Intracellular Activity of Antibiotics: the knowns, the uncertainties and the failures

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(Drug Discovery & Development / Rational) therapeutic choices)

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* with slides borrowed from Françoise Van Bambeke

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- Research grants
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  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)

- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - **Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*]** (governance)

Slides: http://www.facm.ucl.ac.be → Lectures

Chester extra and intra…

Why do we wish to look at intracellular activity of antibiotics ?

- Beyond truly obligate intracellular parasites (e.g., *Legionella*, *Chlamydia*, *Mycobacteriae*, …many more "common" bacteria are facultative (e.g. ***Listeria***) or occasional (e.g. ***Staphylococci***, *Pseudomonas*…) intracellular parasites …

- These bacteria form a **reservoir** from where bacteria may escape causing **relapses** and **recurrences** of the infection…

- Natural defenses often restrict their growth and decrease their persistence, but not always…

- You may need to help host defenses with **antibiotics**

Intracellular activity of antibiotics

- **What has been know for long about pharmacokinetics…**
- **What has surprised us …**
- **Adding pharmacodynamics …**
- **A renewed model ?**

Intracellular activity of antibiotics

- **What has been know for long about pharmacokinetics…**
- **What has surprised us …**
- **Adding pharmacodynamics …**
- **A renewed model ?**

