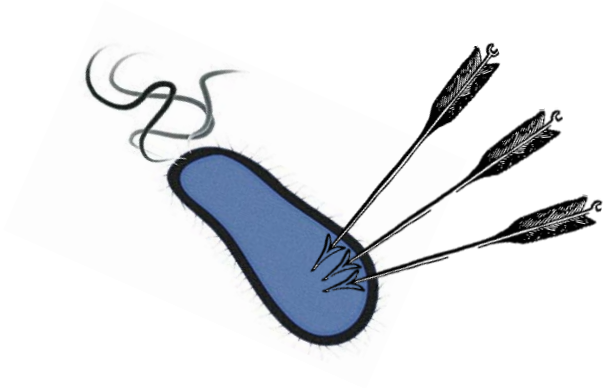
37ème Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse
Lundi 18 et mardi 19 décembre 2017
Palais des Congrès de Paris

DISCOVERY AND EXPLOITATION OF NEW TARGETS FOR ANTIBIOTICS

Action on intracellular targets



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Disclosures

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

- GSK
- Debiopharm

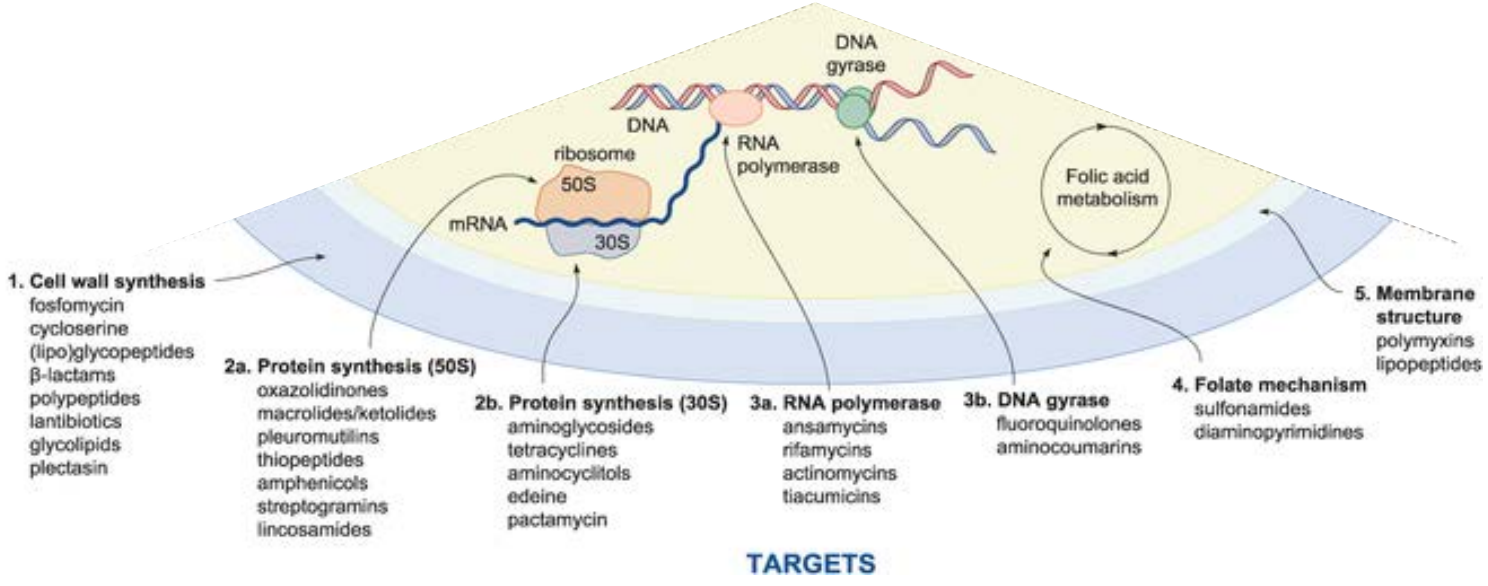
Member of advisory board for

- Morphochem AG

Resistance to current drugs

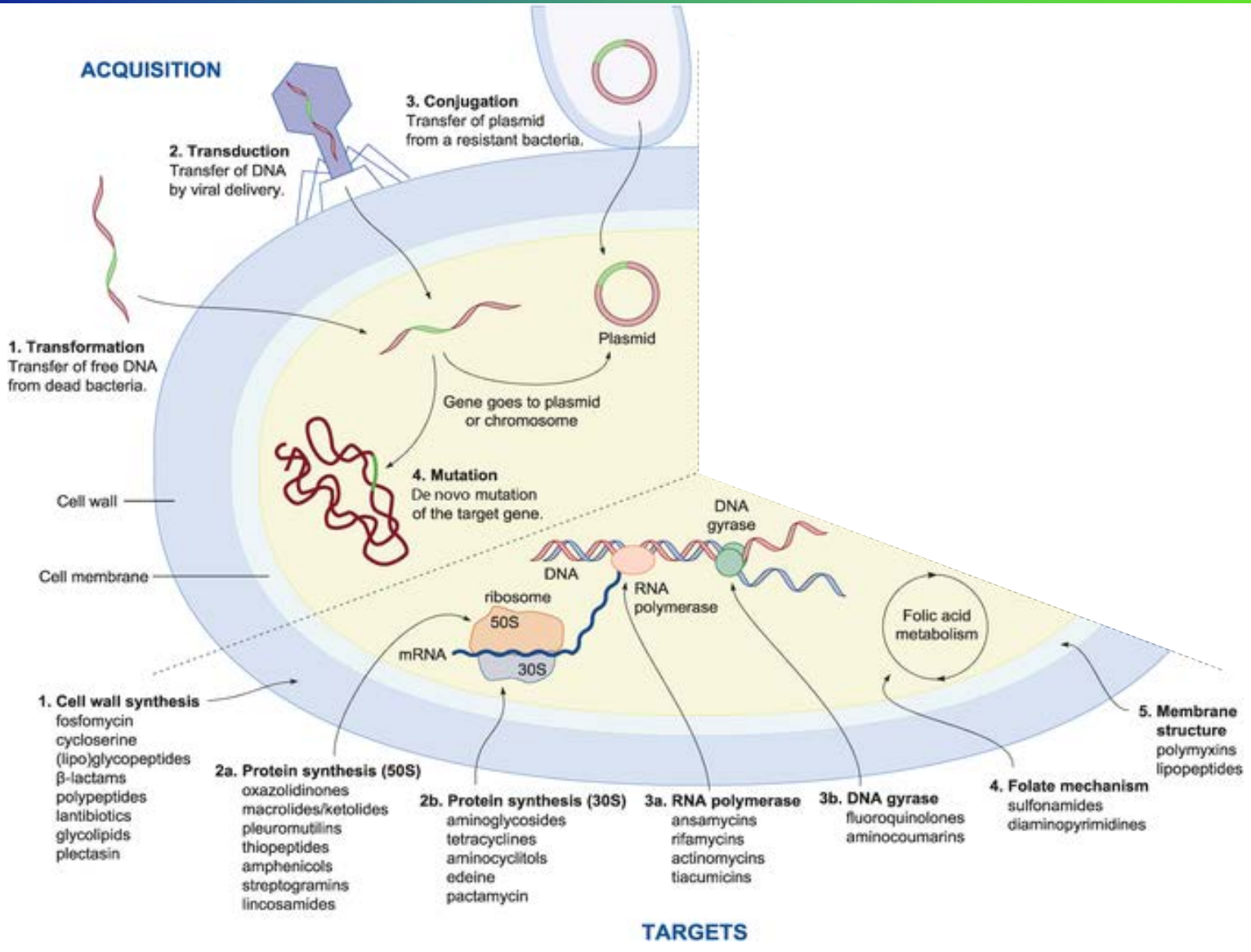
Folon

Current targets and resistance mechanisms



Chellat et al, Angew.Chem. Int.Ed. 2016; 55:6600 –26

Current targets and resistance mechanisms



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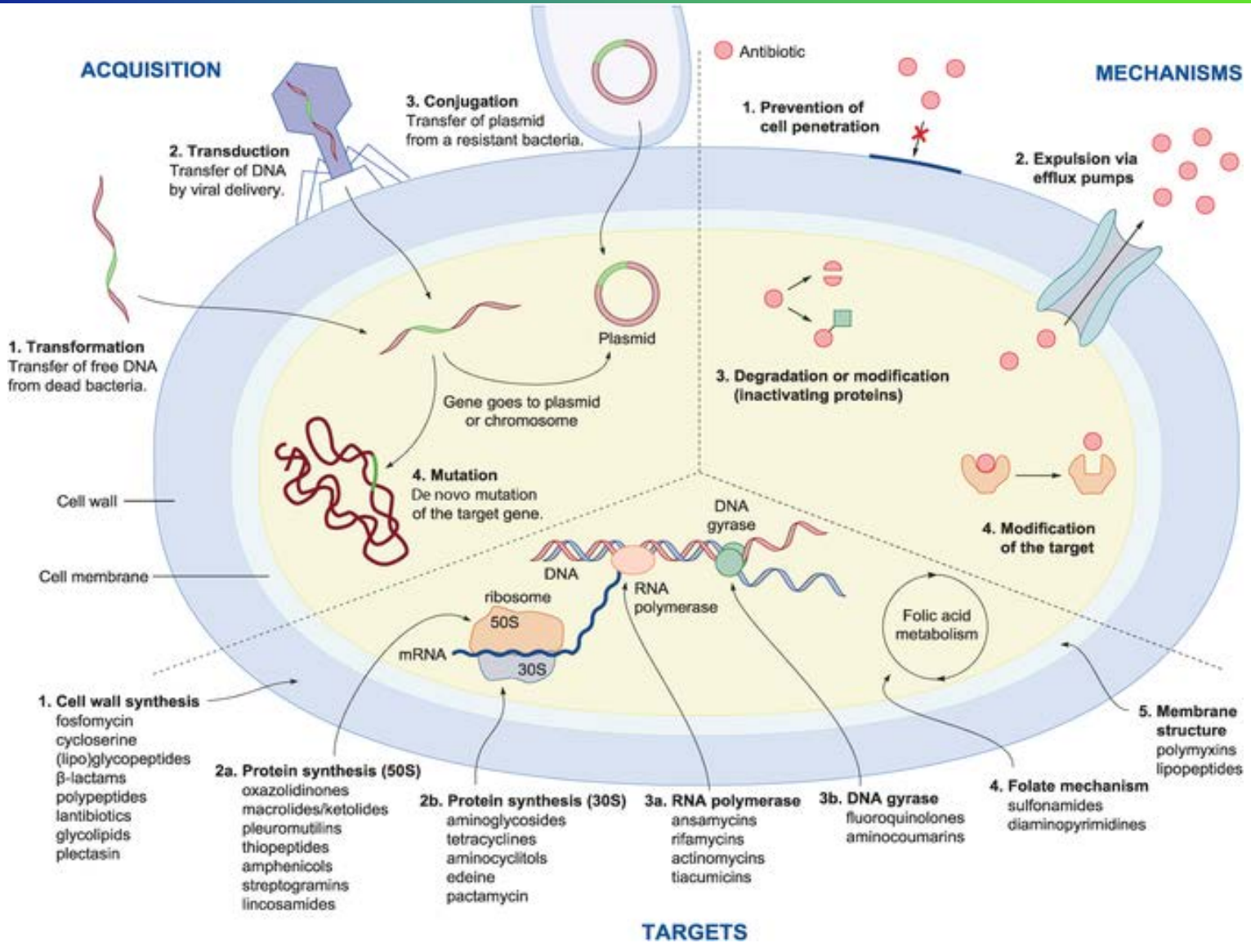

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Acting on intracellular targets: 'wish list' for new drugs

