Efflux Mechanisms of Fluoroquinolones and β-lactams

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http://www.md.ucl.ac.be/facm

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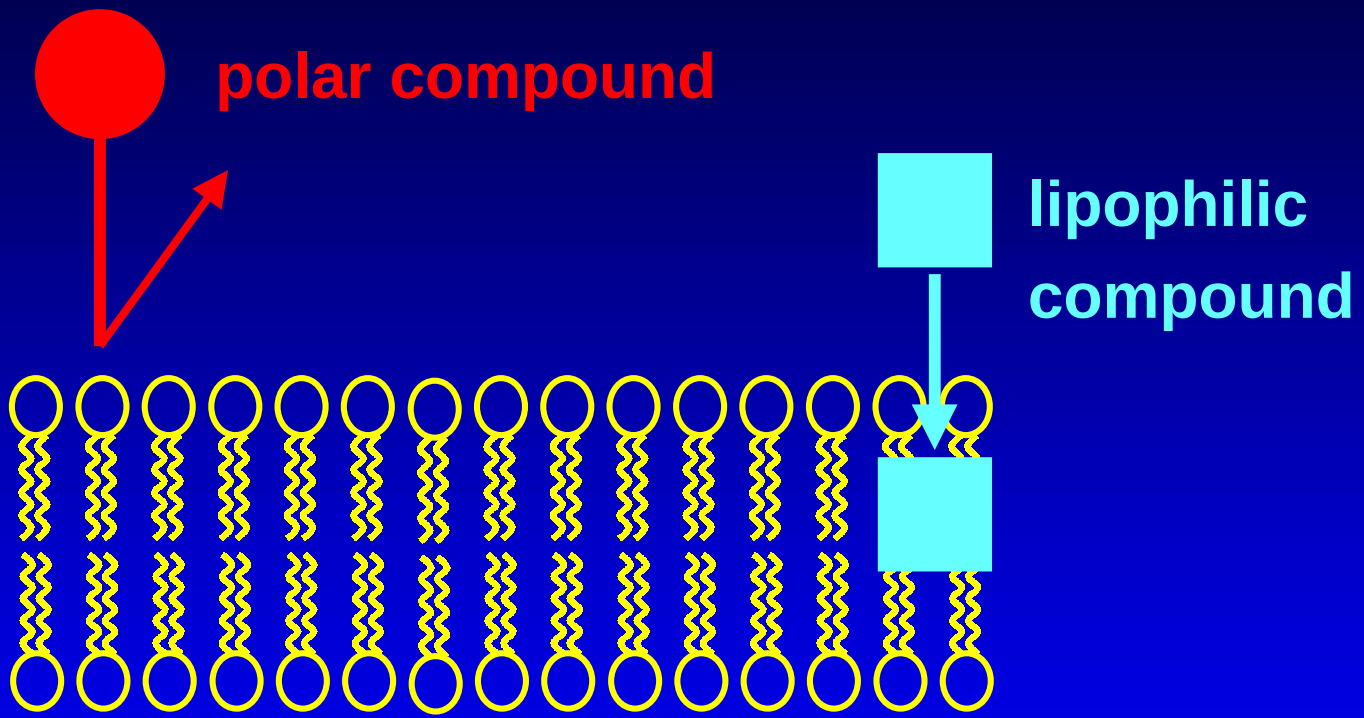
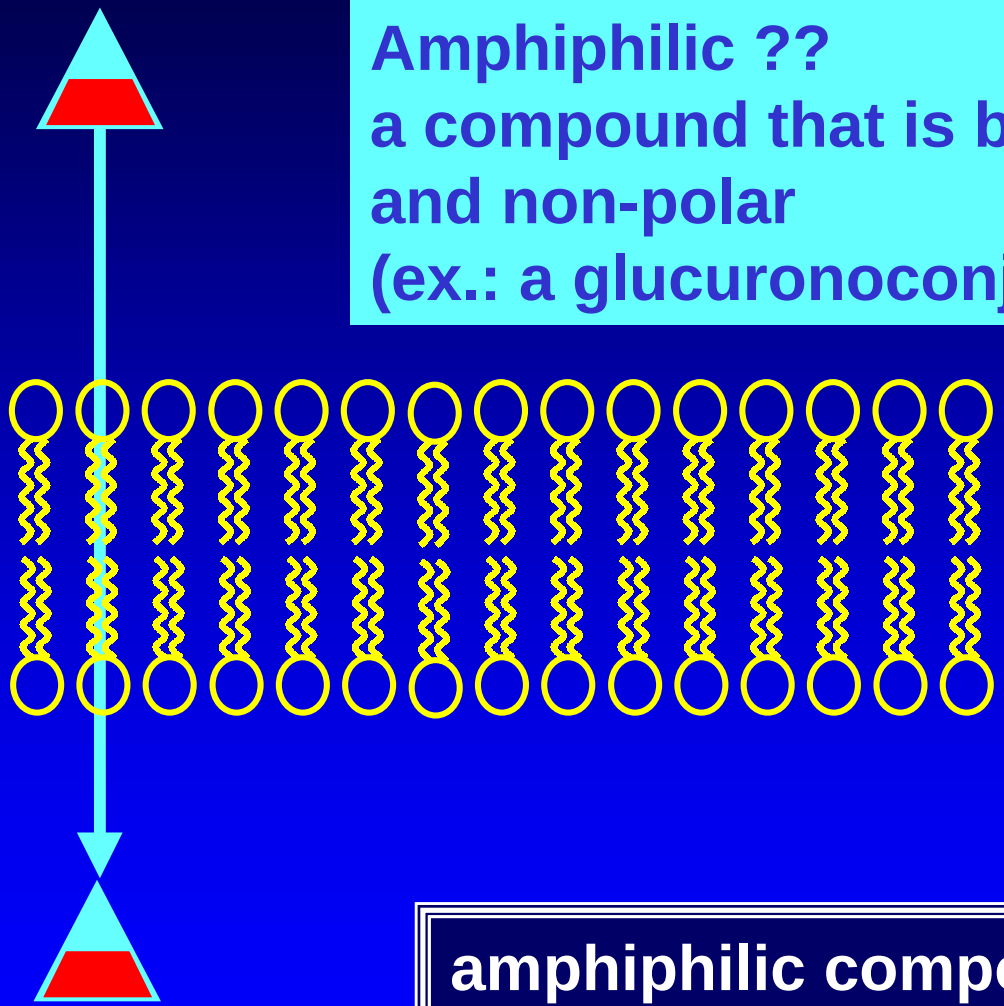
Why efflux ?



highly polar or highly lipophilic compounds do not easily pass across membranes ...

Why efflux ?

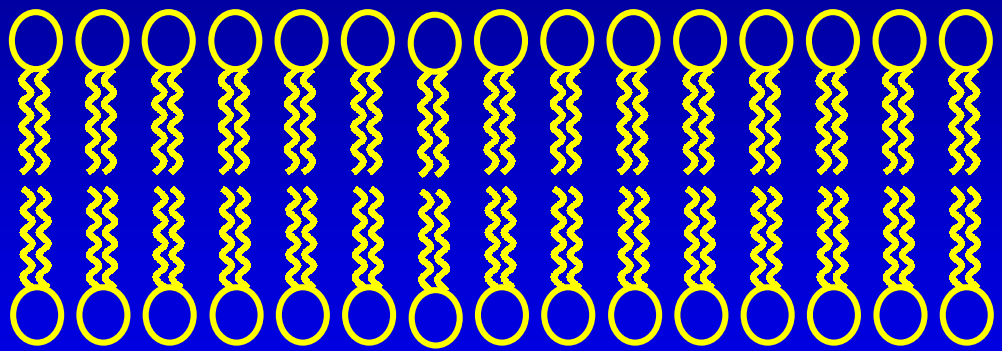
amphiphilic compound

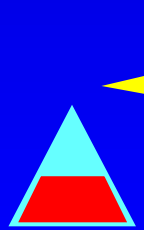


Amphiphilic ??
a compound that is both polar and non-polar
(ex.: a glucuronoconjugate)

amphiphilic compounds <u>easily</u> invade cells

Why efflux ?



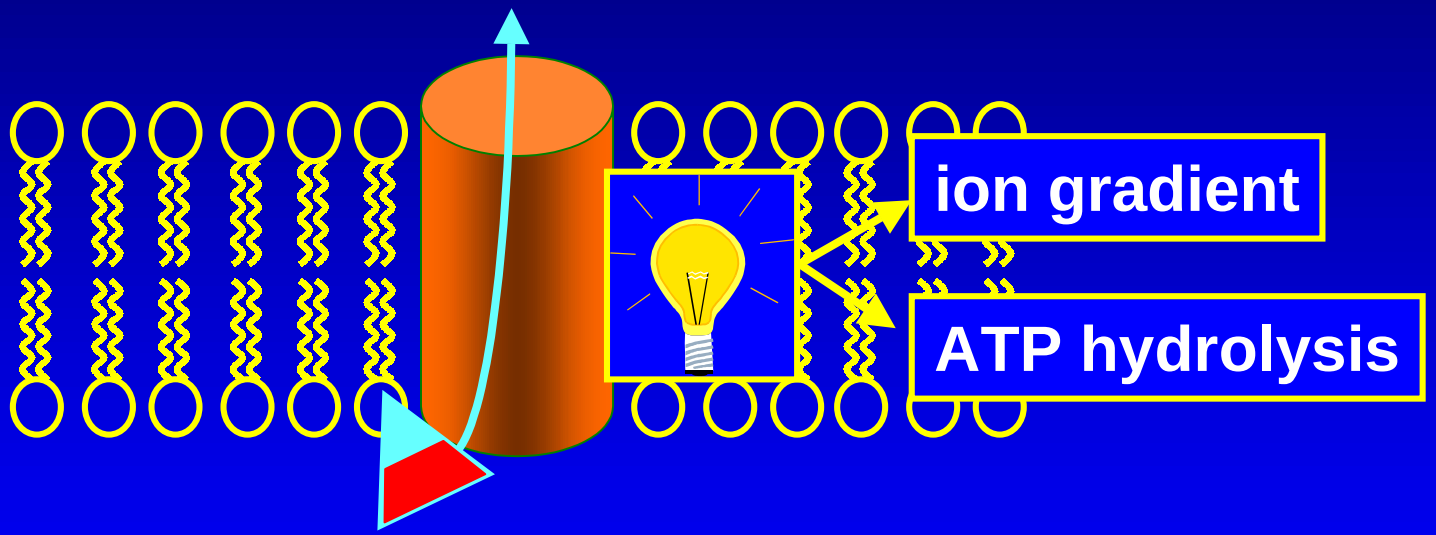


But a diffusible compound

may have

potentially harmful effects in cells !

Why efflux ?



Efflux transporters are a general mean of protection of the cell against invasion by diffusible molecules

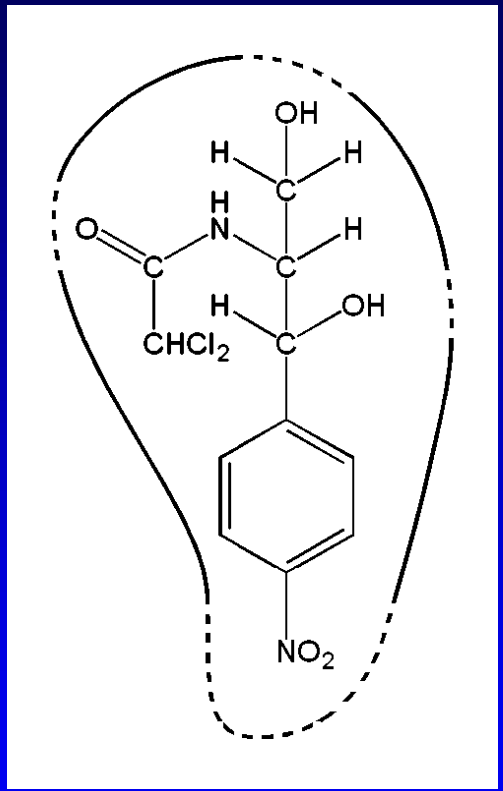
Why **DRUG** efflux transporters ?

Most of our drugs are made amphiphilic !

to allow them to diffuse and penetrate in cells and tissues ...

Most antibiotics are amphiphilic !

Neutral



chloramphenicol

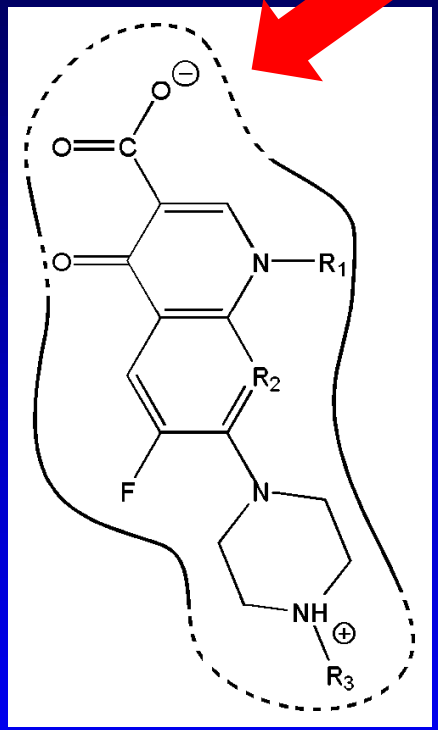
apolar

polar

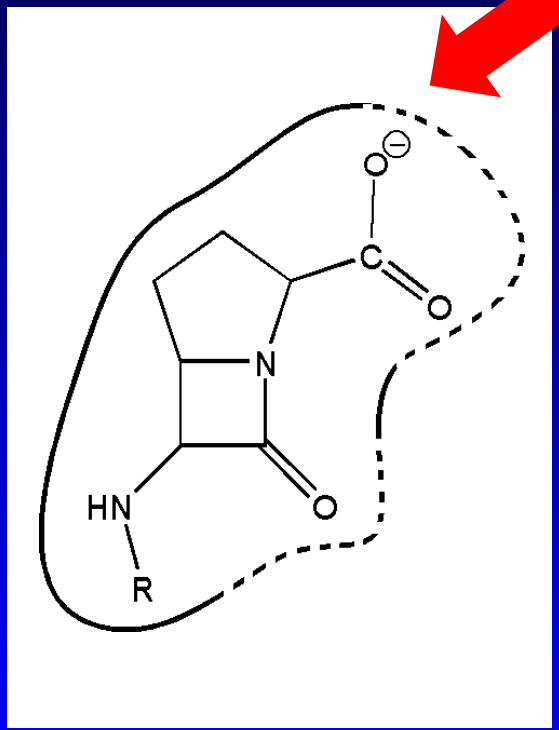
Van Bambeke *et al*. Biochem. Pharmacol. (2000) 60: 457-470

Most antibiotics are amphiphilic !

