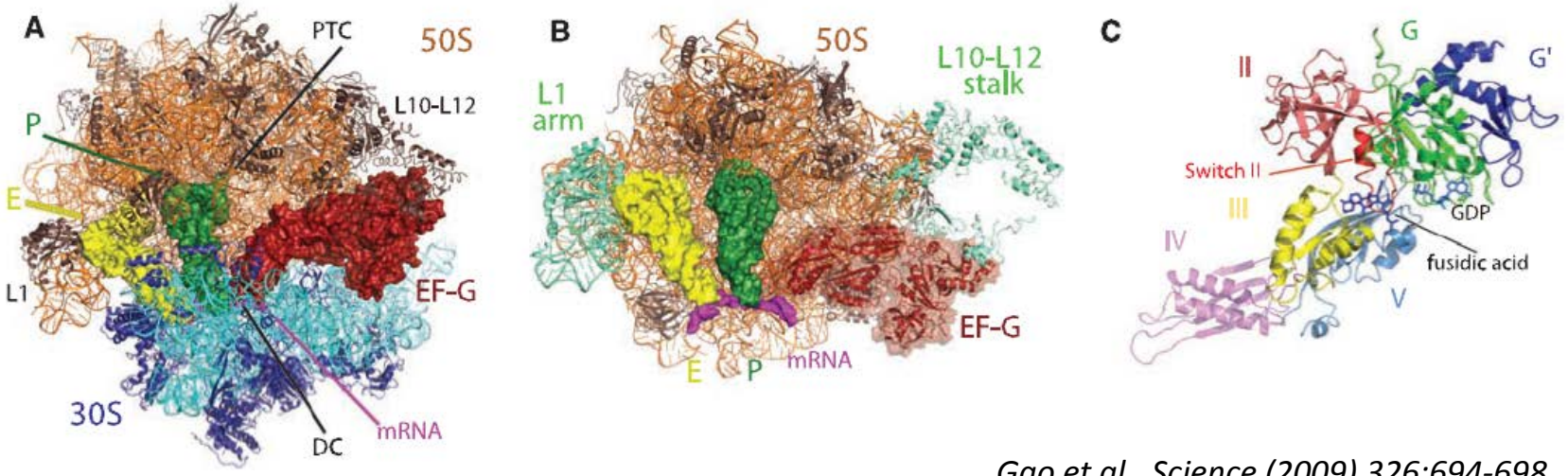
Constructed based on www.pewtrusts.org

Fusidic acid



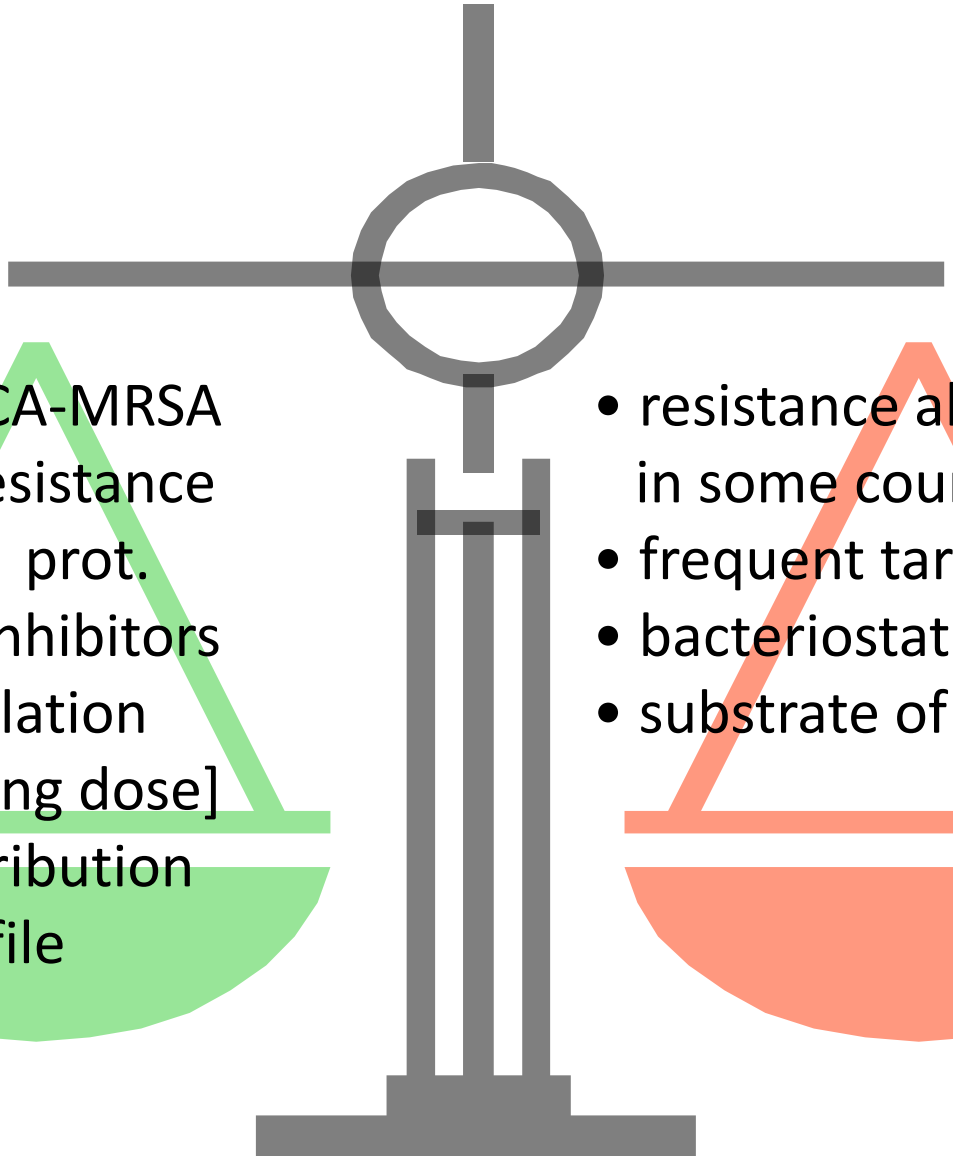
Elongation factor G = GTP-ase
~ translocation of tRNA-mRNA

Fusidic acid prevents EF-G release from the ribosome



Gao et al., Science (2009) 326:694-698

Fusidic acid: pros and cons



- active on CA-MRSA
- no cross resistance with other prot. synthesis inhibitors
- oral formulation [with loading dose]
- tissue distribution
- safety profile

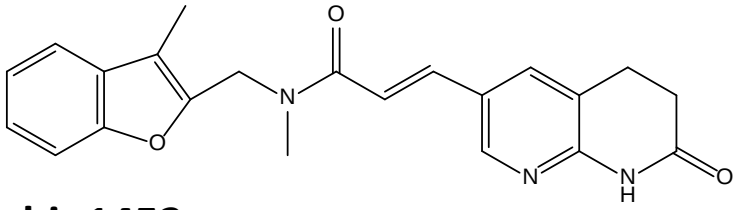
- resistance already spread in some countries
- frequent target mutations
- bacteriostatic
- substrate of CYP 3A4