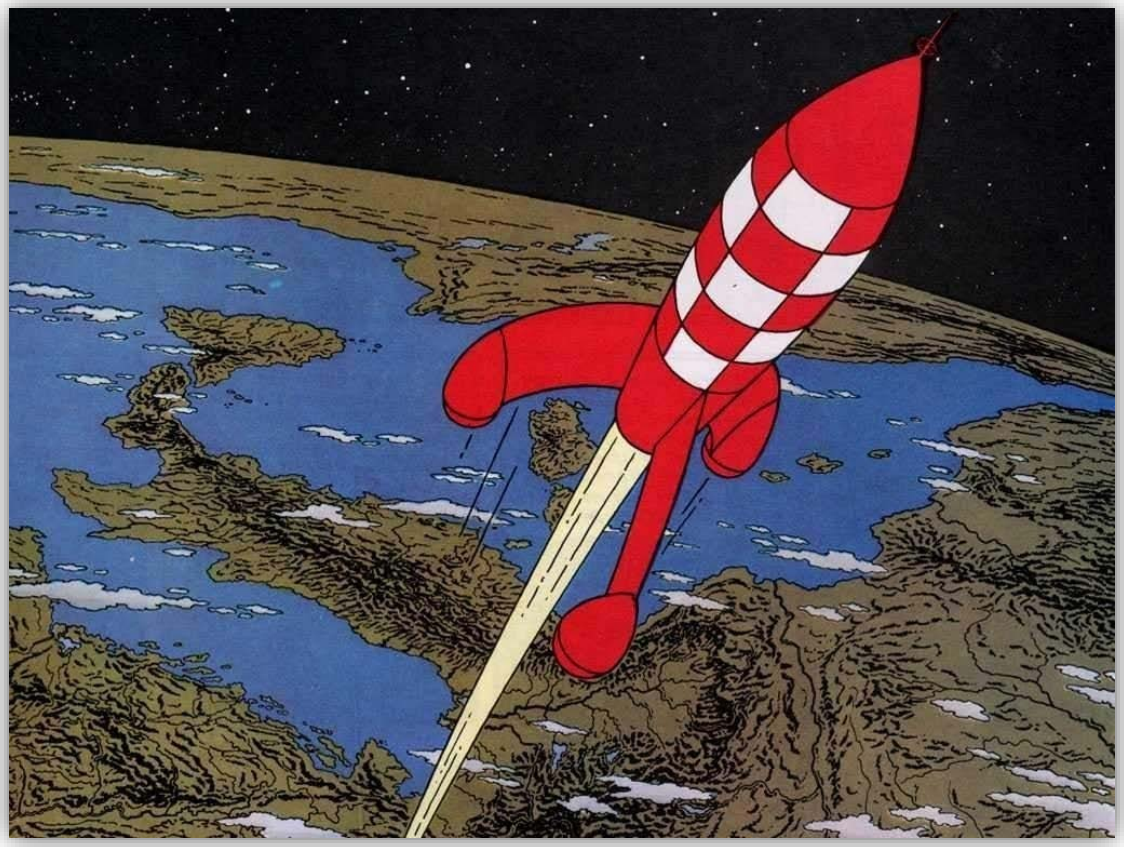
- **Essentiality ?** Inactivation prevents bacterial growth / kills bacteria → bacteriostatic/cidal effect
- **Selectivity ?** Inexistent target in eukaryotic cells → safety
- **Novelty ?** No preexisting resistance mechanism
- **Function ?** If known, make easier the screening of inhibitors
- **Spectrum ?** Highly conserved in most bacteria → broad spectrum
  Specific for a few species → narrow spectrum

All antibacterial drugs

- **Accessibility ?** Compartment accessible to antibiotics
  Crossing of membranes (porins & efflux !!!)

Intracellular targets: Anti-Gram(-) ⩛ Anti-Gram(+)

In progress in (early stages of) clinical trials



Hergé

Molecules in clinical development acting on new intracellular targets

	Target	Compound	Chemical family	Company	Phase
New binding site on known target	Topoisomerase II (A subunit site)	Gepotidacin	Triazaacenaphthylene	GlaxoSmithKline PLC	2
	Topoisomerase II (ATP site)	Zoliflodacin	Spiropyrimidenetrione	Entasis Therapeutics Inc.	2
New target	FabI	Afabicin	Benzofuran naphthyridine	Debiopharm Intern. SA	2
		CG400549	Benzyl pyridinone	CrystalGenomics Inc	2
	Met-aminoacyl-tRNA synthetase	CRS3123	Fluorovinylthiophene	Crestone Inc.	1
	DNA minor groove	MGP-BP3	Lexitropsin	MGB Biopharma Ltd	1
Hybrids	Topoisomerase + ribosome	Cadazolid	fluoroquinolone + oxazolidinone	Actelion Pharmaceuticals Ltd.	3
		MCB3837		Morphochem AG	1

www.pewtrusts.org/antibiotic-pipeline [Dec. 2017]

Molecules in clinical development acting on new intracellular targets

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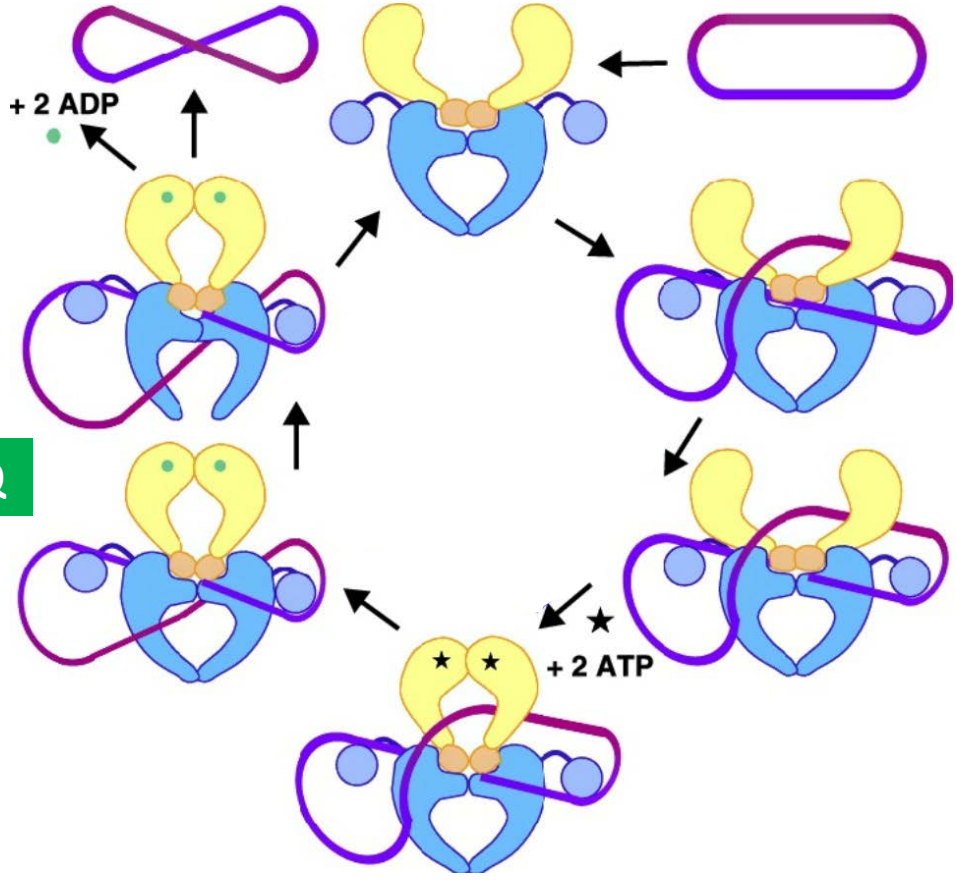
Drugs acting on new binding sites of known targets: the example of topoisomerase II inhibitors



FQ

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

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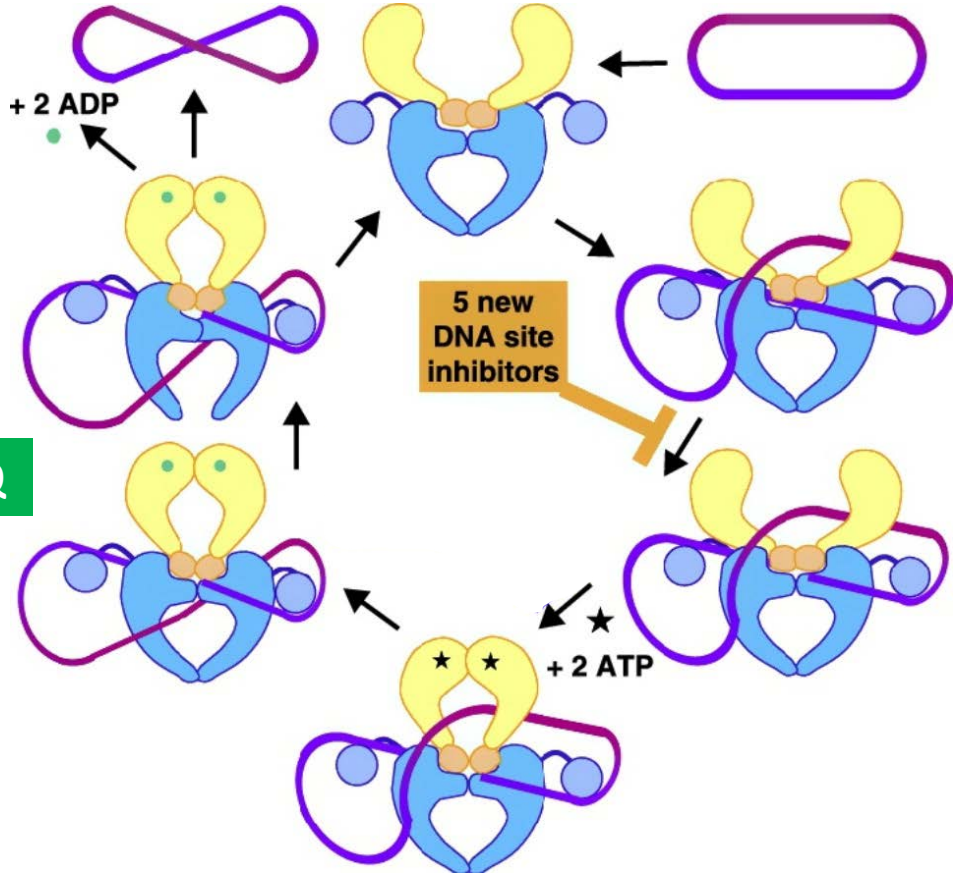

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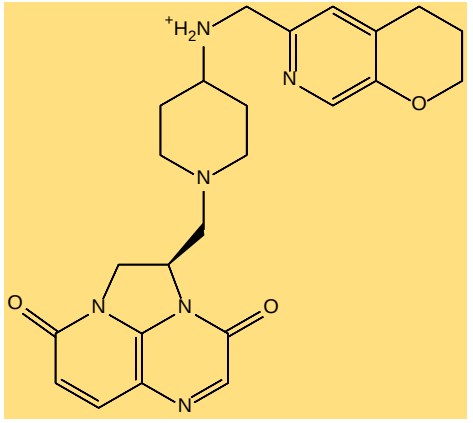
Gepotidacin



