ACADÉMIE UNIVERSITAIRE WALLONIE-BRUXELLES

Journée des Doctorants en Sciences Pharmaceutiques
2007-2008

Antibiotic transporters: From Discovery to Clinical Implications

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Influenced largely by

- **Françoise Van Bambeke, Béatrice Marquez, Youri Glupczynski (UCL) and Martine Prevost (ULB)**
- **my participation to the *European Committee for Antibiotic Susceptibility Testing* (EUCAST)**

The slides are available from **http://www.facm.ucl.ac.be** – follow "Lectures"

Steps and Challenges of efflux in antibacterial chemotherapy

- **recognizing its existence:**
  is it a significant mechanism of resistance ?
- **which pumps …**
  is antibiotic efflux different from other drug efflux ?
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Historical observations on tetracyclines …

1: Nature. 1963 Oct 26;200:384-5.

DISAPPEARANCE OF OXYTETRACYCLINE ACCUMULATION IN THE CELLS OF MULTIPLE DRUG-RESISTANT ESCHERICHIA COLI.

IZAKI K, ARIMA K.

PMID: 14087909 [PubMed - indexed for MEDLINE]

Who remembers that car ?

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Who remembers that graph ?

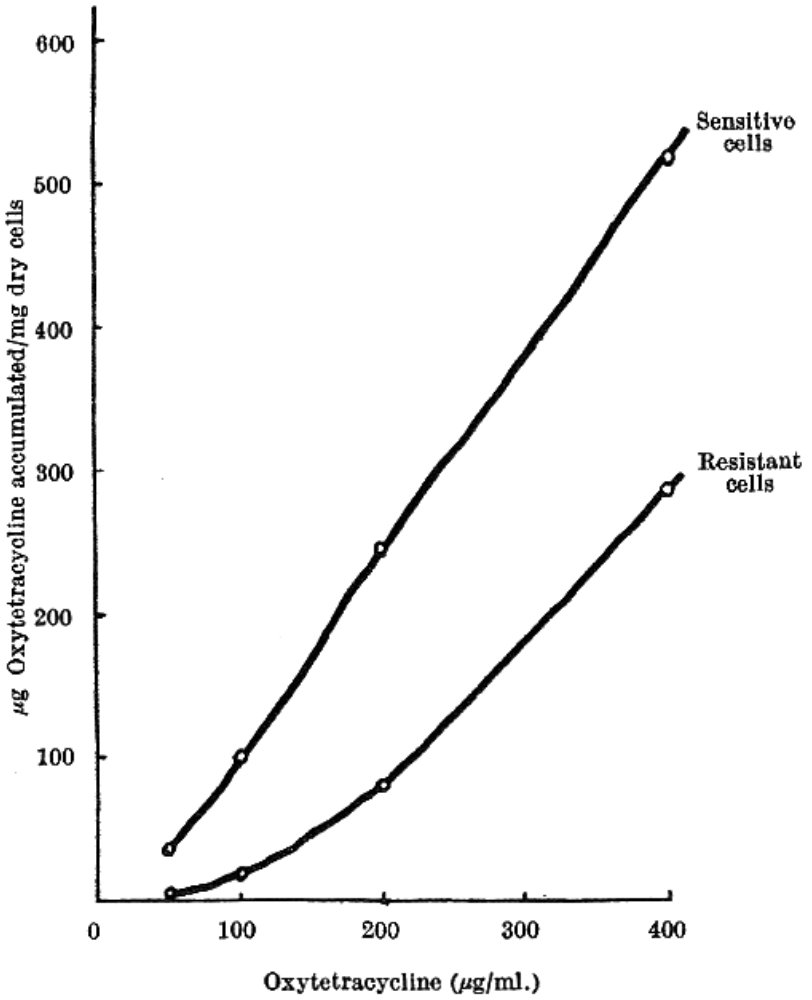

Fig. 1. Accumulation of oxytetracycline in *E. coli* K-12 at various concentrations of oxytetracycline added. The reaction mixture contains 1 ml. suspension (0·7 mg dry weight) oxytetracycline hydrochloride, 1 ml. (0·5–4·0 mg/ml.) and 1 ml. of 10 per cent (w/v) glucose, 2 per cent K_2HPO_4 and 0·1 per cent $MgSO_4.7H_2O$ respectively in a total volume of 10 ml. Incubation was carried out aerobically at 30° C for 90 min

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Biochem. J. (1965) **94**, 54

Resistance of *Escherichia coli* to Tetracyclines

BY T. J. FRANKLIN AND A. GODFREY
Imperial Chemical Industries Ltd. (Pharmaceuticals Division), Alderley Park, Macclesfield, Cheshire

(*Received* 23 *March* 1964)

1. A strain of *Escherichia coli* highly resistant to chlortetracycline and partially cross-resistant to tetracycline has been isolated. 2. The nitro-reductase system of the resistant cells was inhibited to a smaller extent by chlortetracycline than was the corresponding enzyme of sensitive cells. 3. The incorporation of leucine *in vitro* into the ribosomal protein of cell-free preparations from sensitive and resistant cells was equally inhibited by chlortetracycline. 4. Resistant cells accumulated much less chlortetracycline and tetracycline than did sensitive cells when both were cultured in the presence of these drugs. 5. The uptake of tetracycline by both sensitive and resistant *E. coli* was dependent on the presence of glucose in the medium. 6. Fractionation of cells cultured in medium containing [^{14}C]chlortetracycline indicated that the largest proportion of radioactivity in sensitive cells was in the fraction consisting mainly of cell-wall material. There was no concentration of radioactivity in any one fraction of the resistant cells. 7. No evidence could be obtained for a specific tetracycline-excretion system in the resistant cells. 8. The significance of these results in relation to current theories of the antibiotic action of and resistance to the tetracycline drugs is discussed.

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Historical observations on tetracyclines …

15 years later...

Proc. Natl. Acad. Sci. USA
Vol. 77, No. 7, pp. 3974–3977, July 1980
Biochemistry

Active efflux of tetracycline encoded by four genetically different tetracycline resistance determinants in *Escherichia coli*

(everted membrane vesicles/tetracycline transport/transposon Tn10/plasmids)

LAURA MCMURRY, RICHARD E. PETRUCCI, JR., AND STUART B. LEVY*

Department of Molecular Biology and Microbiology and Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts 02111

Communicated by Boris Magasanik, April 21, 1980

Historical observations on tetracyclines …

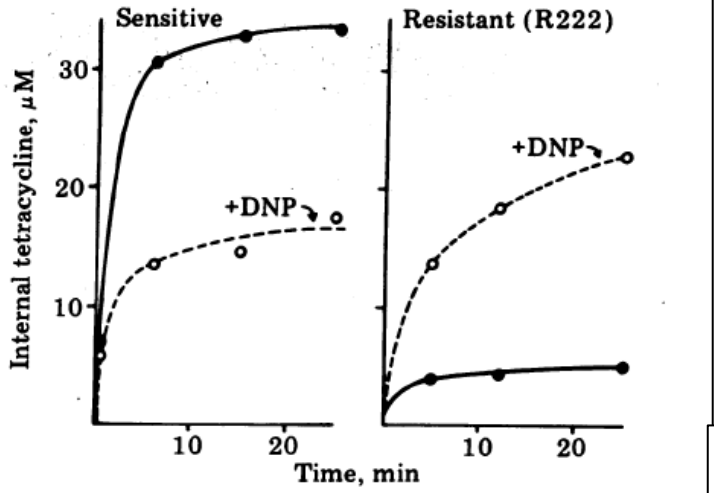


FIG. 1. Tetracycline uptake by *E. coli* ML308-225 (sensitive) and by R222-containing induced (resistant) cells with (○) and without (●) 1 mM DNP. Cells were grown overnight in medium A containing glucose and uptake was measured in the absence of added energy source.

Whole bacteria

Everted membranes

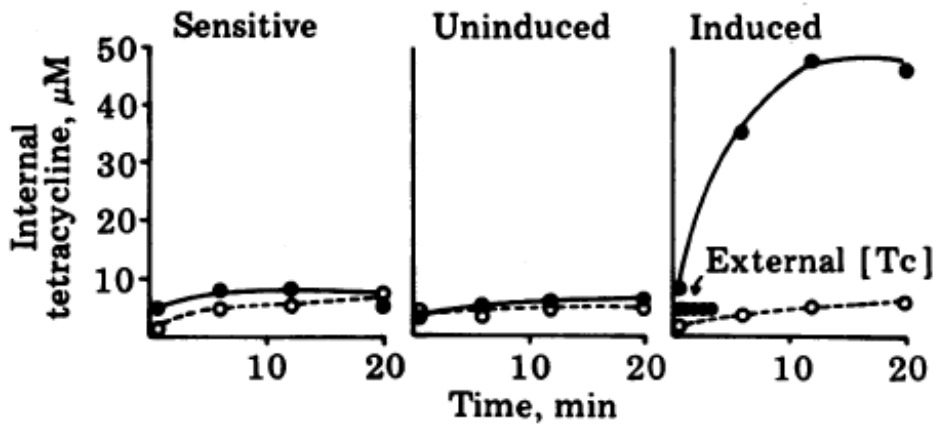
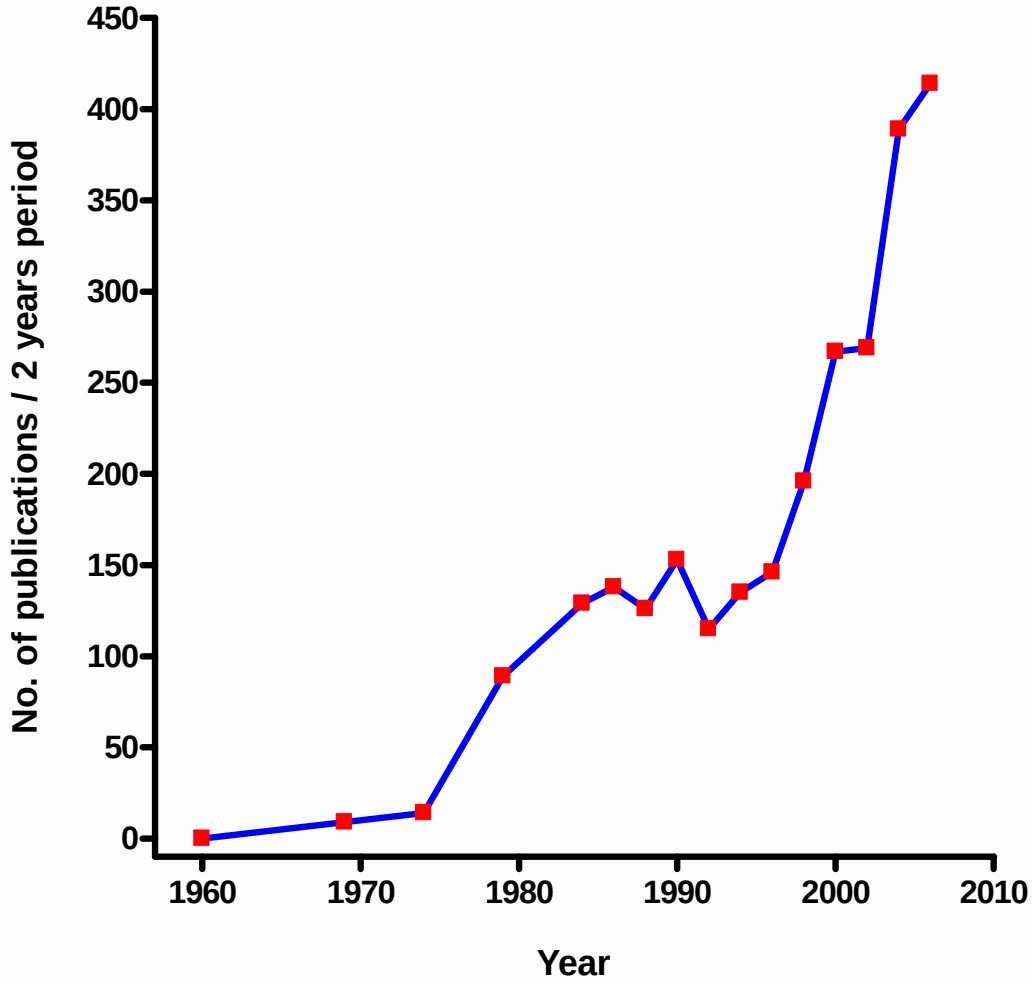


FIG. 2. Tetracycline (Tc) uptake by everted membrane vesicles made from sensitive ML308-225 cells and from uninduced and induced R222-containing cells. ○, No energy; ●, D-lactate. Cells were grown in glycerol and vesicles were frozen in 5 mM Tris·HCl, pH 7.2/70 mM KCl/0.25 mM dithiothreitol/50% glycerol. The assay was done at pH 6.6.

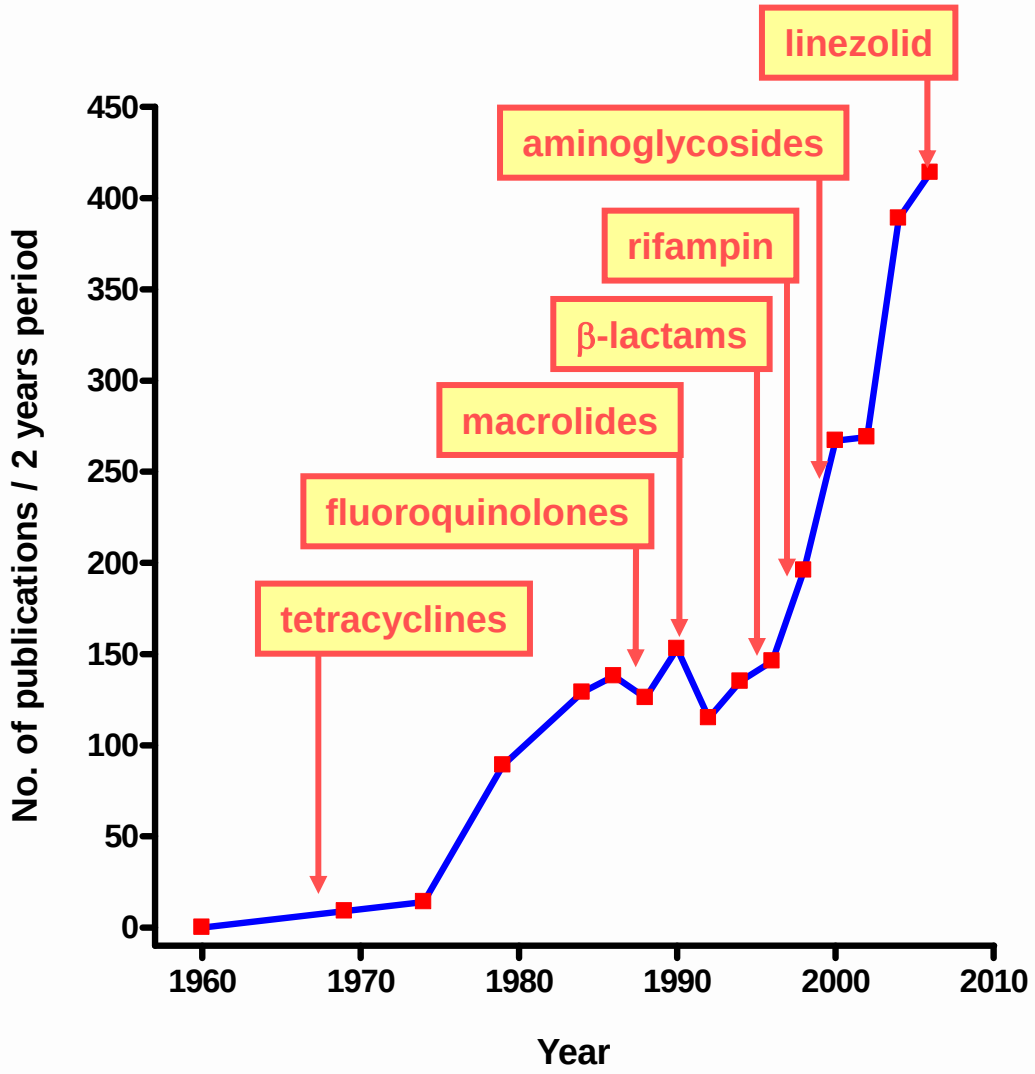
McMurry et al., PNAS 1980; 77:3974-3977

Historical trends …



No. of publications in PubMed with keywords: antibiotic & efflux

Historical landmarks …



Successive description of efflux-mediated resistance for major antibiotics

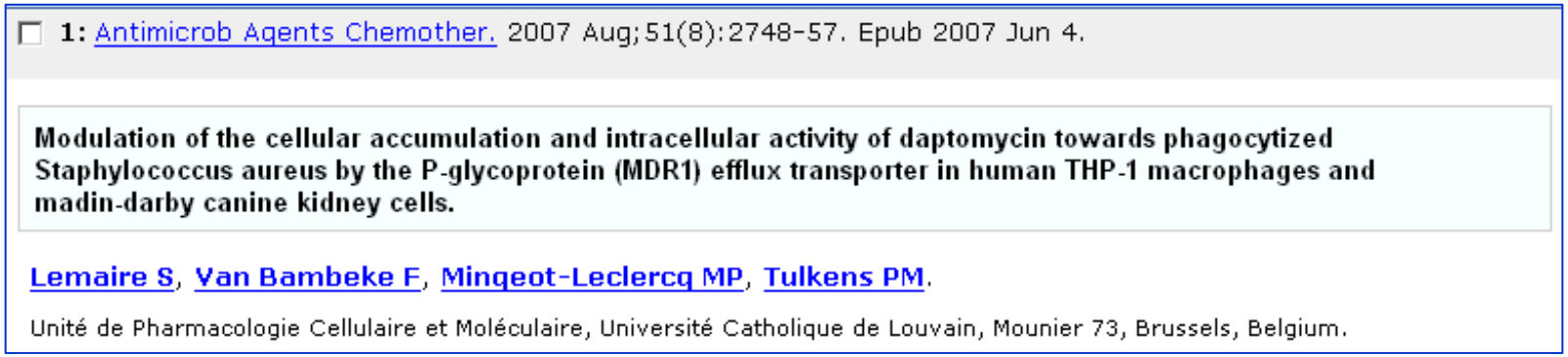
The present situation …

- Efflux has, slowly but surely, been shown to affect most if not all major antibiotic classes …

  ? Are they classes that will never show efflux-mediated resistance ?