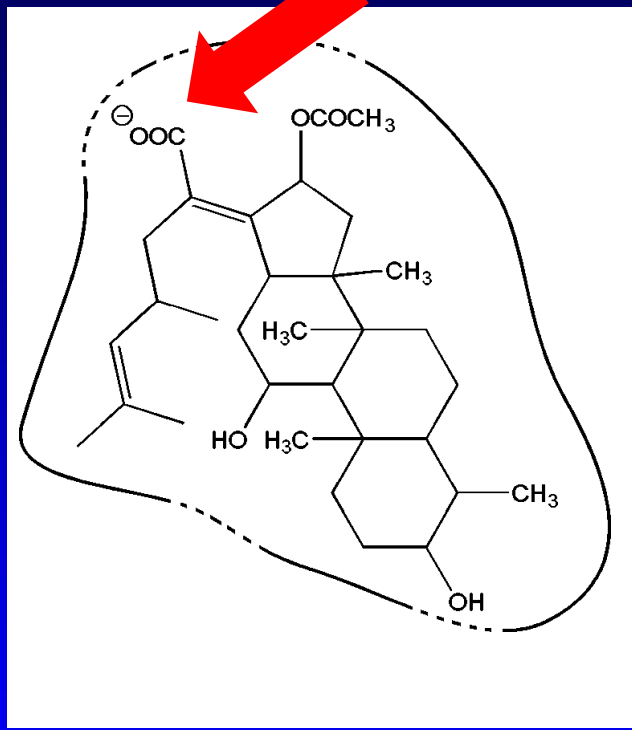
anionic



fluoroquinolones



beta-lactams

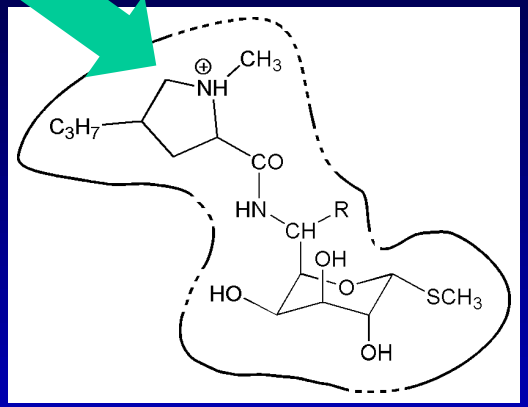


fusidic acid

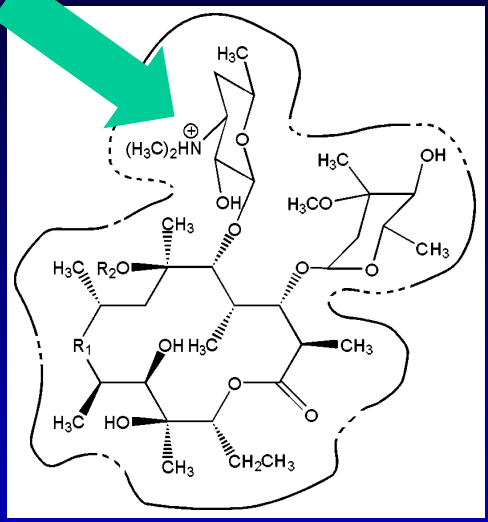
Van Bambeke *et al*. Biochem. Pharmacol. (2000) 60: 457-470

Most antibiotics are amphiphilic !

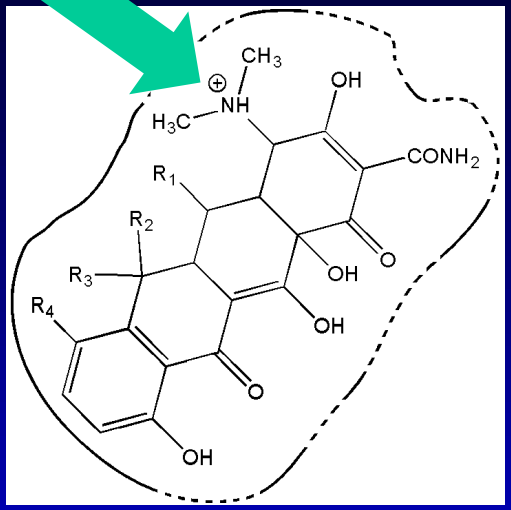
cationic



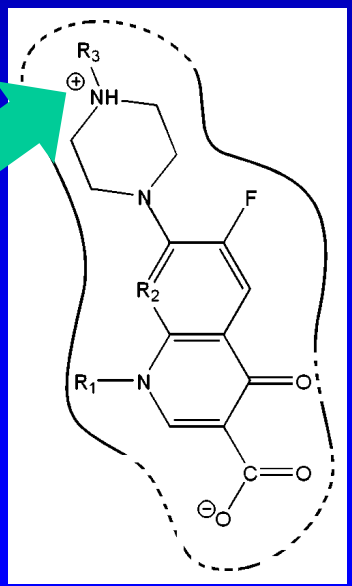
lincosamides



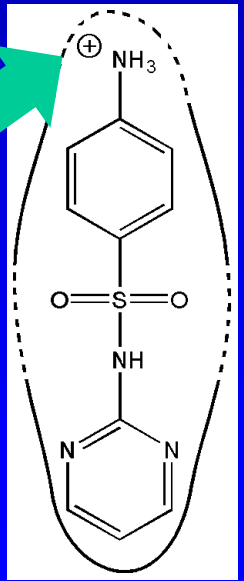
macrolides



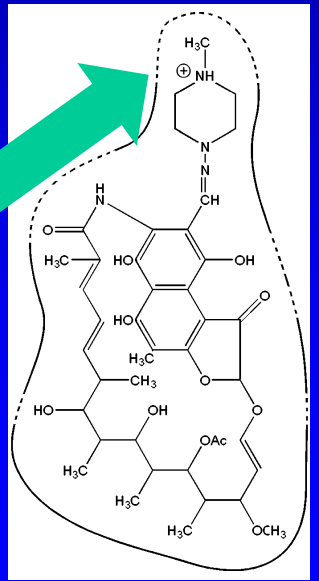
tetracyclines



fluoroquinolones



sulfamides



rifampicin

Antibiotic classes recognized by efflux pumps in different types of organisms

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

Identification of efflux pumps based on genome sequencing data

http://www-biology.ucsd.edu/~msaier/transport/

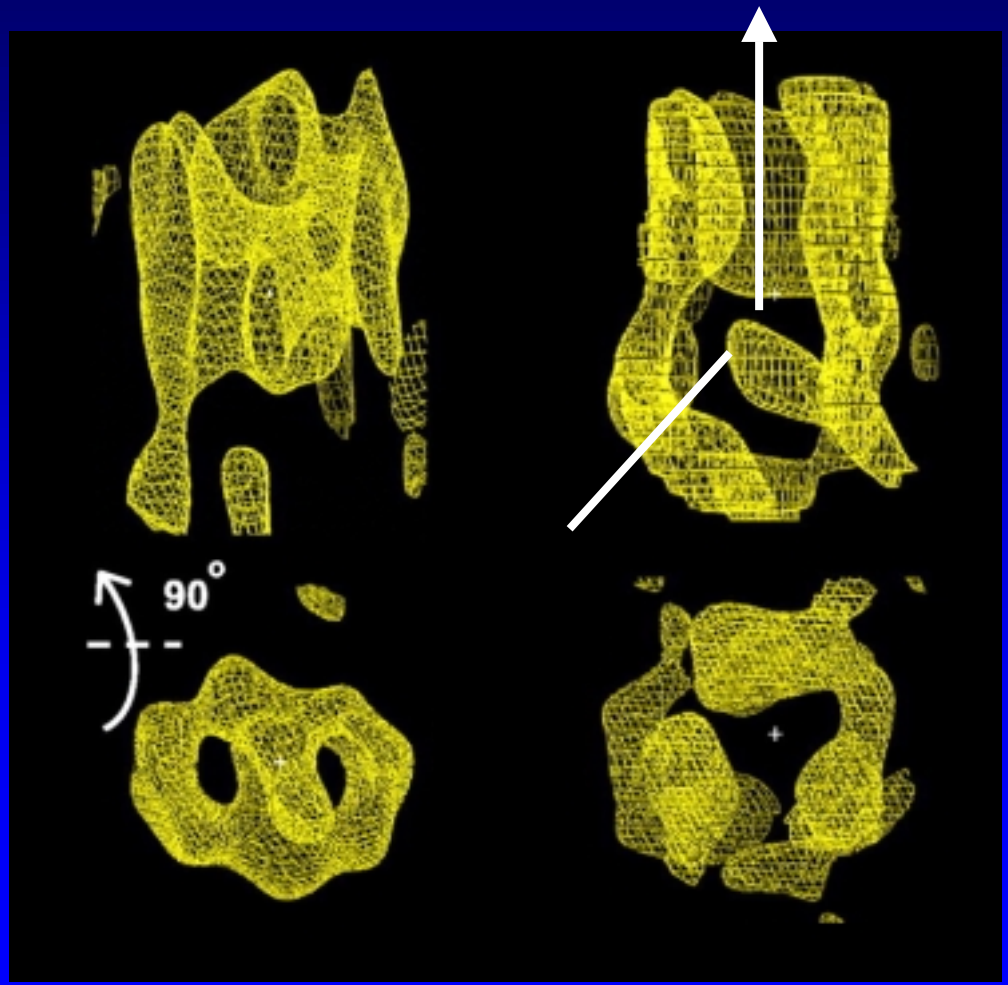
identification of genes encoding for putative transporters in the genome of

- **87 bacteria** *S. aureus, S. pneumoniae, E. coli, P. aeruginosa, ...*
- **14 archea**
- **4 eucaryotes** *S. cerevisiae, P. falciparum, ...*

Structure of pumps in eucaryotic cells

Current view of the structure of P-glycoprotein

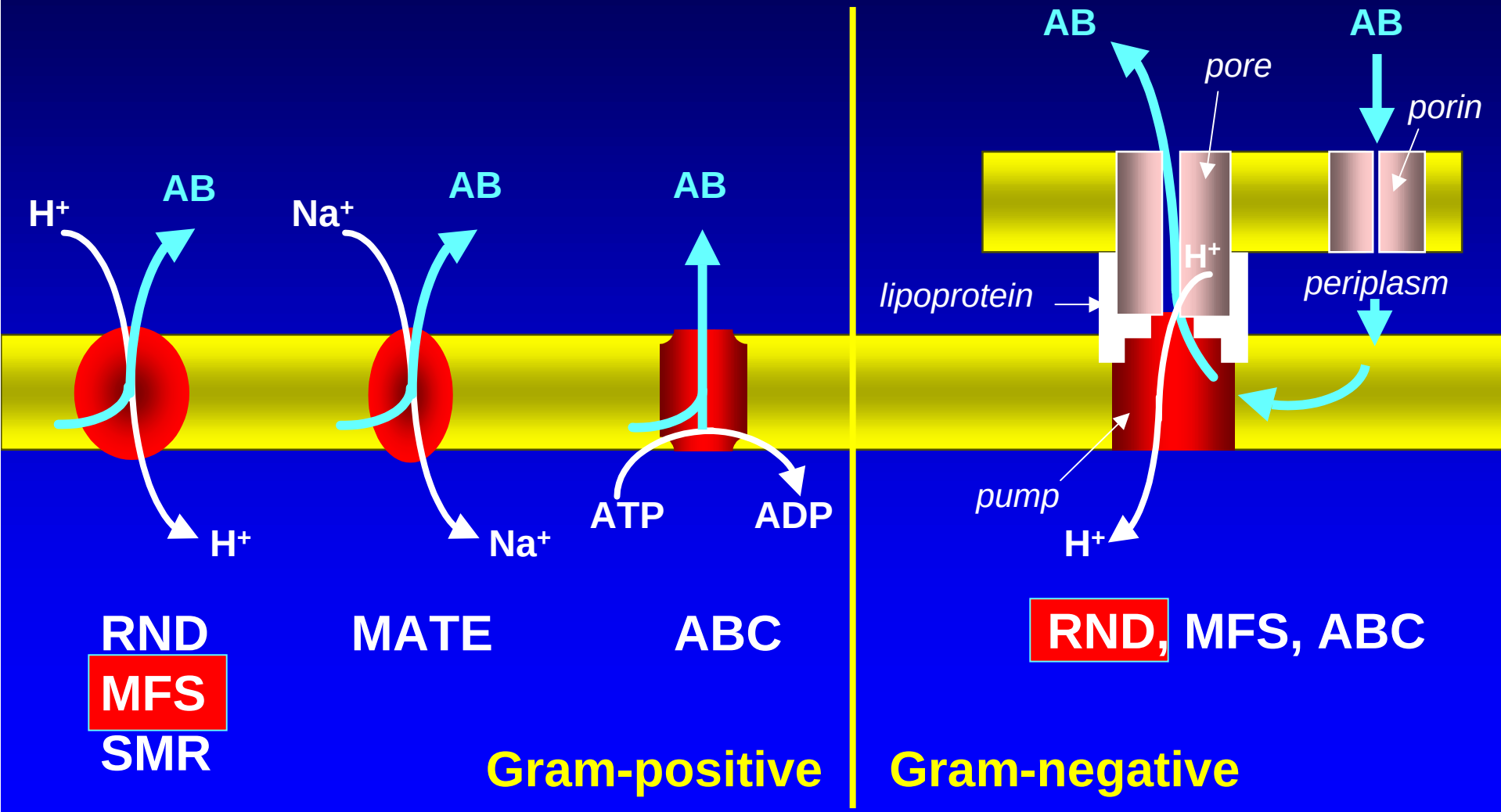
- ATP



+ ATP

Rosenberg *et al*. (2003) JBC 278: 8294-8299

Structure of pumps in procaryotic cells



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

Efflux pumps in bacteria: what does it mean for resistance ?