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

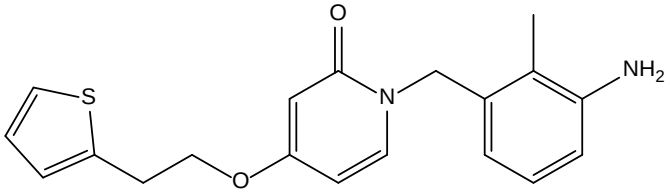
company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

Constructed based on www.pewtrusts.org

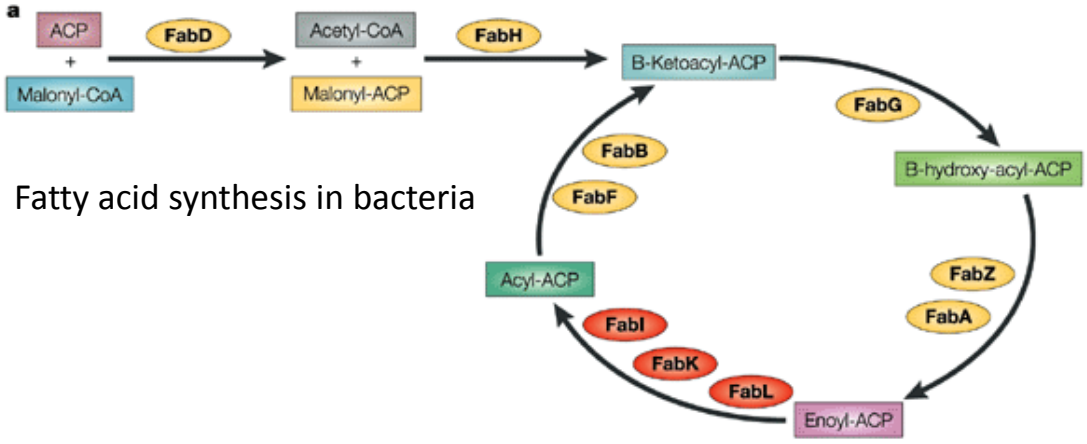
FabI (Enoyl-[acyl-carrier-protein] reductase) inhibitors



Debio1452

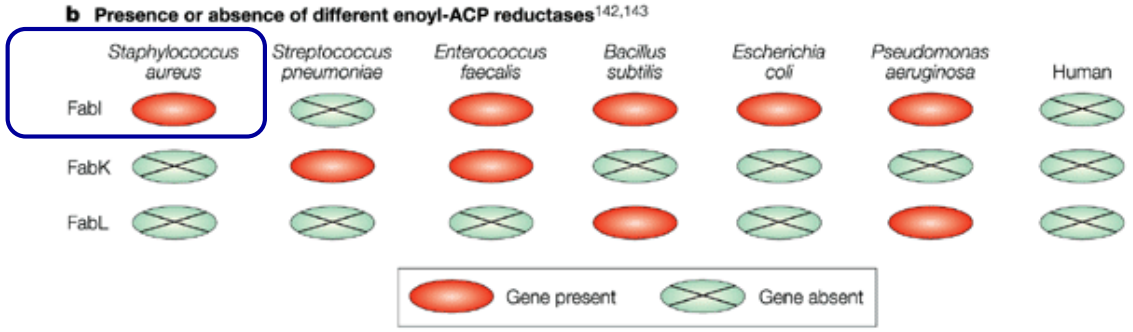


CG-400549



Fatty acid synthesis in bacteria

Specifically active on *S. aureus*



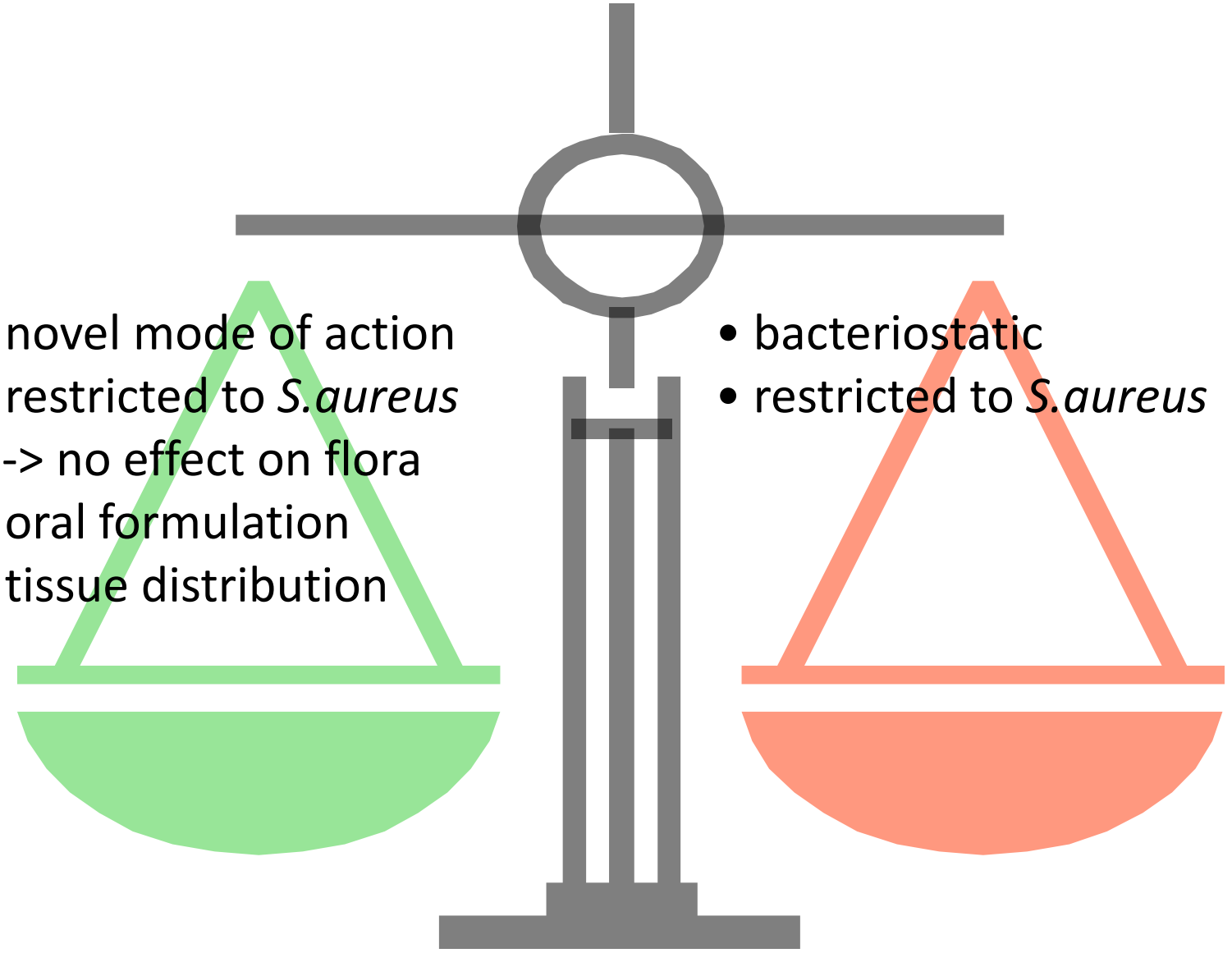
Miesnel et al, Nature Rev. Gen. (2003) 4: 442-456