A simple view in 1991

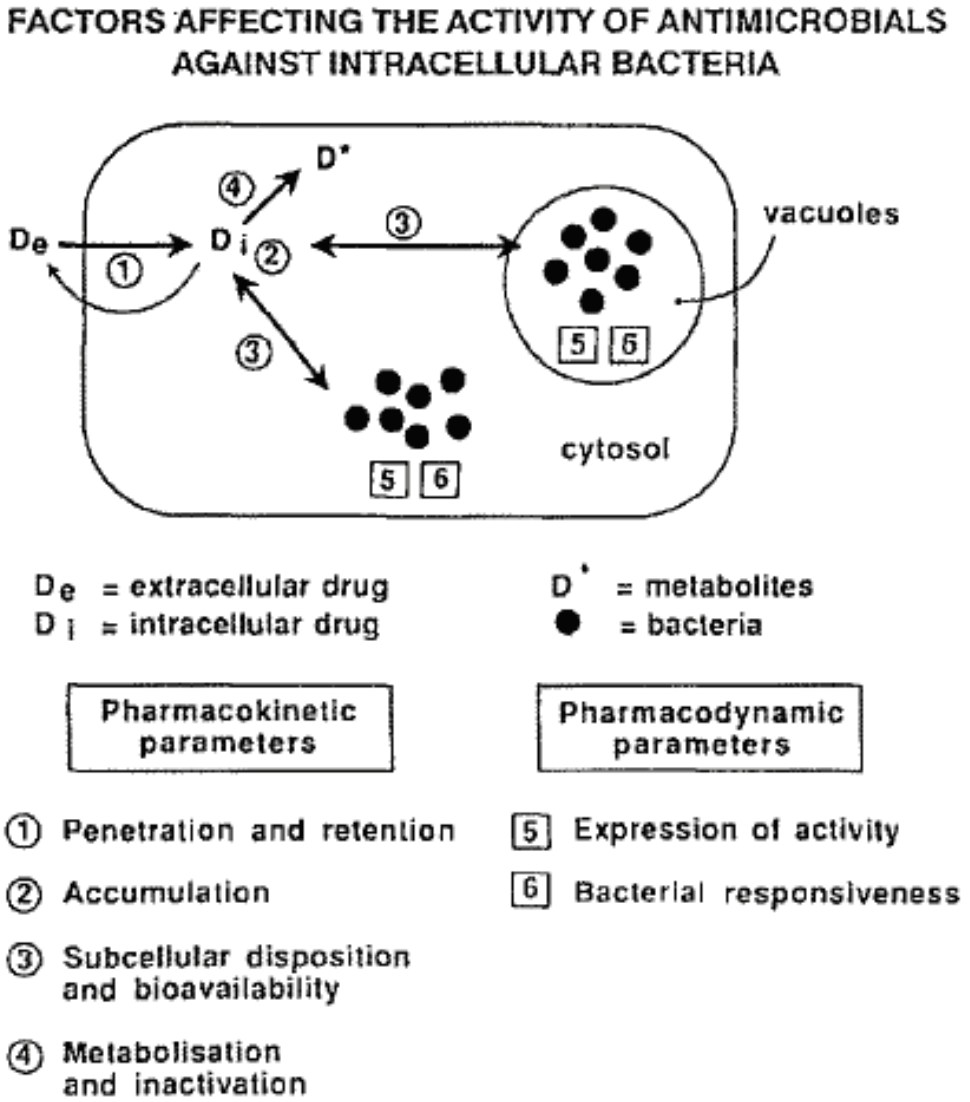


Figure 1: Pharmacokinetic and pharmacodynamic parameters involved in the activity of antimicrobial drugs against intracellular microorganisms.

Tulkens PM. Intracellular distribution and activity of antibiotics. Eur J Clin Microbiol Infect Dis. 1991 10:100-6. PubMed PMID: 1864271.

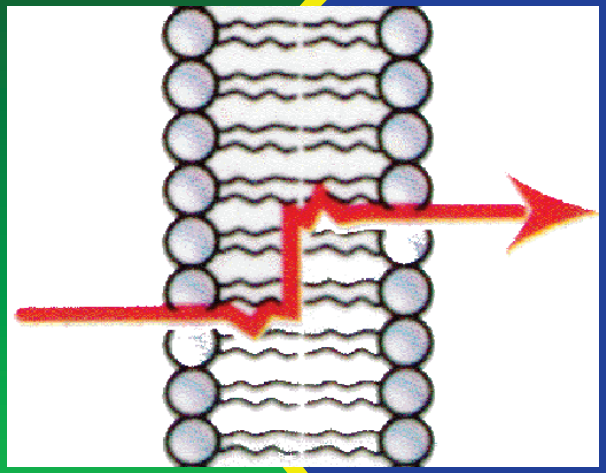
Which antibiotics accumulate in cells ?

- beta-lactams: ≤ 1x
- aminoglycosides: <1 to 2 x
- ansamycins: 2-3 x
- tetracyclines: 2-4 x
- fluoroquinolones: 5 - 20 x
- macrolides: 4 to > 100 x *
- glycopeptides: 1 to 400 x !! **

* azithromycin, ketolides
** oritavancin

How do antibiotics penetrate in cells ?