  May be only those which must act on bacterial surface ?

  - ? glycopeptides [vancomycin…],
  - ? lipoglycopeptides [telavancin],
  - ? lipopeptides [daptomycin], …



1: Antimicrob Agents Chemother. 2007 Aug;51(8):2748-57. Epub 2007 Jun 4.

Modulation of the cellular accumulation and intracellular activity of daptomycin towards phagocytized Staphylococcus aureus by the P-glycoprotein (MDR1) efflux transporter in human THP-1 macrophages and madin-darby canine kidney cells.

Lemaire S, Van Bambeke F, Mingeot-Leclercq MP, Tulkens PM.

Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, Mounier 73, Brussels, Belgium.

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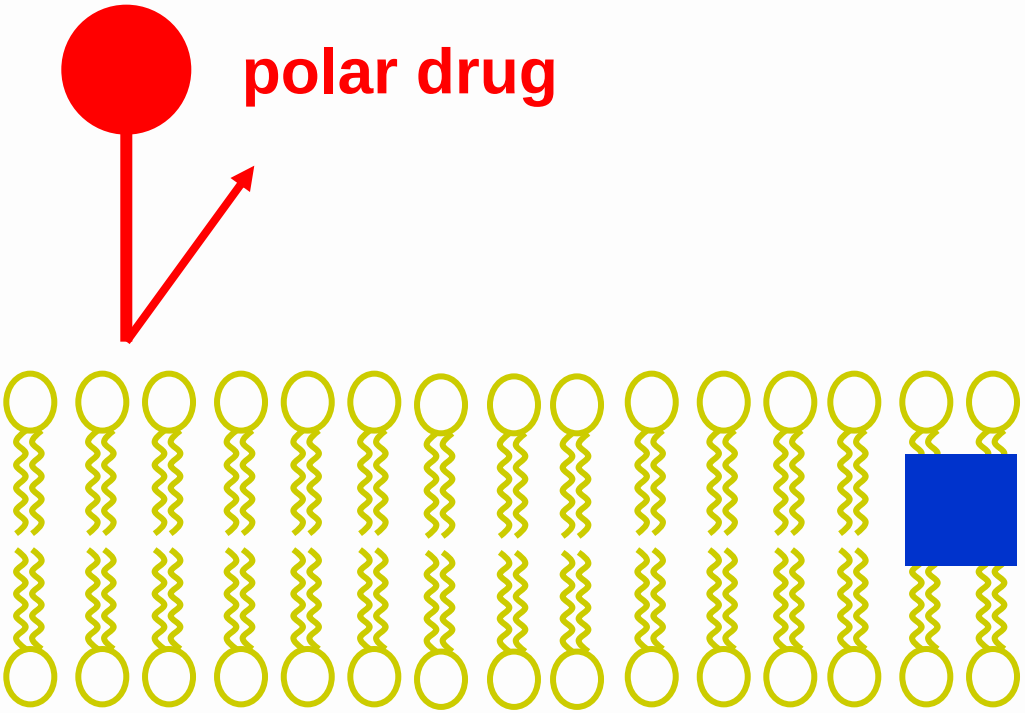
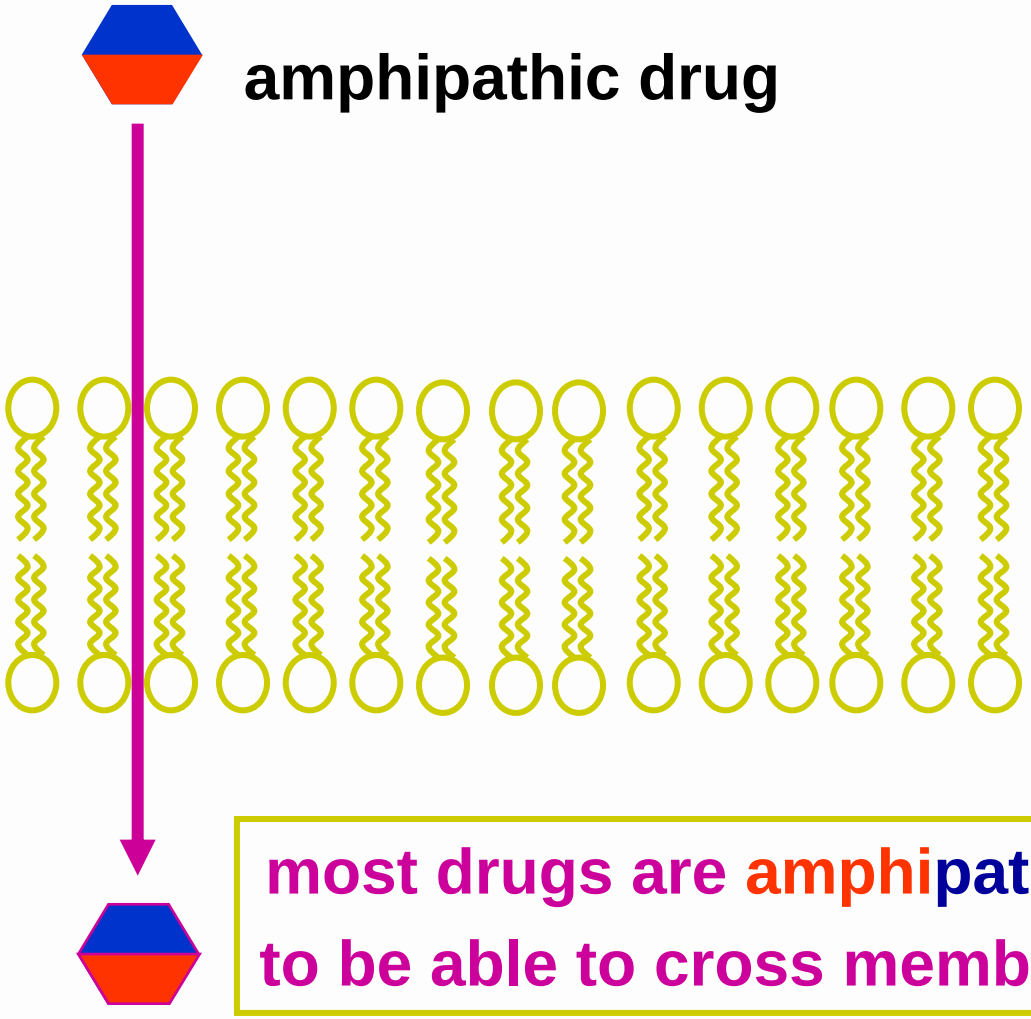
Why do we have efflux ?



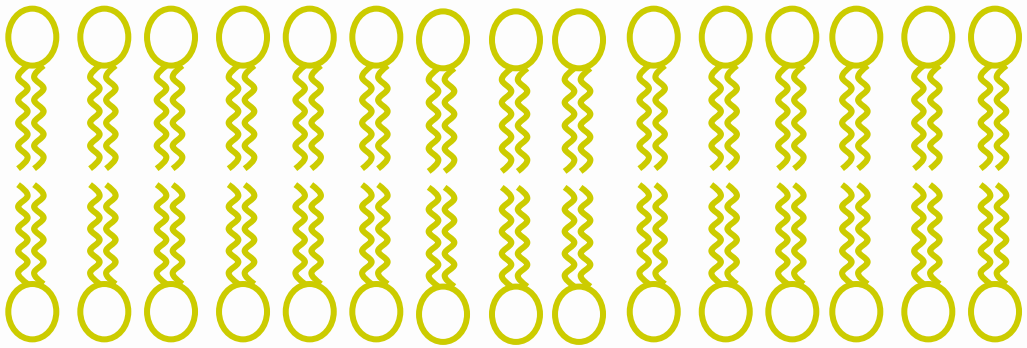
- **polar drugs do not reach intracellular targets !**
- **Lipophilic drugs get stucked in the bilayer !**

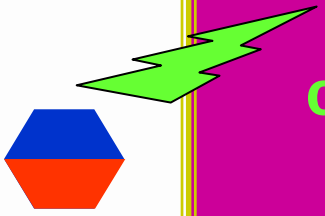
Reaching an intracellular target …



most drugs are amphipathic by design, to be able to cross membrane barriers !

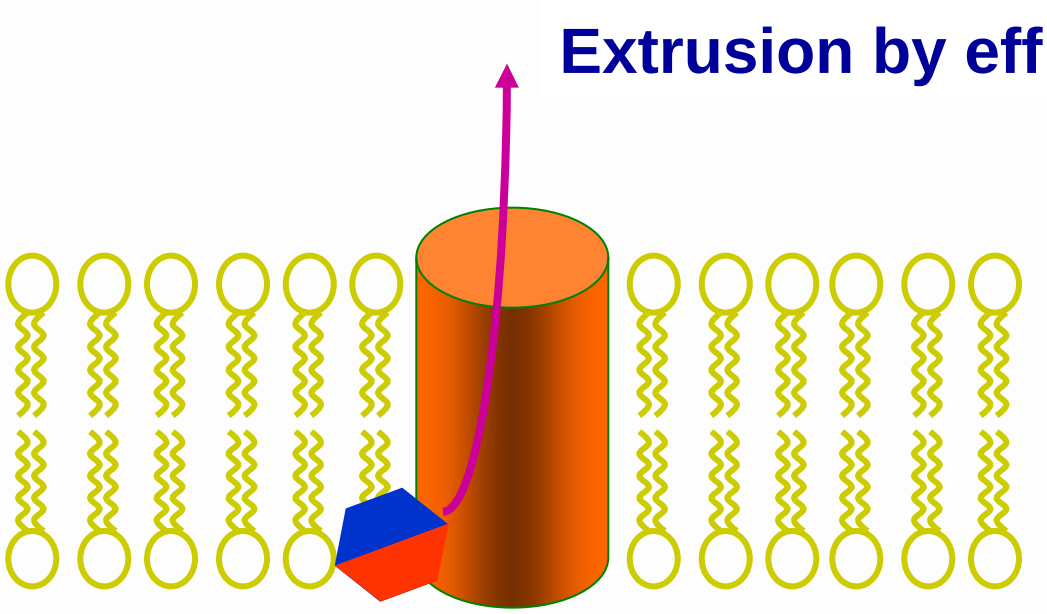
Intracellular chemotherapeutic agents



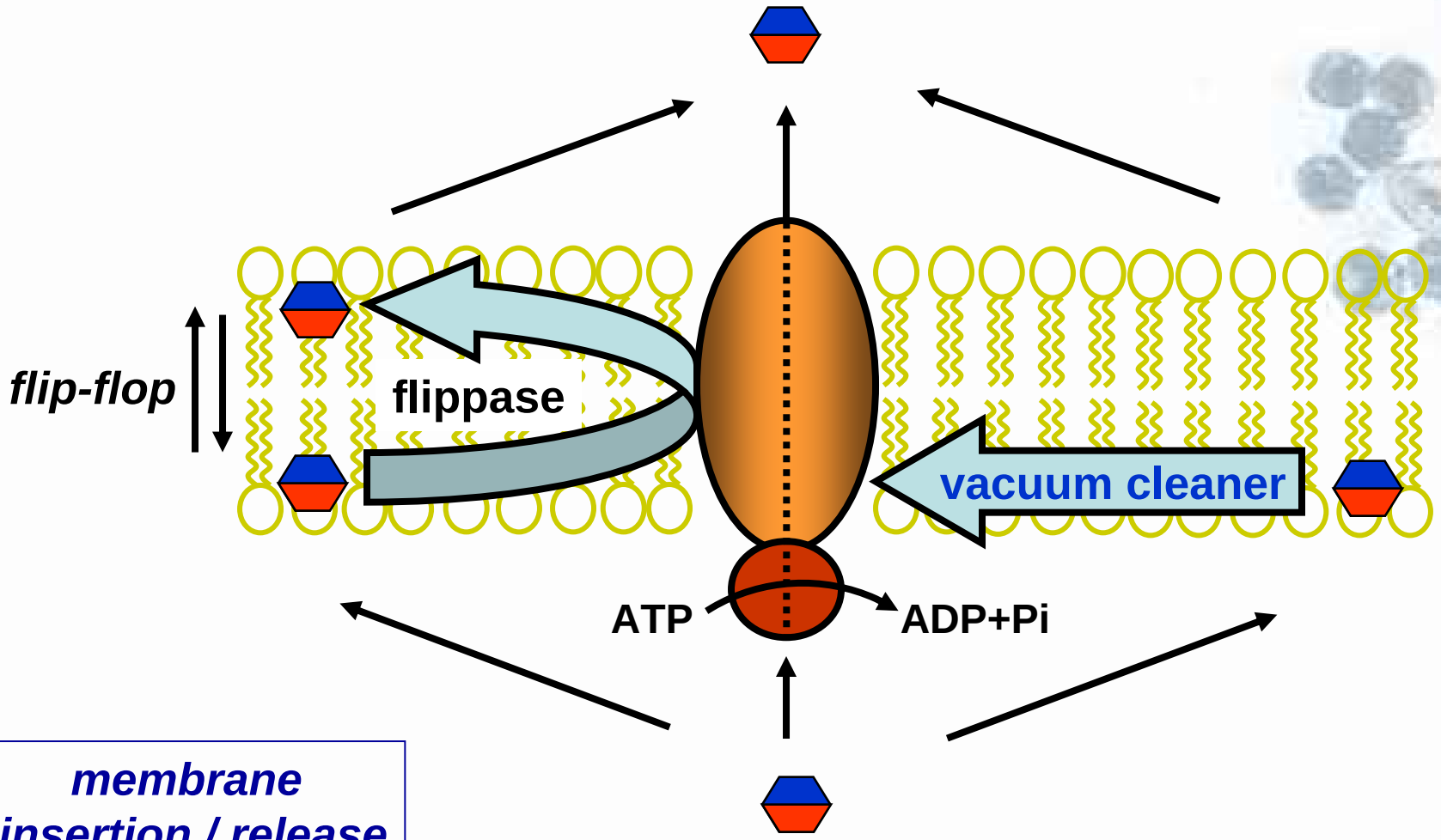


But once inside the cell, any compound may have potentially harmful effects

Proteins with efflux capabilities may have been selected out to help cells getting rid of diffusible, potentially toxic compounds



General mechanisms of drug efflux



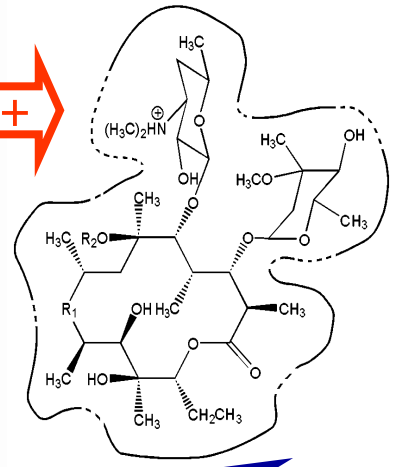
membrane insertion / release

Van Bambeke *et al*. (2000) Biochem. Pharmacol. 60:457-70

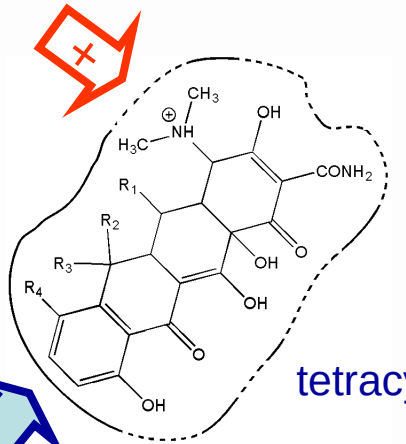
Most antibiotics are amphiphilic !

cationic amphiphiles

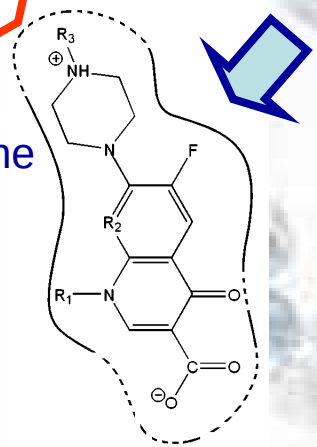
macrolide



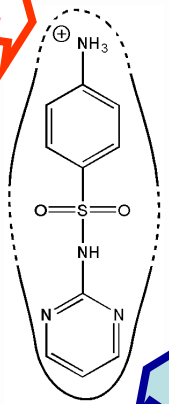
tetracycline



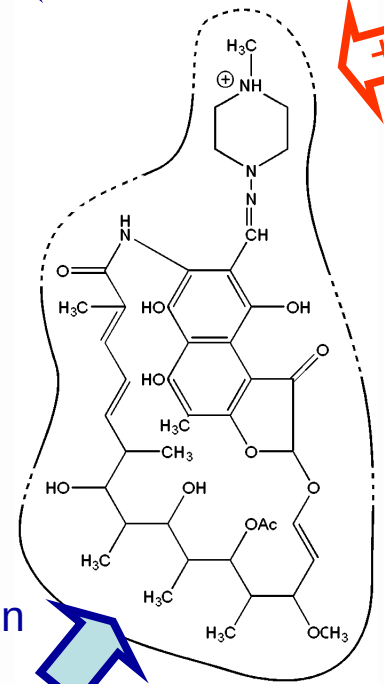
fluoroquinolone



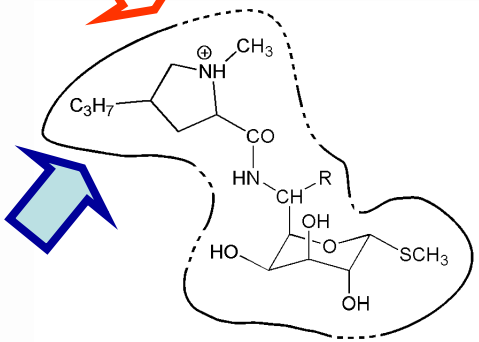
sulfamide



rifampicin



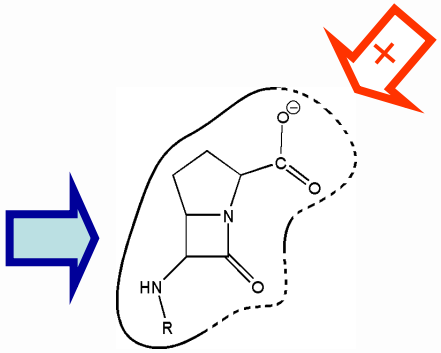
lincosamide



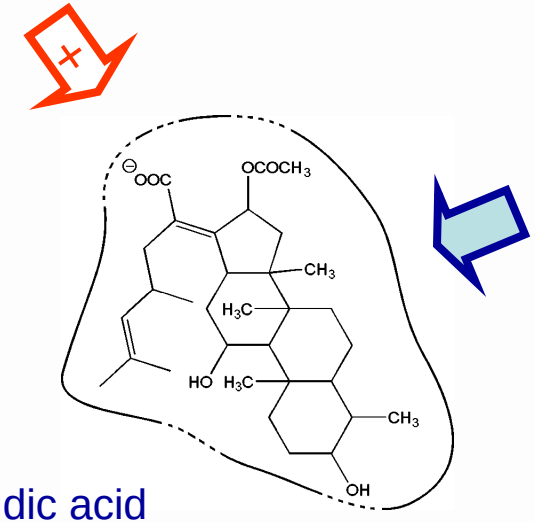
Van Bambeke *et al*. (2000) Biochem. Pharmacol. 60:457-70

Most antibiotics are amphiphilic !