- **Constitutive expression of efflux pumps**
  ➔ intrinsic resistance
- **Inducible expression of efflux pumps**
  ➔ acquired resistance
- **Cooperation with other mechanims of resistance**
- **Selection of other mechanisms of resistance**

P. aeruginosa seems to be constitutively resistant to many antibiotics ...

Drug	MIC (μg/ml)[a] for strain: K372 (wild type)
Norfloxacin	>8
Ciprofloxacin	2 (0.2)
Tetracycline	8–16 (2.5)
Chloramphenicol	16 (12.5)
Novobiocin	128
Penicillin G	>1,024 (512)
Carbenicillin	32 (16)
Azlocillin	16 (2)
Cefoperazone	4 (2)
Ceftriaxone	64 (4)
Carumonam	8 (0.12)
Moxalactam	8
Cefepime	2 (0.5)
Cefpirome	4 (0.5)
Imipenem	2

Li *et al*. AAC (1995) 39:1948-1953

Disruption of MexAB-OprM restores the activity of several antibiotics against *P. aeruginosa*

Drug	MIC (μg/ml)[a] for strain: K372 (wild type)	K590 (*mexA*::*tetA*)
Norfloxacin	>8	1
Ciprofloxacin	2 (0.2)	0.1 (0.1)
Tetracycline	8–16 (2.5)	ND[c]
Chloramphenicol	16 (12.5)	4 (3)
Novobiocin	128	16
Penicillin G	>1,024 (512)	512 (256)
Carbenicillin	32 (16)	≤0.25 (0.12)
Azlocillin	16 (2)	1 (≤0.06)
Cefoperazone	4 (2)	0.5 (0.12)
Ceftriaxone	64 (4)	8 (0.25)
Carumonam	8 (0.12)	8 (≤0.06)
Moxalactam	8	2
Cefepime	2 (0.5)	1 (0.25)
Cefpirome	4 (0.5)	2 (0.25)
Imipenem	2	1–2

Li *et al*. AAC (1995) 39:1948-1953

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- **Constitutive expression of efflux pumps**

➔ **intrinsic resistance**

- **Inducible expression of efflux pumps**

➔ **acquired resistance**

- **Cooperation with other mechanims of resistance**

- **Selection of other mechanisms of resistance**

Overexpression of efflux pumps in *P. aeruginosa* upon exposure to fluoroquinolones in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
Control	0.25	0.12				

Jalal et al, AAC (2000) 44:710-712

Overexpression of efflux pumps in *P. aeruginosa* upon exposure to fluoroquinolones in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
CF166	2	1		R82L		
CF59	2	0.5		R82L		wk
Control	0.25	0.12				

Regulator of MexAB expression

Jalal et al, AAC (2000) 44:710-712

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➔ **acquired resistance**

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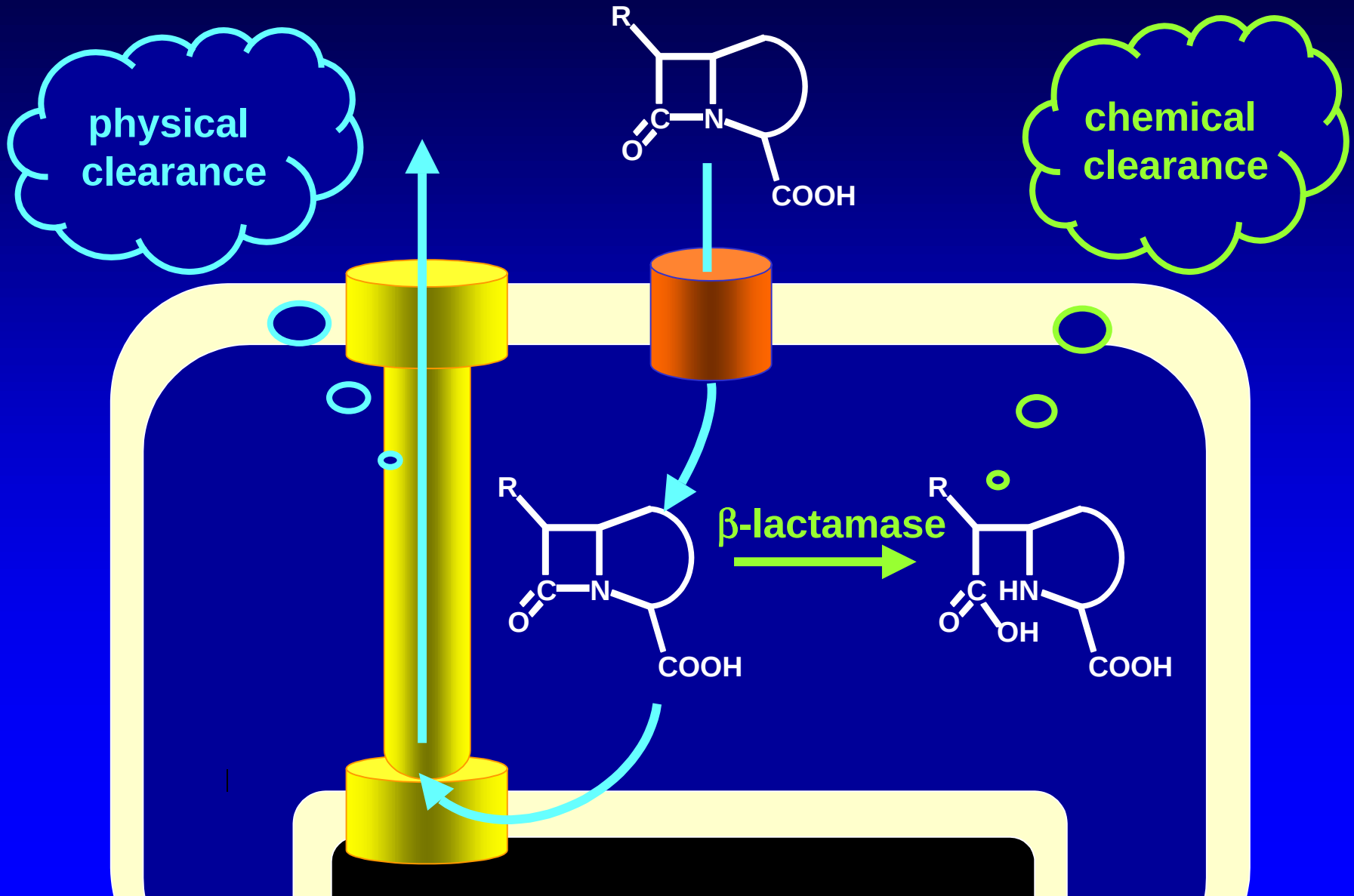
Efflux in cooperation with other resistance mechanisms



Efflux in cooperation with other resistance mechanisms

Contributions of the AmpC β-lactamase and the AcrAB Multidrug Efflux System in Intrinsic Resistance of *E. coli* to β -lactams

Efflux	β-lactamase	MIC carbenicillin
-	-	0.2
+	**-**	**12.5**

Intrinsic low level resistance !

Mazzariol *et al*, AAC (2000) 44:1387-1390

Efflux in cooperation with other resistance mechanisms

Contributions of the AmpC β-lactamase and the AcrAB Multidrug Efflux System in Intrinsic Resistance of *E. coli* to β -lactams

Efflux	β-lactamase	MIC carbenicillin
-	-	0.2
+	**-**	**12.5**
+++	-	50
-	+	100
+	+	**200**
+++	+	**400**

Intrinsic low level resistance !

high level resistance !

Mazzariol *et al*, AAC (2000) 44:1387-1390

Overexpression of efflux pumps in *P. aeruginosa* upon exposure to fluoroquinolones in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
CF166	2	1		R82L		
CF59	2	0.5		R82L		wk
Control	0.25	0.12				

Regulator of MexAB expression

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Cooperation of efflux pumps and target mutation in *P. aeruginosa* in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
CF166	16	4	T83I	R82L		
	2	1		R82L		
CF59	2	0.5		R82L		wk
Control	0.25	0.12				

+ Mutation in FQ target

Regulator of MexAB expression

Jalal et al, AAC (2000) 44:710-712

Cooperation of efflux pumps and target mutation in *P. aeruginosa* in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
CF166	16	4	T83I	R82L		
	2	1		R82L		
CF222	16	8	T83I	R82L	wk	wk
	2	0.5			wk	
CF86	16	8	T83I	R82L	wk	+
	8	2	D87N	R82L		wk
CF59						
	2	0.5		R82L		wk
Control	0.25	0.12				

+ Mutation in FQ target

Regulator of MexAB expression

Jalal et al, AAC (2000) 44:710-712

Cooperation of efflux pumps and target mutation in *P. aeruginosa* in CF patients

Patient	Characteristics of 1997 isolate(s)					
	MIC (μg/ml) of:		Amino acid change			
	Nor	Cip	GyrA	NfxB	OprN	OprJ
CF166	16	4	T83I	R82L		
	2	1		R82L		
CF222	16	8	T83I	R82L	wk	wk
	2	0.5			wk	
CF86	16	8	T83I	R82L	wk	+
	8	2	D87N	R82L		wk
CF59	8	4	D87Y	R82L		
	2	0.5		R82L		wk
CF21	16	4	T83I	R82L		wk
	2	1			+	
CF89	8	2	T83I	R82L		+
Control	0.25	0.12				

+ Mutation in FQ target

Regulator of MexAB expression

Jalal et al, AAC (2000) 44:710-712

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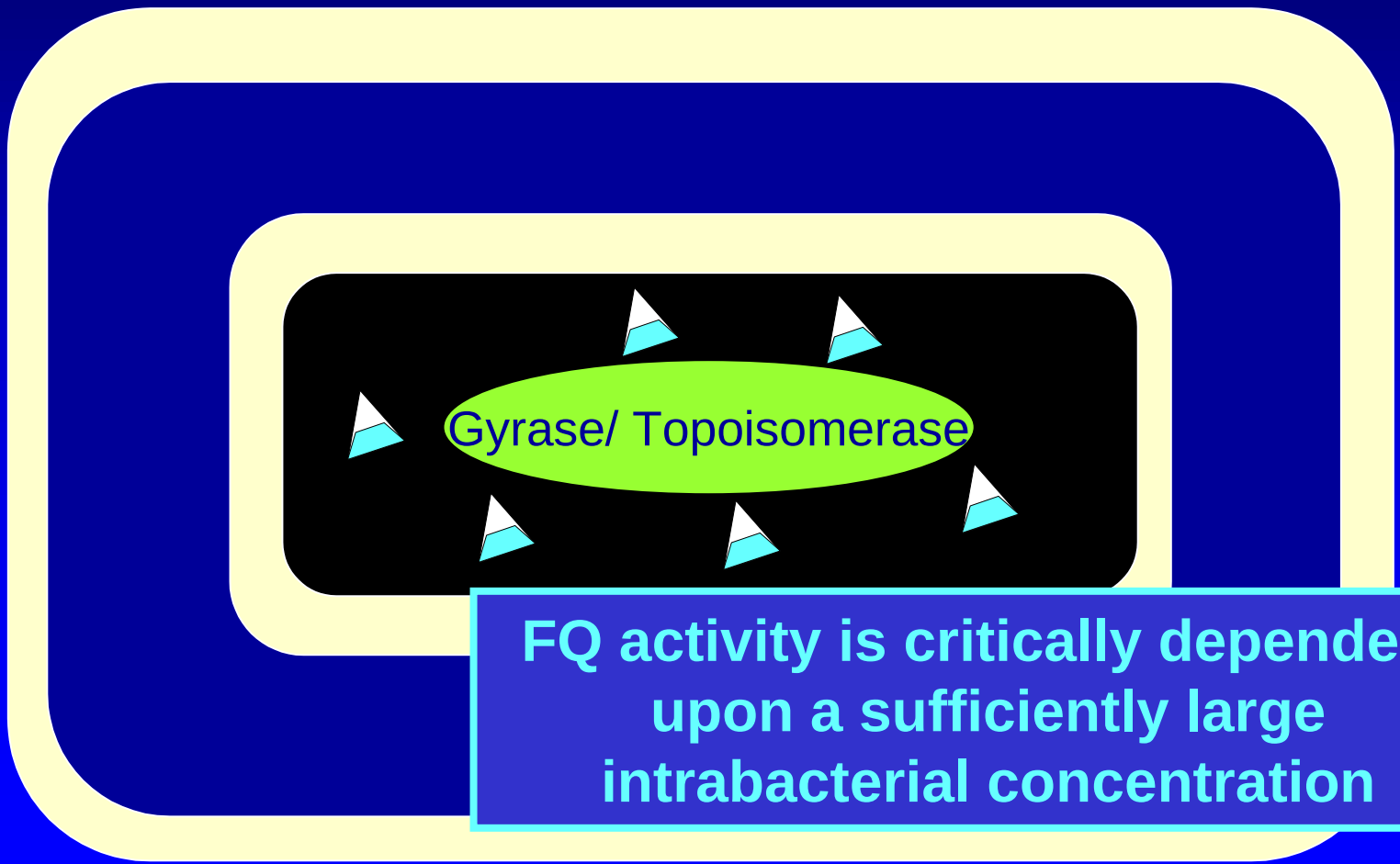
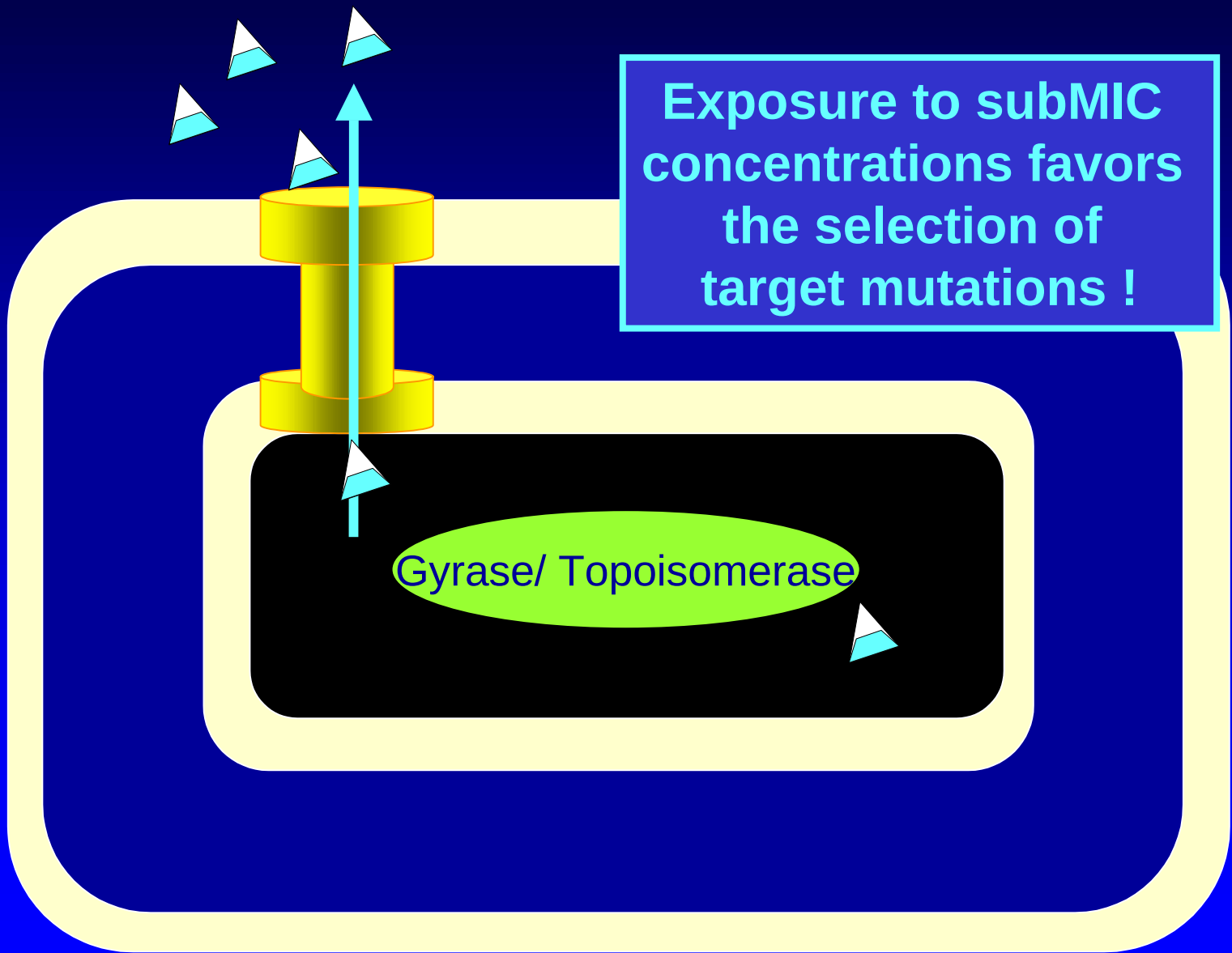
Efflux and selection of resistance to FQ