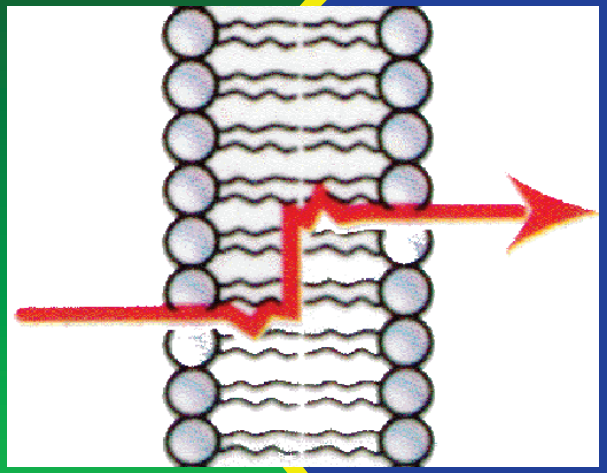
1. diffusion

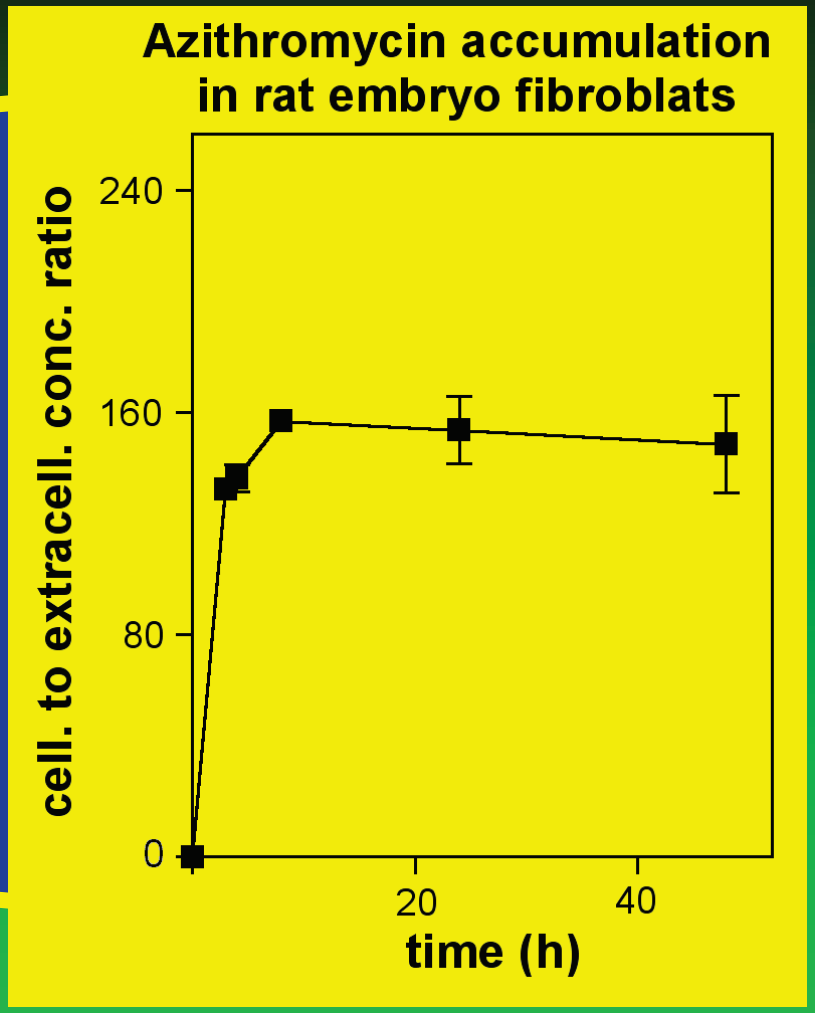


- macrolides
- fluoroquinolones
- tetracyclines
- ansamycines
- β-lactams,
- ...

How do antibiotics penetrate in cells ?