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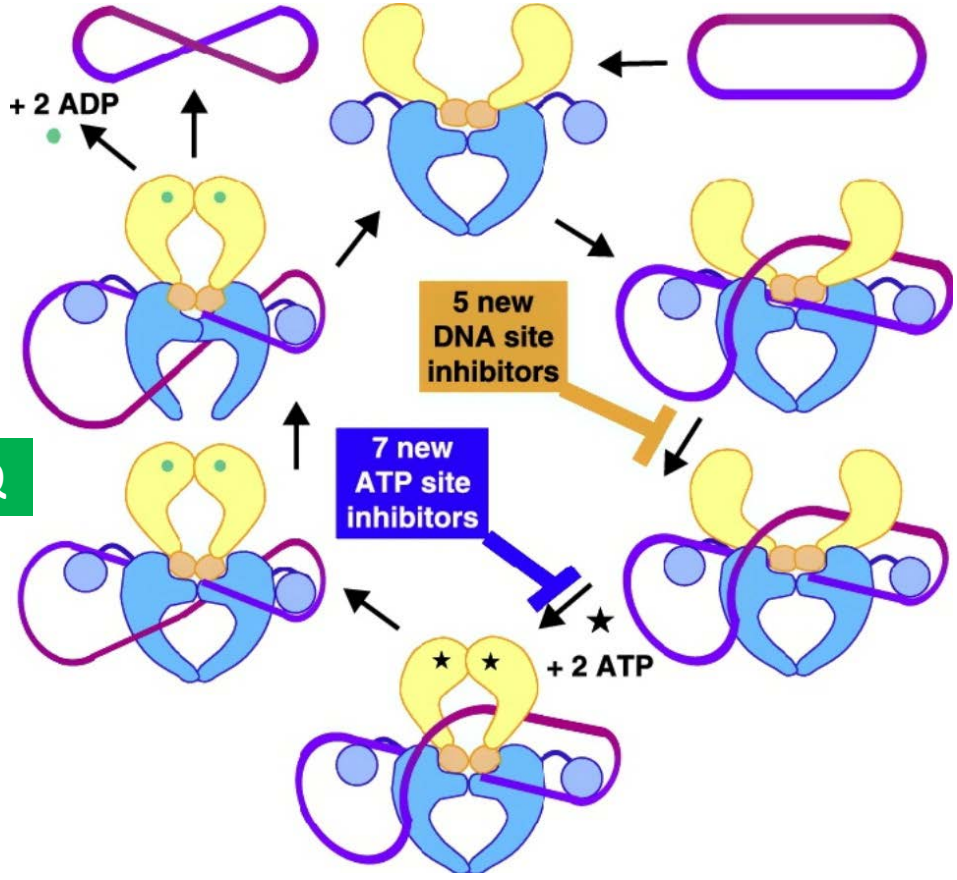

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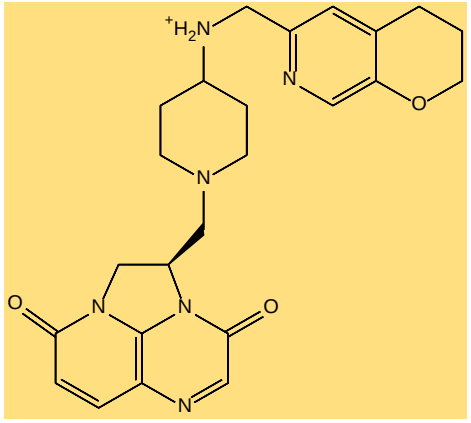
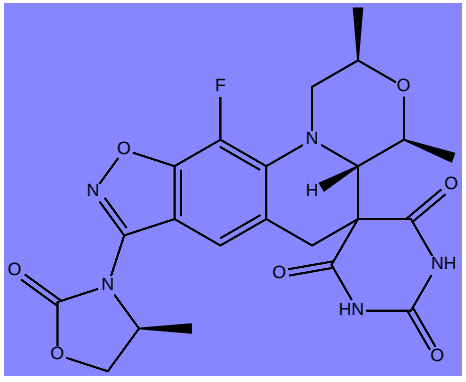


Zoliflodacin



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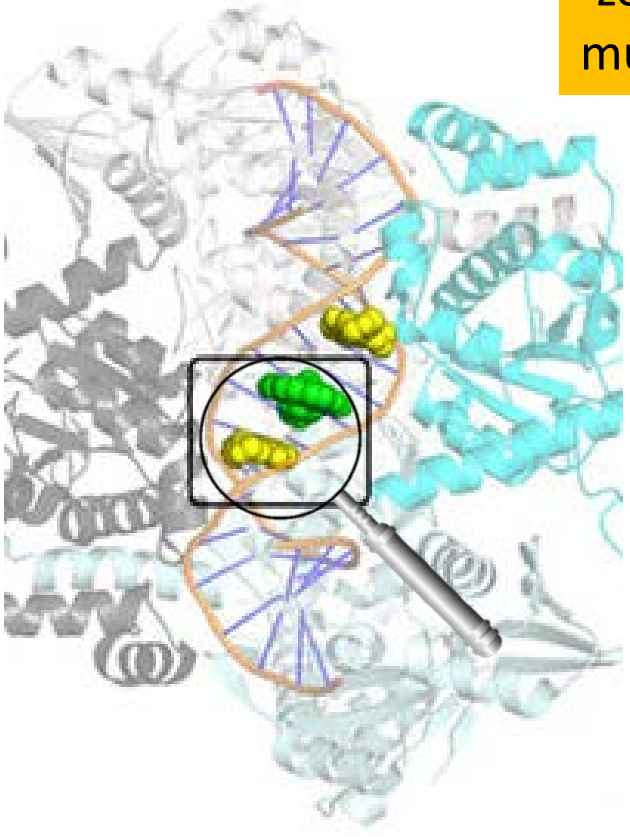
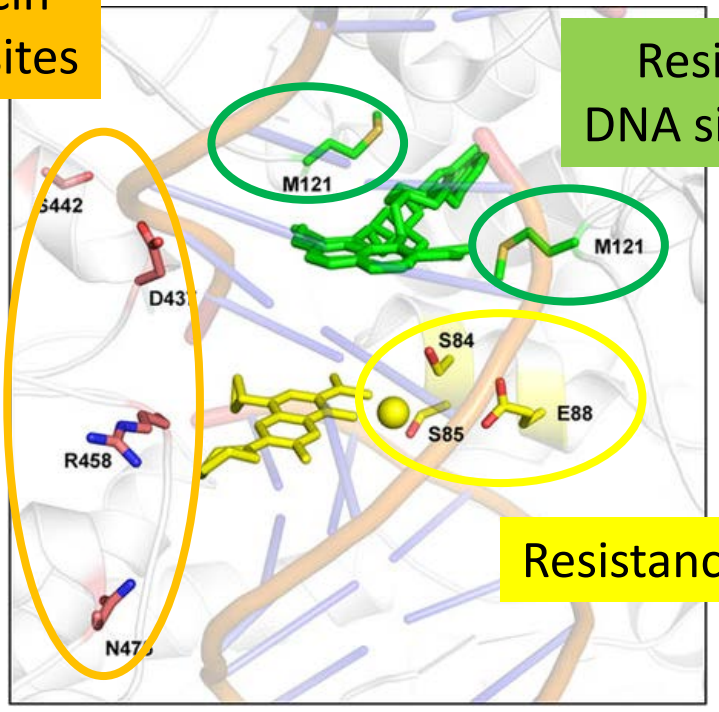


zoliflodacin mutable sites



Resistance to DNA site inhibitors

Resistance to FQ

Basarab et al, Sci Rep. 2015; 5:11827

Gepotidacin

strains	gepotidacin			moxifloxacin *(levofloxacin)*		
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range
MRSA	0.25	0.5	≤ 0.06 - 1	> 1	> 1	0.03 - > 1
FQ-R Sa	0.25	0.5	≤ 0.06 - 1	> 1	> 1	0.12 - > 1
S. pneumoniae	0.12	0.25	0.03 - 1	0.02	0.12	≤ 0.03 - > 2
FQ-R Sp	0.12	0.25	0.06 – 0.5	2	> 2	2 - > 2
H. influenzae	0.5	1	≤ 0.015 - 8	0.015	0.03	≤ 0.004 - > 1
M. catarrhalis	≤ 0.06	≤ 0.06	≤ 0.06 – 0.12	*≤ 0.06*	*0.12*	*≤ 0.06 – 0.5*
E. coli	2	2	≤ 0.03 - 16	*0.03*	*0.5*	*≤ 0.004 - 2*
FQ-R Ec	2	4	0.06 - > 2	*> 4*	*> 4*	*4 - > 4*
N. gonorrheae	0.12	0.25				

- Oral and IV formulations
- Skin & soft tissue infections
- Community acquired pneumonia
- Complicated urinary tract infections
- Gonorrhea

Biedenbach et al, AAC 2014; 60: 1918–1923
Farrell et al, AAC 2017; 61. pii: e02047-16

Zoliflodacin

	Topoisomerase resistance determinants/mutable sites				MIC (µg/mL)			
	GyrA	GyrB	ParC	ParE	AZD 0914	2 cipro	3 NBTI	4 novo
S. aureus ARC516	none	none	none	none	0.12	0.25	0.06	0.25
S. aureus ARC2796	$M_{121}K$	none	none	none	0.12	0.25	4	0.25
S. aureus ARC3445	none	$R_{144}I$	none	none	0.25	0.25	0.12	16
S. aureus ARC2381	$S_{84}L^a$, $S_{85}P$	none	$S_{80}Y^a$	none	0.5	>64	0.12	0.12
S. aureus ATCC33591	none	none	none	none	0.25	1	0.5	0.12
S. aureus ATCC33591-D1[e]	none	$D_{437}N^a$	none	none	2	1	1	0.12
S. aureus ATCC33591-D2[e]	none	$S_{442}P$	none	none	4	2	<0.06	0.12
S. pneumoniae ARC548	none	none	none	none	0.25	1	0.12	0.5
S. pneumoniae ARC2480	$S_{81}F^a$	none	$S_{79}Y^a$	none	0.12	32	0.12	0.25
S. pneumoniae ARC2800	none	$T_{172}A$	none	$T_{172}A$	0.25	1	0.12	8
N. gonorrhoeae FA1090	none	none	none	none	0.06	0.004	0.25	0.25
N. gonorrhoeae ARC4672	$S_{91}F^a$, $D_{95}G^b$	none	$S_{87}R^a$	none	0.12	16	0.25	1
N. gonorrhoeae ARC4680	$S_{91}F$, $D_{95}G$	none	$S_{87}R$	none	0.06	32	4	1
N. gonorrhoeae ARC1612	none	none	none	none	0.12	0.004	0.5	2
N. gonorrhoeae 49226-TF	none	$K_{450}T^{c,d}$	none	none	1	0.001	1	2
N. gonorrhoeae ARC4676	$S_{91}F$, $D_{95}A$	none	none	none	0.12	32	1	1
N. gonorrhoeae ARC4676-D1[e]	$S_{91}F$, $D_{95}A$	$K_{450}T$	none	none	2	0.5	1	1
N. gonorrhoeae ARC4676-D3[e]	$S_{91}F$, $D_{95}A$	$D_{429}N^a$	none	none	2	16	0.5	0.5
N. gonorrhoeae ARC4676-D3-2[e]	$S_{91}F$, $D_{95}A$	D429N, S467N	none	none	8	32	1	1

[e]: in vitro generated mutants

Oral formulation
→ *N. gonorrheae*

Basarab et al, Sci Rep. 2015; 5:11827

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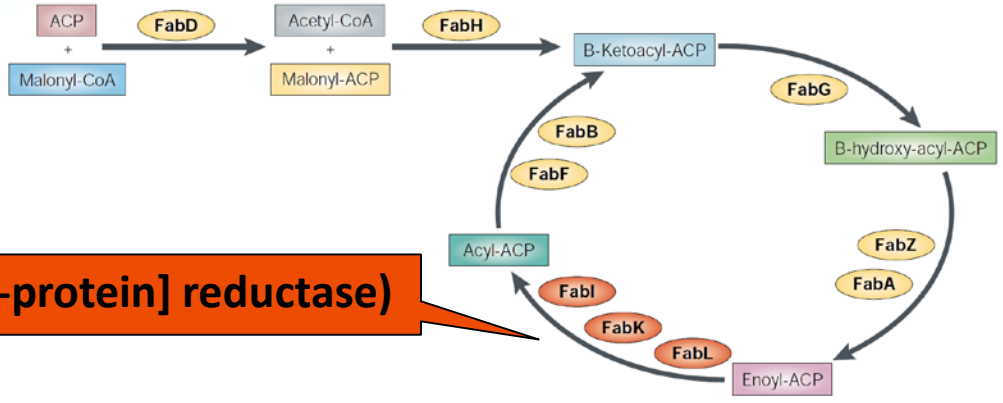
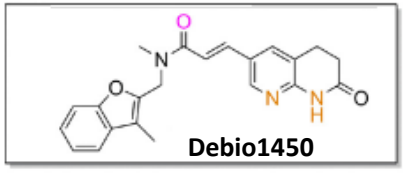
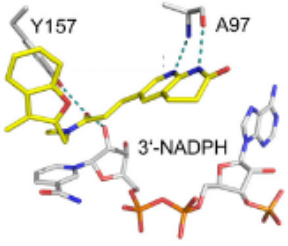
Drugs acting on new targets - XXS spectrum: the example of FabI inhibitors