FQ activity is critically dependent upon a sufficiently large intrabacterial concentration

Efflux and selection of resistance to FQ



Efflux and selection of resistance to FQ

Frequency of Levofloxacin-resistant mutants in *Pseudomonas aeruginosa* with deletions of the efflux pump operons

Pump status	LVX MIC	Frequency of LVX-resistant mutants
WT	0.25	2×10^7 - 4×10^7
Δ mexAB-oprM	0.015	2×10^7 - 4×10^7
Δ mexCD-oprJ	0.25	2×10^7 - 4×10^7
Δ mexEF-oprN	0.25	2×10^7 - 4×10^7
Δ mexAB-oprM;Δ mexEF-oprN	0.015	2×10^7 - 10^7
Δ mexCD-oprJ; Δ mexEF-oprN	0.25	2×10^6
Δ mexAB-oprM; Δ mexCD-oprJ	0.015	1×10^9
Δ mexAB-oprM; Δ mexCD-oprJ; Δ mexEF-oprN	0.015	**$<1 \times 10^{11}$**

Selection of mutants in FQ target undetectable if ALL pumps are disrupted

Lomovskaya *et al,*
AAC (1999) 43:1340-1346

How to cope with efflux pumps in anti-infective therapy ?

- ***S. pneumoniae and the correct choice of "respiratory fluoroquinolones"***
- ***P. aeruginosa***
  - **quinolones**
  - **carbapenems**

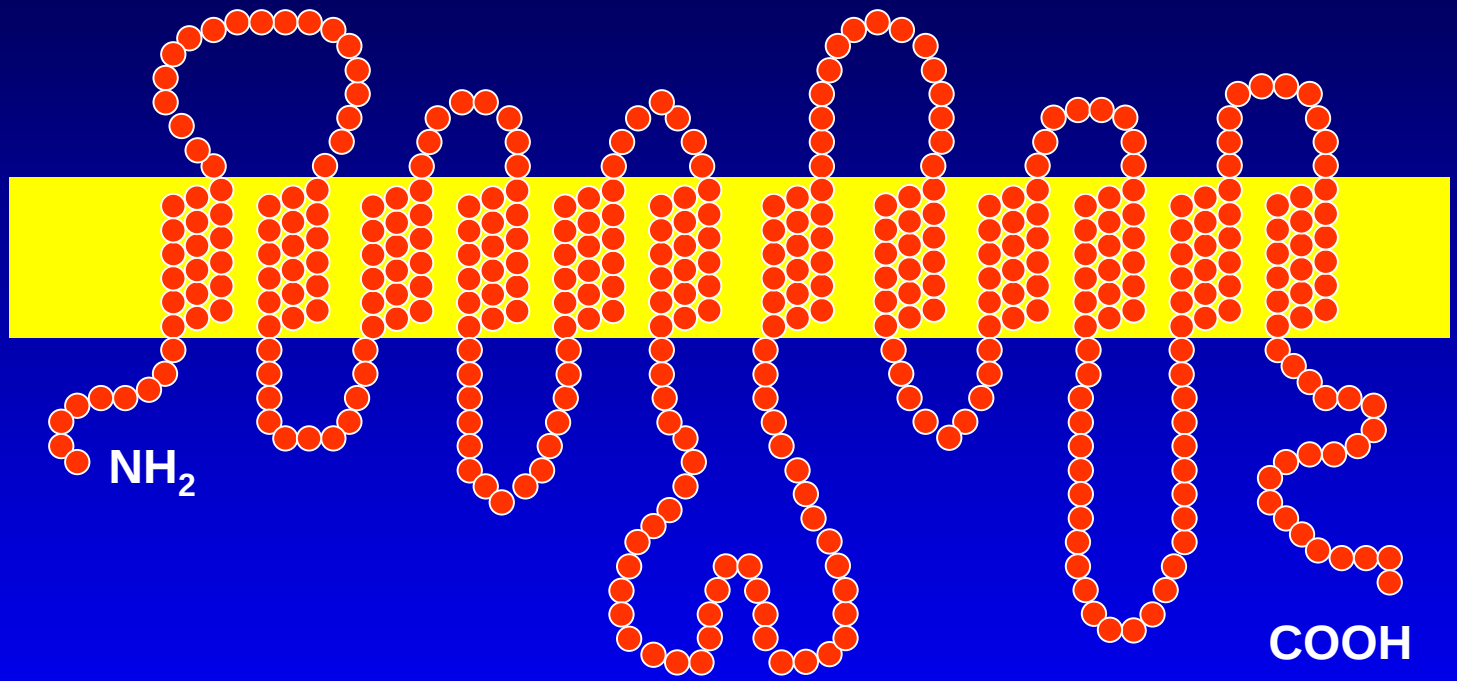
MIC considerations ...

	Wild-type strain
Quinolone	**MIC**
CIP	**0.5**
LVX	**1**
MXF	**0.25**
GAT	**0.25**

Are those differences important ?

Coyle *et al*. AAC (2001) 45:1654-1659

Enters the quinolone pmrA efflux pump ...



12 transmembrane segments

member of the Major Facilitator Superfamily (MFS)

energized by H^+ gradient

Gill *et al*. AAC (1999) 43:187-189

Van Bambeke *et al*. (2000) Biochem. Pharmacol. 60:457-470

MIC considerations ...

Quinolone	Wild-type strain MIC	Efflux resistant strain MIC
CIP	0.5	8
LVX	1	4
MXF	0.25	0.5
GAT	0.25	0.5

And look at this, now ...

Coyle *et al*. AAC (2001) 45:1654-1659

PK / PD considerations ...

For fluoroquinolones,

- efficacy is linked to AUC/MIC ratio
  (must be > 30 for *S. pneumoniae*)
- prevention of resistance is linked to
  C_{max}/MIC ratio
  (must be > 10 to prevent mutations)

Optimisation based on pharmacodynamics

	Wild-type strain		
Quinolone	MIC	AUC/MIC	C_{max}/MIC
CIP	0.5	92.8	11.2
LVX	1	63.6	6.4
MXF	0.25	213.6	18.8
GAT	0.25	151.8	14.8

moderate risk of selection of resistance !

Coyle *et al*. AAC (2001) 45:1654-1659

Optimisation based on pharmacodynamics

Quinolone	Wild-type strain MIC	Wild-type strain AUC/MIC	Wild-type strain Cmax/MIC	Efflux resistant strain MIC	Efflux resistant strain AUC/MIC	Efflux resistant strain Cmax/MIC
CIP	0.5	92.8	11.2	8	5.8	0.7
LVX	1	63.6	6.4	4	15.9	1.6
MXF	0.25	213.6	18.8	0.5	106.8	9.4
GAT	0.25	151.8	14.8	0.5	75.9	7.4

m
selec

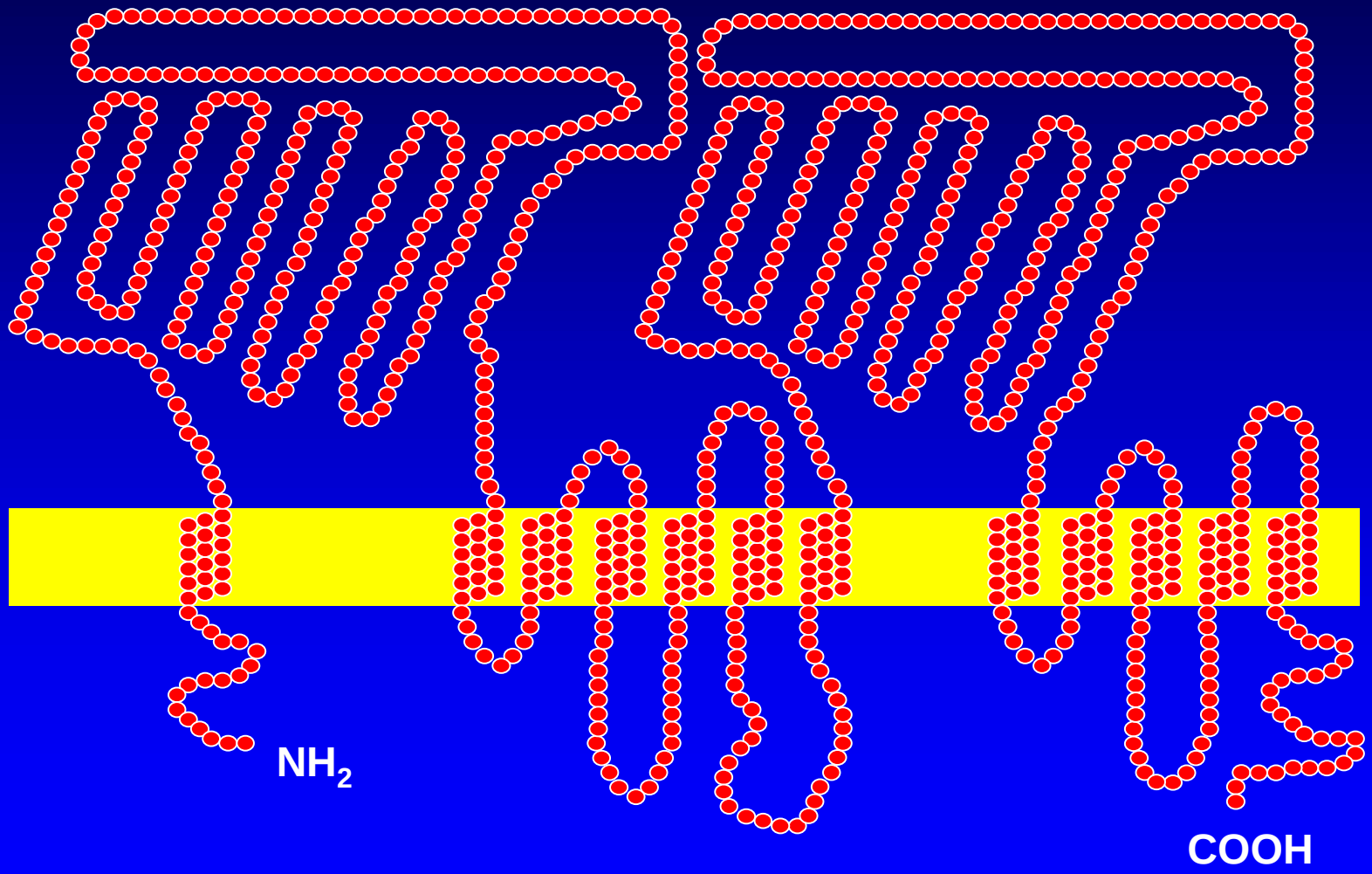
High risk of selection of resistance !

Coyle *et al*. AAC (2001) 45:1654-1659

How to cope with efflux pumps in anti-infective therapy ?