1. diffusion

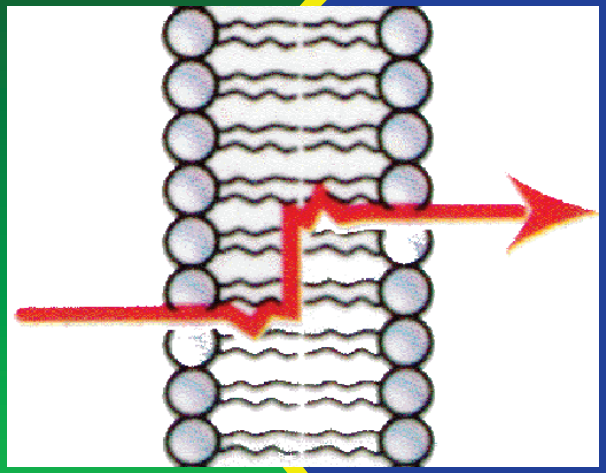


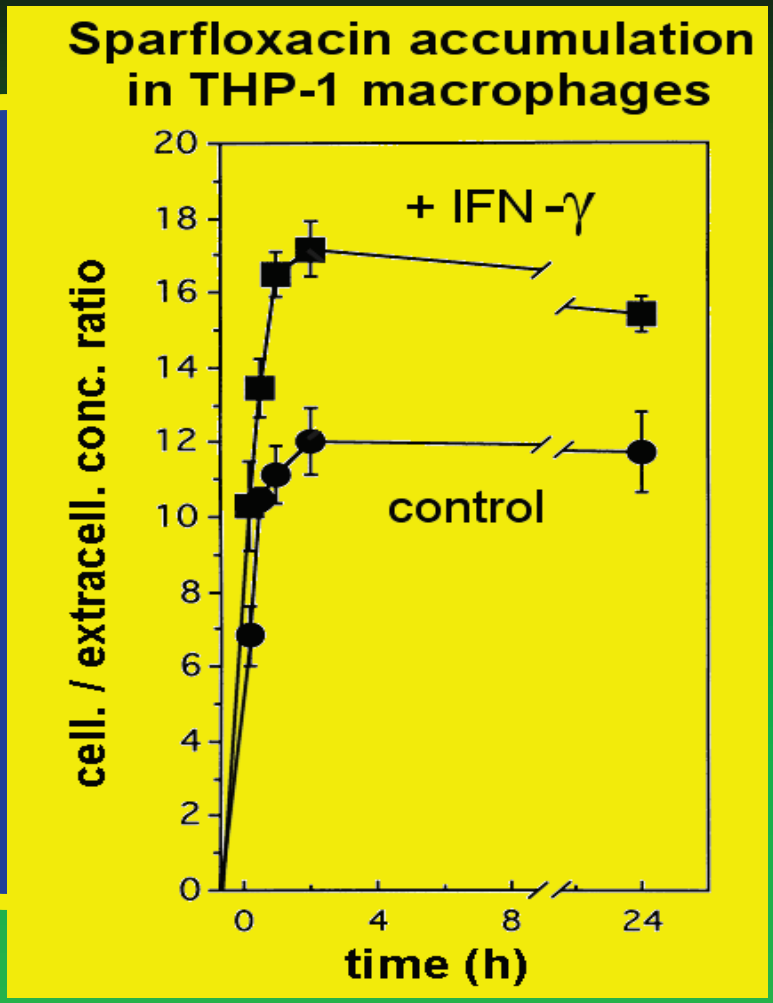


Tyteca et al., EJCB, 2001, in press

How do antibiotics penetrate in cells ?

1. diffusion





Ouadrhiri et al., AAC, 1999

How do antibiotics penetrate in cells ?

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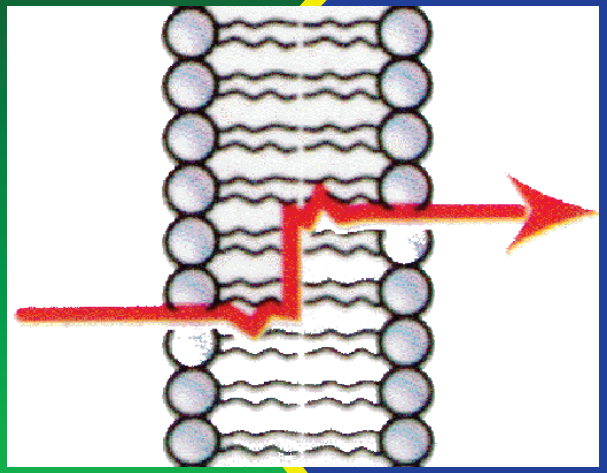
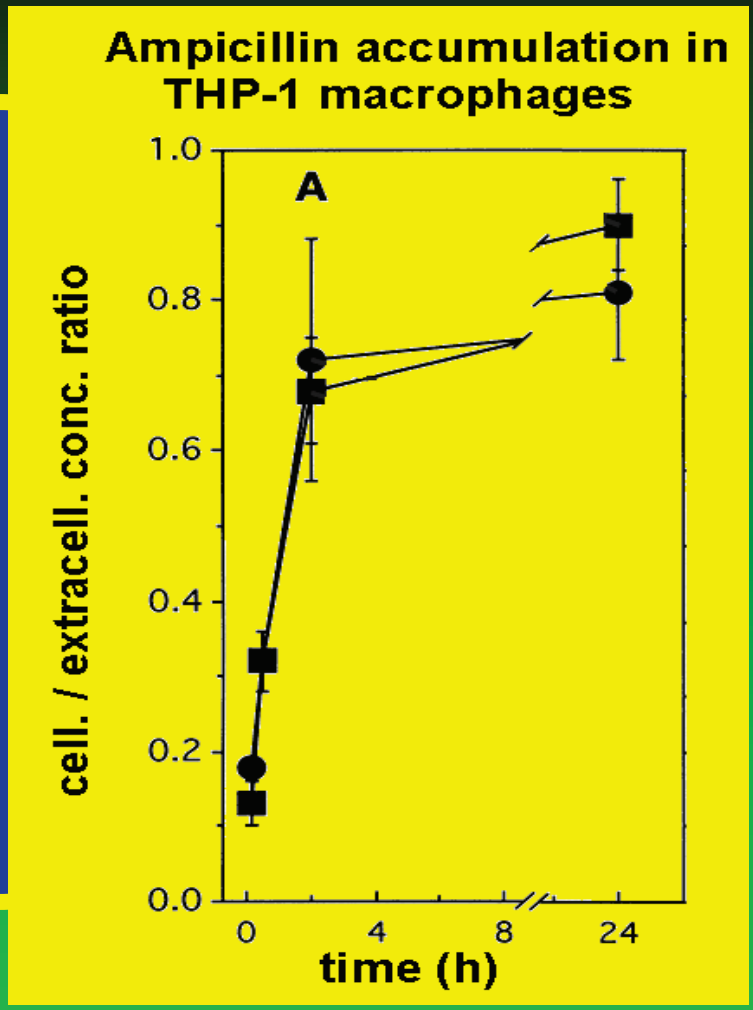
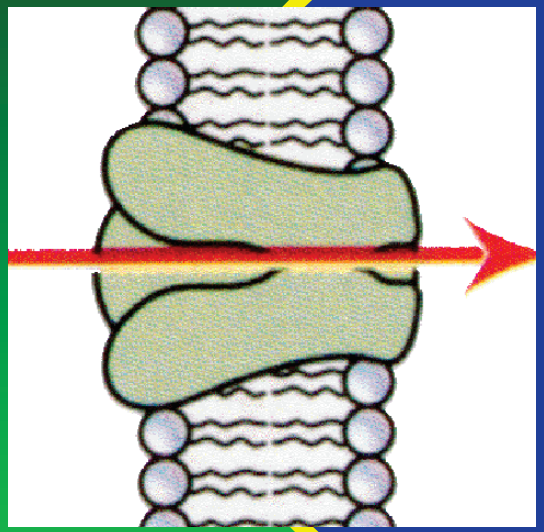