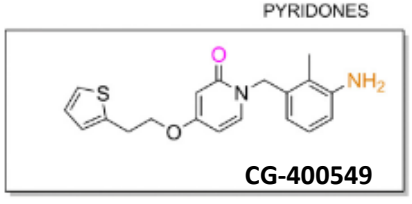
Fatty acid synthesis in bacteria

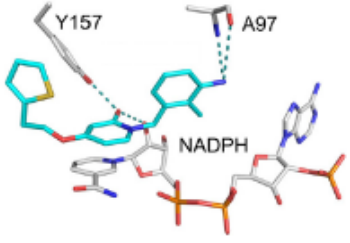


FabI (Enoyl-[acyl-carrier-protein] reductase)









Miesnel et al, Nature Rev. Gen. 2003; 4: 442-456; Schiebel et al, JBC 2014; 289:15987-16005

Drugs acting on new targets - XXS spectrum: the example of FabI inhibitors

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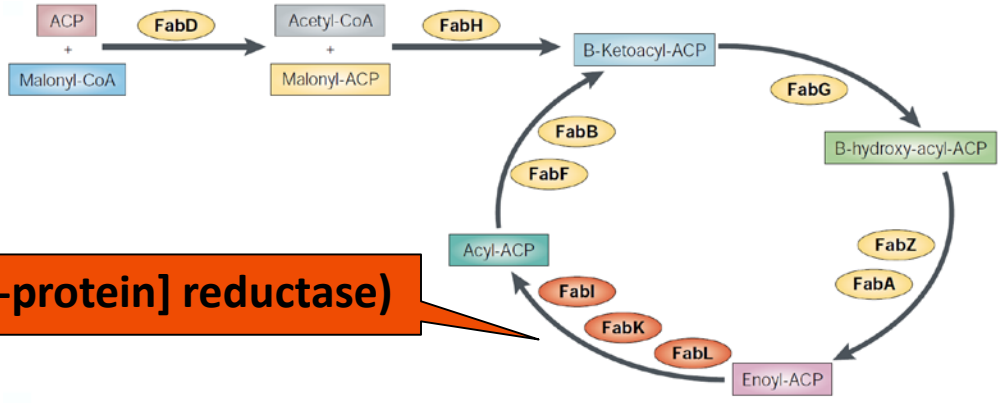
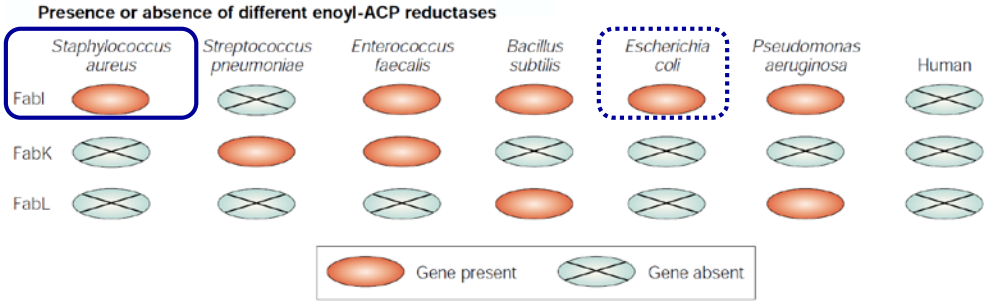
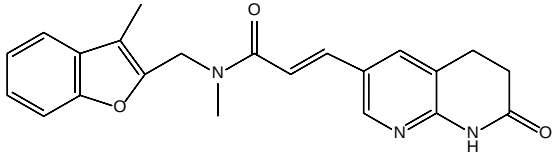


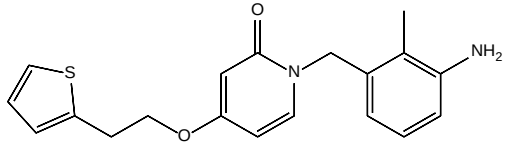
FabI (Enoyl-[acyl-carrier-protein] reductase)

Specifically active on *S. aureus*





Debio1450 [Afabicin]



CG-400549

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

FabI inhibitors are inactive on *E. coli*

- Permeability barrier

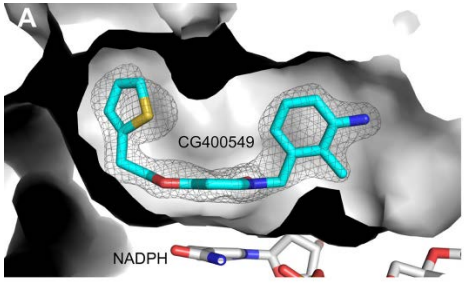
Spectrum of antibacterial activity for different FabI inhibitors

Organism	MIC (μM) CG400549	MIC (μM) PT166
S. aureus RN4220	5.9	0.8
E. coli MG1655	>375	>425
E. coli MG1655 Δ*acrAB*[b]	>375	6.7

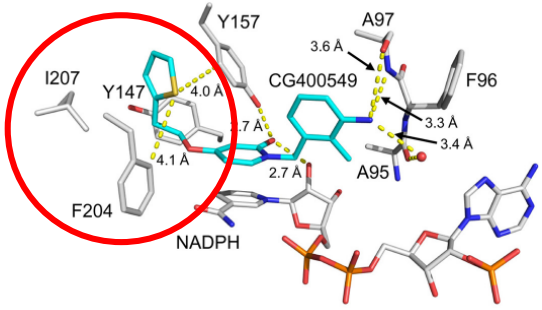
PT166 is inactive on *E. coli* due to active efflux

CG400549 is inactive on *E. coli* due to lack of affinity for the target

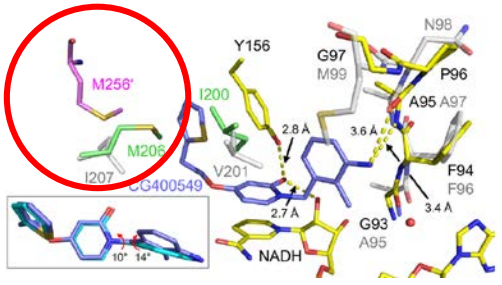
- Binding to the target



S. aureus enzyme



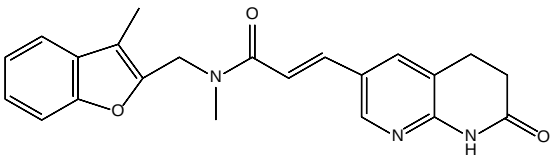
E. coli enzyme



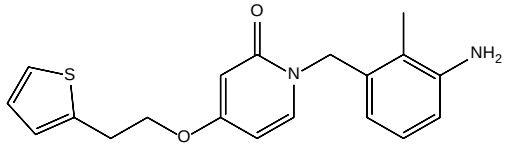
Steric hindrance …

Schiebel et al, JBC 2014; 289:15987-16005

FabI inhibitors: activity on Staphylococci



Debio1450 [Afabicin]



CG-400549

Pheno-type	drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range
MRSA	Debio	≤ 0.008	≤ 0.008	≤ 0.008 – 0.06
	Linezolid	2	4	0.25 – 4
	Vanco	1	1	≤ 0.25 - 2
MRSE	Debio	≤ 0.008	≤ 0.008	≤ 0.008
	Linezolid	1	1	0.5 – 1
	Vanco	> 4	> 4	4 - > 4

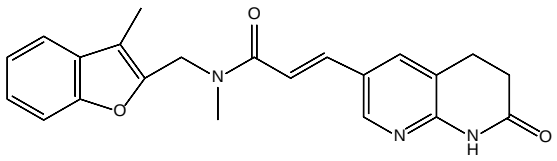
Pheno-type	drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range
MRSA	CG	0.25	0.25	0.06 - 1
	Linezolid	1	2	0.25 - 2
	Vanco	1	2	1 - 64
Coag(-) staph	CG	0.5	4	0.12 – 16
	Linezolid	1	2	0.5 – 4
	Vanco	1	2	0.5 - 16

Acute bacterial skin and skin structure infections,
Osteomyelitis caused by Staphylococci

Karlowsky et al, AAC 2009; 53:3544-48

Bogdanovich et al, AAC 2007; 51: 4191-5
Yum et al, AAC 2007; 51: 2591–3

FabI inhibitors: activity on Staphylococci



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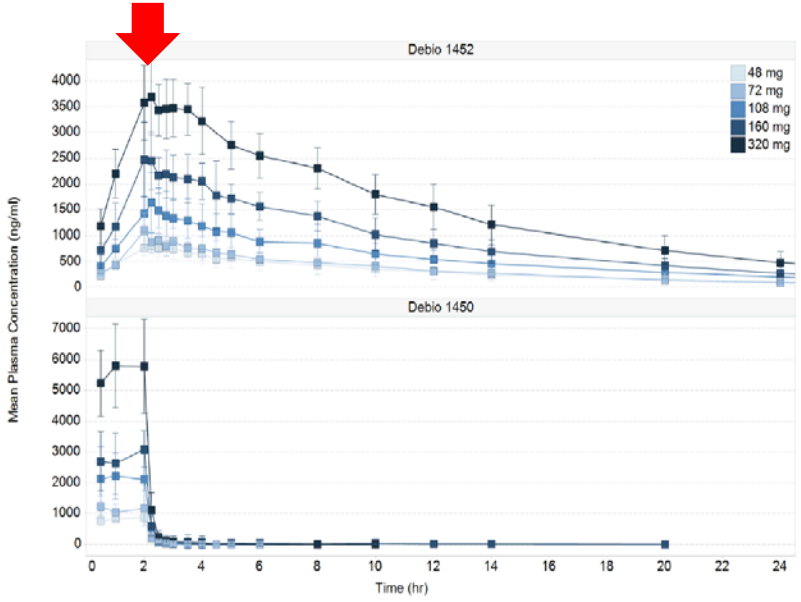
Pheno -type	drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range
MRSA	Debio	≤ 0.008	≤ 0.008	≤ 0.008 – 0.06
	Linezolid	2	4	0.25 – 4
	Vanco	1	1	≤ 0.25 - 2
MRSE	Debio	≤ 0.008	≤ 0.008	≤ 0.008
	Linezolid	1	1	0.5 – 1
	Vanco	> 4	> 4	4 - > 4

Time-concentration Profiles of Debio 1452 and Debio 1450 after IV Administration of Debio 1450 to Healthy Human Subjects