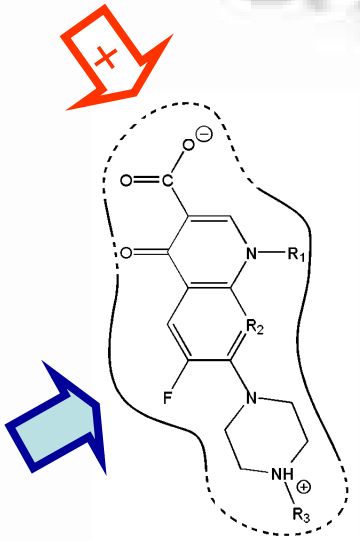
anionic amphiphiles



β-lactam

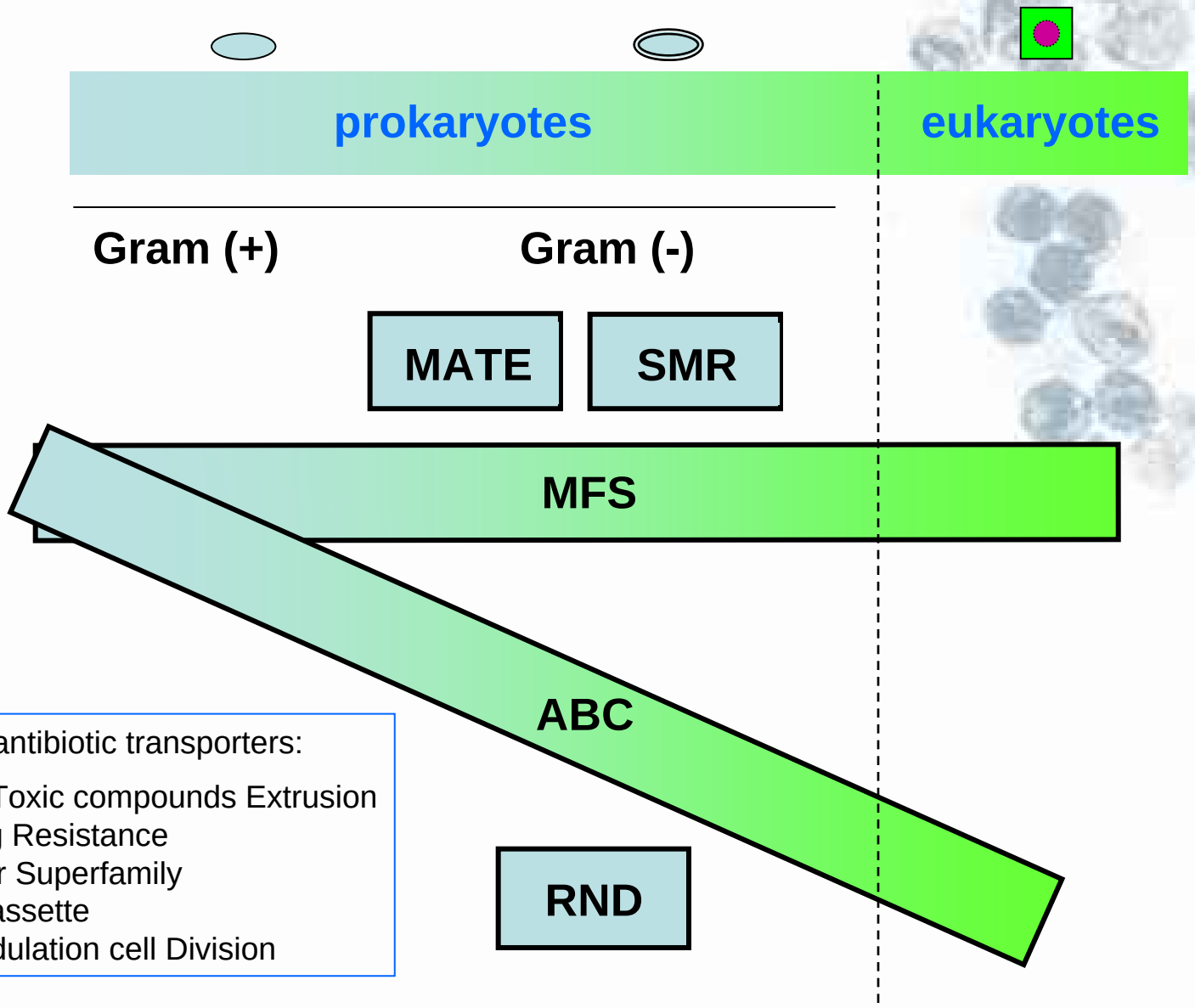


fusidic acid



fluoroquinolone

But antibiotic efflux transporters are everywhere



Main (super)families of antibiotic transporters:

- MATE: Multidrug And Toxic compounds Extrusion
- SMR: Small Multidrug Resistance
- MFS: Major Facilitator Superfamily
- ABC: ATP Binding Cassette
- RND: Resistance Nodulation cell Division

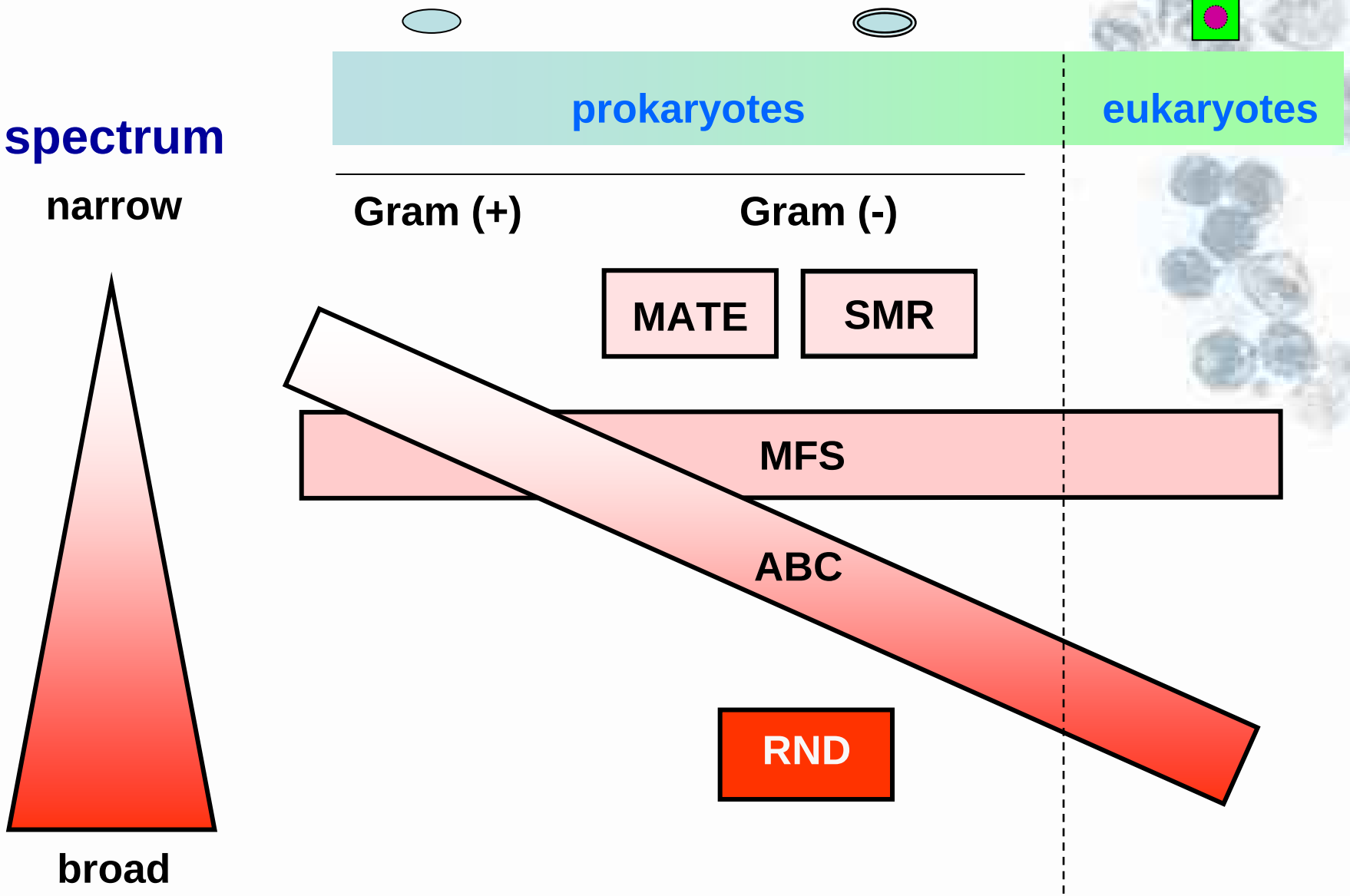
Mesaros *et al*. (2005) Louvain médical. 124:308-20

Antibiotics as substrates of efflux pumps accross living organisms

Antibiotic class	bacteria Gram (+)	bacteria Gram(-)	fungi	superior eucaryotes
β-lactams	●	●	●	●
fusidic acid		●		
macrolides	●	●	●	●
streptogramins	●			●
tetracyclines	●	●	●	●
aminoglycosides		●	●	
chloramphenicol	●	●	●	
rifamycins				●
sulfamides			●	
trimethoprim		●		
fluoroquinolones	●	●		●

Van Bambeke *et al*. (2000) Biochem. Pharmacol. 60:457-70

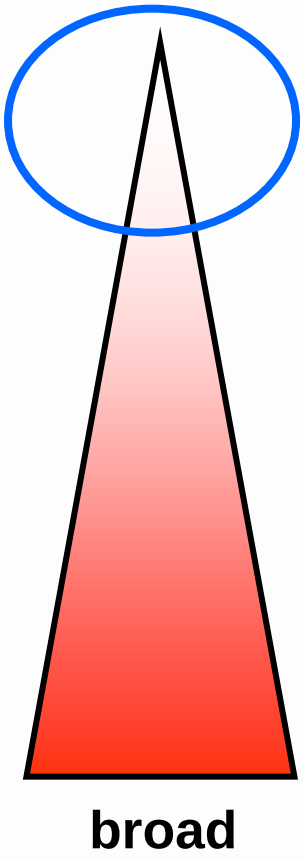
Antibiotic transporter spectra …



Mesaros *et al*. (2005) Louvain médical. 124:308-20

Efflux as a mechanism of export in antibiotic producers

spectrum



specific for the produced antibiotic

ABC

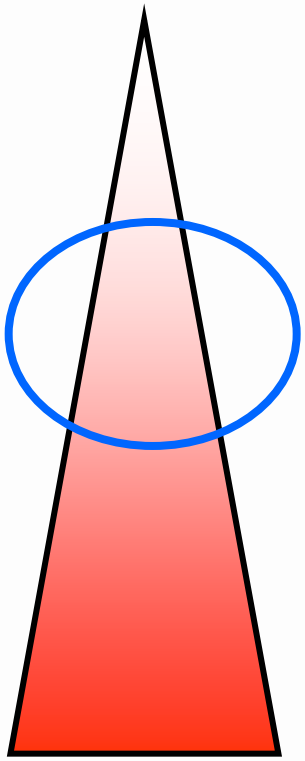
OleB or C of *S. antibioticus*
→ oleandomycin
SmB of *S. ambofaciens*
→ macrolides
Tlrc of *S. fradiae*
→ tylosin

MFS

Ptr of *S. pristinaespiralis*
→ pristinamycin
LmrA of *S. lincolnensis*
→ lincomycin
RifP of *A. mediterranei*
→ rifampicin

Efflux as a mechanism of resistance in Gram-positive bacteria

spectrum



specific for one (or a few) families of drugs

ABC

PatA/PatB of *S. pneumoniae*
→ FQ, chl
MsrA of *S. epidermidis*
→ erythromycin

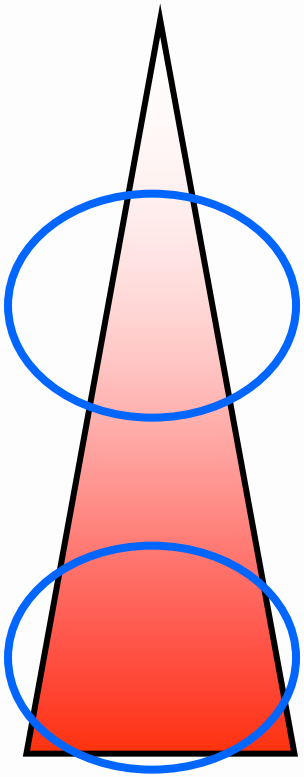
MFS

NorA of *S. aureus*
→ FQ,Tet, chl
MefE of *S. pneumoniae*
→ ML
PmrA of *S. pneumoniae*
→ FQ
MefA of *S. pyogenes*
→ ML

Efflux as a mechanism of resistance in Gram-negative bacteria

spectrum

narrow



broad

specific for one (or a few) families of drugs

MFS

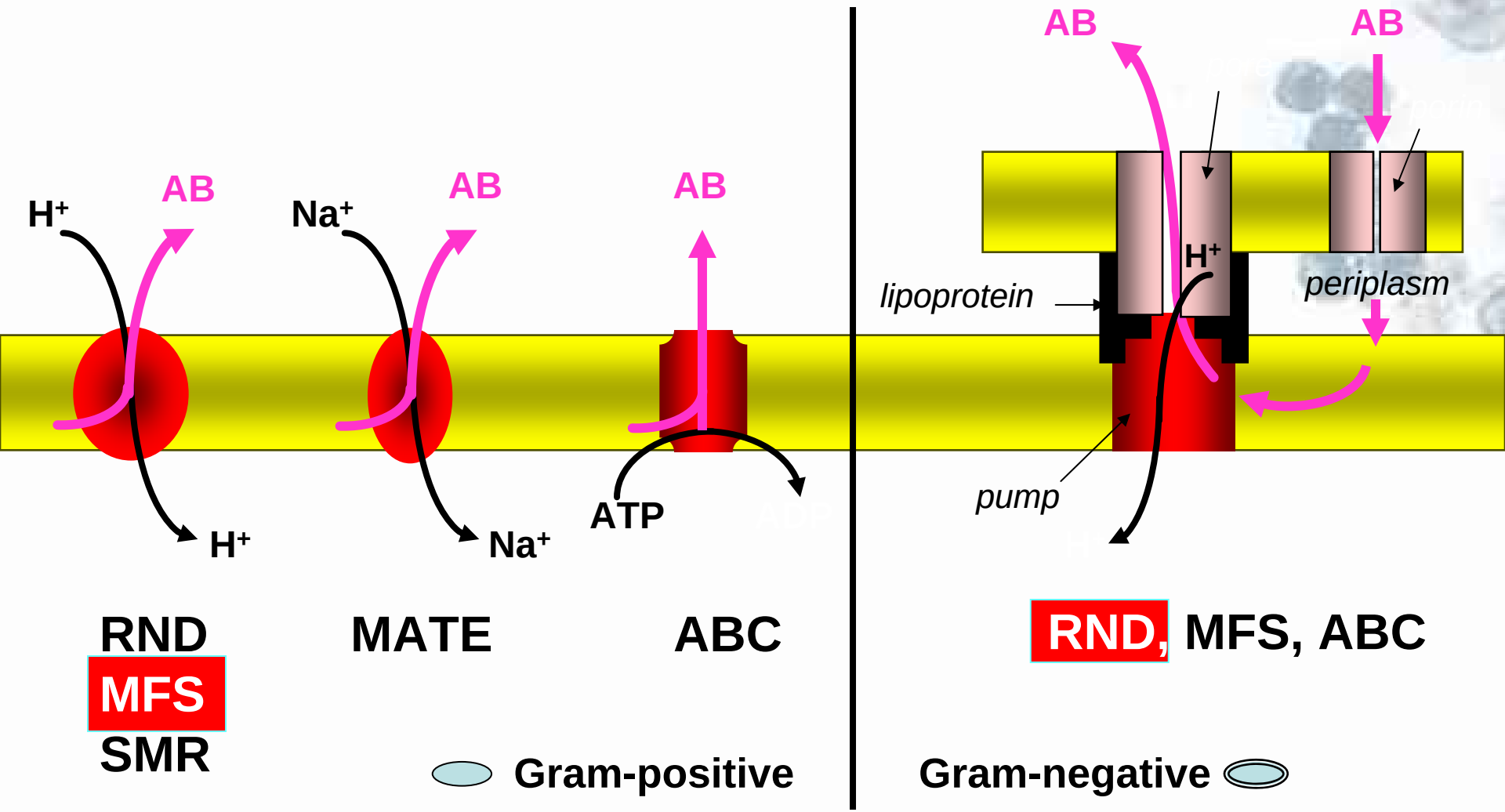
TetA of *E. coli*
→Tet
MsrA of *S. epidermidis*
→ erythromycin

broad spectrum, conferring cross-resistance

RND

MexAB-OprM of *P. aeruginosa*
→ β-lac, FQ,Tet, ML, chl, rif, sulf
AcrAB-TolC of *E. coli*
→ β-lac, FQ,Tet, ML, chl, rif, sulf