Ouadrhiri et al., AAC, 1999

How do antibiotics penetrate in cells ?

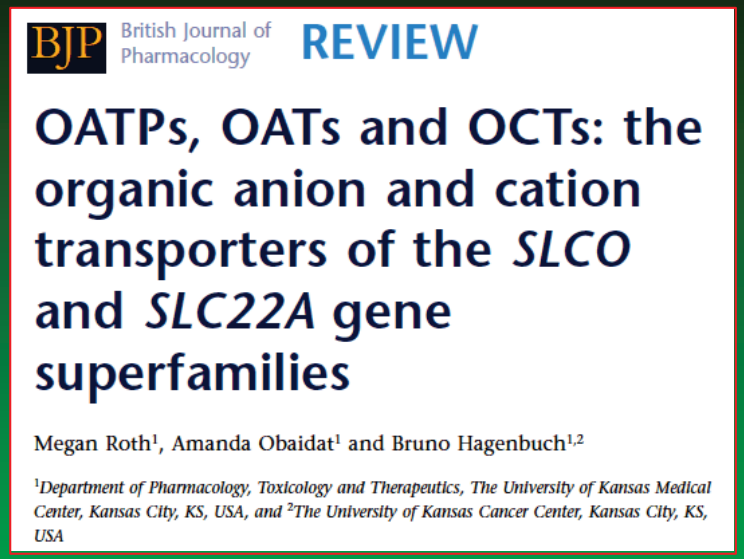
2. carrier-mediated influx



- specific structure
- (some energy-dependent)
- saturable
- competition by analogues

highly variable rom on cell type to another

Carrier-mediated transport



BJP British Journal of Pharmacology REVIEW

OATPs, OATs and OCTs: the organic anion and cation transporters of the *SLCO* and *SLC22A* gene superfamilies

Megan Roth[1], Amanda Obaidat[1] and Bruno Hagenbuch[1,2]

[1]*Department of Pharmacology, Toxicology and Therapeutics, The University of Kansas Medical Center, Kansas City, KS, USA, and* [2]*The University of Kansas Cancer Center, Kansas City, KS, USA*