Debio (AFN) 1252 *in vitro* activity

Species or isolate group (no. of isolates)	Agent	MIC (μg/ml)		
		50%	90%	Range
Methicillin-resistant *S. aureus* (127)	AFN-1252	≤0.008	≤0.008	≤0.008–0.06
	Cefazolin	64	>128	32–>128
	Ciprofloxacin	>16	>16	0.25–>16
	Clindamycin	>8	>8	≤0.12–>8
	Gentamicin	≤0.5	>32	≤0.5–>32
	Linezolid	2	4	0.25–4
	Trimethoprim-sulfamethoxazole	≤0.12	8	≤0.12–>8
	Vancomycin	1	1	≤0.25–2
Methicillin-resistant *S. epidermidis* (9)	AFN-1252	≤0.008	≤0.008	≤0.008
	Cefazolin	64	128	32–128
	Ciprofloxacin	>16	>16	8–>16
	Clindamycin	>8	>8	≤0.12–>8
	Gentamicin	16	>32	≤0.5–>32
	Linezolid	1	1	0.5–1
	Trimethoprim-sulfamethoxazole	4	8	≤0.12–>8
	Vancomycin	1	2	1–2
Streptococcus pneumoniae (489)	AFN-1252	>4	>4	4–>4
	Penicillin	0.06	0.25	≤0.03–>8
	Levofloxacin	0.5	1	≤0.06–32
	Ceftriaxone	≤0.06	0.12	≤0.06–4
	Linezolid	0.5	1	≤0.12–2
	Trimethoprim-sulfamethoxazole	≤0.12	1	≤0.12–>8
	Vancomycin	≤0.25	≤0.25	≤0.25–0.5
Enterococcus faecalis (81)	AFN-1252	>4	>4	>4
	Cefazolin	32	128	0.5–>128
	Ciprofloxacin	2	>16	0.25–>16
	Clindamycin	>8	>8	≤0.12–>8
	Linezolid	2	2	0.5–4
	Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–>8
	Vancomycin	1	2	0.5–4

Karlowsky et al, AAC (2009) 53: 3544-48

FabI inhibitors: pros and cons



- novel mode of action
- restricted to *S.aureus*
  -> no effect on flora
- oral formulation
- tissue distribution

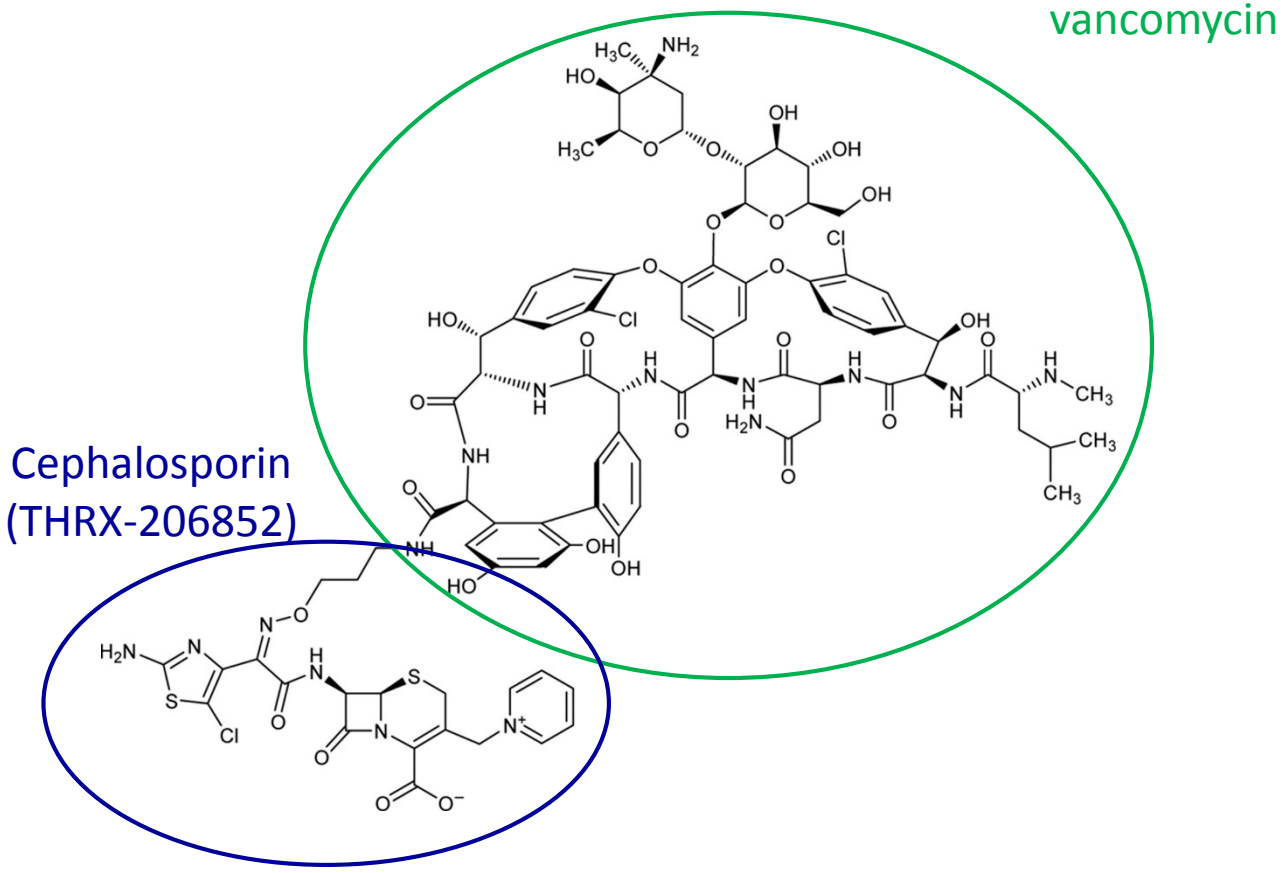
- bacteriostatic
- restricted to *S.aureus*

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

Constructed based on www.pewtrusts.org

TD-1792



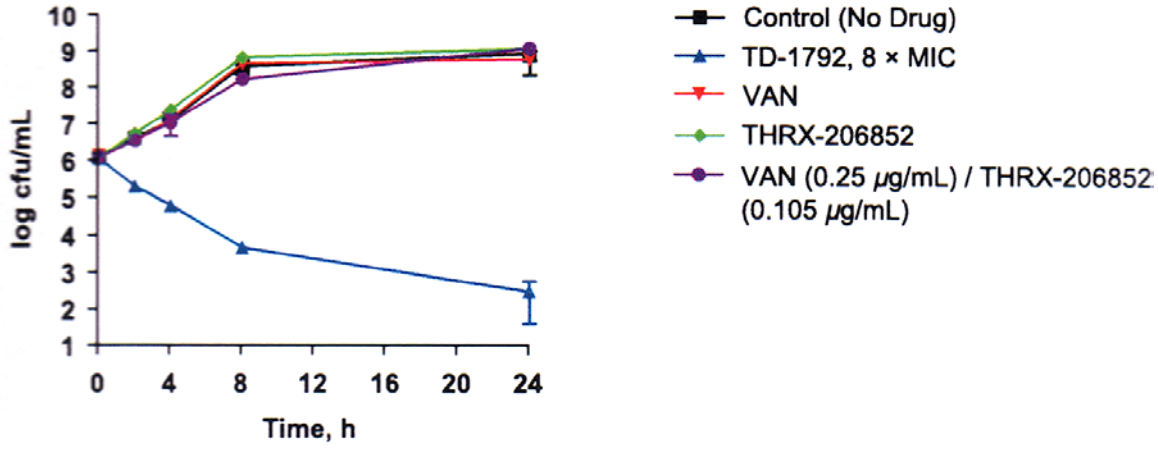
Long et al, J. Antibiot. (2008) 61:603-14