Topological organization of efflux transporters in procaryotes

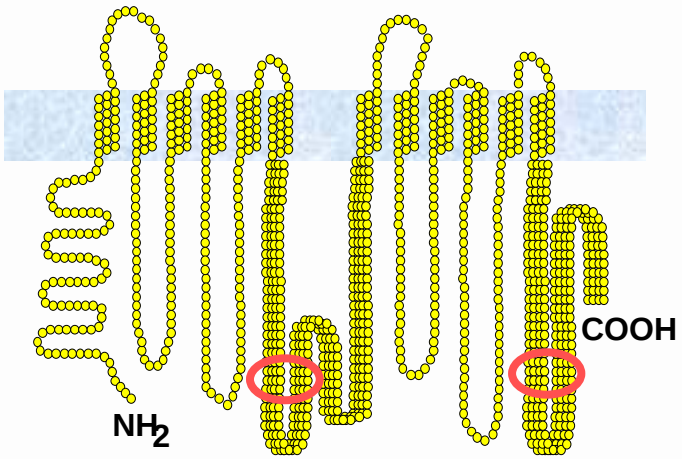


Van Bambeke et *al*. JAC (2003) 51: 1055-1065

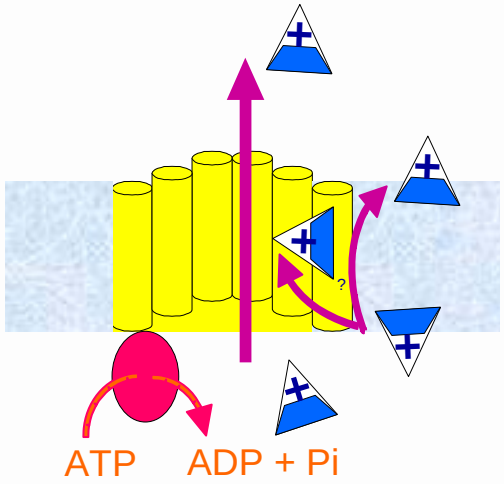
Common antibiotic-efflux pumps in eucaryotes (1/2)

- **Multiple Drug Resistance (PgP)**

TOPOLOGY



MECHANISM



ANTIBIOTICS

tetracyclines
fluoroquinolones
macrolides
lincosamides
rifampicin

daptomycin

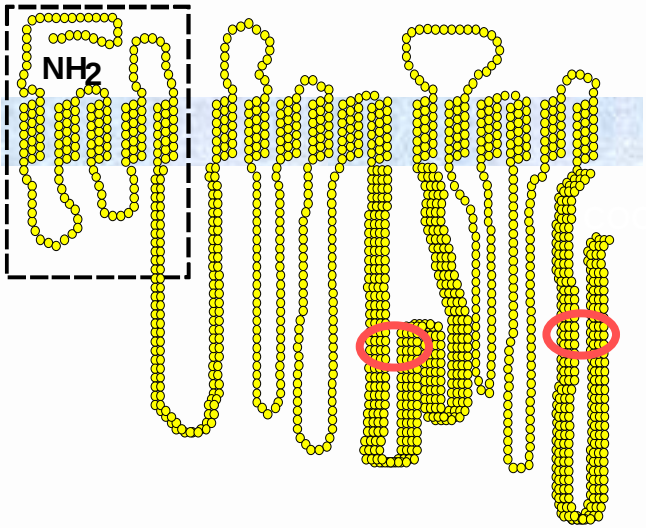
chloramphenicol

aminoglycosides

Common antibiotic-effluc pumps in eucaryotes (2/2)

- **Multidrug Resistance Proteins (MRP)**

TOPOLOGY



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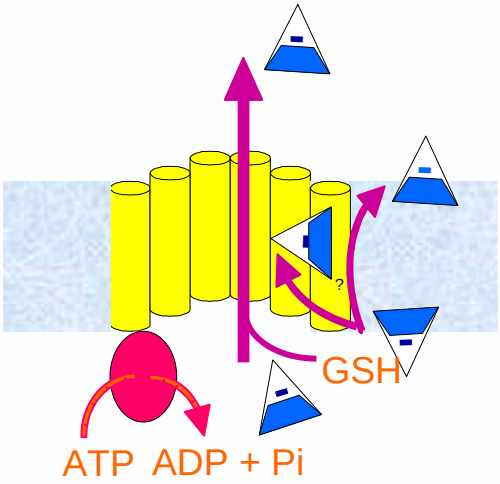


ANTIBIOTICS

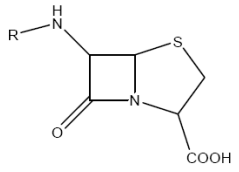
fluoroquinolones

tetracyclines
macrolides

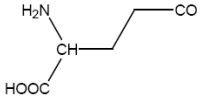
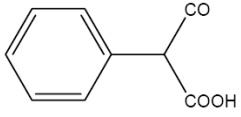
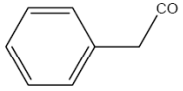
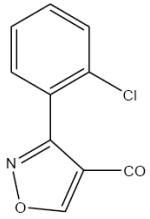
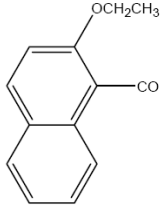
Molecular determinants of antibiotic efflux

- lipophilicity
- modulation by (small) structural changes
- anionic / cationic character
- capacity to bind to phospholipids
- and … multi-ligand binding sites …

Differential efflux of β-lactams by AcrB of *S. typhimurium*



Relationship between structure, lipophilicity of the side chain of selected penicillins and MIC of bacteria resistant by efflux

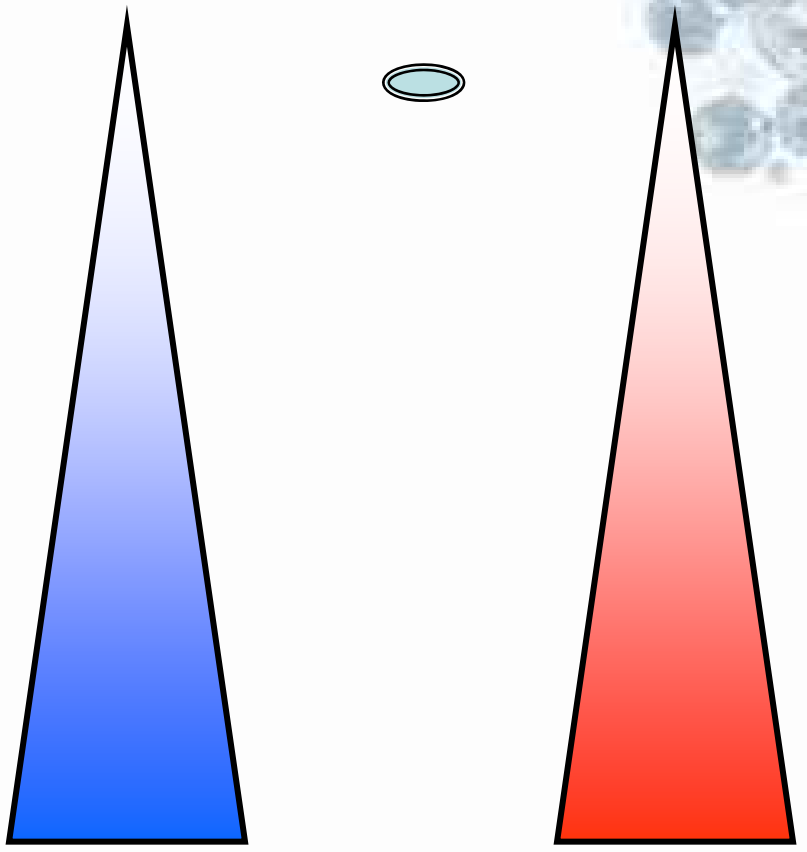
R (Side chain)	molecule	side-chain partition coefficient	MIC ratio[a]
	penicillin N	0	1
	carbenicillin	80	4
	penicillin G	270	32
	cloxacillin	890	256
	nafcillin	4200	128

[a] ratio between the MIC of a *S. typhimurium* resistant mutant (AcrAB-TolC overproducer) and of its susceptible parental strain

β-lactams & broad spectrum RND

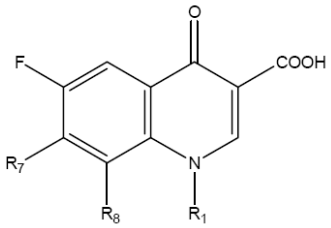
Lipophilicity of the side chain

Resistance

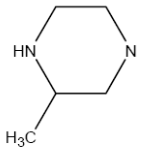
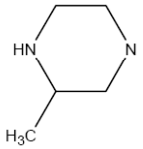
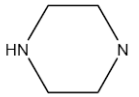
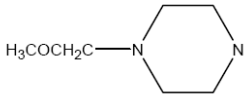
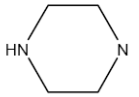


Nikaido *et al.* (1998) J. Bacteriol. 180:4686-92

Differential efflux of fluoroquinolones by NorA of *S. aureus*



Relationship between structure, bulkiness, and hydrophobicity of selected quinolone substituents and MIC of bacteria resistant by efflux.

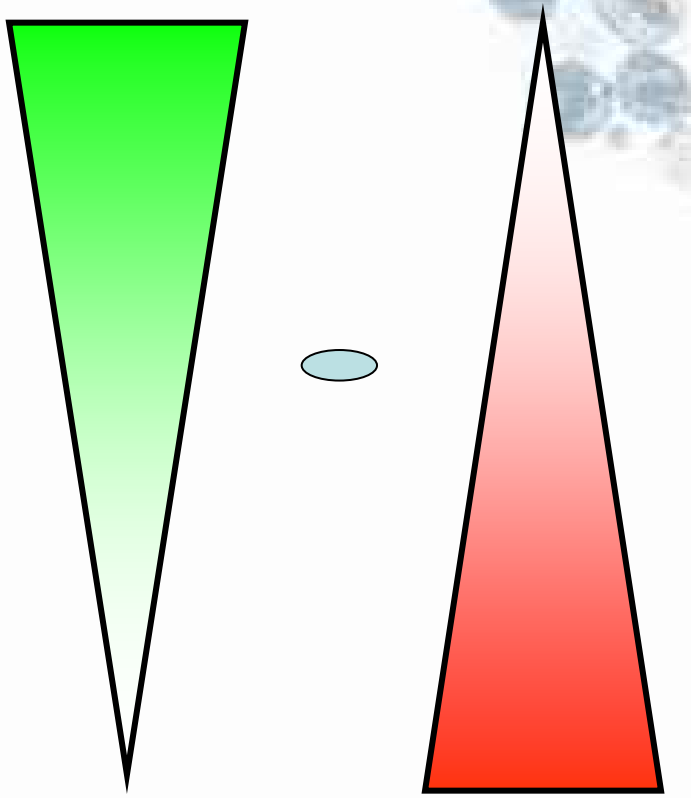
molecule	R_1	R_7	R_8	MIC ratio[a]
(a)			OCF_3	2
(b)			OCH_3	4
ciprofloxacin			H	16
(c)	C_2H_5		H	16
norfloxacin	C_2H_5		H	64

[a] ratio between the MIC of a *S. aureus* resistant mutant (NorA overproducer) and of its susceptible parental strain.

Quinolones & narrow spectrum MFS

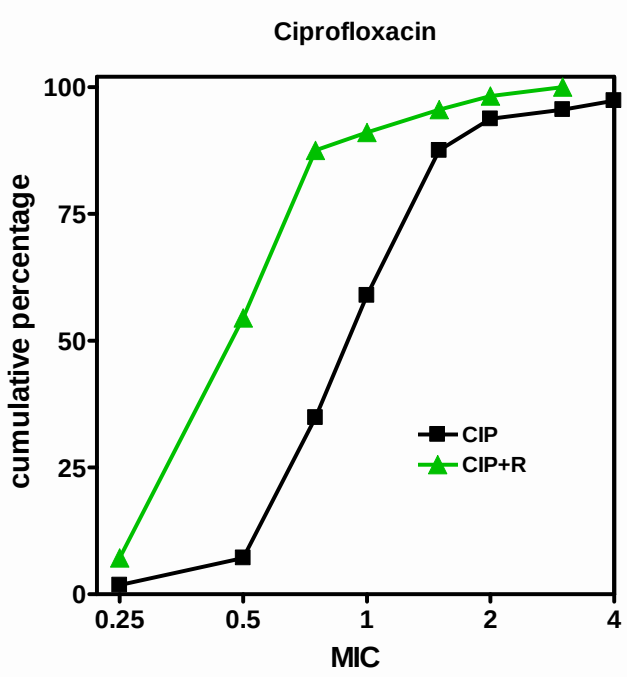
Bulkiness in 7 and 8

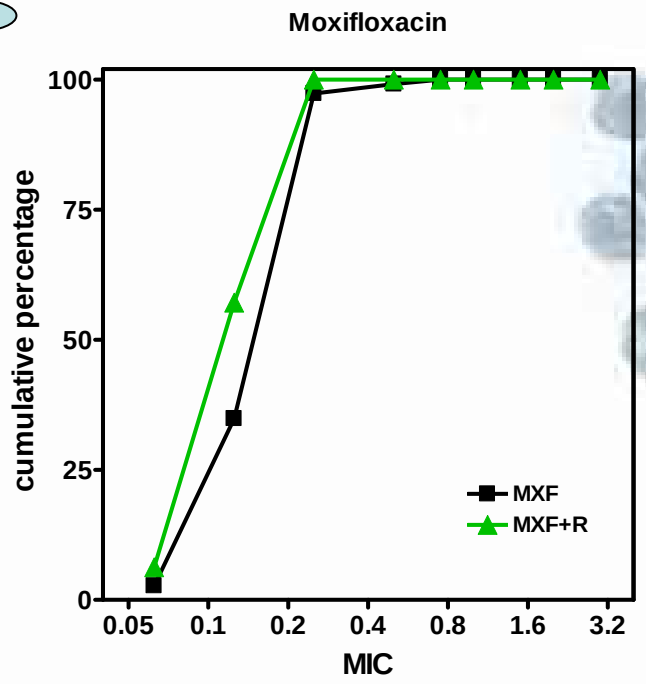
Resistance

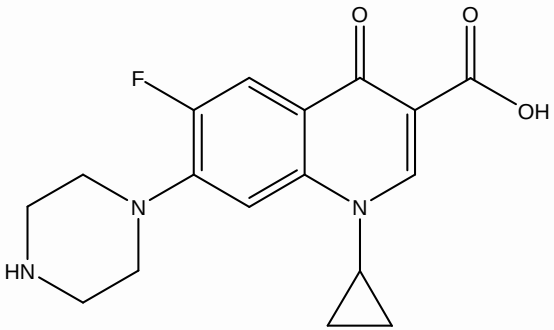


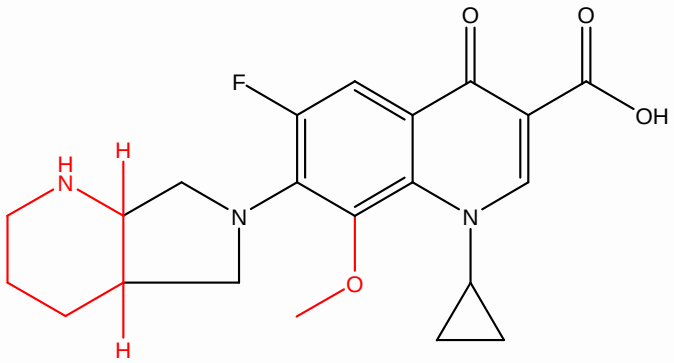
Takenouchi *et al.* (1996) AAC 40:1835-42

Moxifloxacin vs. ciprofloxacin for *S. pneumoniae* in Brussels : influence of reserpine … (**MFS** [PmrA ?])