Roth et al. Br J Pharmacol. 2012;165:1260-87 -- PMID: 22013971

Carrier-mediated transport

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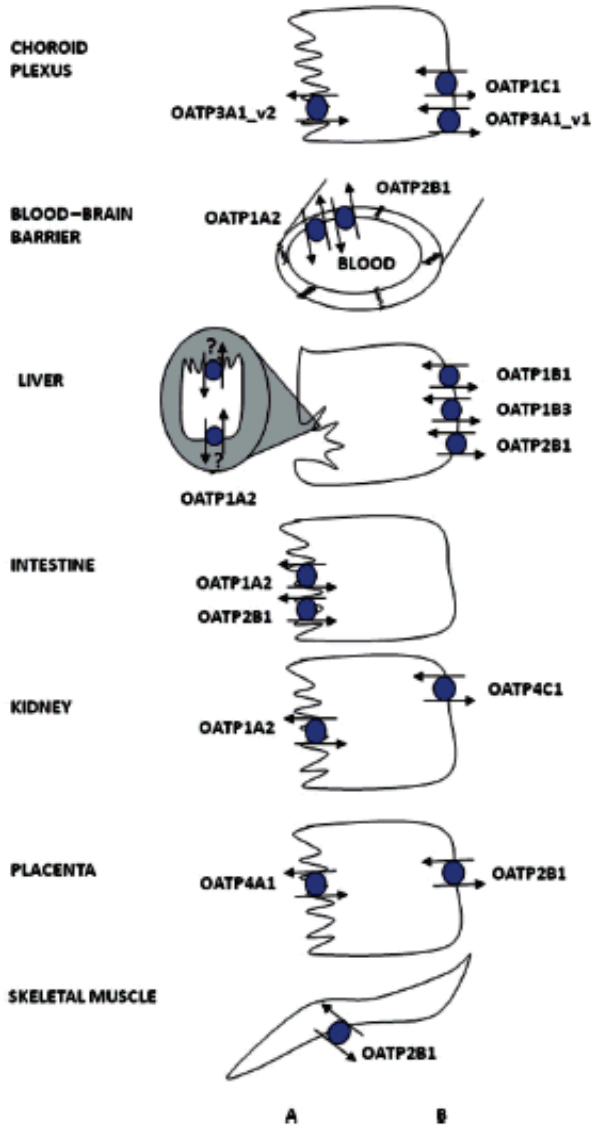
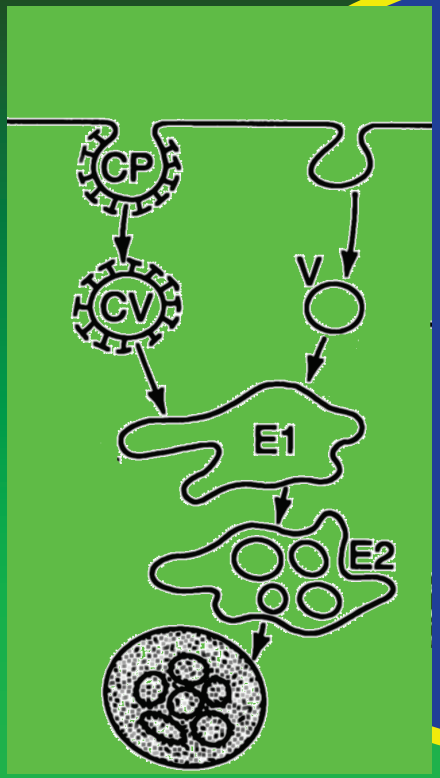


Figure 1
Expression of OATPs in selected human epithelial cells. For more details, see the text. OATP1A2 expression in cholangiocytes has been demonstrated, but it has not yet been localized to a distinct cell membrane. (A) apical; (B) basolateral.

How do antibiotics penetrate in cells ?