TD-1792 : *in vitro* activity

1 In Vitro Activities of TD-1792 and Related Substructures

Antimicrobial Agent	MIC, μg/mL		
	MSSA	MRSA	VISA
TD-1792	0.015	0.03	0.03-0.06
VAN	1	1	8
THRX-206852	2	16	16-32
VAN / THRX-206852[a]	1 / 0.42	1 / 0.42	4 / 1.68

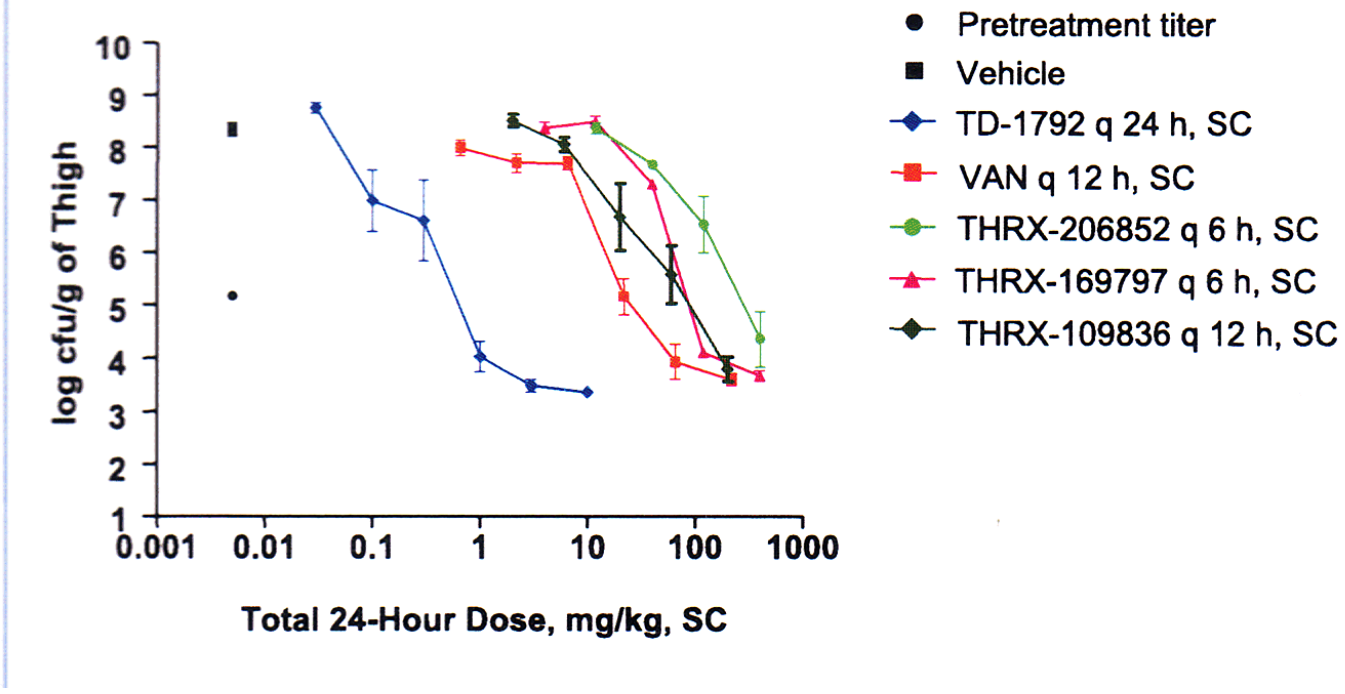
3 Bactericidal Activity of TD-1792 and Related Substructures Tested at 0.25 μg/mL Against MRSA



ICAAC (2007) F1-2110

TD-1792 : *in vivo* activity

4 Dose-Response Curve for TD-1792 and Related Substructures Against MRSA



ICAAC (2007)