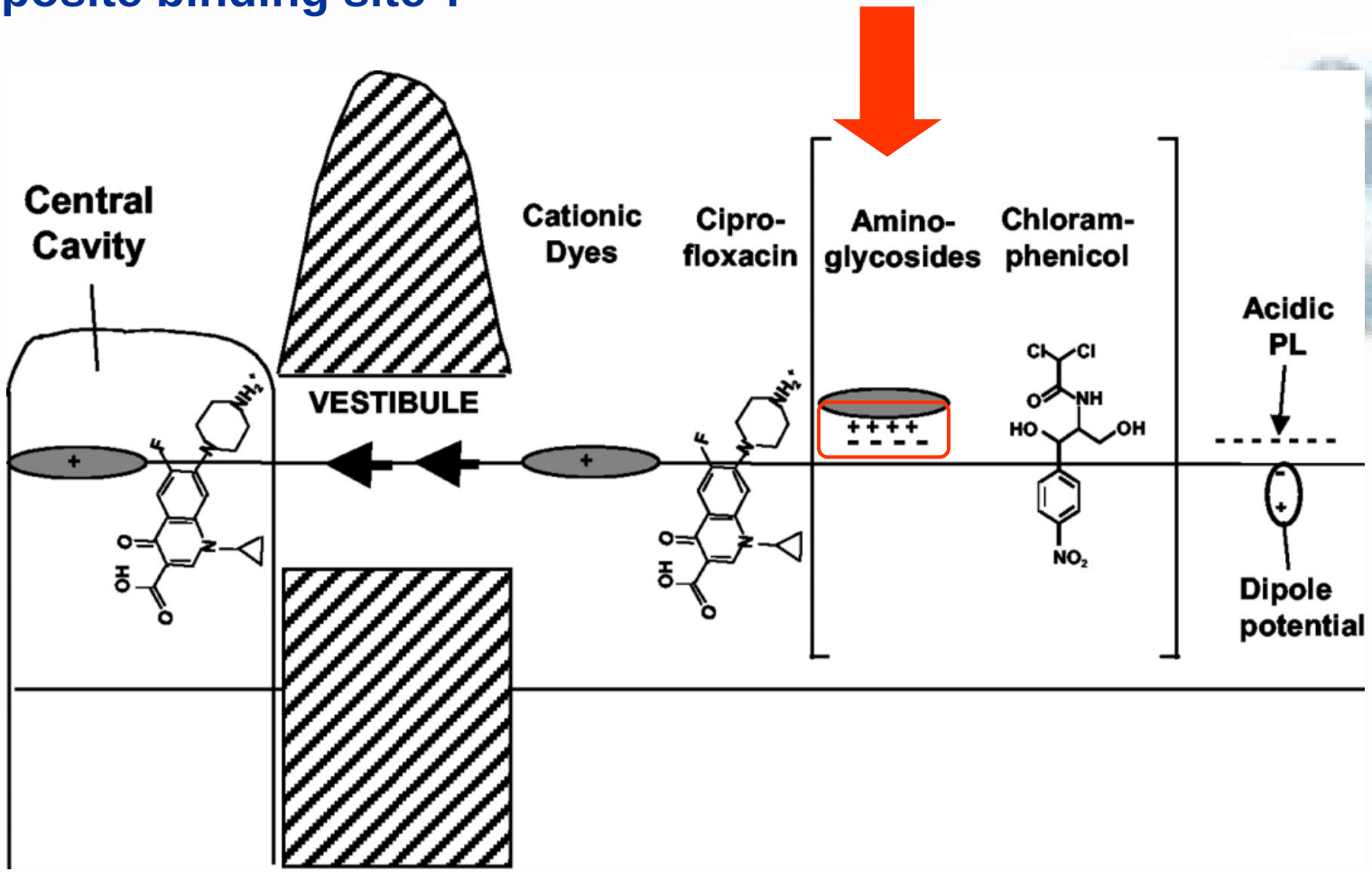




A. Lismond et al., ECCMID 2008

Aminoglycosides as unexpected substrates for efflux pumps (RND)

Composite binding site ?



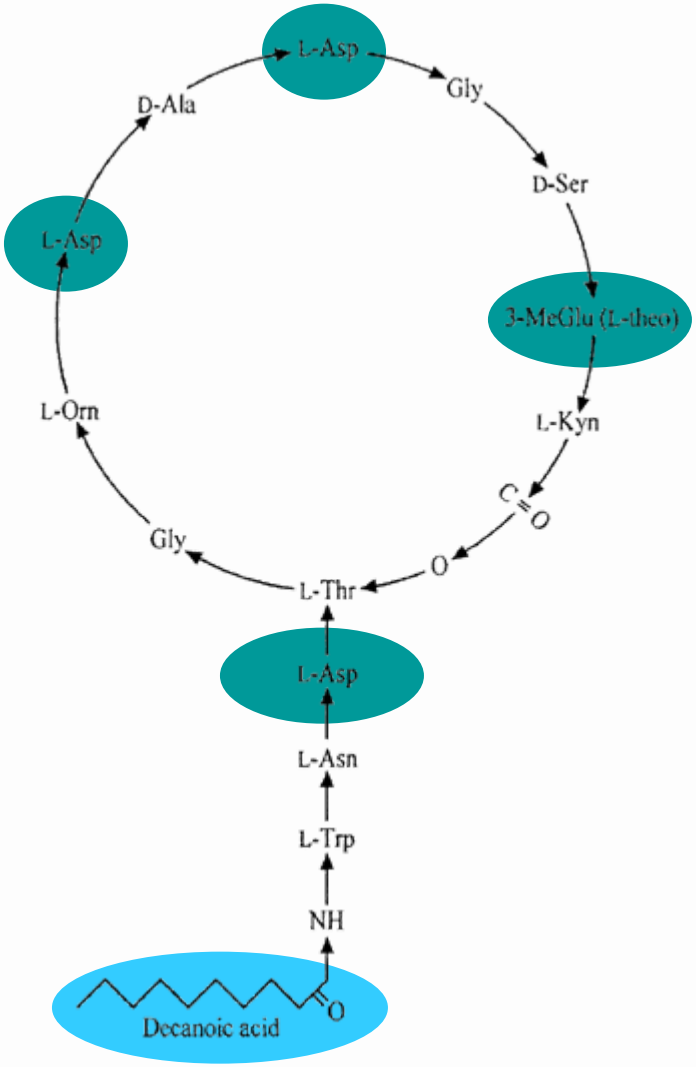
Yu *et al.* (2003) J. Bacteriol. 185:5657-64

Another unexpected substrate

daptomycin

Log P = - 4
Log D = -9.5 at pH 7

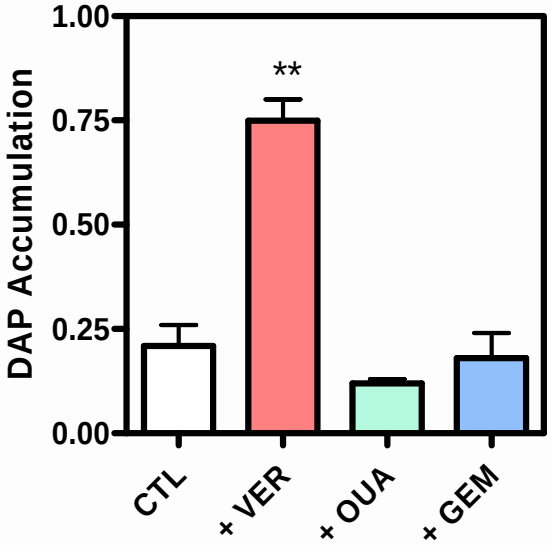
Highly polar molecule !



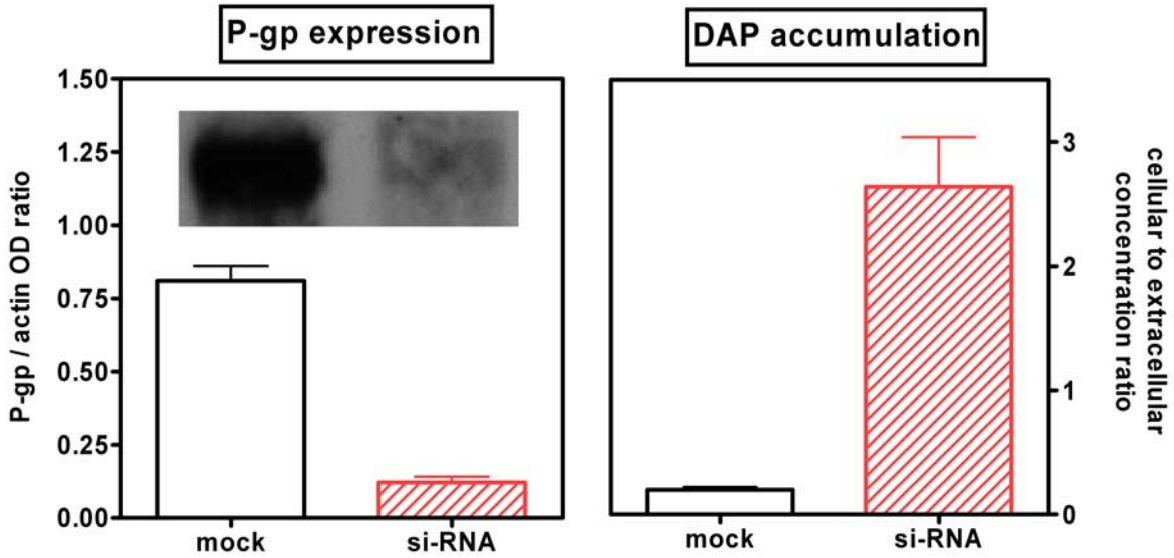
polyanionic
cyclic peptide

lipophilic chain

Daptomycin is substrate of P-gp

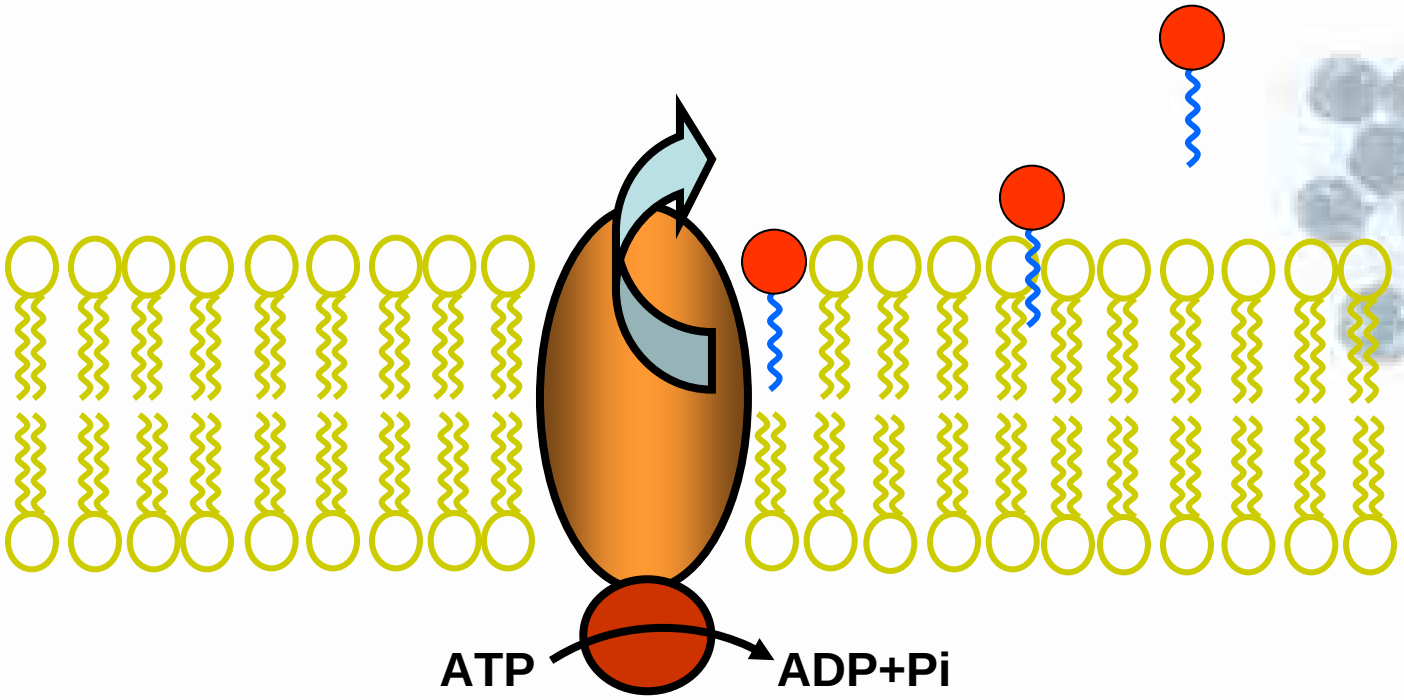


Daptomycin accumulation in macrophages is inversely proportional to P-gp activity and expression level



Lemaire *et al.* AAC 2007; 51(8):2748-57

Putative mechanism of daptomycin transport by P-gp

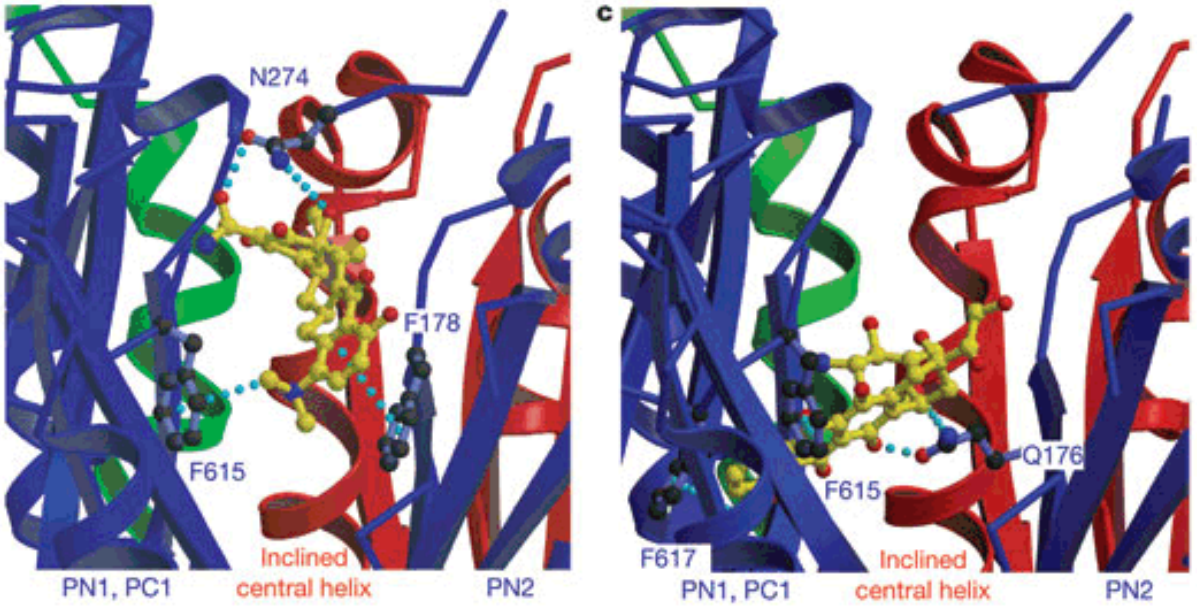


anchoring in the membrane towards the hydrophobic chain
and extrusion from the membrane

Lemaire *et al.* AAC 2007; 51(8):2748-57

Multi-ligand biding sites: the binding domain of AcrB (RND) in *E. coli*

minocycline **doxorubicine**



- The methyl moiety of the 7-dimethylamino group and the C-ring of minocycline interact with Phe 178 and Phe 615, respectively. Two oxygen atoms of the 1-oxo and 2-amido groups interact with Asn 274
- Doxorubicin interacts with Phe 615, similar to minocycline, but interacts with Gln 176 and Phe 617 instead of Asn 274 and Phe 178, respectively.

Murakami et al. Nature 2006;443:173-9

Steps and Challenges of efflux in antibacterial chemotherapy

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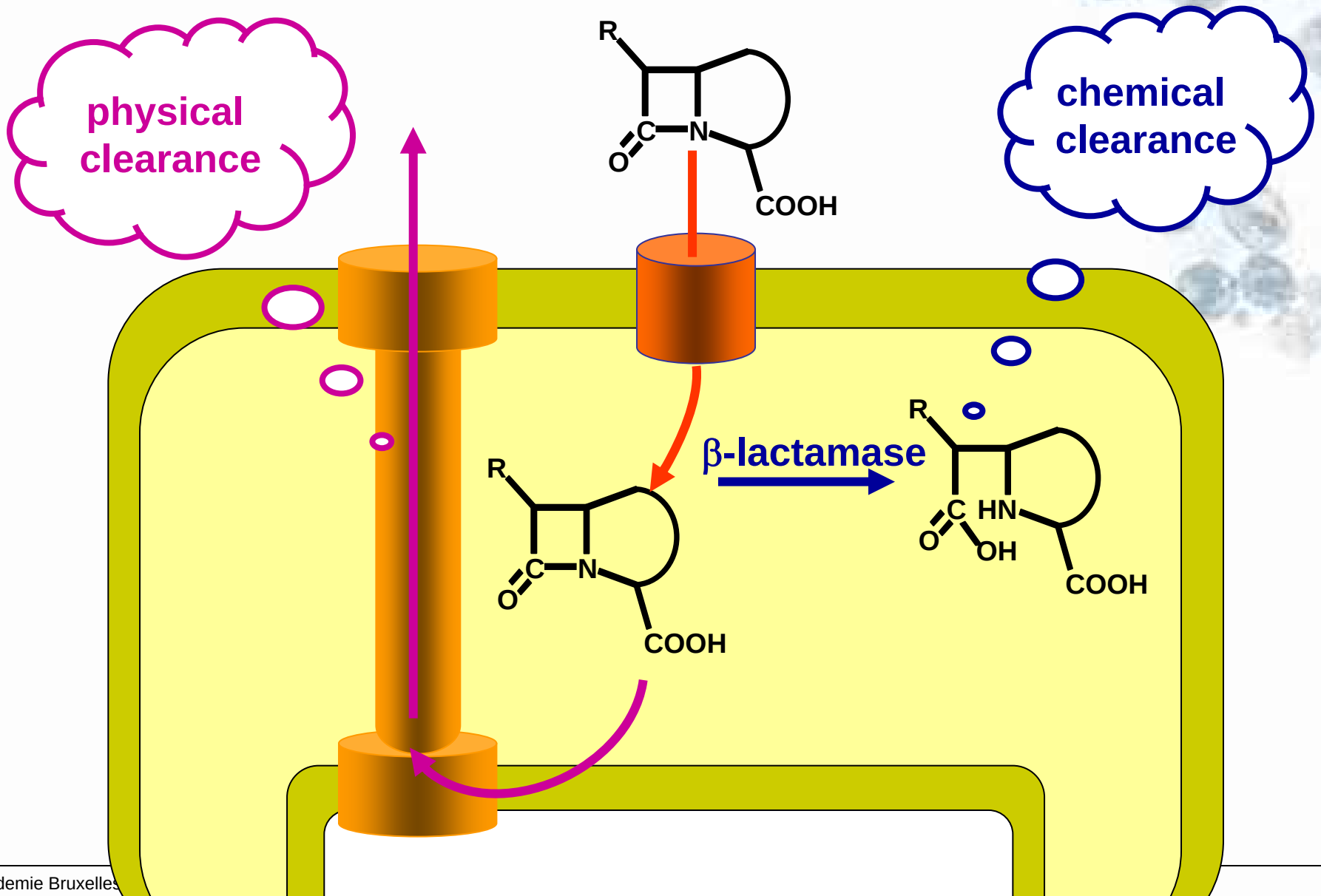
  - and what about efflux inhibitors ?
  - is efflux important in pharmacokinetics/drug interactions ?