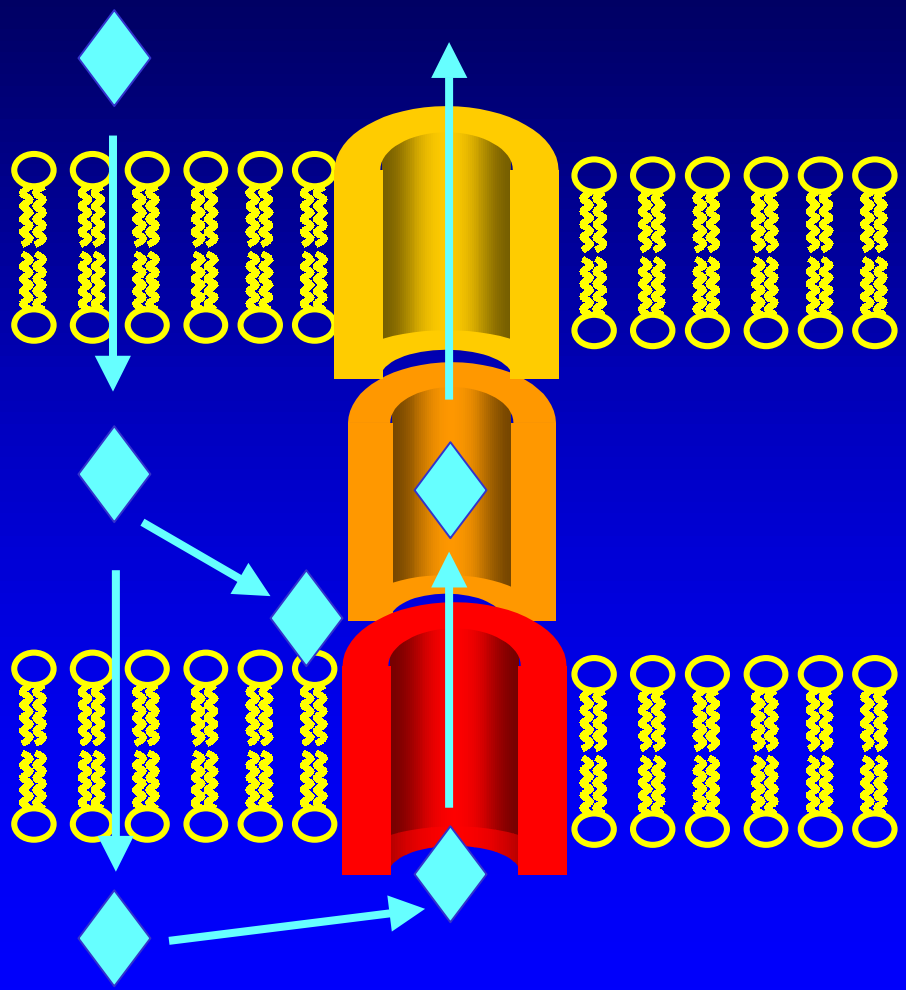
- ***S. pneumoniae and the correct choice of "respiratory fluoroquinolones"***
- ***P. aeruginosa***
  - **quinolones**
  - **carbapenems**

Topology of the wide spectrum Mex pumps in *Pseudomonas* *(RND superfamily)*



Van Bambeke *et al*. (2000) Biochem. Pharmacol. 60:457-470

Functionning of the wide spectrum Mex pumps in *Pseudomonas*



outer membrane

inner membrane

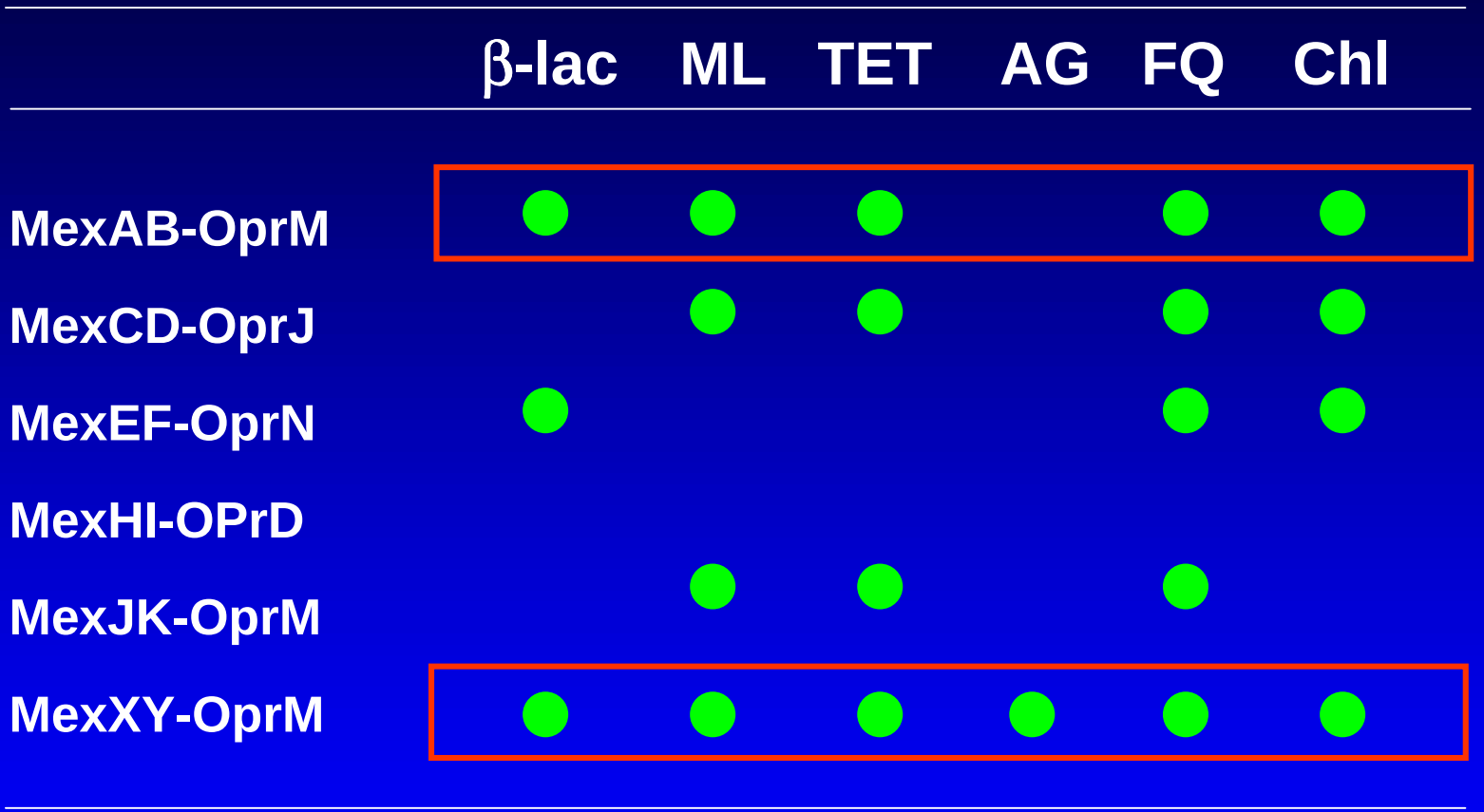
outer membrane protein
OprM, J, N

linker protein
MexA, C, E, X

RND exporter protein
MexB, D, F, Y

adapted from Aeschlimann, Pharmacotherapy (2003) 23:916-924

Wide spectrum pumps in *Pseudomonas*



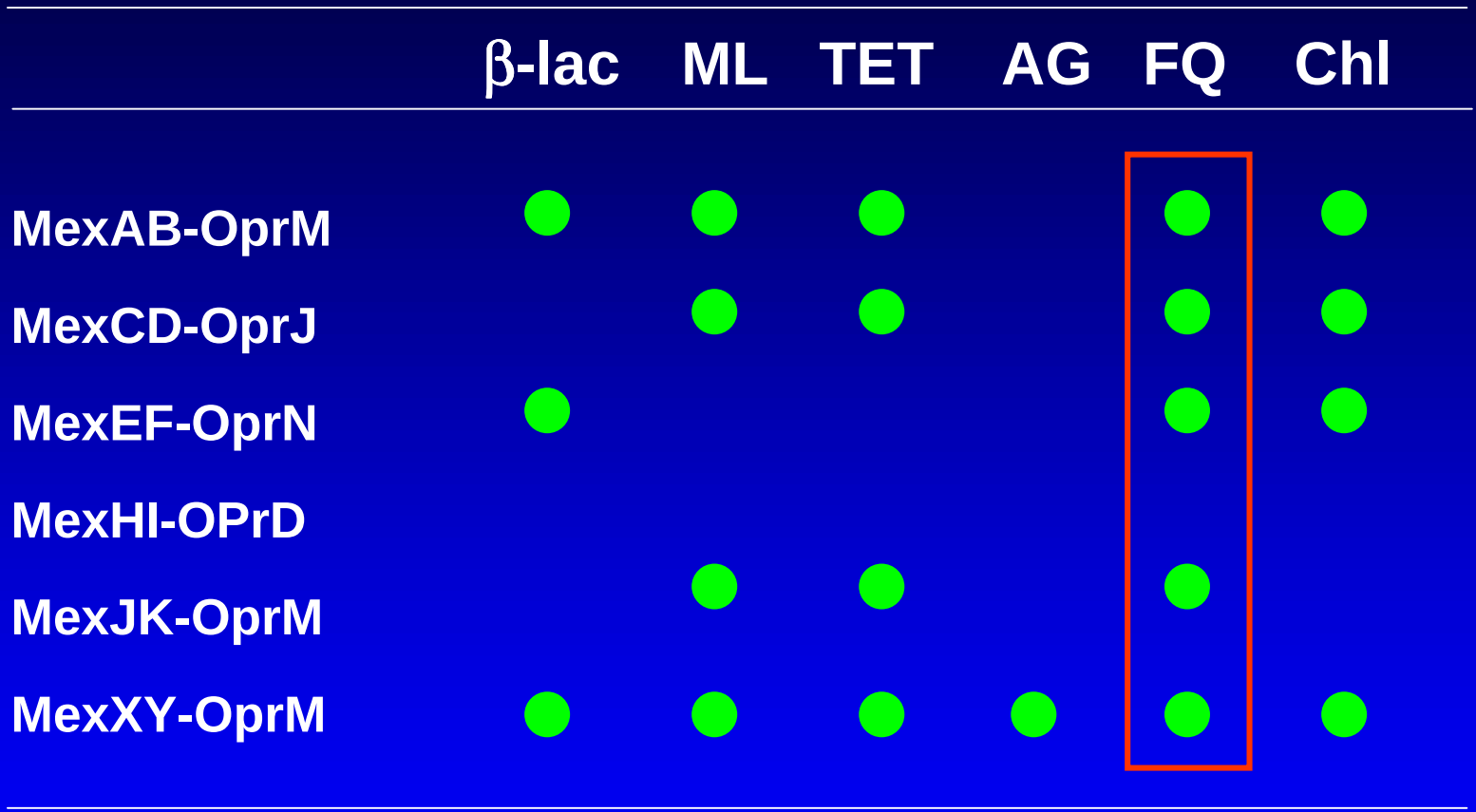
1. wide spectrum transporters

➔ cross-resistance among most AB classes

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

Aeschlimann, Pharmacotherapy (2003) 23:916-924

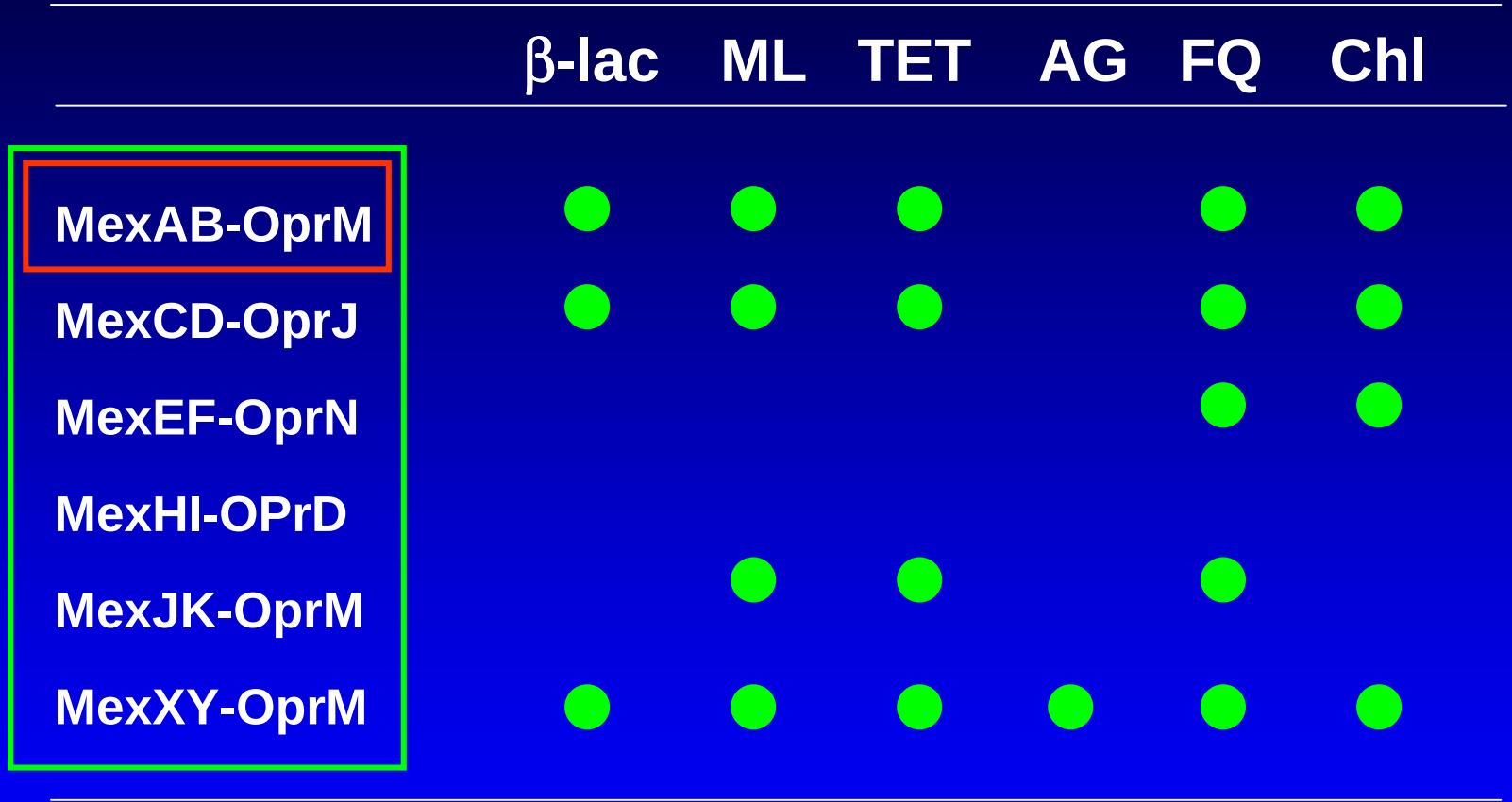
Wide spectrum pumps in *Pseudomonas*



2. FQ are « universal » substrates
➔ easy selection of resistance

Van Bambeke et *al*. JAC (2003) 51: 1055-1065
Aeschlimann, Pharmacotherapy (2003) 23:916-924