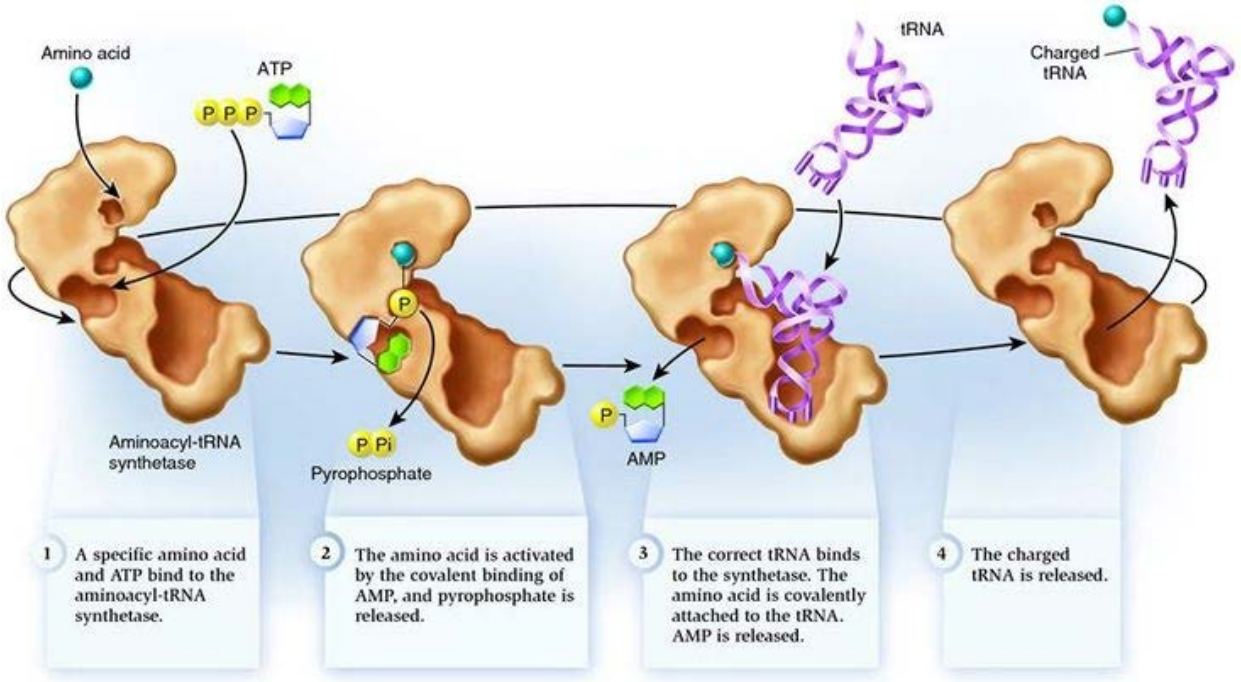


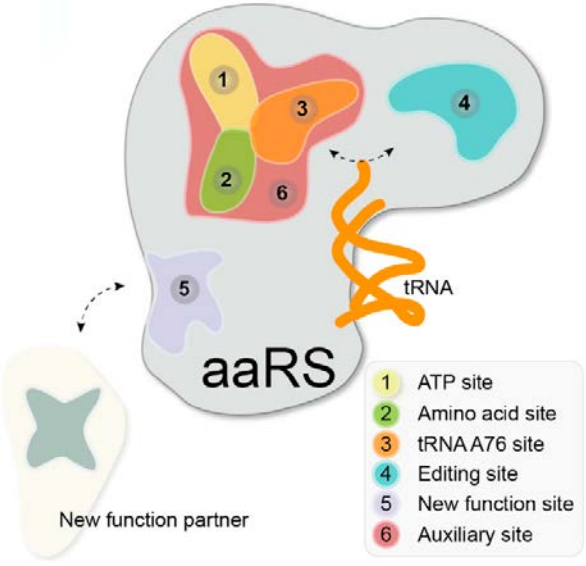
Debio 1450 Dose (mg)	Debio 1452 (active metabolite) T_{max} (hr)	C_{max} (ng/ml)	Half life (hr)	AUC_{inf} (hr*ng/ml)
48	2.25	837	7.0	8,704
72	2.38	1,101	7.3	9,990
108	2.25	1,596	7.9	17,010
160	2.25	2,960	7.6	29,066
320	2.25	3,740	7.8	45,414

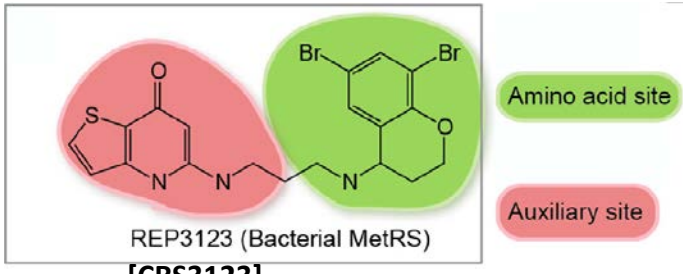
Karlowsky et al, AAC 2009; 53:3544-48

Hafkin & Kaplan, ECCMID 2014

Drugs acting on new targets - M spectrum: the example of Met-aminoacyl-tRNA synthetase inhibitors



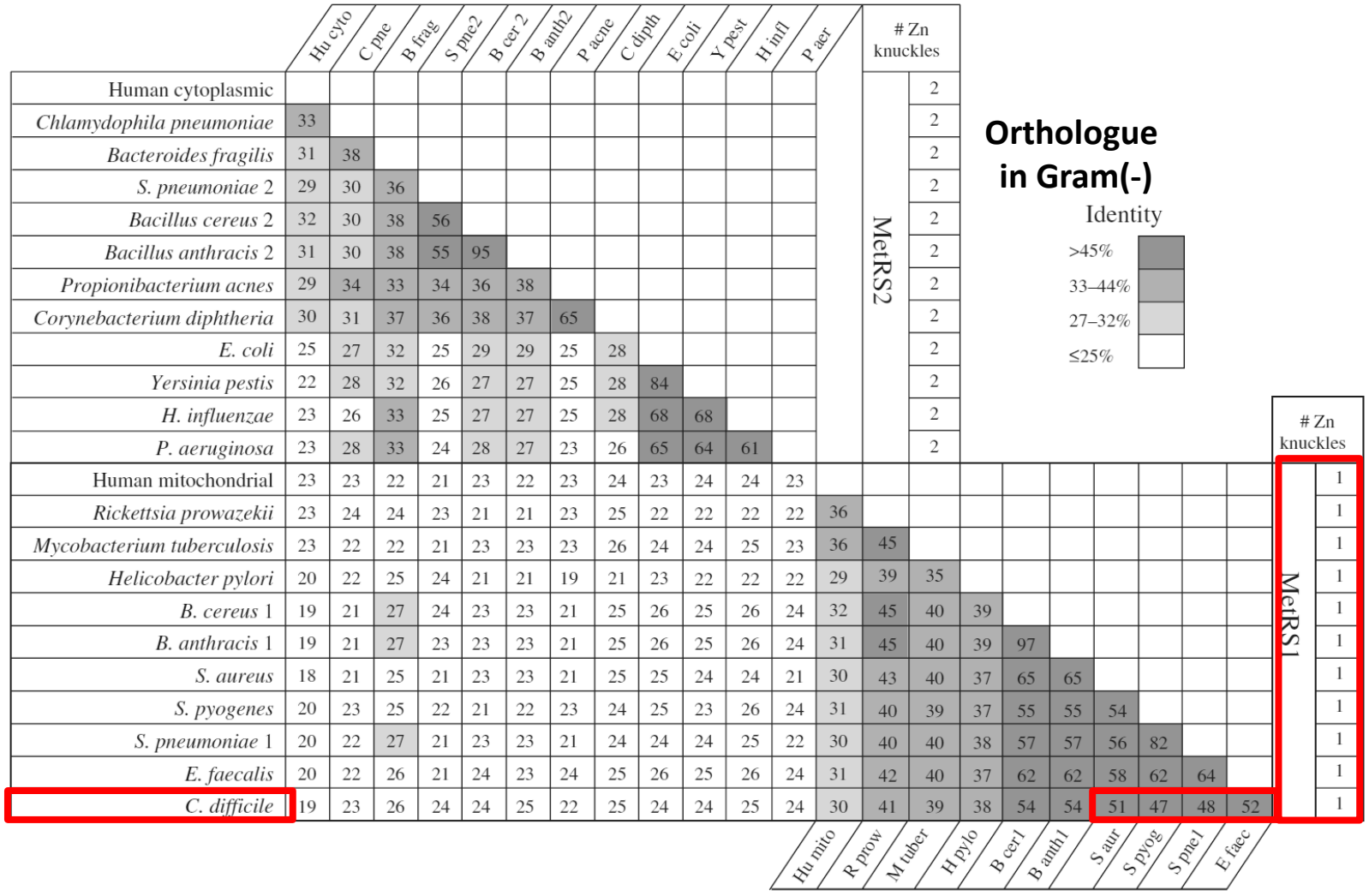




[CRS3123]

Fang & Guo, Life 2015; 5:1703–25

Drugs acting on new targets - M spectrum: the example of Met-aminoacyl-tRNA synthetase inhibitors



Orthologue in Gram(-)

Orthologue in Gram(+)

Critchley et al, JAC 2009; 63:954–63

CRS3123 (REP3123) activity

MetRS orthologue	REP3123 K_i (nM)	REP3123 MIC_{90} (mg/L)
MetRS1		
C. difficile	0.020	1
S. aureus	0.017	0.5
S. pneumoniae (MetRS1)	0.080	0.5
human mitochondrial	28	NA
MetRS2		
H. influenzae	178	32
E. coli	1900	>32
S. pneumoniae (MetRS2)	>20000	>16
human cytoplasmic	>20000	NA

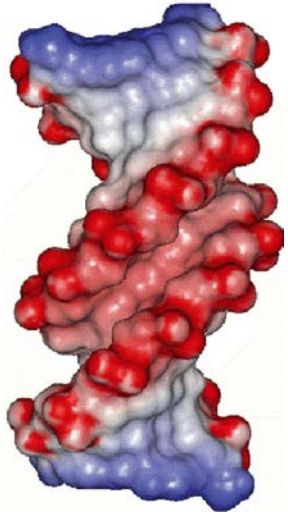
Oral formulation → *C. difficile*

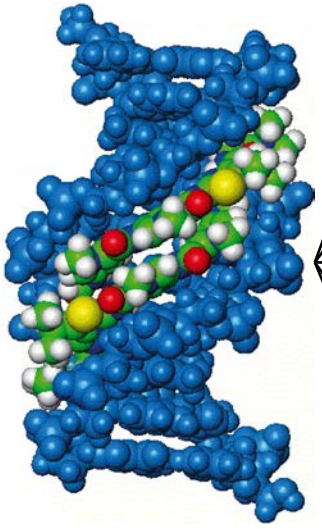
Species	phenotype	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range
C. difficile		1	1	0.5 – 1
S. aureus	MRSA	0.06	0.25	0.015 – 0.5
E. faecium	vanco-R	≤ 0.004	≤ 0.004	≤ 0.004
S. pneumoniae	peni-R	0.25	32*	0.25 - 64
H. influenzae		32	32	32
enterobacteriacae		> 32	> 32	> 32

* Strains expressing MetRS2

Critchley et al, JAC 2009; 63:954–63

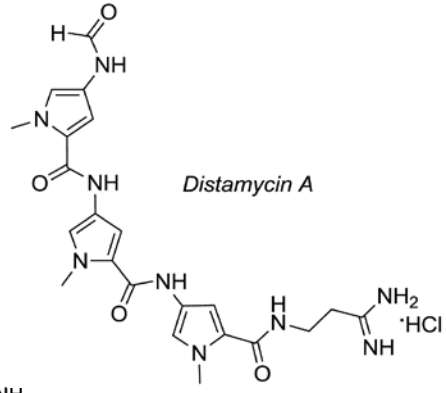
Drugs acting on new targets - XXL spectrum: the example of DNA minor grove binders

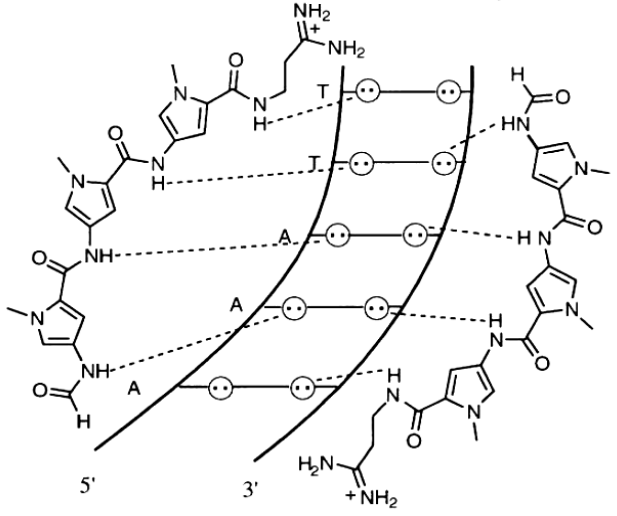




Surface of DNA minor groove in a region composed of A/T base pairs only. Red coloration indicates areas of negative charge

- antibacterial → preferentially targeting A/T rich sites within bacterial DNA
- antiparasitic
- antiviral
- antifungal
- anticancer

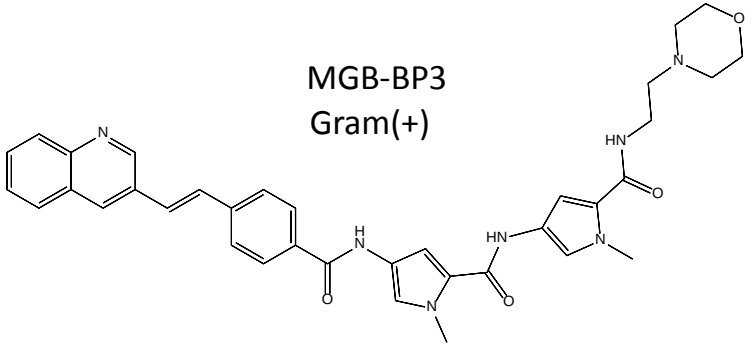




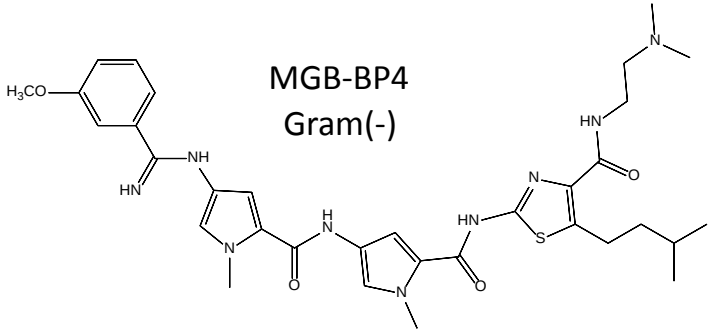
Anthony et al, Bioorg Med Chem Lett 2004; 14:1353–6
Dervan et al, Bioorg Med Chem. 2001; 9:2215–35

Drugs acting on new targets - XXL spectrum: the example of DNA minor grove binders

MGB-BP3
Gram(+)



MGB-BP4
Gram(-)



organism	MIC_{80} (µM)	MIC_{80} with efflux inhibitor (µM)
P. aeruginosa	> 100	1.36
E. coli	> 100	0.78

In general MGBs bind AT-rich or CG-rich sequences within the minor groove of bacterial DNA in a sequence and in a conformation-specific fashion, interfering with transcription factors and altering genetic regulation of bacteria.