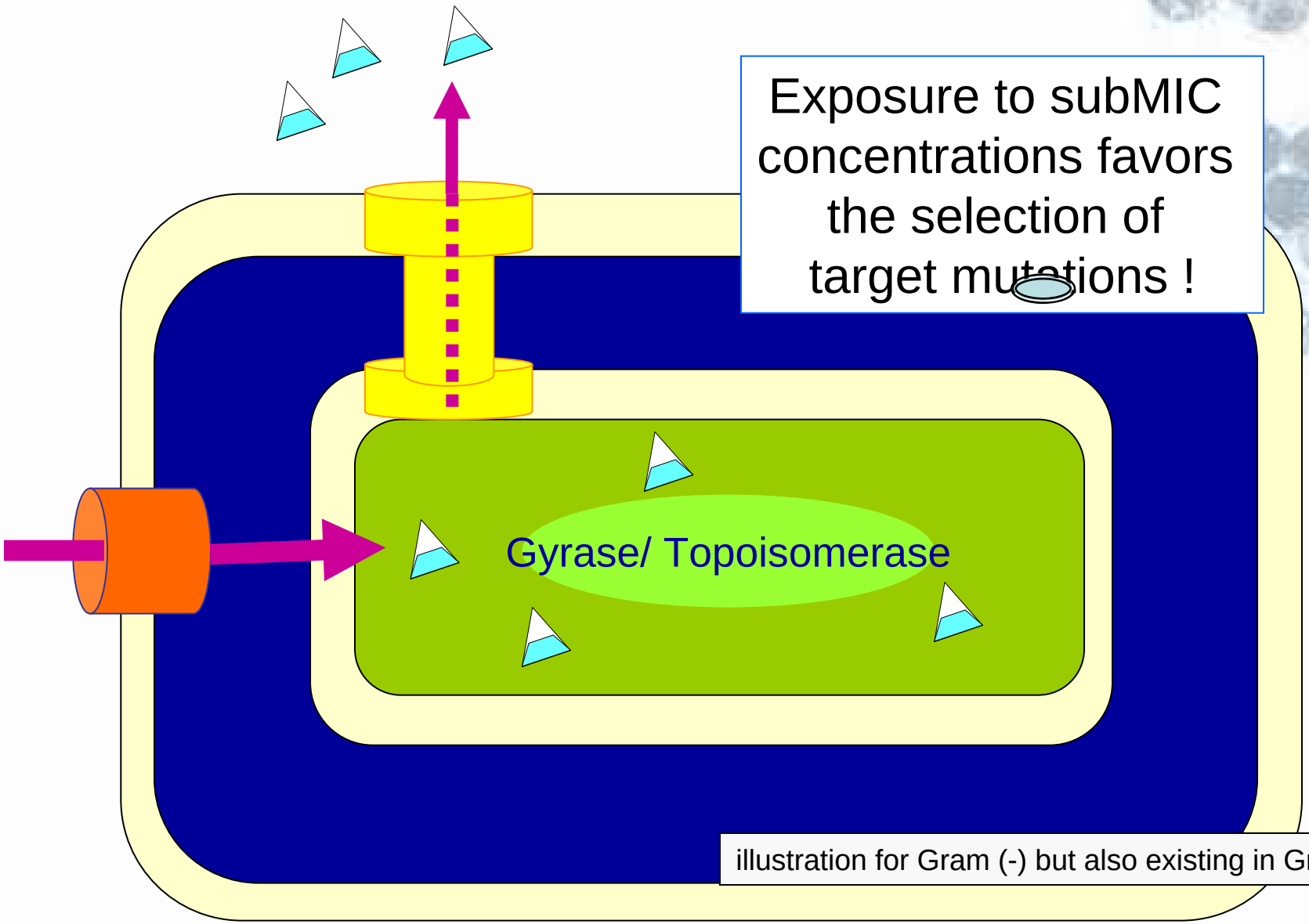
Impact of efflux on bacterial susceptibility

- Bacterial efflux
  - cooperation with other mechanisms of resistance, leading to high level resistance
  - suboptimal exposure of the antibiotic target, leading to selection of less susceptible mutants
  - low level resistance if alone, but nearing the limit of the PK/PD breakpoint (and new EUCAST breakpoints)
- Efflux from eucaryotic cells
  - decrease of intracellular activity

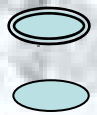
β-lactams: cooperation between efflux and β-lactamase(s) in Gram-negative bacteria



Efflux and selection of resistance to Floroquinolones



Efflux and resistance in pathogenic bacteria

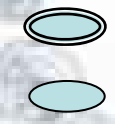


1 bacteria → **several pumps** → **multiresistance**

1 pump → **several classes of antibiotics** → **crossresistance**

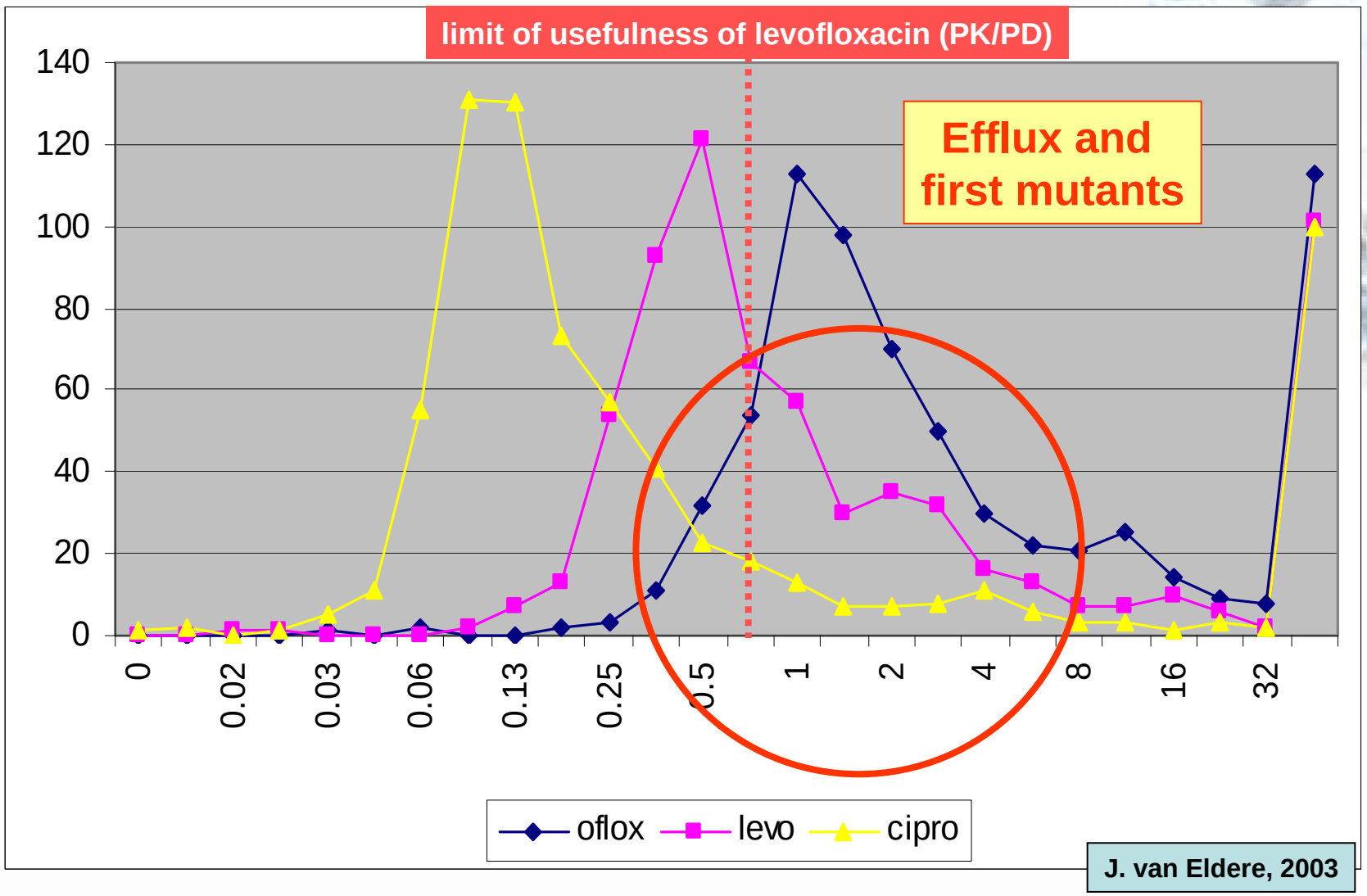
1 class of antibiotics → **several pumps** → **efficacy of inhibitors ?**

Efflux and resistance in pathogenic bacteria

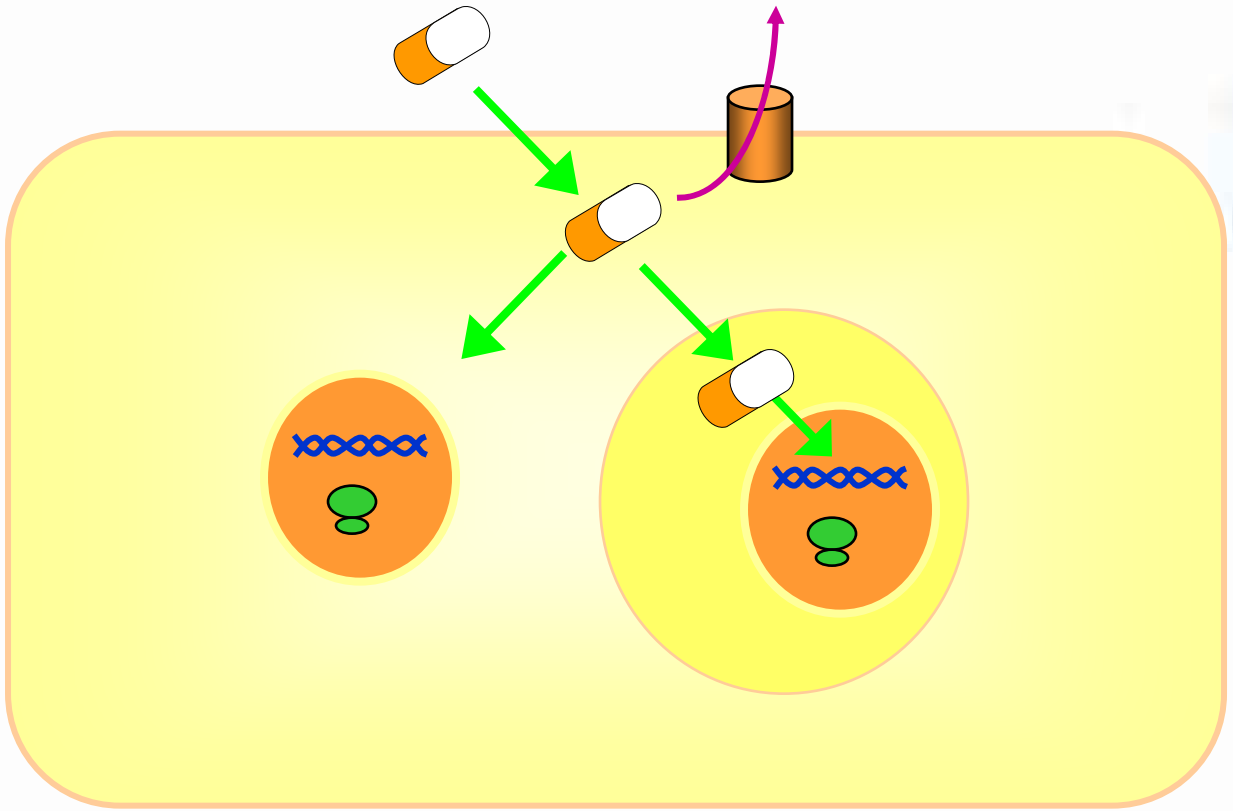


bacteria	efflux pump		β-lactams					FA	AG	Tet	OX	ML	LM	CP	Rif	Q		SM	TM
			penams	cephems	penems	mbact.	inhib β-ase									NA	FQ		
S.aureus	NorA	MFS												●			●		
	TetK-L	MFS								●									
S. pneumoniae	mefE	MFS										●							
	pmrA	MFS															●		
	TetK-L	MFS																	
S. pyogenes	mefA	MFS								●		●							
L. monocytogenes	mdrL	MFS		●								●	●						
M. tuberculosis	tap	MFS							●	●									
	TetK-L	MFS								●									
	LfrA	MFS															●		
Enterococcus	mef?	MFS										●							
	TetK-L	MFS								●									
H. influenzae	TetB, K	MFS								●									
	homl AcrAB	RND										●			●				
N. gonorrheae	MtrCDE	RND	●					●		●		●		●	●				
Salmonella	acrAB	RND	●	●				●		●		●		●	●	●	●		
	TetA-D	MFS								●									
	FloR	MFS												●					
S. dysenteriae	TetA-D	MFS								●									
E. coli	EmrE	SMR								●		●						●	
	SetA	MFS							●										
	EmrB	MFS														●			
	TetA-E	MFS								●				●		●			
	Bcr	MFS																●	
	MdfA	MFS							●	●		●		●	●		●		
	acrAB	RND	●					●		●	●	●		●	●	●	●		
	acrD	RND							●										
S. maltophila	SmeDEF	RND							●	●		●		●			●		
P. aeruginosa	CmlA	MFS												●					
	TetA,C,E	MFS								●									
	MexAB OprM	RND	●	●	●	●	●	●		●		●	●	●	●		●	●	●
	MexCD OprJ	RND	●	●		●				●		●	●	●			●		●
	MexEF OprN	RND					●							●			●		●
	MexXY	RND	●	●		●			●	●		●	●	●			●		

Fluoroquinolones and *P. aeruginosa* at the Gaslhuisberg Academic Hospital (Belgium)



Antibiotic efflux from eucaryotic cells and "intracellular resistance"



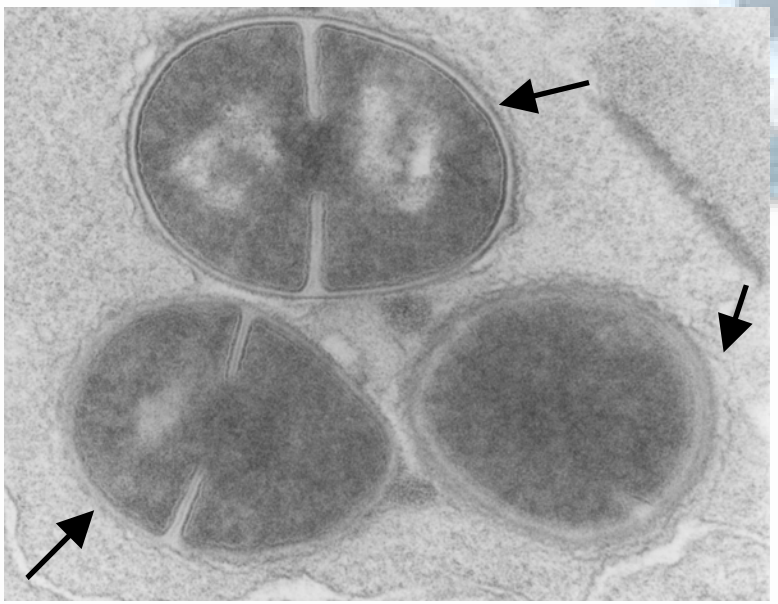
Reduction in intracellular drug concentration
can result in inefficacy against intracellular bacteria