Wide spectrum pumps in *Pseudomonas*



3. constitutive expression and/or inducible expression

➔ **increase of resistance level higher upon antibiotic exposure**

Van Bambeke et *al*. JAC (2003) 51: 1055-1065
Aeschlimann, Pharmacotherapy (2003) 23:916-924

Pseudomonas and quinolone efflux

Overexpressed Mex pumps			MICs		
AB	CD	EF	CIP[1]	LVX[2]	MXF[1]
			0.1	0.125	0.8
+			0.4	2	**3.2**
	+		0.8	2	**6.4**
		+	1.6	**4**	**12.8**

[1] Zhang *et al*. JAC (2001) 48: 549-552

[2] Lomovskaya et al. AAC (2001)5: 105-116

Pseudomonas and penem efflux

Mex pumps			MICs					
AB	CD	XY	MERO	IMI	BIA	PANI	FARO	RITI
-	-	-	0.032	0.25	0.25	0.25	1	2
+ *	-	-	**0.25**	1	0.5	4	512	128
++	-	-	**1**	0.25	0.25	1	4096	256
-	++	-	**0.25**	0.125	0.063	0.25	16	4
-	-	++	0.063	0.25	0.25	2	4	8

* clinical isolate, basal level of expression

Okamoto *et al*. J. Infect. Chemother (2002) 8: 371-373

Okamoto *et al.* AAC (2002) 46:2696-2699

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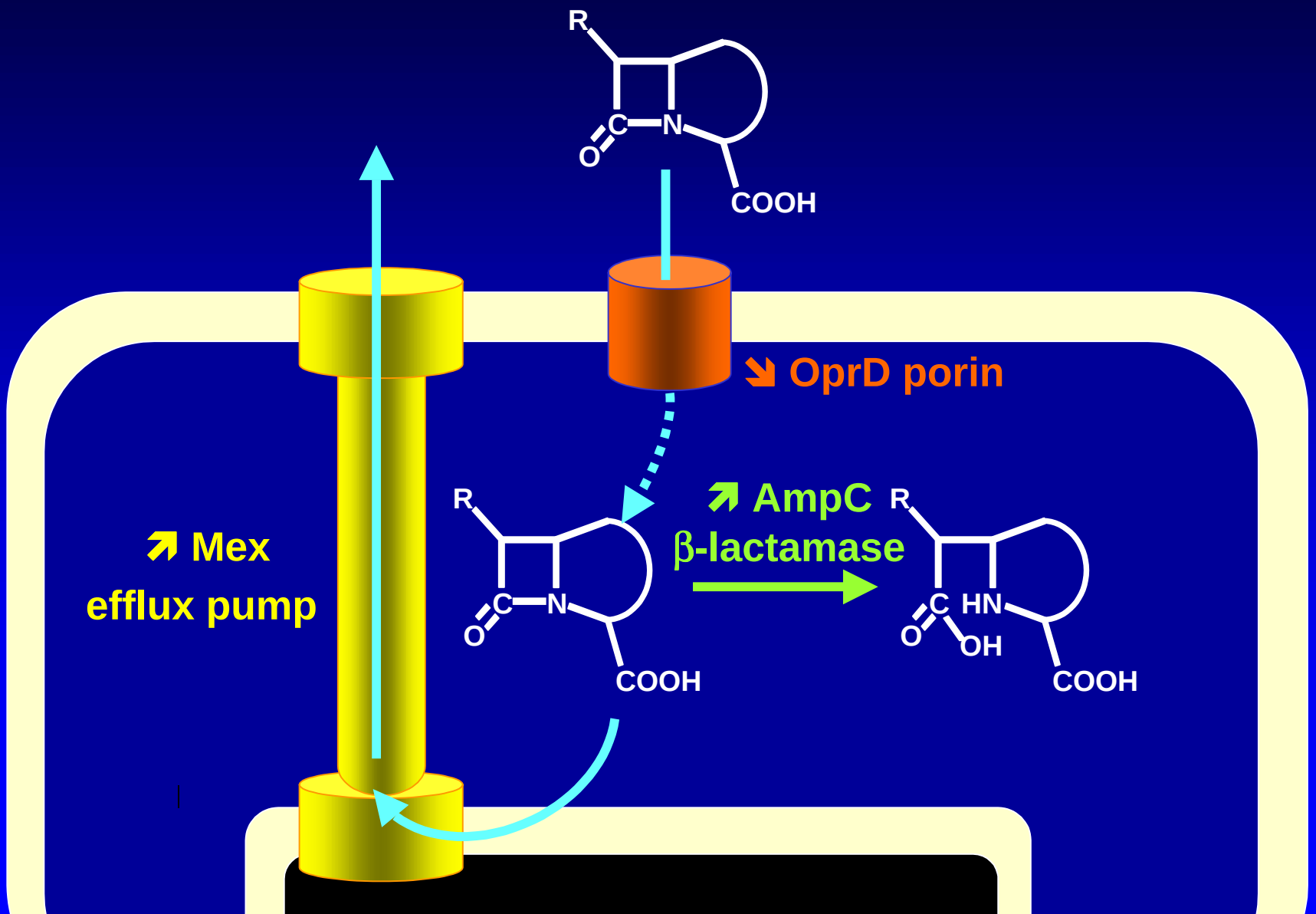
Combined mechanisms of resistance in *Pseudomonas*



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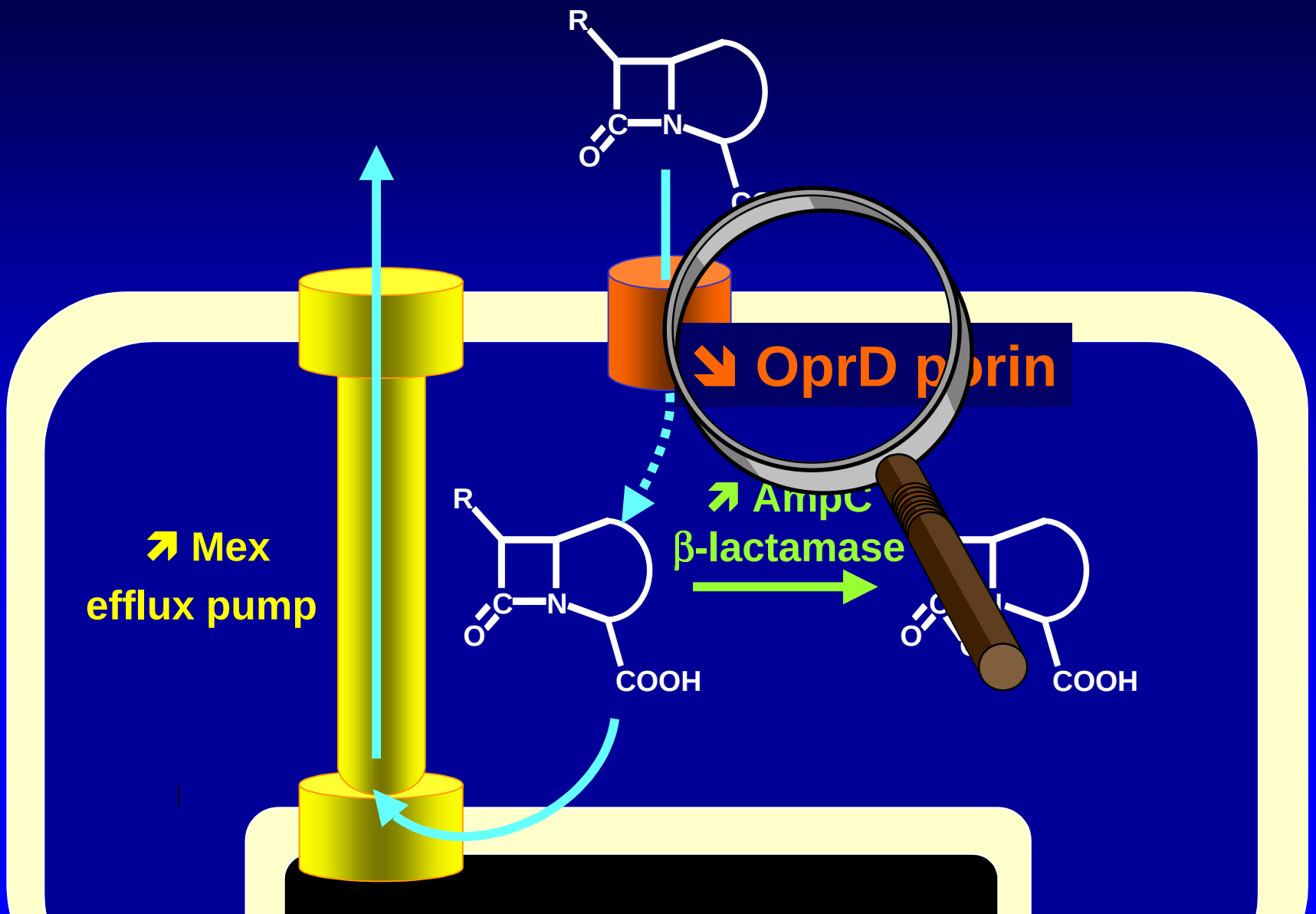

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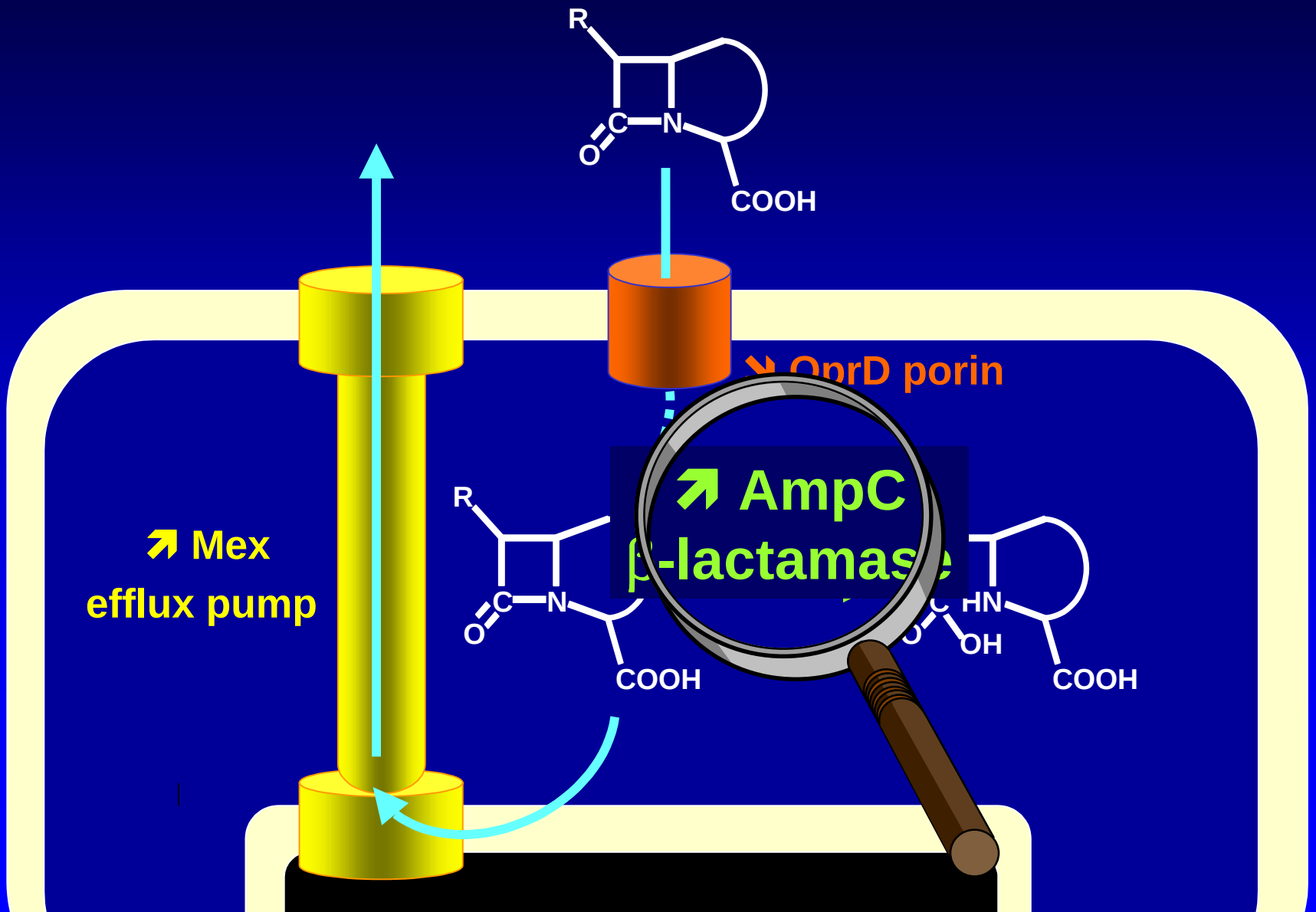