TD-1792 : cSSSI Phase II data

TD-1792 : 2 mg/kg once daily vs vancomycin 1 g twice daily

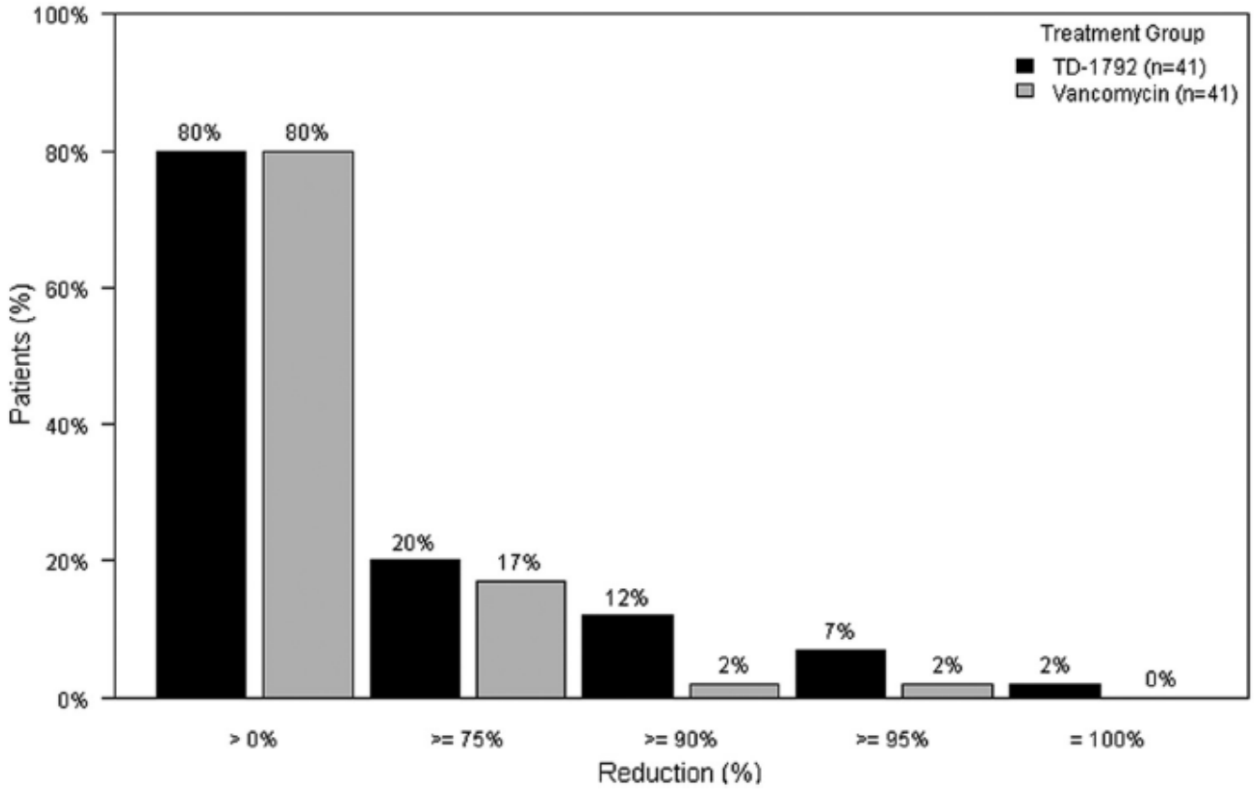
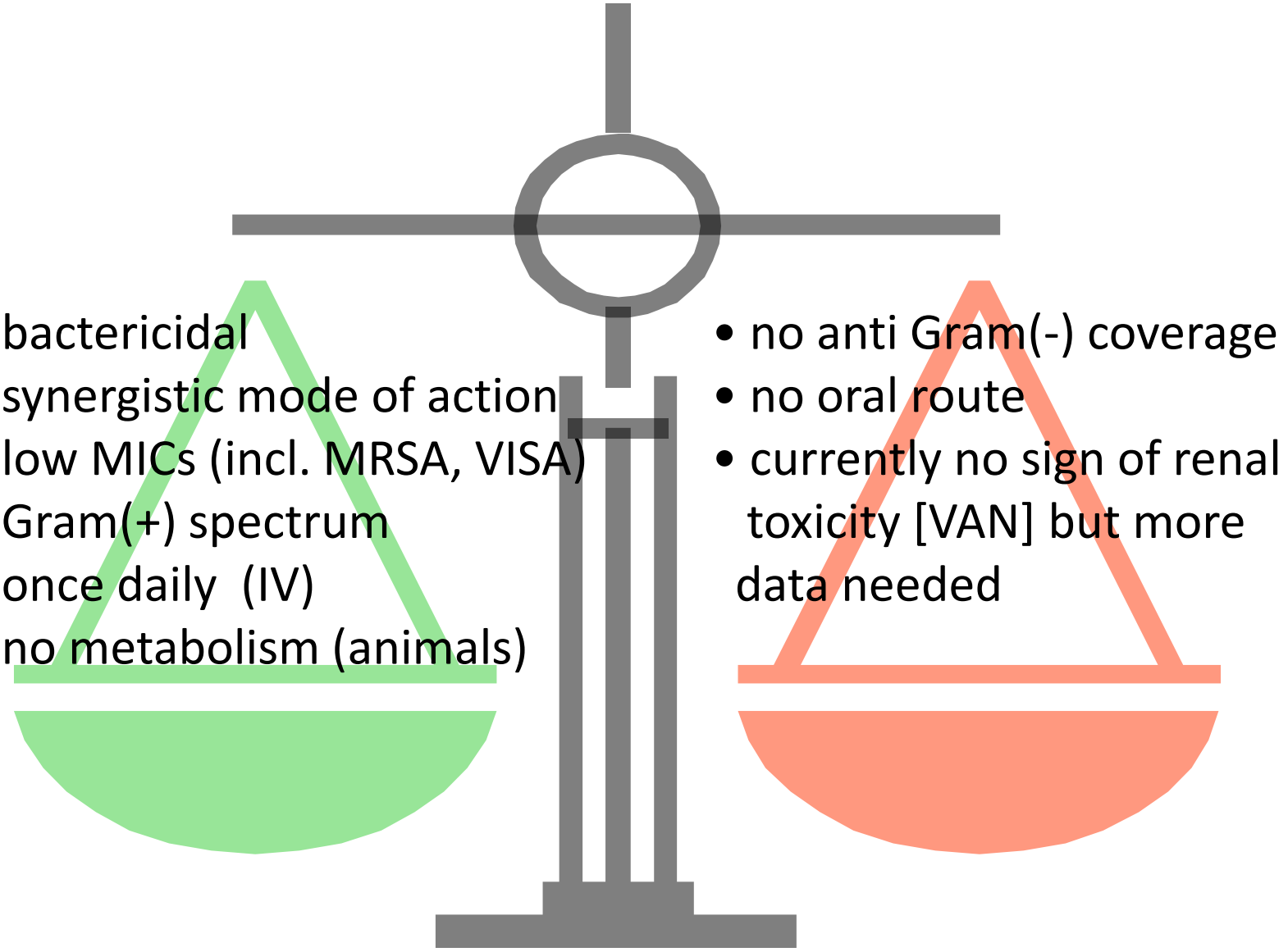


FIG 1 Percentage of patients achieving cessation of spread or reduction of lesion size and temperature of <37.7°C at 72 h after initiation of treatment (early clinical endpoint). Only patients with baseline lesions ≥75 cm^2 and Gram-positive infection were included. Patients with missing percentage of change and/or missing temperature were excluded.

Stryjewski et al, AAC (2012) 56:5476-83

TD-1792: pros and cons



- bactericidal
- synergistic mode of action
- low MICs (incl. MRSA, VISA)
- Gram(+) spectrum
- once daily (IV)
- no metabolism (animals)

- no anti Gram(-) coverage
- no oral route
- currently no sign of renal toxicity [VAN] but more data needed

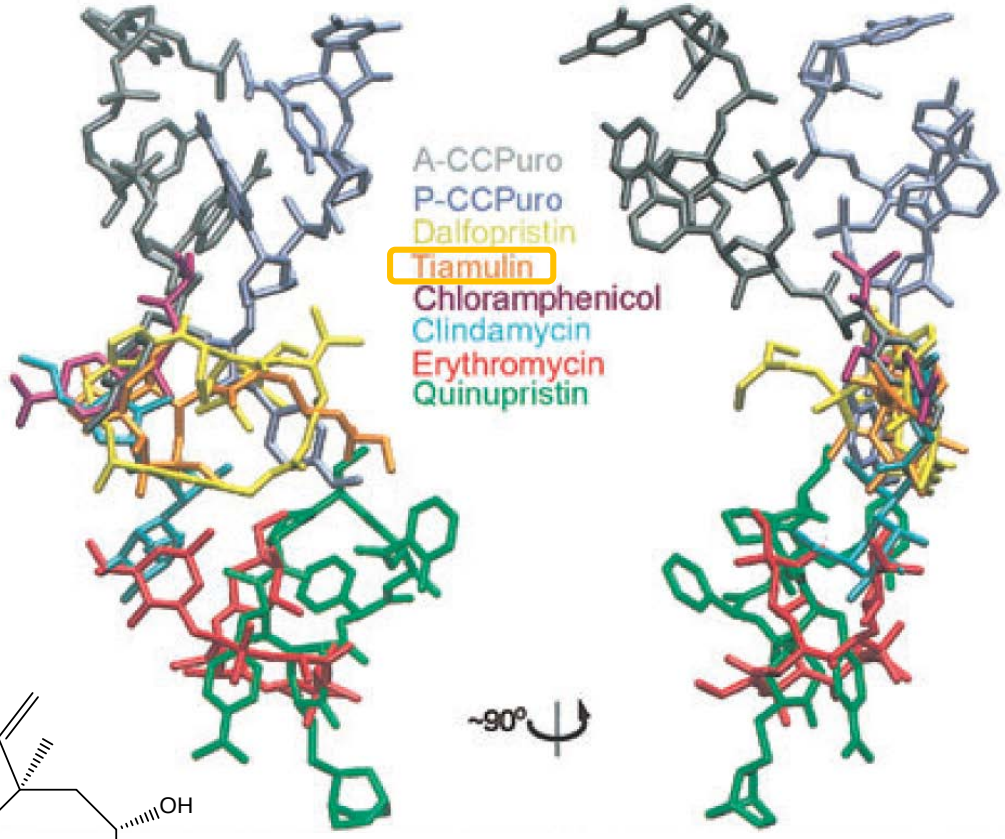
Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