Models of intracellular infection

L. monocytogenes

cytosol

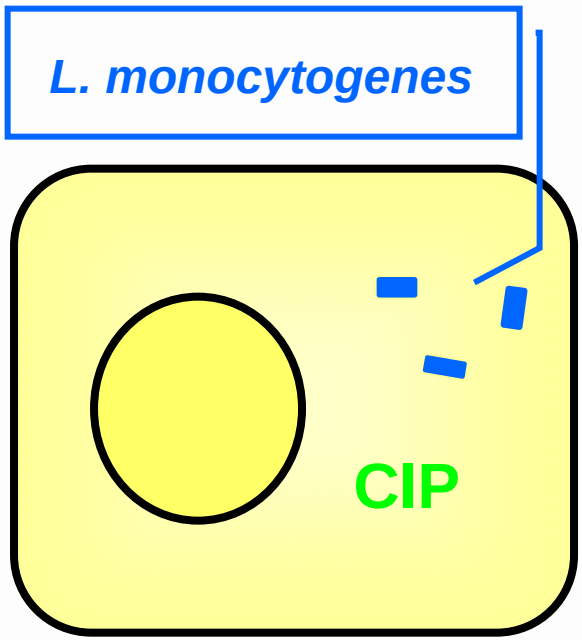
S. aureus

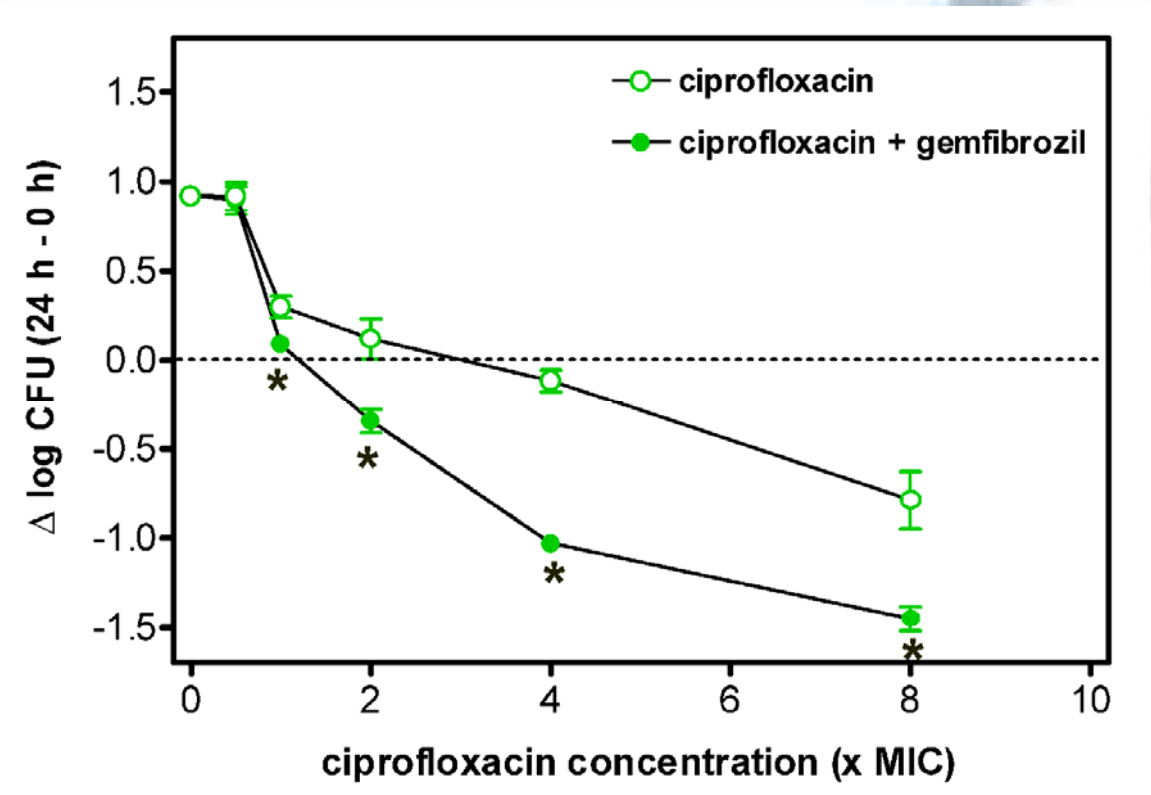


phagolysosomes

Influence of an inhibitor * of an eucaryotic antibiotic transporter (MRP) on the intracellular activity of an antibiotic

ciprofloxacin and *L. monocytogenes*



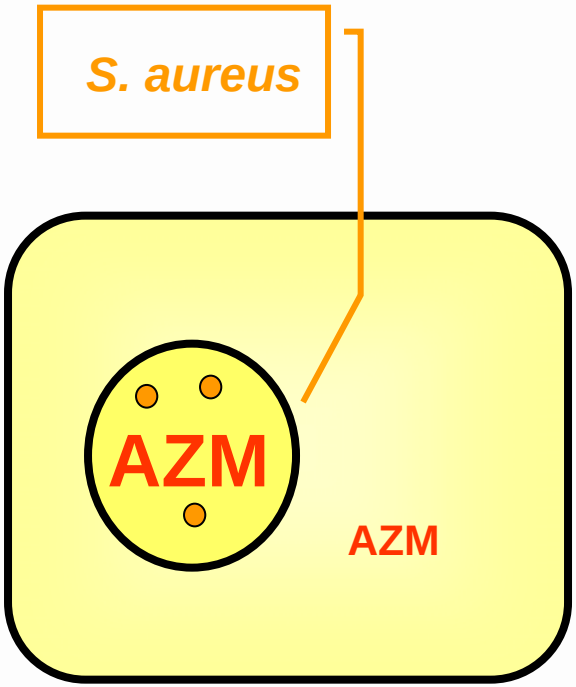


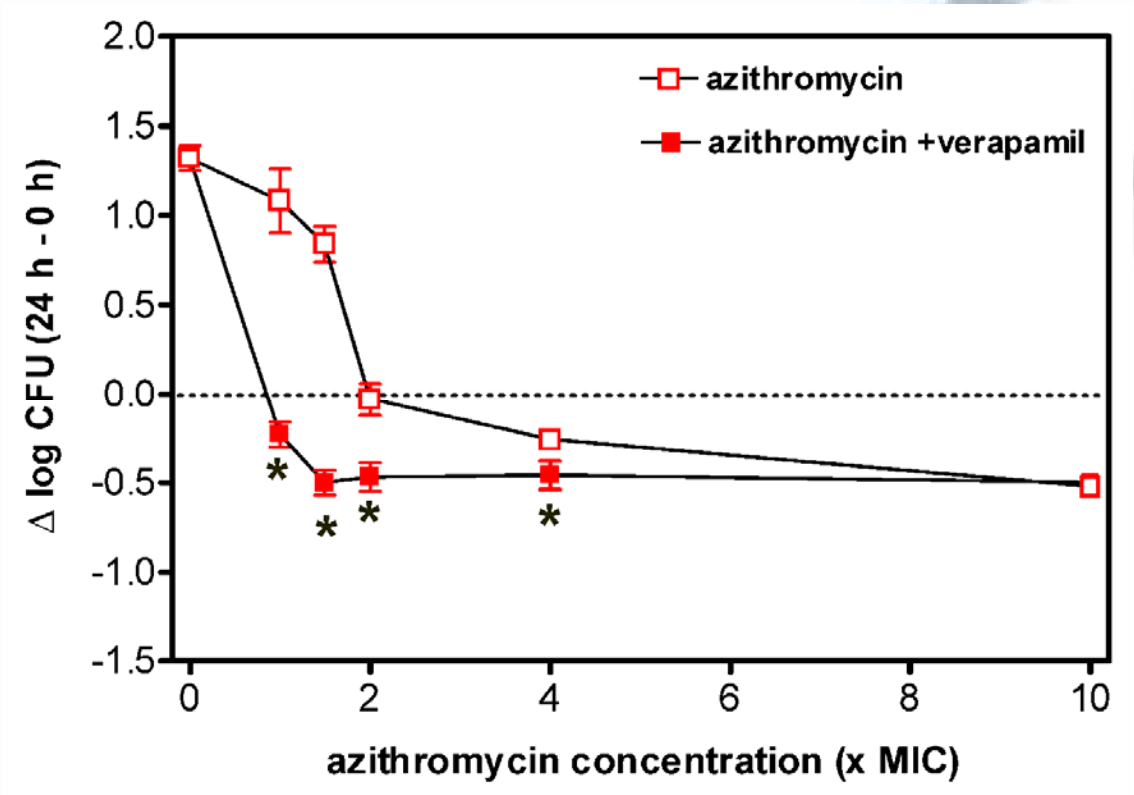
* *gemfibrozil 250 µM; 24 h*

Seral *et al.* (2003) JAC 51:1167-73

Influence of an inhibitor * of an eucaryotic antibiotic transporter (P-gp) on the intracellular activity of an antibiotic

azithromycin and *S. aureus*

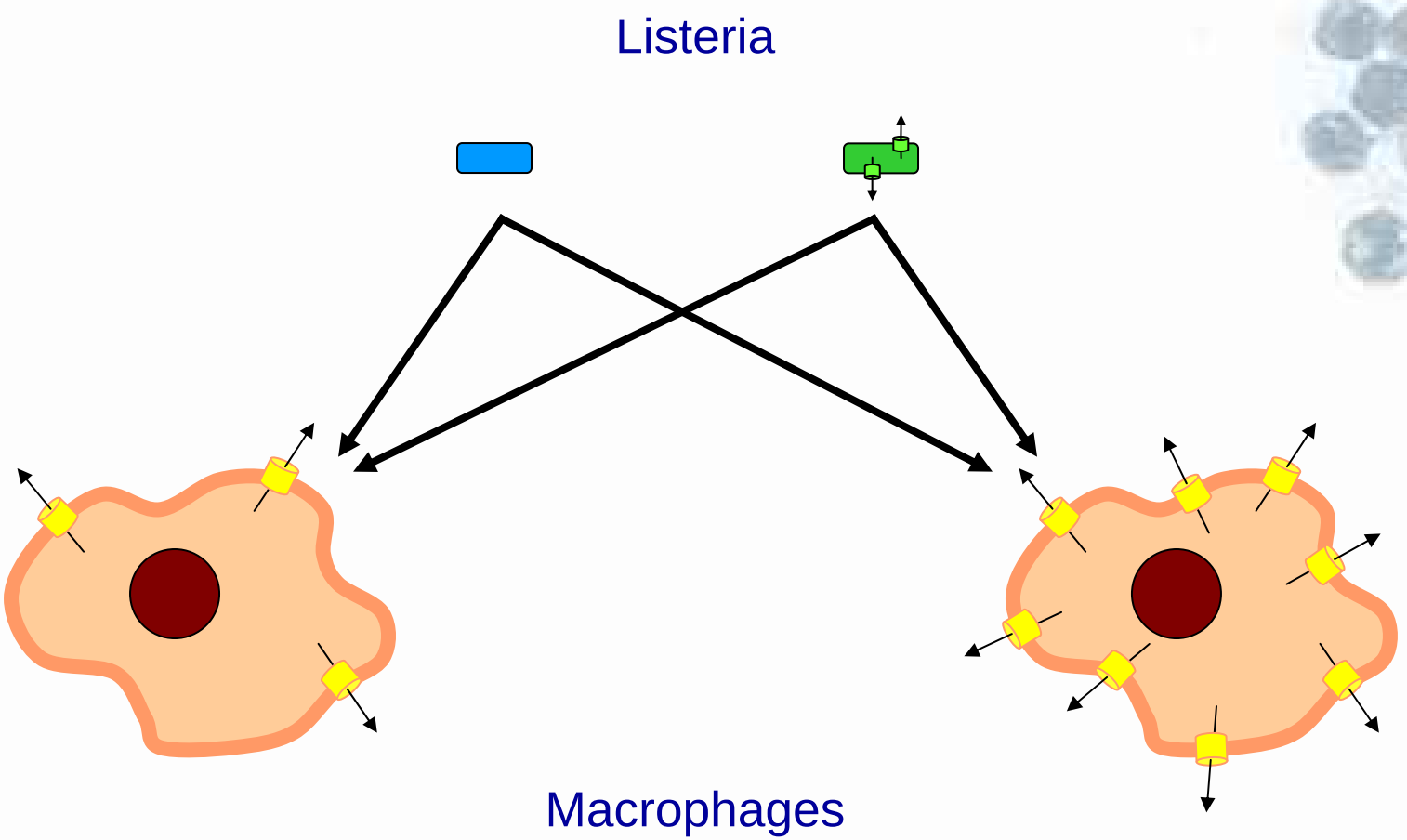




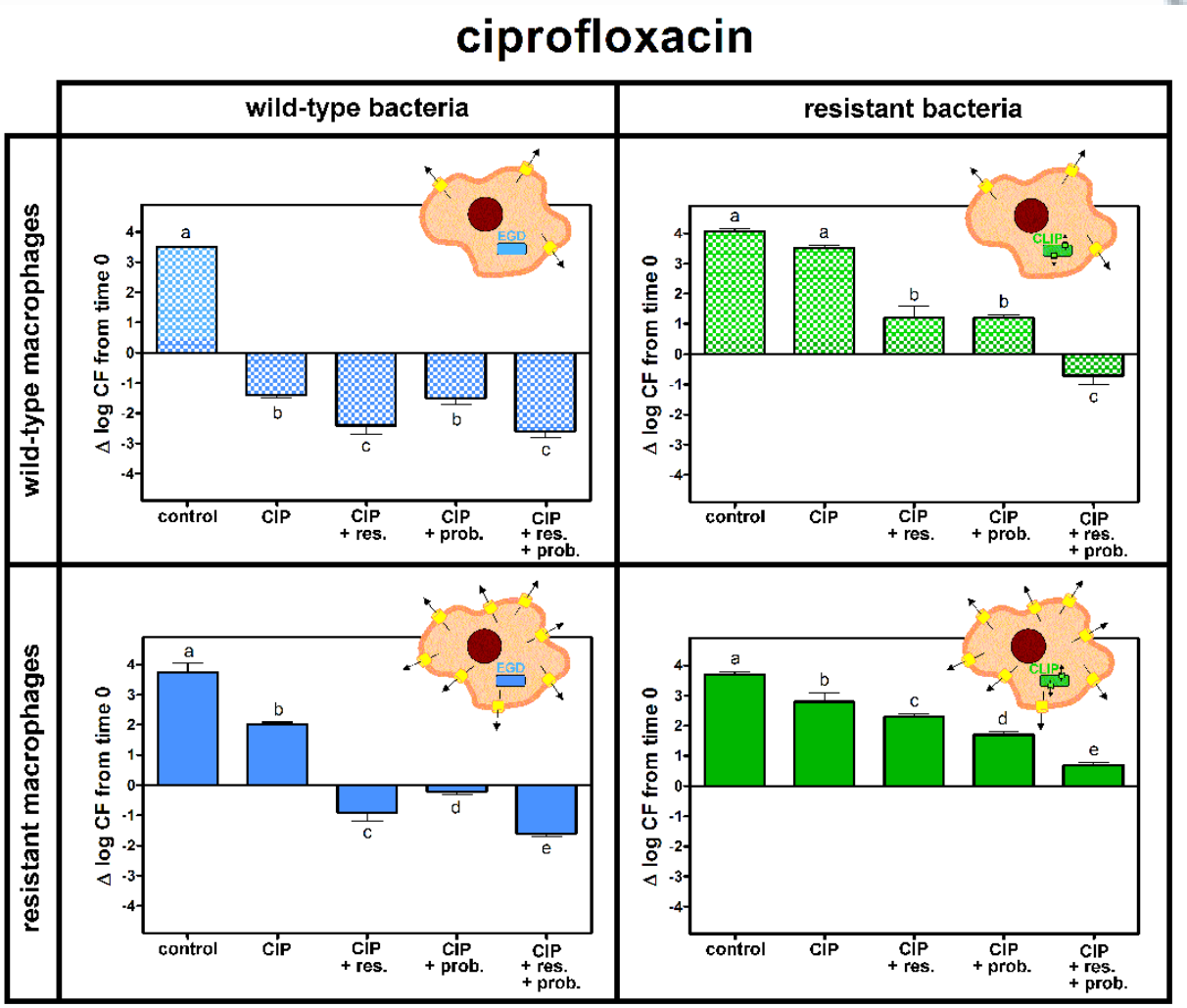
** verapamil 20 µM; 24 h*

Seral *et al.* (2003) JAC 51:1167-73

Cooperation between bacterial and eucaryotic efflux pumps…



Cooperation between bacterial and eucaryotic efflux



Lismond *et al.* (2006) ICAAC-A1108 and submitted

Steps and Challenges of efflux in antibacterial chemotherapy

- **recognizing its existence:**
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- **which pumps …**
  is antibiotic efflux different from other drug efflux ?
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  - and what about efflux inhibitors ?
  - is efflux important in pharmacokinetics/drug interactions ?