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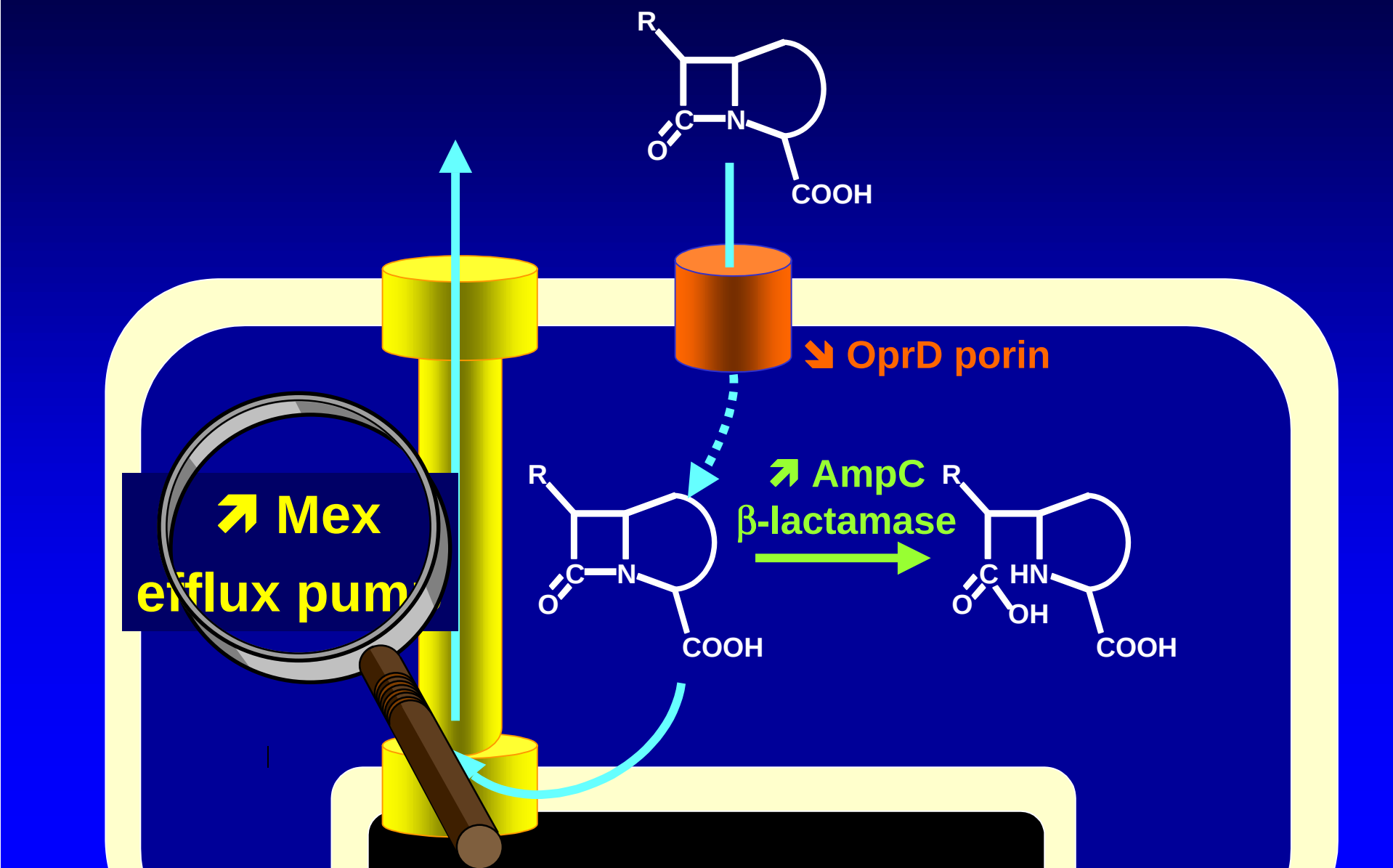

Contribution of resistance mechanisms to carbapenem resistance in *Pseudomonas*

1. Laboratory strains

Resistance mechanism			fold increase in MIC	
AmpC	MexAB	ΔOprD	IMI	MERO
+	-	-	X 1	X 2

Kohler *et al*. AAC (1999) 43: 424-427

Nakae *et al.* AAC (1999) 43:1301-1303

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-	+	-	X 1	X 2 - 10

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-	-	+	X 16	X 4

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-	-	+	X 16	X 4
-	+	+	X 16	X 32 - 128

Kohler *et al*. AAC (1999) 43: 424-427

Nakae *et al.* AAC (1999) 43:1301-1303

Contribution of resistance mechanisms to carbapenem resistance in *Pseudomonas*

2. Clinical strains

	Resistance mechanism			MIC (mg/L)	
	AmpC	MexAB	ΔOprD	IMI	MERO
# 1	low	-	-	1	0.5

Pai *et al.* AAC (2001) 45:480-484

Contribution of resistance mechanisms to carbapenem resistance in *Pseudomonas*

2. Clinical strains

	Resistance mechanism			MIC	
	AmpC	MexAB	ΔOprD	IMI	MERO
# 1	low	-	-	1	0.5
# 2	low	-	+	8 - 16	2 - 4

Imipenem is affected by a defect in OprD (porin)

Pai *et al.* AAC (2001) 45:480-484

Contribution of resistance mechanisms to carbapenem resistance in *Pseudomonas*

2. Clinical strains

	Resistance mechanism			MIC	
	AmpC	MexAB	ΔOprD	IMI	MERO
# 1	low	-	-	1	0.5
# 2	low	-	+	8 - 16	2 - 4
# 3	low	+	+	16	16

Meropenem is affected by the expression of Mex AB (efflux)

Pai *et al.* AAC (2001) 45:480-484

Contribution of resistance mechanisms to carbapenem resistance in *Pseudomonas*

2. Clinical strains

	Resistance mechanism			MIC	
	AmpC	MexAB	ΔOprD	IMI	MERO
# 1	low	-	-	1	0.5
# 2	low	-	+	8 - 16	2 - 4
# 3	low	+	+	16	16
#4	high	-	+	8 - 16	2 - 16

AmpC does not markedly affect imipenem or meropenem

Pai *et al.* AAC (2001) 45:480-484

An what about ertapenem ?

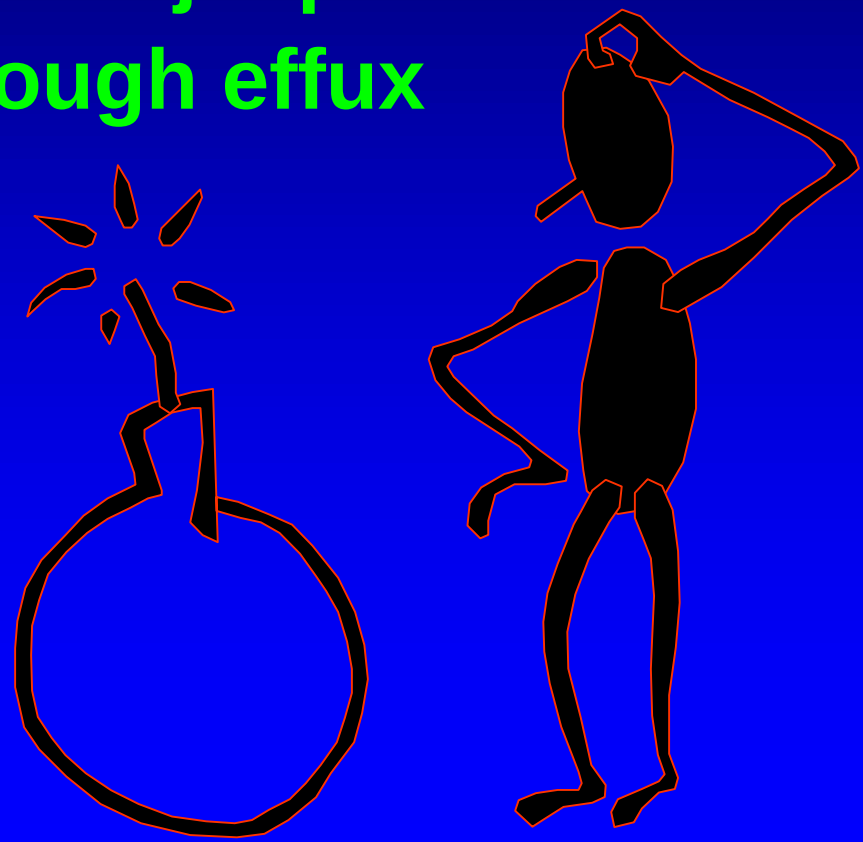
Susceptibility Patterns of Resistant Mutants (PAO -1 and Derivatives)

Resistance mechanism	D2	β-la	OprM	ETP	IPM	MER	CAZ	LVF
None (PAO-1)	+	Ind	+	4-8	1-2	0.5-1	2-4	0.5
D2 (porin) ↓	-	Ind	+	8	8-16	2-4	2	0.5
OprM (efflux)↑	+	Ind	↑	32	1	4	16	4
βla↑	+	Con	+	16	2	1	64	0.5
MK- X	**+**	**Ind**	**+**	**32**	**2**	**2**	**4**	**0.5**

The major ertapenem resistance seen in PAO-1 is not due to D2 loss, OprM overexpression or βla constitutivity - suggesting a new mechanism

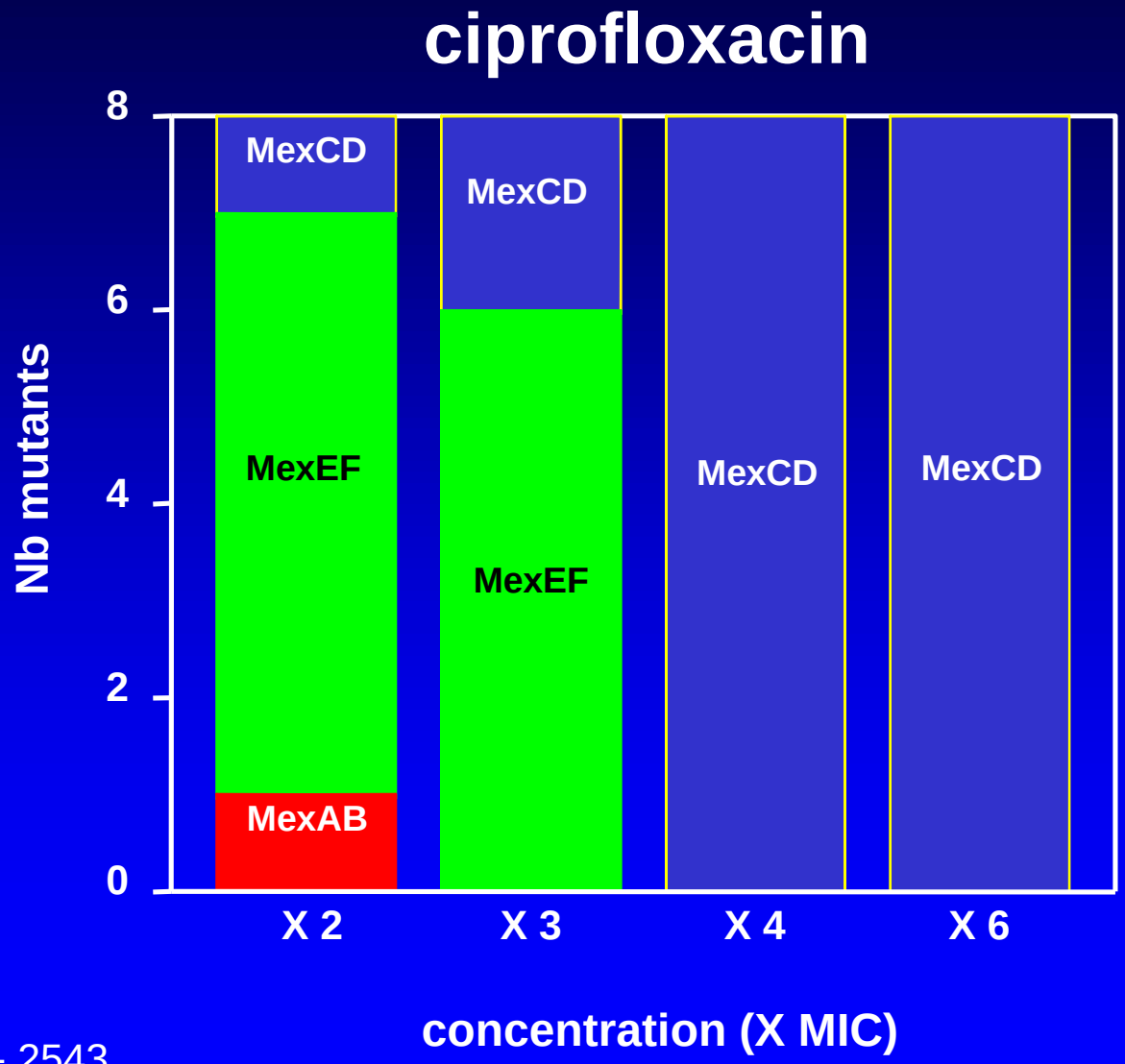
A burning question ...

- **Could fluoroquinolones jeopardize other antibiotics through effux pumps ?**



Fluoroquinolones-exposed *P. aeruginosa* overexpress wide spectrum efflux pumps

Incubation of P.aeruginosa with (too) low concentrations of fluoroquinolones triggers the expression of the Mex transporters BEFORE it affects the gyrase !



Kohler *et al*. AAC (1997) 41: 2540 - 2543

Mex-expressing strains become highly resistant to many antibiotics

MIC profiles of the PAO1 wild-type strain and MDR derivatives selected by quinolones

Antimicrobial agent	MIC (μg/ml) for: PAO1 wild type	MDR derivative MexAB-OprM	MexCD-OprJ	MexEF-OprN
Erythromycin	256	128–256	512–2,048	128–256
Chloramphenicol	64	256–512	128–256	≥1,024
Trimethoprim	128	1,024–2,048	256–1,024	512–1,024
Carbenicillin	32	128–256	8–32	32–64
Cefpirome	1	4–8	8–16	1–2
Ceftazidime	2	4–8	1–2	0.5–1
Ciprofloxacin	0.125	0.25–0.5	0.5–1	0.5–1

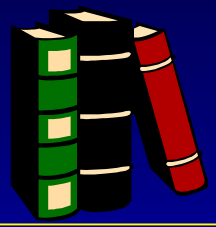
Risk of cross resistance !