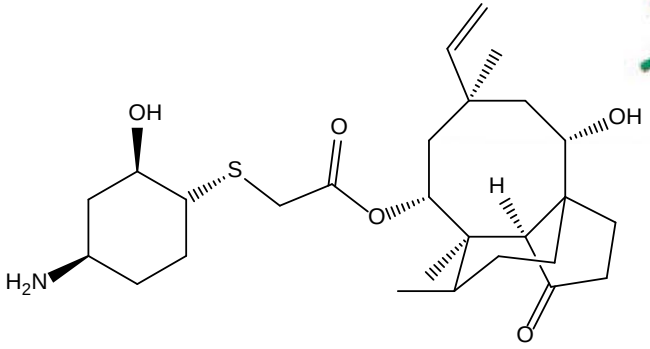
Constructed based on www.pewtrusts.org

Lefamulin (BC-3781) vs retapamulin

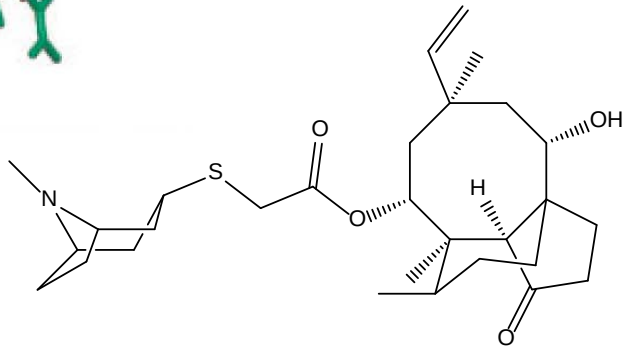
Antibiotic binding to peptidyl transferase center of 50S ribosome



lefamulin



retapamulin



Schlünzen et al, Mol. Microbiol. (2004) 54: 1287–94

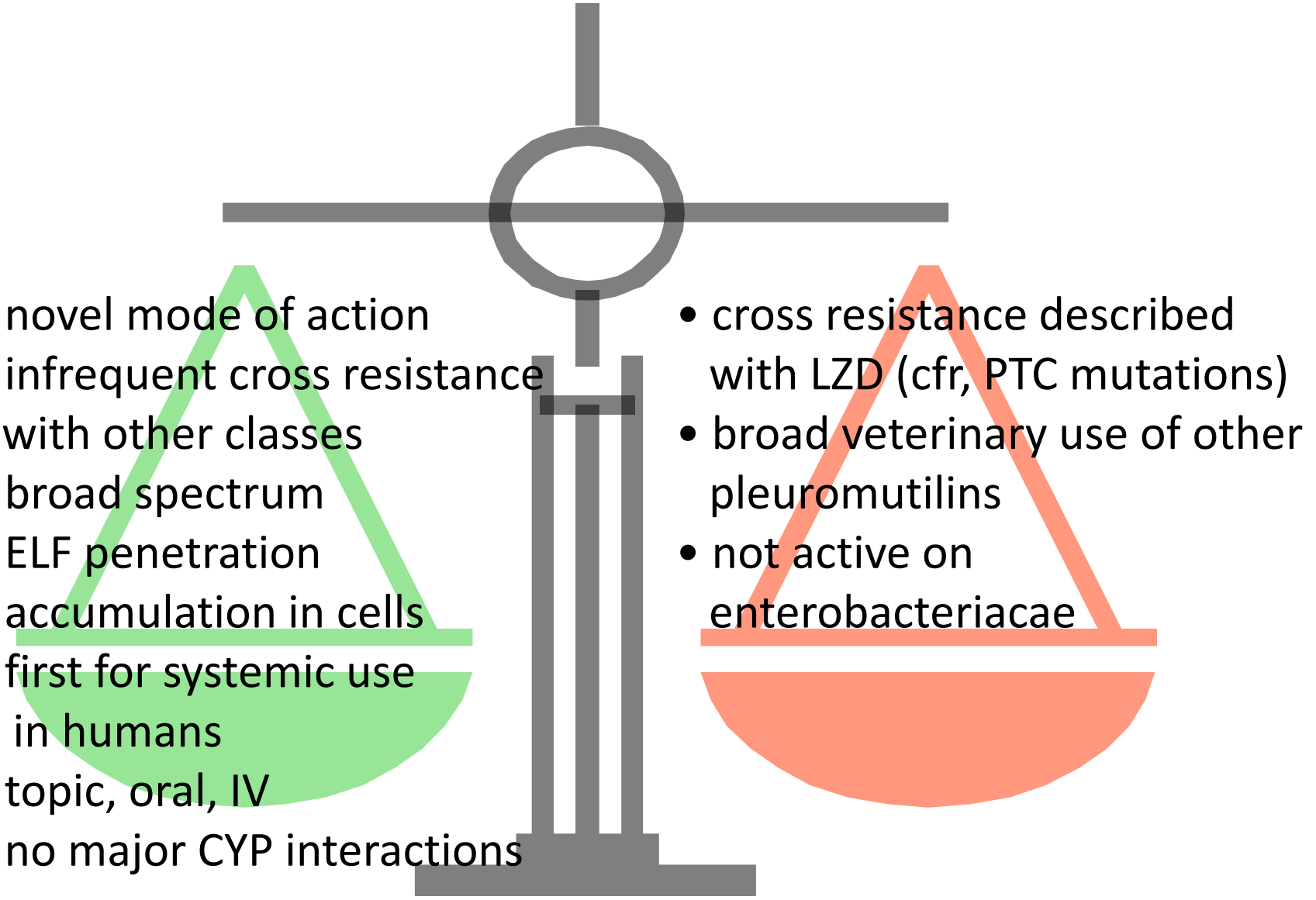
Lefamulin: ABSSSI Phase II data

Microbiological Eradication and Clinical Success Rates at TOC by Baseline Pathogen

Study Population	Pathogen	Treatment Arm: BC-3781 100 mg q12h	BC-3781 150 mg q12h	Vancomycin ≥ 1 g* q12h
Microbiological Eradication Rate [%] at TOC [1,2]				
MITT	All pathogens	80.0	84.3	82.4
	S. aureus	79.5	87.2	85.1
	MRSA	82.4	87.5	82.1
ME	All pathogens	84.8	90.7	95.0
	S. aureus	82.9	90.2	94.9
	MRSA	84.4	92.6	93.5
Clinical Success Rate [%] at TOC [1]				
CE	All pathogens	90.0	88.9	92.2
MITT	All pathogens	82.0	82.4	82.4
	S. aureus	81.8	87.2	85.1
	MRSA	85.3	87.5	82.1
	MRSA USA300	84.0	94.7	77.8
ME	All pathogens	87.0	88.4	95.0
	S. aureus	85.4	90.2	94.9
	MRSA	87.5	92.6	93.5
	MRSA USA300	87.0	94.1	90.5

ICAAC (2012) L1-1660

Lafamulin: pros and cons



- novel mode of action
- infrequent cross resistance with other classes
- broad spectrum
- ELF penetration
- accumulation in cells
- first for systemic use in humans
- topic, oral, IV
- no major CYP interactions