Suckling et al, Chemistry & Biology Interface 2015; 5:166-74

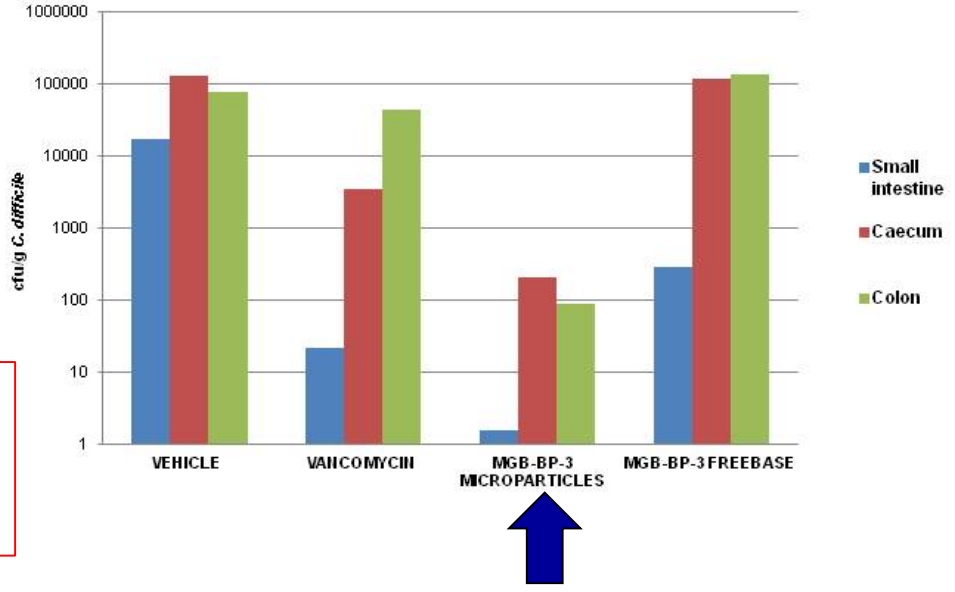
MGB-BP3 activity

Gram(+)

MGB-BP3 MIC_{50} and MIC_{90} ($\mu g\ mL^{-1}$) in comparison with vancomycin.

Target organism	MGB-BP3 MIC_{50}	MGB-BP3 MIC_{90}	Vancomycin MIC_{50}	Vancomycin MIC_{90}
MRSA	1	1	1	1
MRSE	0.25	0.5	2	2
MSSA	0.5	1	1	1
MSSE	0.25	0.25	2	2
Strep. pyrogenes	0.25	0.25	0.5	0.5
Ent. faecalis (vanc. sensitive)	1	>32	1	16
Ent. faecalis (vanc. insensitive)	2	>32	1	32

Clostridium difficile (hamster model)



- Oral formulation → *C. difficile* colitis
- IV formulation → Gram(+) infections
- Topical formulation → *S. aureus* infections

Barrett et al, Pharmacology & Therapeutics 2013; 139:12–23
Ravic et al, ICAAC 2013

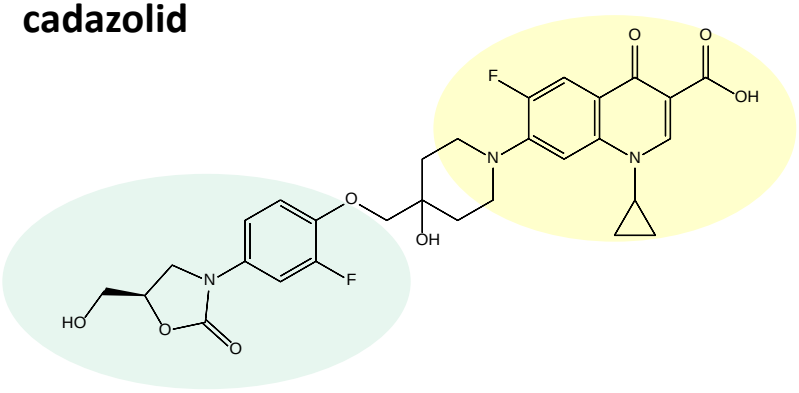
Molecules in clinical development acting on new intracellular targets

	Target	Compound	Chemical family	Company	Phase
New binding site on known target	Topoisomerase II (A subunit site)	Gepotidacin	Triazaacenaphthylene	GlaxoSmithKline PLC	2
	Topoisomerase II (ATP site)	Zoliflodacin	Spiropyrimidenetrione	Entasis Therapeutics Inc.	2
New target	FabI	Afabicin	Benzofuran naphthyridine	Debiopharm Intern. SA	2
		CG400549	Benzyl pyridinone	CrystalGenomics Inc	2
	Met-aminoacyl-tRNA synthetase	CRS3123	Fluorovinylthiophene	Crestone Inc.	1
	DNA minor groove	MGP-BP3	Lexitropsin	MGB Biopharma Ltd	1
Hybrids	Topoisomerase + ribosome	Cadazolid	fluoroquinolone + oxazolidinone	Actelion Pharmaceuticals Ltd.	3
		MCB3837		Morphochem AG	1

www.pewtrusts.org/antibiotic-pipeline [Dec. 2017]

Hybrids: oxazolidinone + fluoroquinolone

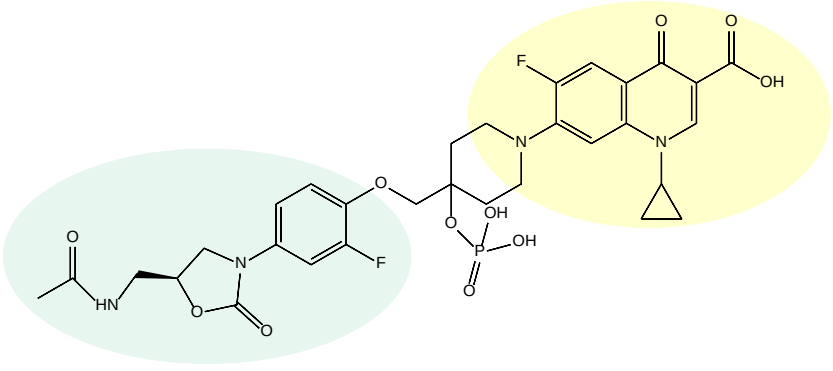
cadazolid



AB	*C. difficile* MIC (mg/L)			
	WT	FQ-R	LZD-R	FQ/LZD R
MXF	2	32	1	32
LZD	2	1	16-32	32-64
cadazolid	0.125-0.25	0.125-0.25	0.25-0.5	0.5

Locher et al, AAC 2014; 58:901–8

MCB3837 (prodrug of MCB3681)



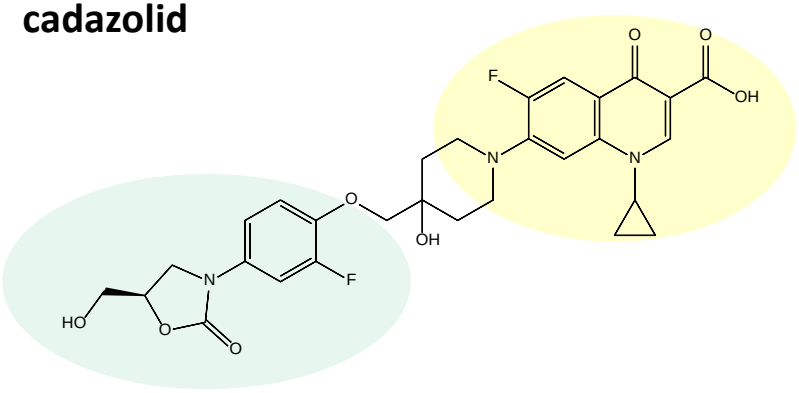
AB	*S. aureus* MIC (mg/L)			*E. coli* MIC (mg/L)	
	WT	CIP-R	LZD-R	WT	Permeab.
CIP	0.5	> 32	0.5	≤ 0.03	≤ 0.03
LZD	2	1	64	> 64	8
MCB3681	0.125	0.125	1	> 32	0.125

Hubschwerlen et al, Bioorg Med Chem Letters 2003; 13:4229–33

Oral formulation → *C. difficile*

Hybrids: oxazolidinone + fluoroquinolone

cadazolid



Metabolic pathway	antibiotic	*C. difficile* (IC_{50} – mg/L)			
		WT	FQ-R	LZD-R	FQ/LZD R
Protein synthesis	moxifloxacin	> 64	> 64	> 64	> 64
	linezolid	1.7	1.8	11.8	68
	cadazolid	0.09	0.08	0.19	0.31
DNA synthesis	moxifloxacin	2.4	46	6	43
	linezolid	> 128	> 128	> 128	> 128
	cadazolid	12	17.6	14.3	18.6

Oral formulation → *C. difficile*

Locher et al, AAC 2014; 58:901–8

Let's have a dream :
Other innovative strategies under investigation

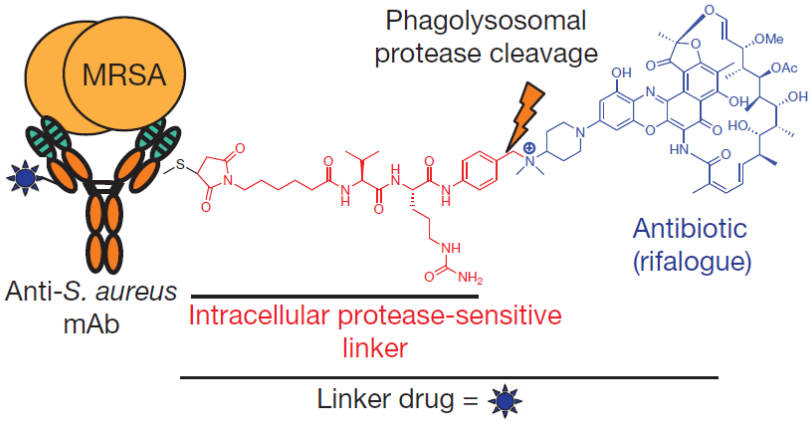
Magritte

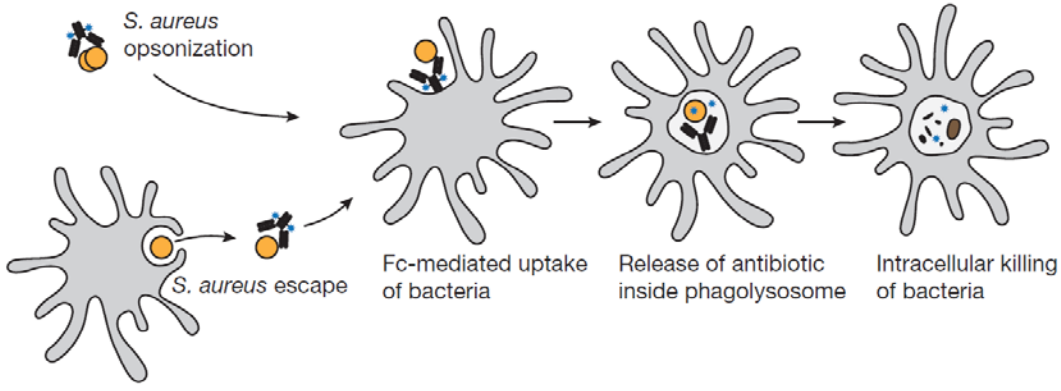
Let's have a dream : Other innovative strategies under investigation