Rearranged from

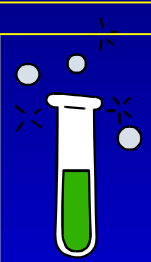
Kohler *et al*. AAC (1997) 41: 2540 - 2543

Perspectives:
strategies to overcome resistance by efflux:
en route to a rational design
of efflux pump inhibitors ?

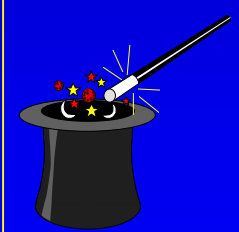
High throughput screening for the discovery of inhibitors of ‘large spectrum’ transporters

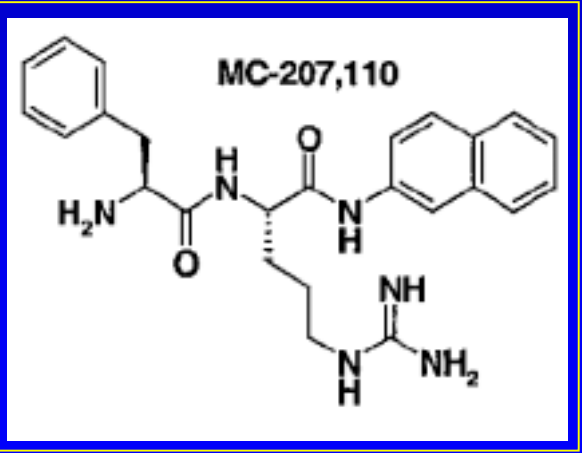


library of 200,000 synthetic and natural compounds



in vitro screening in combination with levofloxacin against *P. aeruginosa* overexpressing Mex pumps



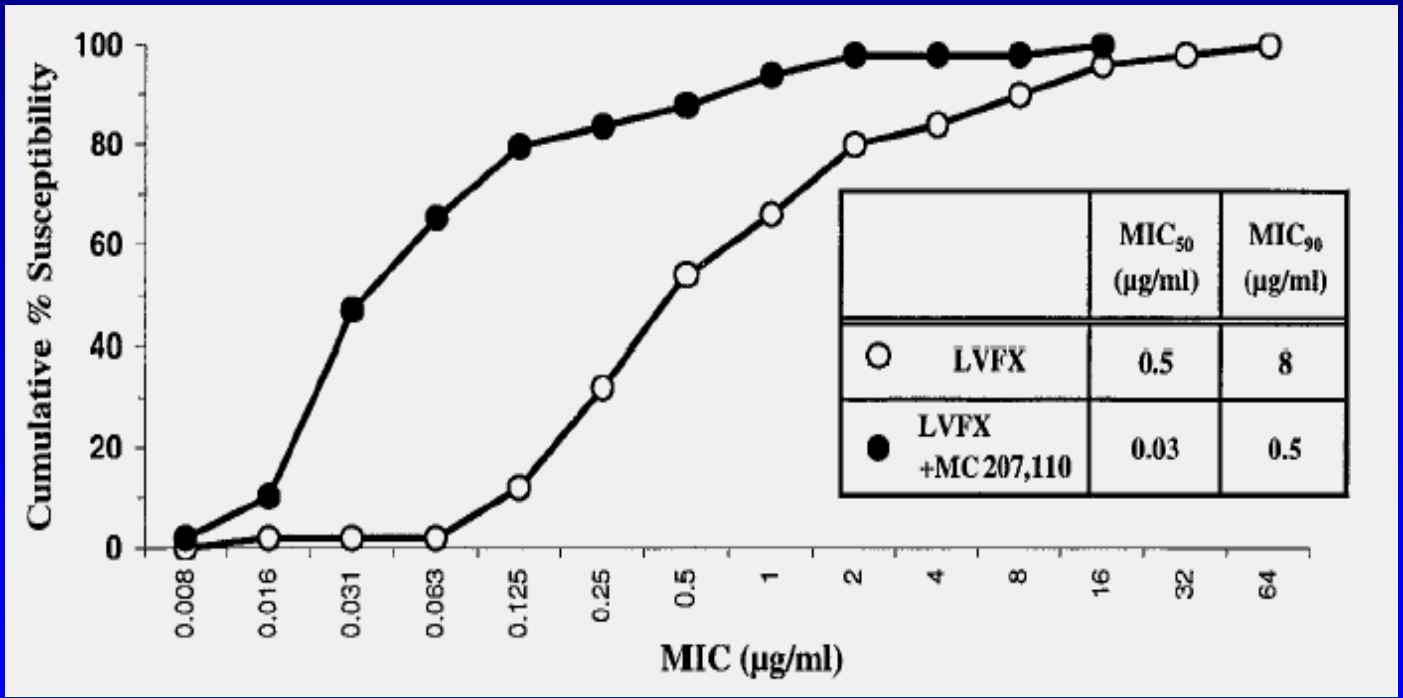


Renau *et al*. J. Med. Chem. (1999) 42: 4928-4931

Lomovskaya *et al*. J. Mol. Microbiol. Biotechnol. (2001) 3: 225-236

High throughput screening for the discovery of inhibitors of ‘large spectrum’ transporters

➔ **increase in susceptibility of clinical isolates**



Lomovskaya *et al*. AAC (2001) 45:106-116

you can win !

Shall we have a better future ?

Do not deny the difficulties ! ...

Thank you for your attention ...

These slides (with a series of additional ones) will be available as PDF file from here ...

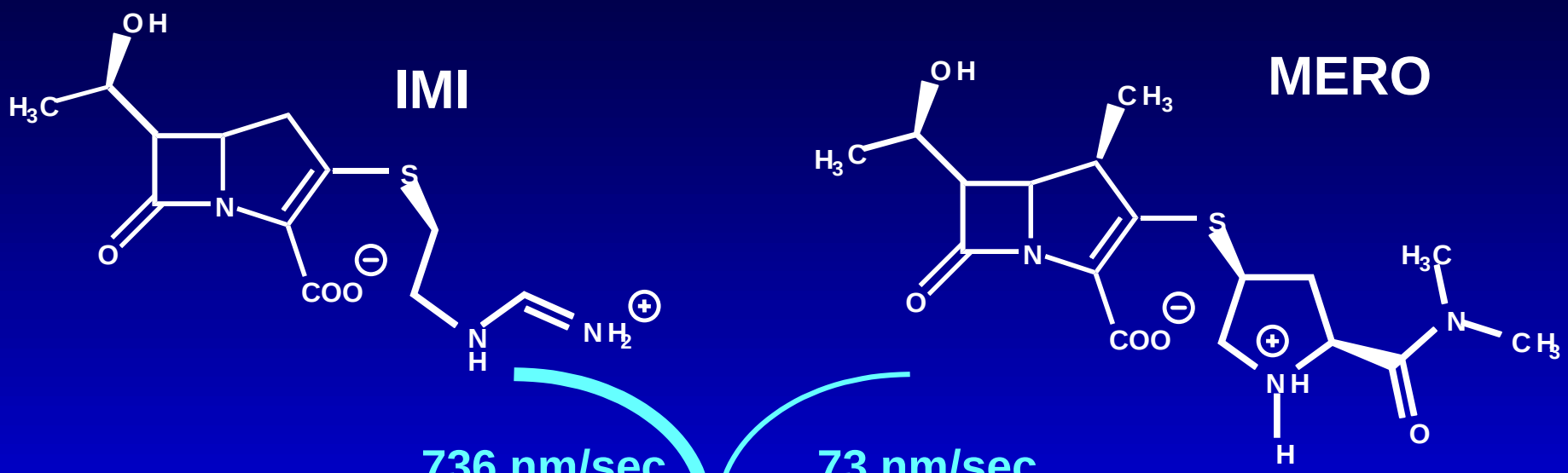
http://www.md.ucl.ac.be/facm

click on "*Conferences*" and look for the link to "*Efflux Mechanisms of Fluoroquinolones and β-lactams*", Chicago, IL, September 14th, 2003"

Additional questions ….

- **Is imipenem more affected than meropenem by ΔOprD (porin) ?**
- **Why is meropenem more affected than imipenem by MexAB (efflux) ?**

Why is IMI more affected than MERO by ΔOprD ?



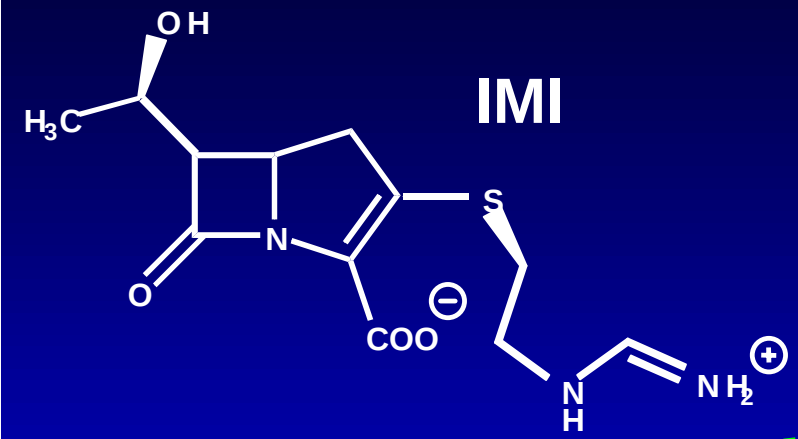
MERO enters only slowly through OprD ...

➔ has MERO another route of entry ?

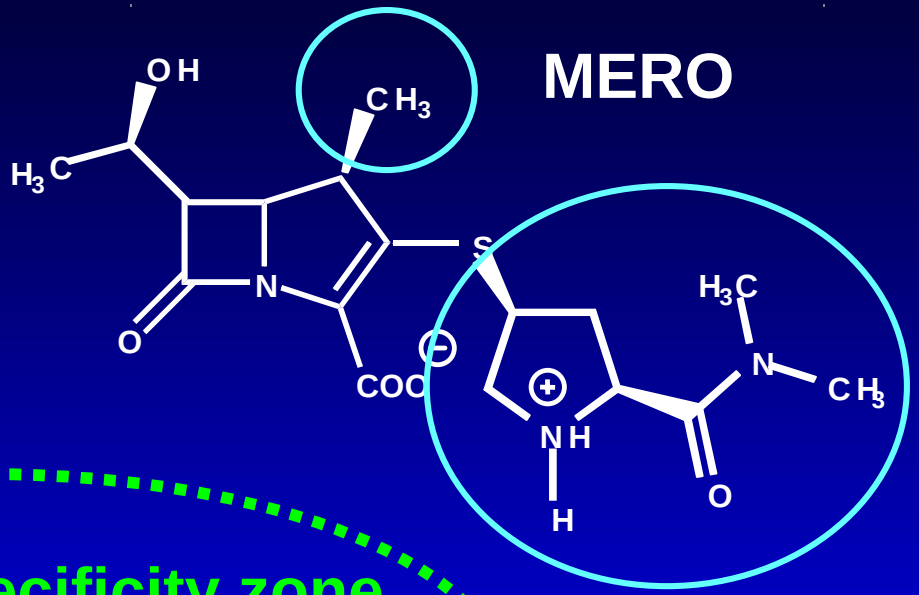
Trias *et al.* AAC (1990) 34:52-57

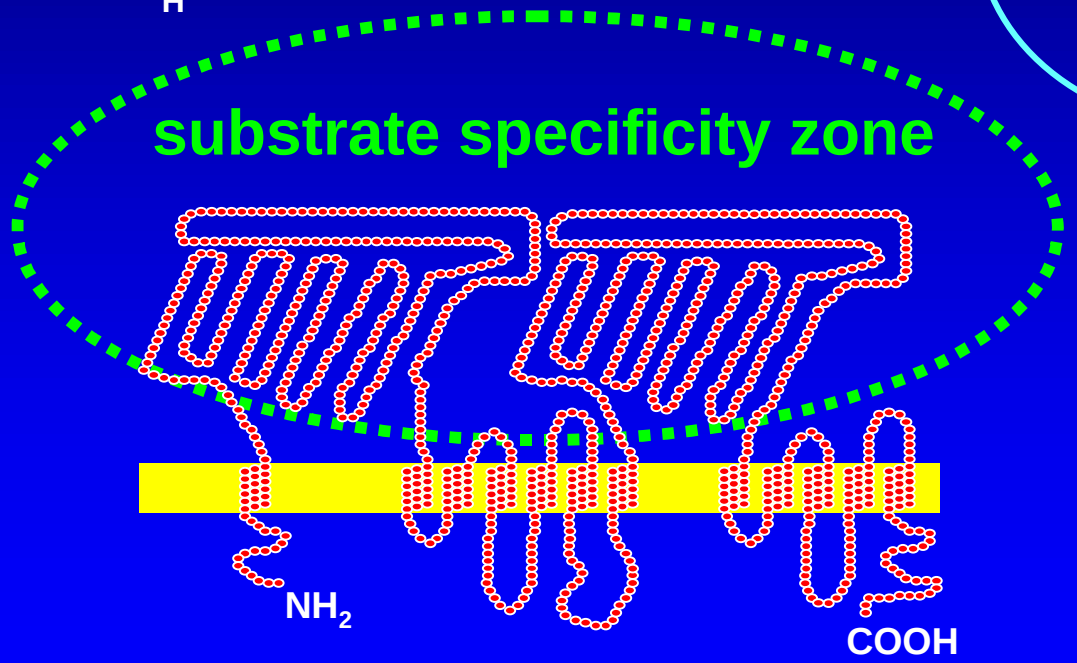
Why is MERO more affected than IMI by MexAB ?

IMI



MERO





differential recognition by the large periplasmic loops

of the inner membrane component ?

Mao *et al.* Mol. Microbiol. 2002 46: 889-901