- cross resistance described with LZD (cfr, PTC mutations)
- broad veterinary use of other pleuromutilins
- not active on enterobacteriacae

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

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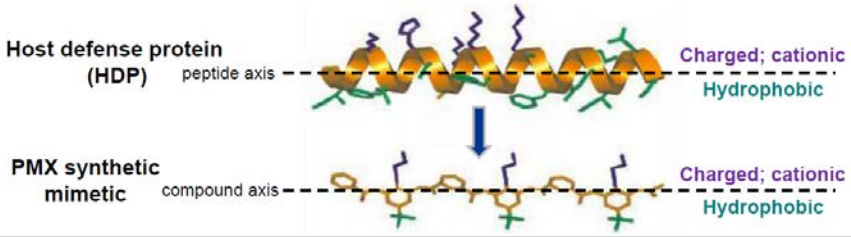
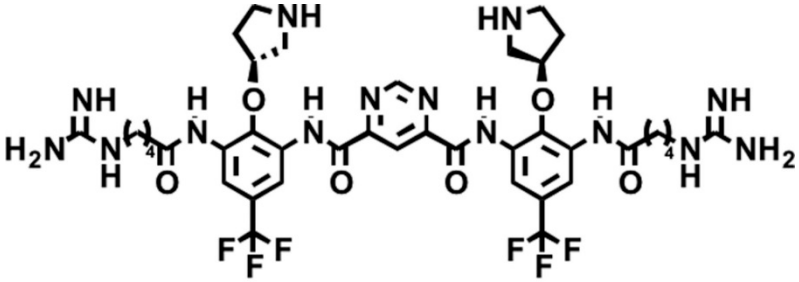
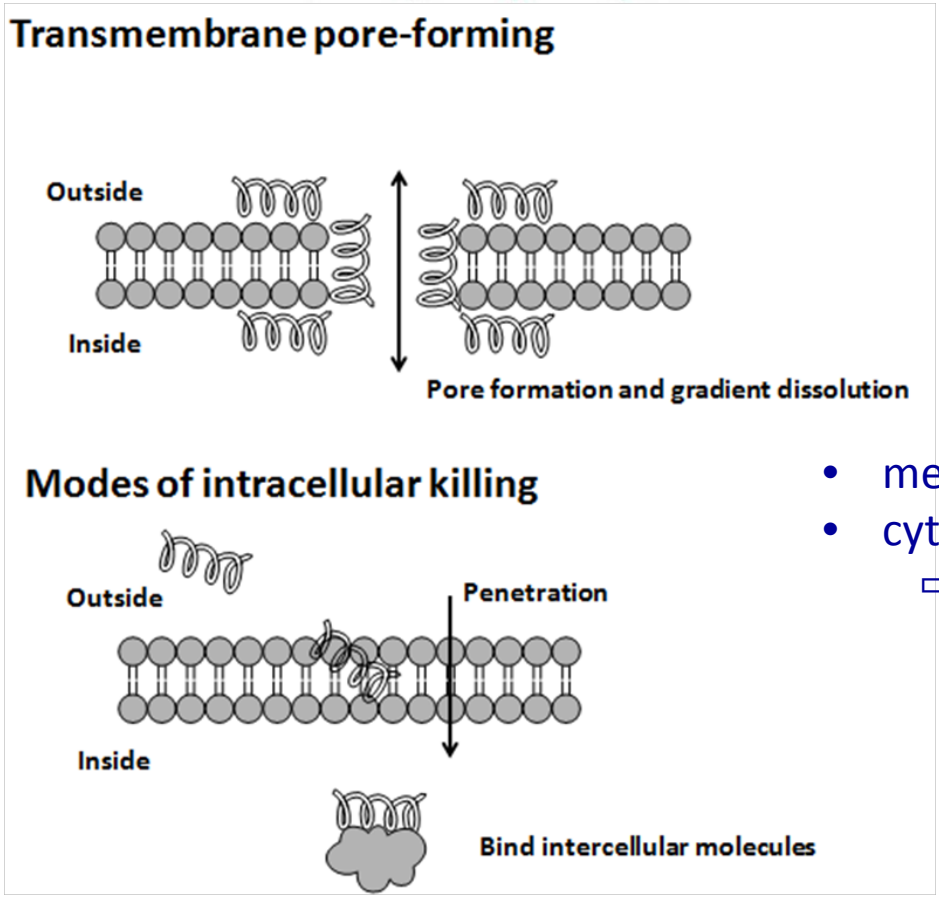
Constructed based on www.pewtrusts.org

Brilacidin







- membrane depolarisation ~ daptomycin
- cytoplasmic protein misfolding
  - ⇨ upregulation of chaperones and proteases (genes involved in stress response) ~ defensins