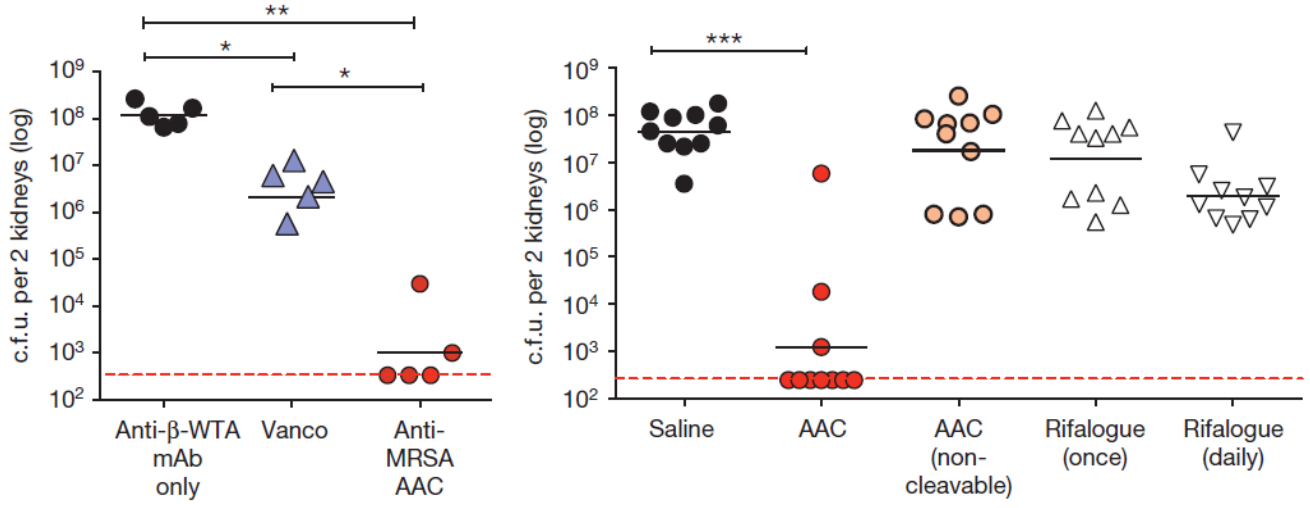
- Specific targeting approach

https://loonylabs.org/2015/01/04/antibiotic-resistance-2/

Antibiotic-antibody conjugates against intracellular *S. aureus*







Lehar et al, Nature 2015; 527: 323–8

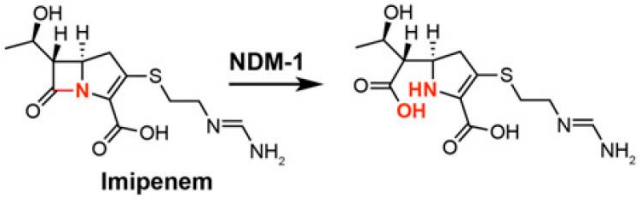
Let's have a dream : Other innovative strategies under investigation

- Specific targeting approach
- Unspecific disruption of bacterial metabolism

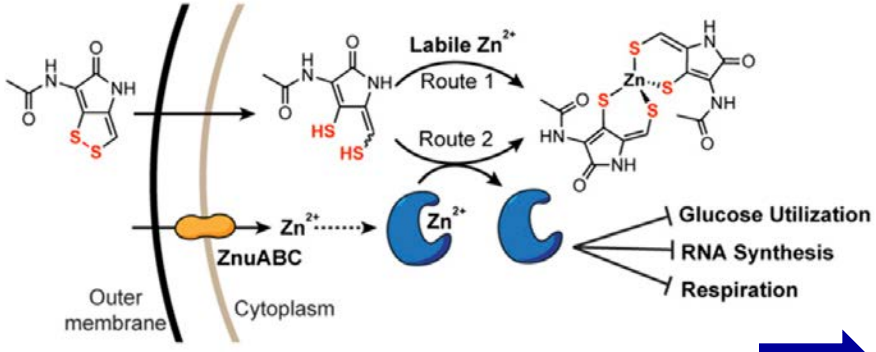
https://loonylabs.org/2015/01/04/antibiotic-resistance-2/

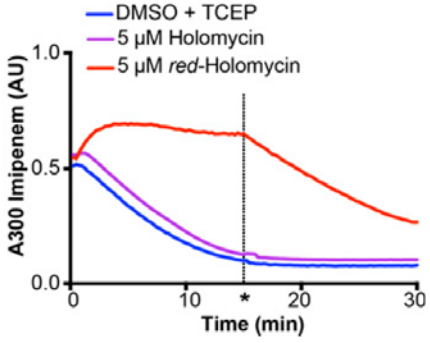
Disrupting metal homeostasis

Inhibition of metallo-β-lactamases

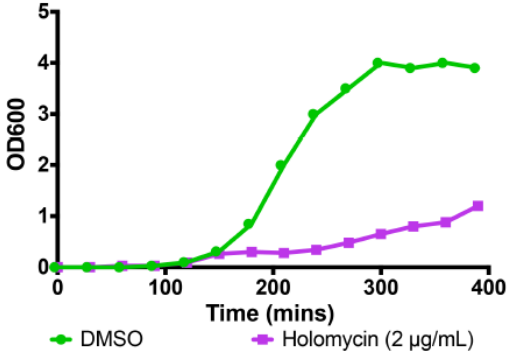


holomycin **holomycin-red**





Inhibition of growth by impairing cation-depending processes



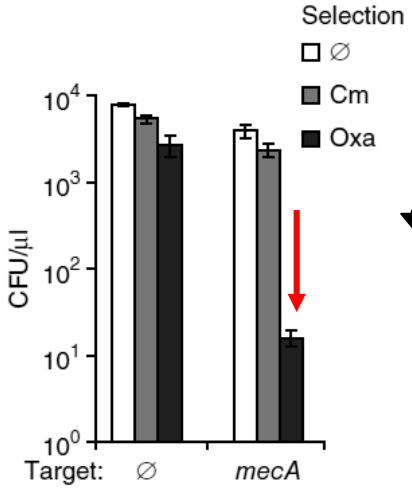
Chan et al, PNAS 2017; 114:2717–22

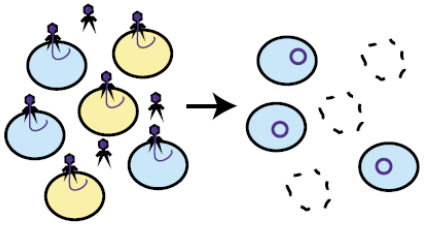
Let's have a dream : Other innovative strategies under investigation

- Specific targeting approach
- Unspecific disruption of bacterial metabolism
- Inactivation of resistance mechanisms

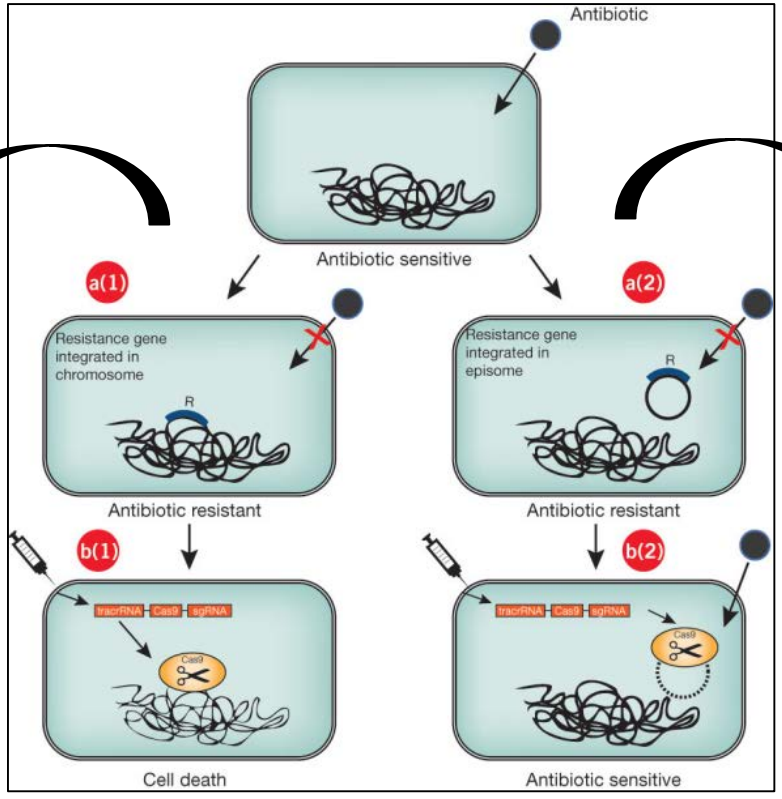
https://loonylabs.org/2015/01/04/antibiotic-resistance-2/

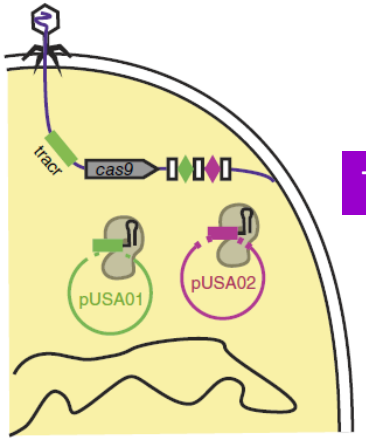
CRISPR/Cas9 to resensitize resistant bacteria



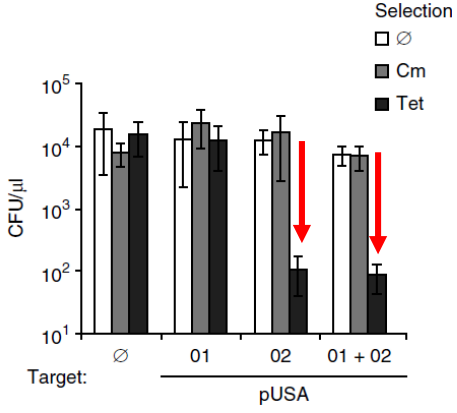


mecA+ *mecA-*





Tet R



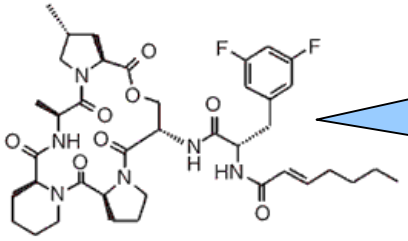
Parmley, S. SciBX 7(41); doi:10.1038/scibx.2014.1198
Bikard et al, Nat Biotechnol 2014; 32:1146-51