Diagnostic approaches …

Journal of Antimicrobial Chemotherapy (2007) **59**, 378–386
doi:10.1093/jac/dkl504
Advance Access publication 8 February 2007

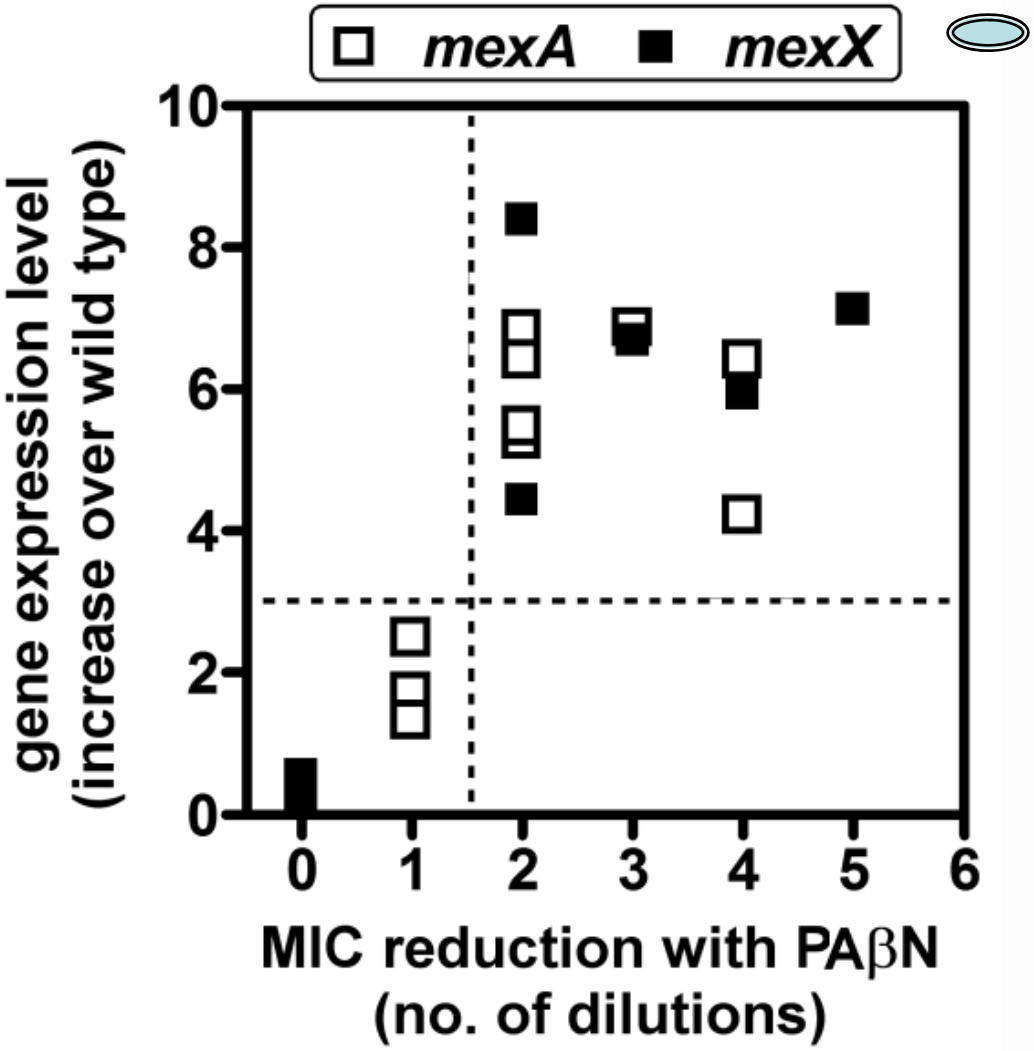
JAC

A combined phenotypic and genotypic method for the detection of Mex efflux pumps in *Pseudomonas aeruginosa*

Narcisa Mesaros[1], Youri Glupczynski[2], Laëtitia Avrain[1], Nancy E. Caceres[1], Paul M. Tulkens[1]* and Françoise Van Bambeke[1]

[1]*Unité de Pharmacologie cellulaire et moléculaire, Brussels, Université catholique de Louvain, UCL 7370 avenue E. Mounier 73, B-1200 Bruxelles, Belgium;* [2]*Laboratoire de Microbiologie, Cliniques universitaires UCL de Mont-Godinne, avenue G. Therasse 1, B-5530 Yvoir, Belgium*

Diagnostic approaches …



Correlation between the level of expression (PCR) of constitutive Mex pumps and the effect of PAβN on the MIC of reporter antibiotics (carbenicillin for mexA and gentamicin for mexX).

Data are grouped in two quadrants of potentially different diagnostic significance

- **lower left, no or minimally meaningful efflux-mediated decrease of susceptibility**
- **upper right, efflux is likely to be the cause of the decreased susceptibility).**

Mesaros et al., J Antimicrob Chemother. 2007; 59:378-86.

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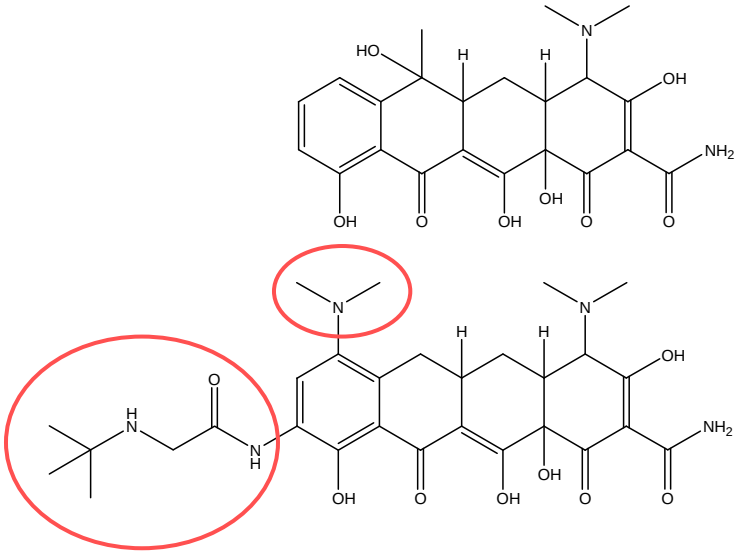
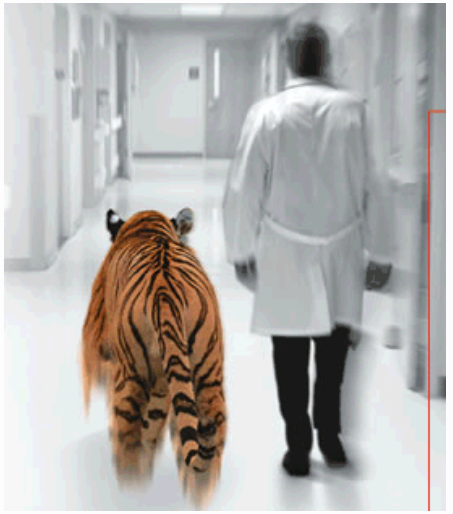
Tigecycline…

- truly <u>made</u> to resist efflux-mediated resistance in Gram(-) bacteria (and also *S. aureus*)
- broad spectrum including MRSA (MIC < 2 mg/L) and VISA
- tet(M) [ribosomal protection] or tet(K) [efflux] have no discernible effect on MICs (AAC 2006 Feb;50(2):505-10).
- approved by the FDA in 2005 and by the EMEA in 2006 for use in patients with complicated skin infections, skin-structure infections and intra-abdominal infections

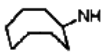
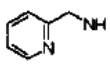




The final selection of tigecycline was the result of a systematic research to combine the hydrophobic moiety AND the additional aminogroup in a substituent attached to position 9

tigecyline

Table 2. In Vitro Antibacterial Activity of Compounds **13–25**.

		Organism; minimum inhibitory concentration (MIC) µg/mg										
	R_1	*E. coli* UBMS 88-1 Tet B	*E. coli* PRP1 Tet A	*E. coli* J3272 Tet C	*E. coli* J3272 Tet D	*E. coli* UBMS 90-4 Tet M	*E. coli* UBMS 90-5 sensitive	*S. aureus* UBMS 88-7 Tet K	*S. aureus* UBMS 90-1 Tet M	*S. aureus* UBMS 90-3 sensitive	*S. aureus* Smith sensitive	Entero-coccus ATCC 29212
13	MeNH	1	16	8	0.5	NT	1	16	1	0.5	0.5	0.5
14	*n*-PrNH	0.5	2	0.5	0.12	0.25	0.5	2	0.5	0.25	0.25	0.25
15	*n*-BuNH	0.5	1	0.5	0.25	0.25	0.5	2	0.5	0.25	0.12	0.12
16	*t*-BuNH	0.5	0.25	0.25	0.12	0.12	0.25	0.5	0.12	0.25	0.25	0.12
17	*n*-HexylNH	0.5	0.5	0.5	0.12	0.25	0.25	2	0.25	0.06	0.12	0.12
18	UndecylNH	32	32	32	32	32	16	2	16	0.5	0.5	2
19		4	32	8	2	2	2	4	0.5	0.5	0.25	0.25
20		0.25	1	0.25	0.12	0.25	0.25	2	0.25	0.12	0.25	0.12
21		4	2	2	0.5	2	4	0.5	1	0.25	0.5	0.25
22		0.5	1	0.5	0.25	0.5	0.5	0.5	0.5	0.25	0.25	0.12
23		0.5	4	0.5	0.25	0.5	0.5	4	1	0.5	0.5	0.25
24	$PhCH_2NH$	2	4	2	0.5	0.5	0.5	2	0.5	0.25	0.25	0.25
25		16	32	16	8	8	16	32	8	4	4	2

Can we make **clinically-useful** inhibitors of bacterial efflux ?

Recent Patents on Anti-Infective Drug Discovery, 2006, *1*, 157-175

Inhibitors of Bacterial Efflux Pumps as Adjuvants in Antibiotic Treatments and Diagnostic Tools for Detection of Resistance by Efflux

Françoise Van Bambeke[1,*], Jean-Marie Pagès[2] and Ving J. Lee[3]

[1]*Unité de Pharmacologie cellulaire et moléculaire, Université catholique de Louvain, Brussels, Belgium* [2]*EA2197 Enveloppe Bactérienne, Perméabilité et Antibiotiques, Faculté de Médecine, Université de la Méditerranée, Marseille, France;* [3]*CB Research and Development, Inc. (Adesis, Inc), New Castle, DE, USA*

BIOCHEMICAL PHARMACOLOGY 71 (2006) 910–918

Practical applications and feasibility of efflux pump inhibitors in the clinic—A vision for applied use

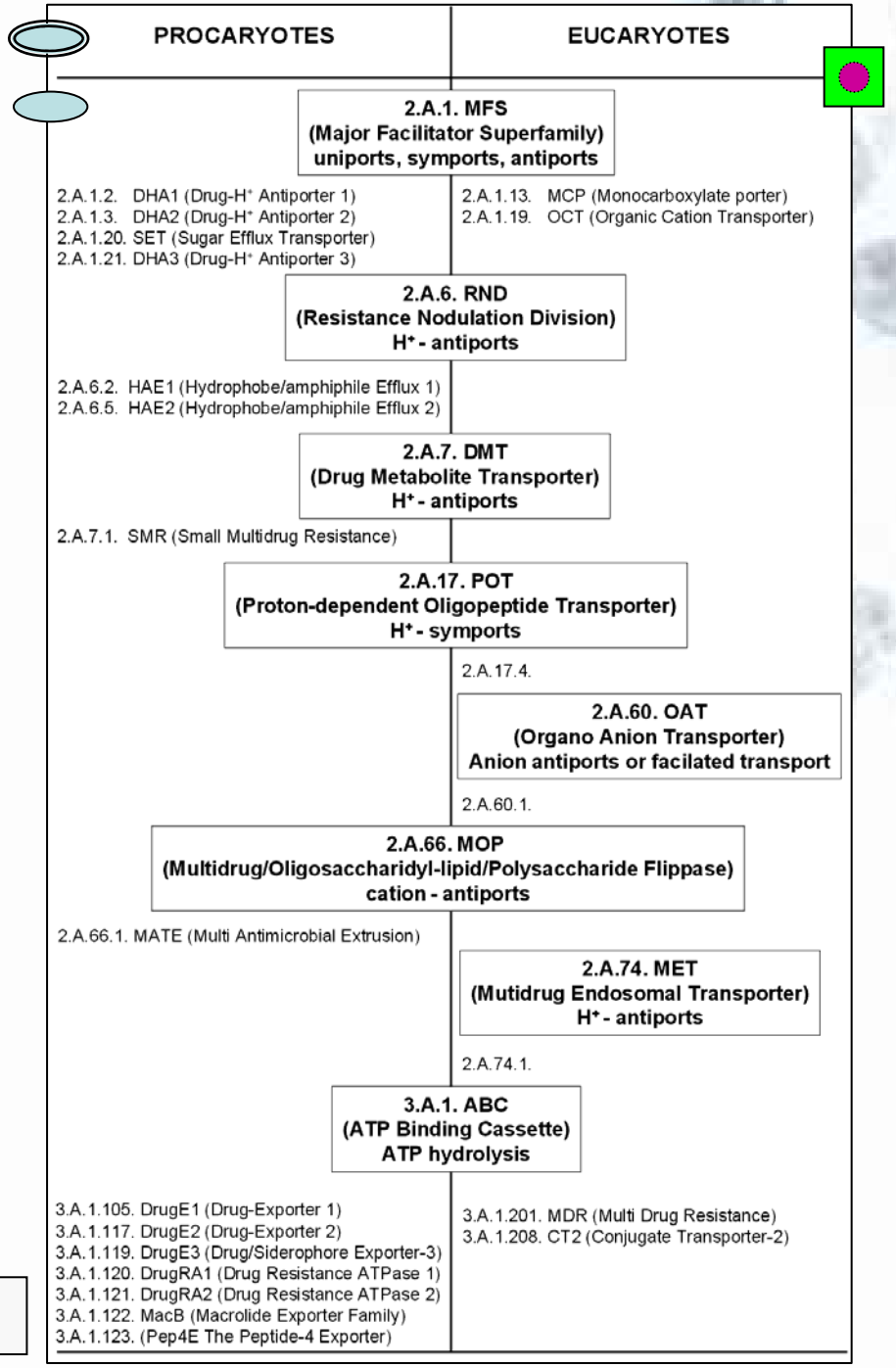
Olga Lomovskaya, Keith A. Bostian *

Mpex Pharmaceuticals Inc., 3030 Bunker Hill Street, San Diego, CA 92109, United States

Clinically useful inhibitors of antibiotic efflux pumps: the bottom line …

It will be difficult because…

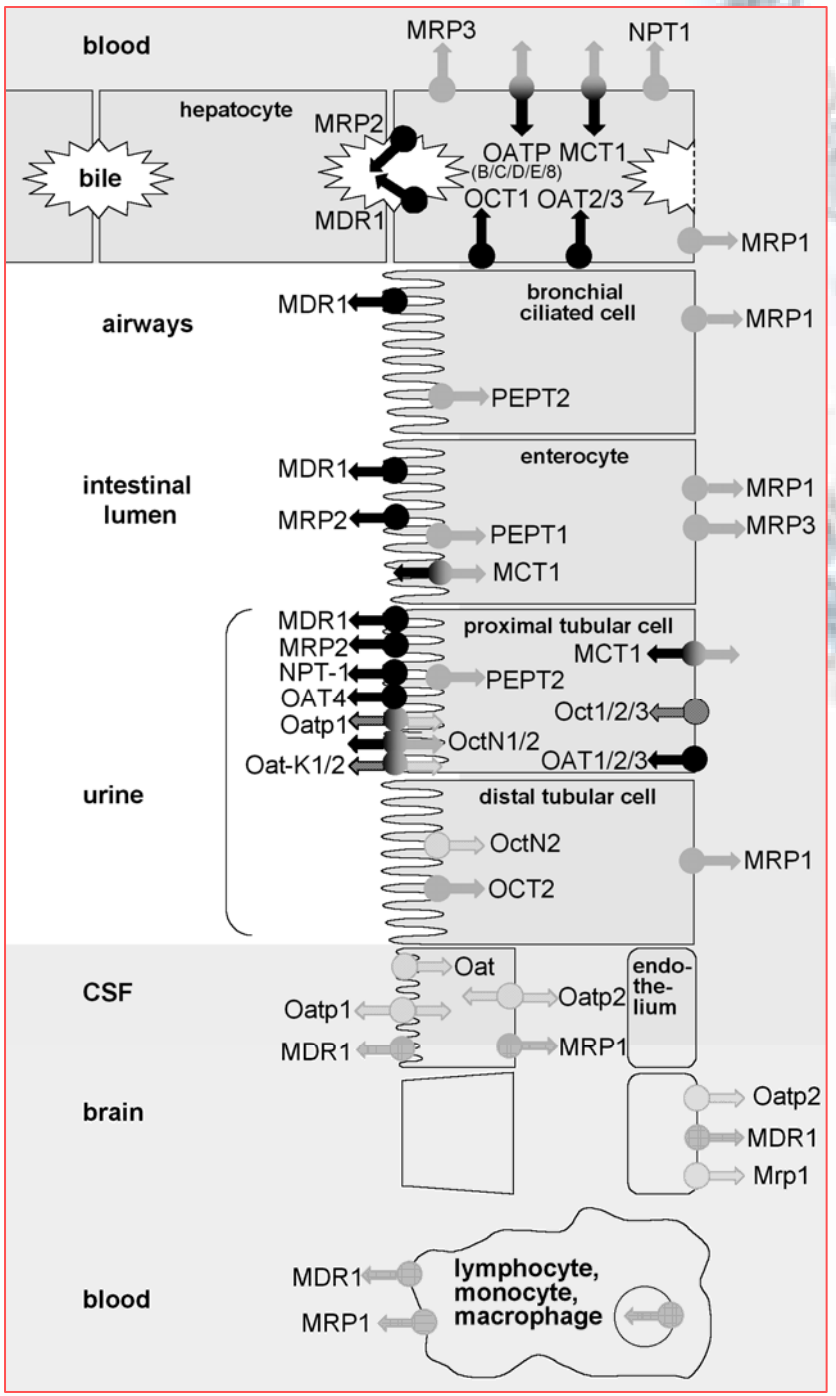
- Many procaryotic transporters have eucaryotic homologues;
- antibiotics are (for that reason or another …) substrate to many of them… (sometimes in an unanticipated fashion)
- and so will probably be many inhibitors…



Van Bambeke et al. (2003)
J Antimicrob Chemother 51: 1055-1065.

Is efflux important in pharmacokinetics ?

Yes, !!!



antibiotic transporters in various human tissues

Van Bambeke et al. (2003)
J Antimicrob Chemother 51: 1055-1065.

Let us believe in pumps…
(each has its own set of challenges)

**the fire pump…
(save your life)**

**the gas pump…
(keeps you moving)**

**the pump for everything …
(white product)**

**the little amateur one…
but with great expectations …**

The past and present "pump team" at UCL


M.P. Mingeot


P. Tulkens


F. Van Bambeke

HOOC


J.M. Michot


H. Chanteux


A. Lismond


S. Lemaire


H. Bensikaddour


F. Huyghe


L. Garcia

H_2N


C. Vallet


M. Riou


F. El Garch


C. Seral


N. Caceres


B. Marquez


N. Mesaros


L. Avrain


M. Heremans


F. Renoird


M.C. Cambier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