http://en.wikipedia.org/wiki/Antimicrobial_peptides

Mensa et al, AAC (2014) 58:5136-45

Brilacidin: phase II data

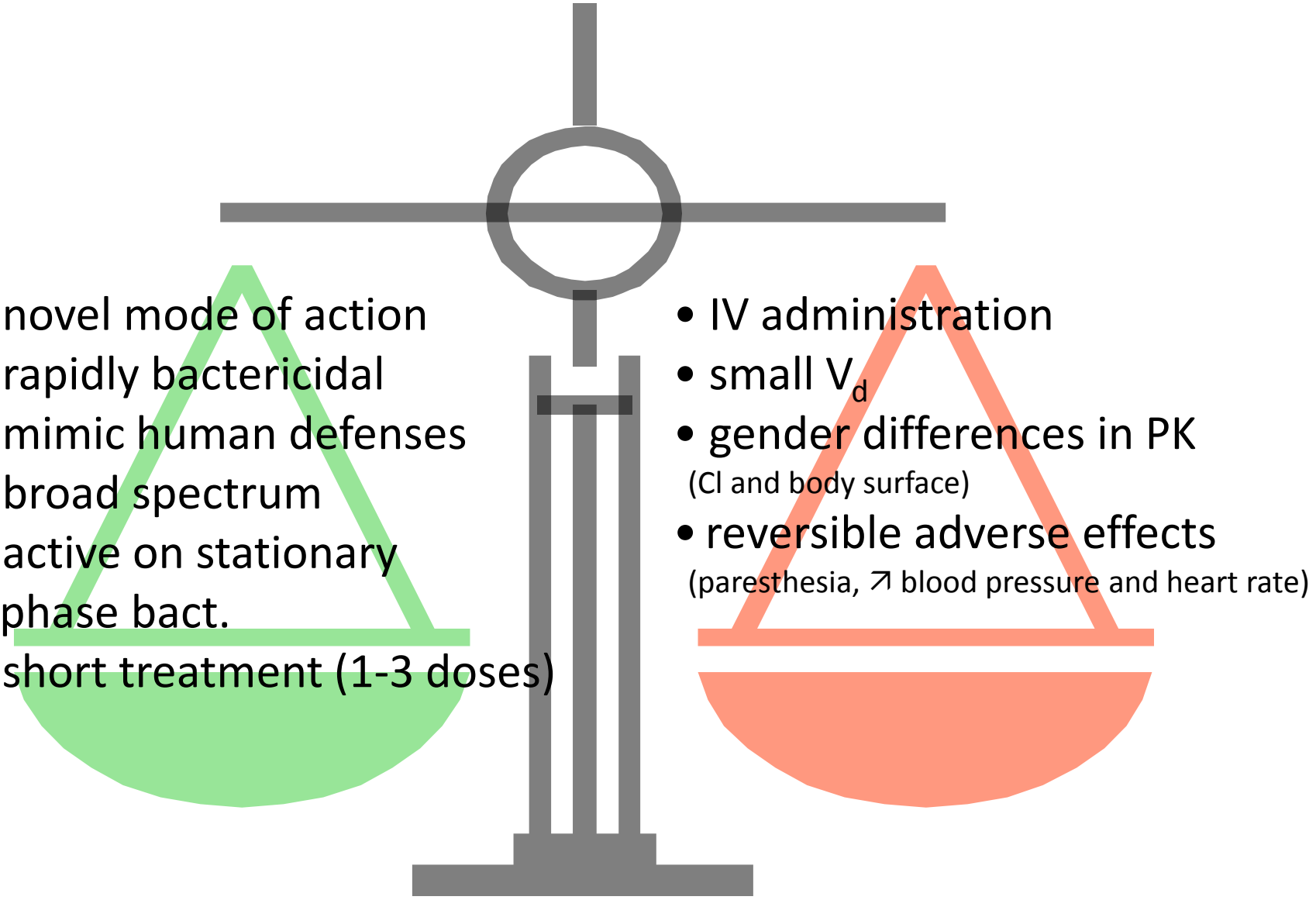
Study CTIX-BRI-204 – Topline Results

Proportions of Subjects with Early Clinical Response (Primary Efficacy Endpoint) - (≥20 % decrease in lesion area) at 48-72 Hours after the First Dose of Study Drug

	Brilacidin: 0.6 mg/kg single dose	Brilacidin: 0.8 mg/kg single dose	Brilacidin: 3-day regimen	Daptomycin 7-day regimen
Intent to Treat (ITT) Population, n assessed	n = 54	n = 53	n = 54	n = 54
≥ 20% decrease in lesion area (%)	47 (87.0)	48 (90.5)	51 (94.4)	45 (83.3)
All Treated / Safety Population, n assessed	n = 51	n = 48	n = 52	n= 48
≥ 20% decrease in lesion area (%)	47 (92.2)	46 (95.8)	51 (98.1)	45 (93.8)
MITT Population (pathogen isolated at baseline), n assessed	n = 29	n = 30	n = 28	n = 36
≥ 20% decrease in lesion area (%)	27 (93.1)	30 (100.0)	27 (96.4)	34 (94.4)

1

Brilacidin: pros and cons



- novel mode of action
- rapidly bactericidal
- mimic human defenses
- broad spectrum
- active on stationary phase bact.
- short treatment (1-3 doses)

- IV administration
- small V_d
- gender differences in PK (Cl and body surface)
- reversible adverse effects (paresthesia, ↗ blood pressure and heart rate)

Antibiotic pipeline: did you change your mind ?

- Large number of molecules in clinical development
  … much more in preclinical development

- More advanced molecules (Phase III) are new derivatives in existing classes with improved properties
  (MIC – resistance – PK- safety)

Antibiotic pipeline: some work ahead

- Susceptibility Breakpoint harmonization

An example with MRSA …

antibiotic	EUCAST		CLSI/FDA	
	S ≤	R >	S ≤	R ≥
rifampicin	0.06	0.5	1	4
azithromycin	1	2	2	8
doxycycline	1	2	4	16
vancomycin	2	2	2	16
linezolid	4	4	4	8
ceftaroline	1	1	0.5	2
telavancin	0.125	0.125	0.125	
dalbavancin	0.125	0.125	0.125	

rule in Europe !

Antibiotic pipeline: can we do better ?

- Equivalence to current options in comparative clinical trials

  ⇨ This will raise issues for reimbursement, especially against the generics of the comparators used in these studies

  ⇨ Need to design superiority trials and to focus pricing and reimbursement for documented cases of infection by resistant organisms

Non-inferiority vs superiority trials ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NON-INFERIORITY if NO evidence of spontaneous resolution rate (more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

→ DRUG/comparator trial

SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)

→ Placebo/ DRUG/comparator trial

LIMITED TRIALS

- Rare MDR organisms
- Few patients

→ DRUG non comparative trial

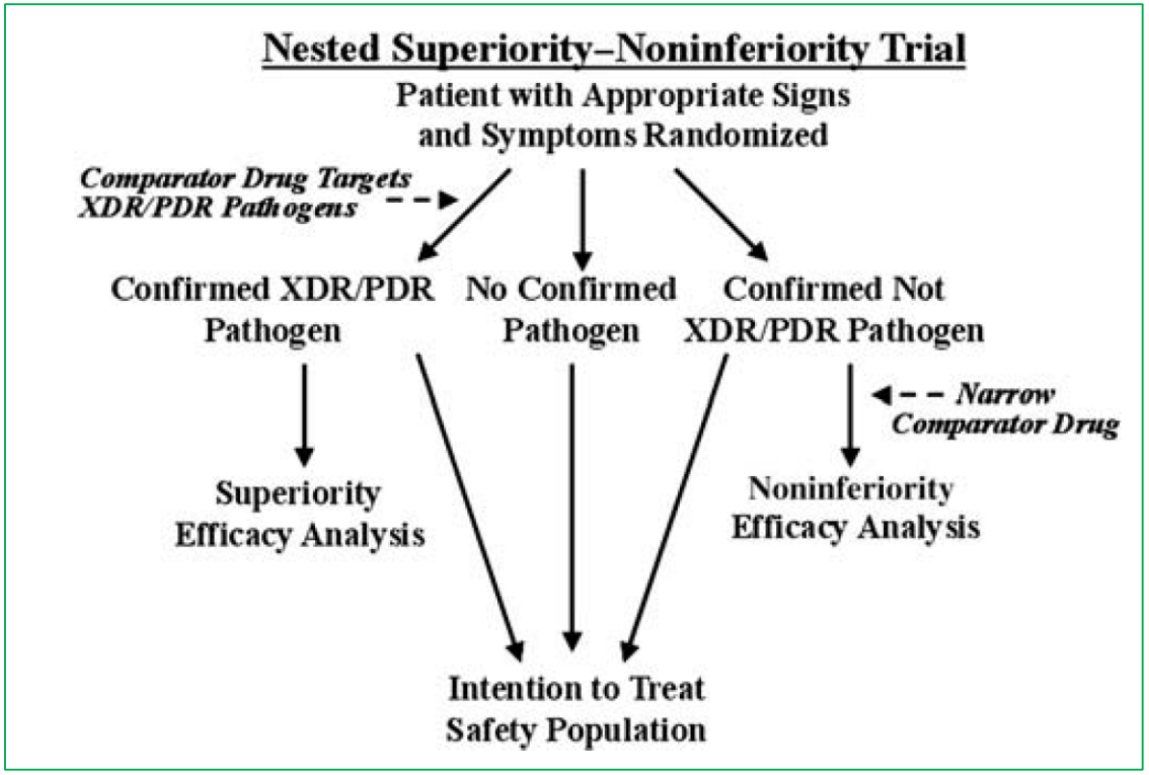
Non-inferiority vs superiority trials ?

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

Infectious Diseases Society of America (IDSA)[a]

IDSA PUBLIC POLICY



What about the future ?