Let's have a dream : Other innovative strategies under investigation

- Specific targeting approach
- Unspecific disruption of bacterial metabolism
- Inactivation of resistance mechanisms
- Waking up dormant bacteria

https://loonylabs.org/2015/01/04/antibiotic-resistance-2/

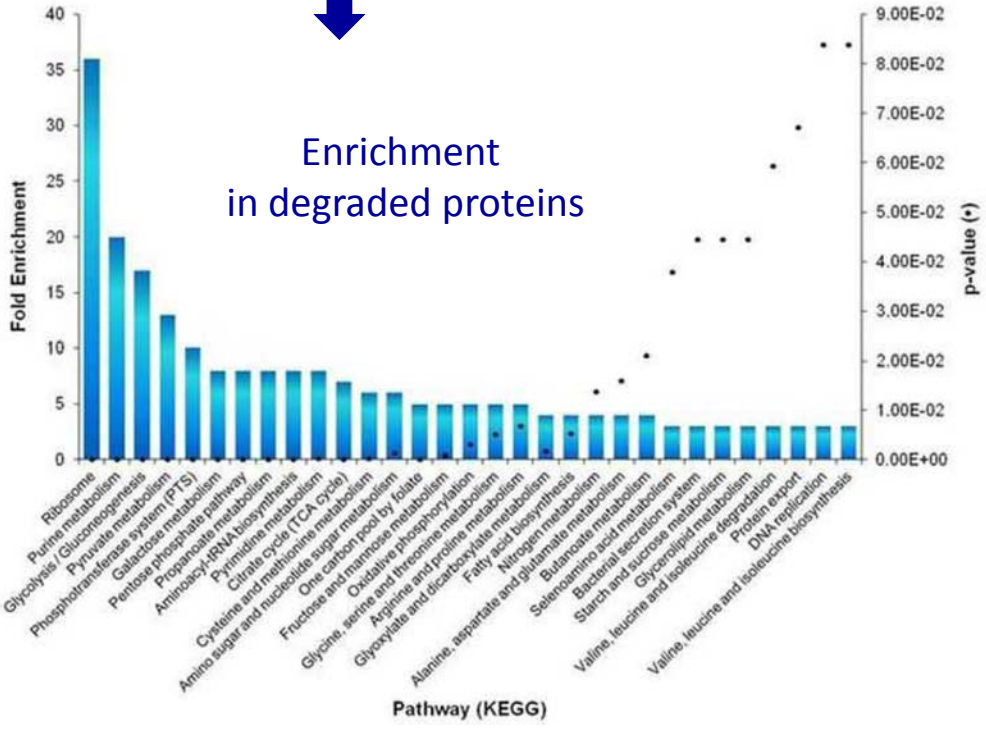
Acting on “tolerant” phenotypes



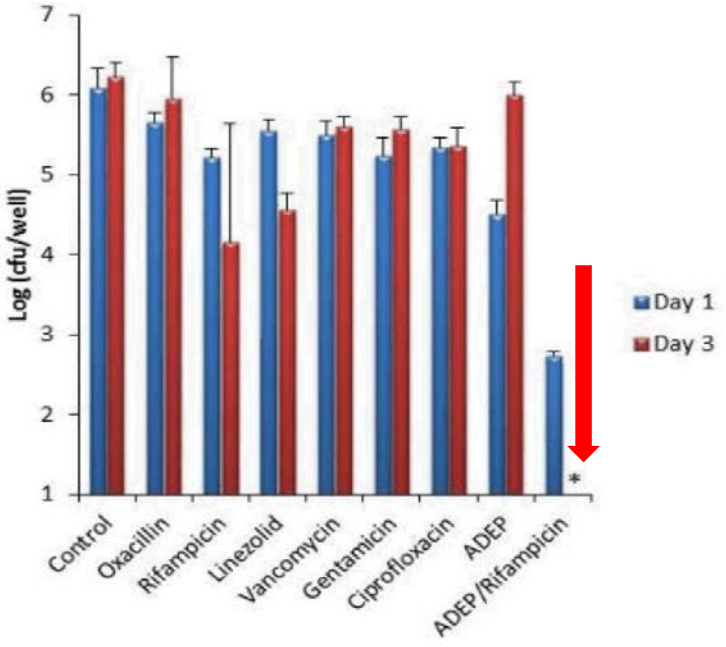
ADEP 4

targets ClpP, core unit of a major bacterial protease complex.

Enrichment
in degraded proteins



Synergistic
with antibiotics in biofilms



Coulon et al, Nature 2013; 503: 365–70

Some food for thought …

Conclusions

- The pipeline is not as dry as you may think at first glance
  → the effort should be maintained

www.pewtrusts.org/antibiotic-pipeline [Dec. 2017]

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  BUT most drugs are developed
  for specific infections / indications
  → reply to current threats

World Health Organization
WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

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World Health Organization
WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

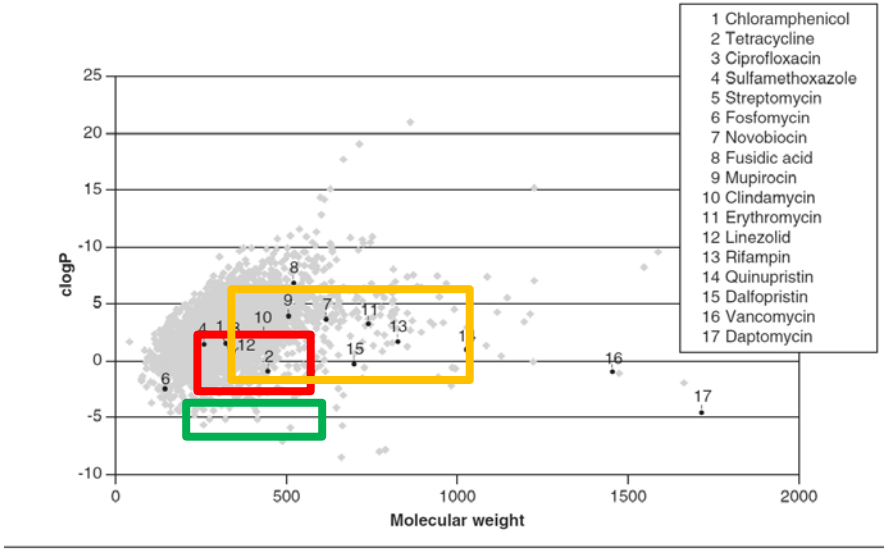
- Most of these new drugs are directed towards Gram(+) bacteria
  → some pieces still missing in the puzzle …

Perspectives for future research: PK & PD issues

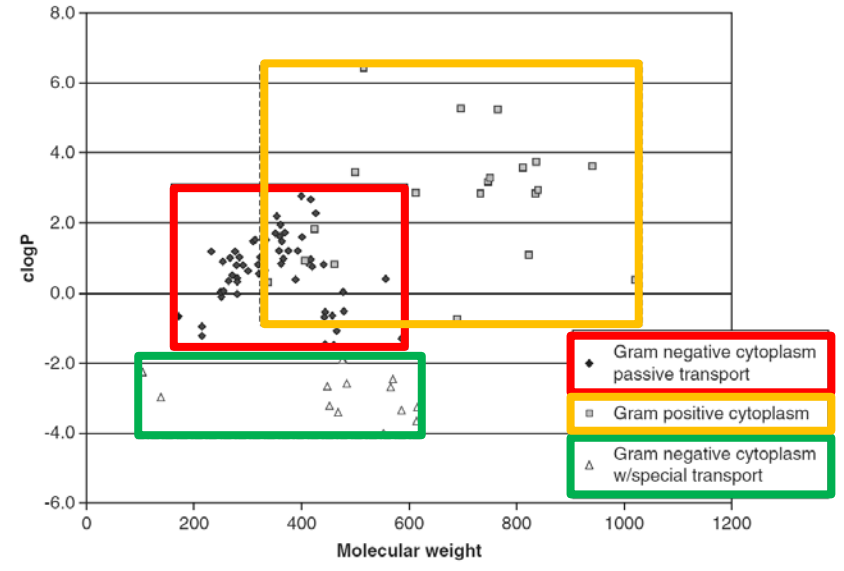
- PK : penetration inside Gram(-) bacteria !
  Most antibiotics do not follow the “rule of five” from C. Lipinsky for drugable compounds

Perspectives for future research: PK & PD issues

- PK : penetration inside Gram(-) bacteria !
  Most antibiotics do not follow the “rule of five” from C. Lipinsky for drugable compounds
  Do we have some guidance ?



Molecular weight versus clogP plotted for non-antibacterial drugs (●) and 17 representative antibacterials

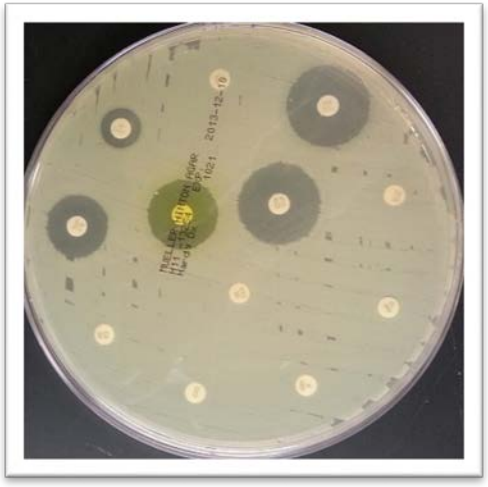


Molecular weight versus clogP plotted for cytoplasm-targeted antibacterials.

Silver, Expert Opin Drug Discov 2008; 3:487-500

Perspectives for future research: PK & PD issues

- PD : tolerant phenotypes non-responsive to antibiotics !
  Antibiotic activity is evaluated by determining susceptibility in broth/agar plate.



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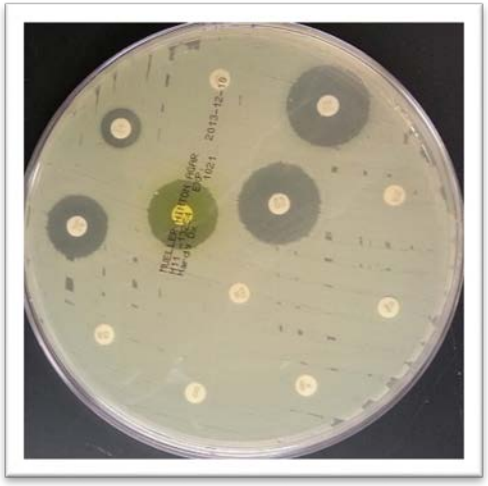
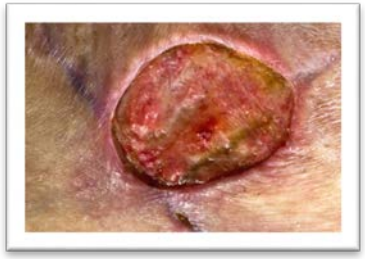
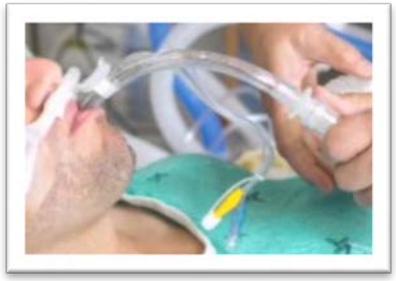
Bacterial growth/metabolic activity is markedly influenced by the environment …



Predictive ?



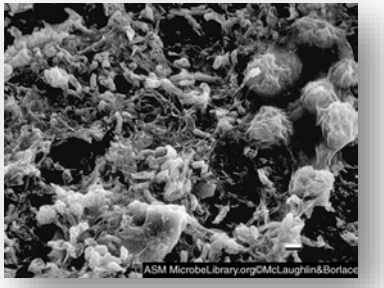


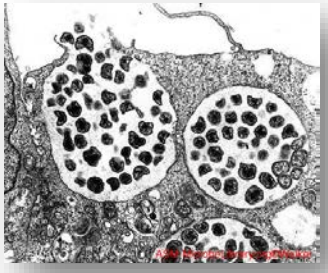
Perspectives for future research: PK & PD issues

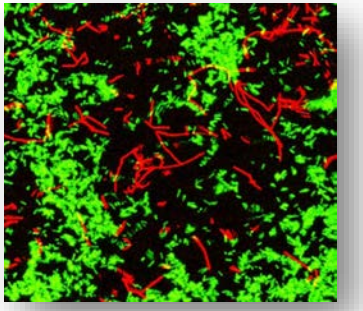
- PD : tolerant phenotypes non-responsive to antibiotics !
  Antibiotic activity is evaluated by determining susceptibility in broth/agar plate.

Bacterial growth/metabolic activity is markedly influenced by the environment …

→ Include in early screening an evaluation of the capacity of the drugs to act upon specific forms of infection (biofilm, intracellular, mixed infections), including in animal models.







Merry Christmas !

Bruxelles, Grand-Place