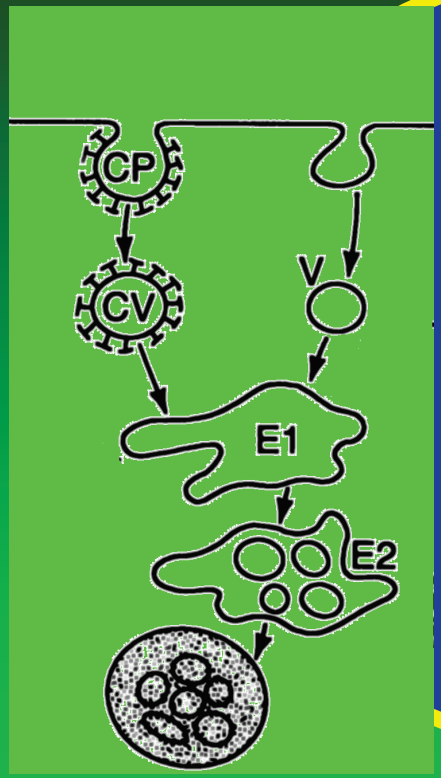
3. pinocytosis

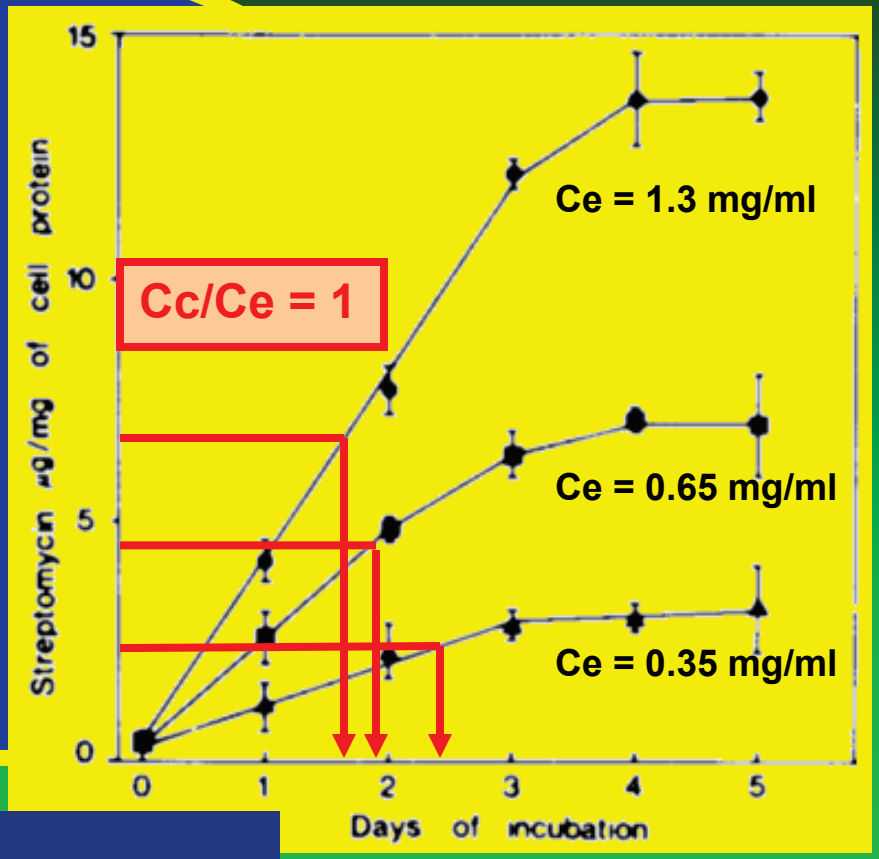


- aminoglycosides
- glycopeptides

How do antibiotics penetrate in cells ?

aminoglycosides in fibroblasts



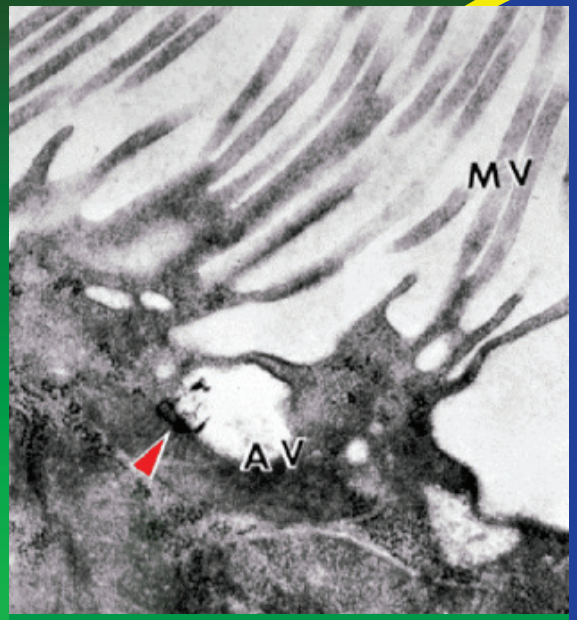


- Slow (days…)
- ill-effective (2-4 fold)

Tulkens & Trouet, 1978

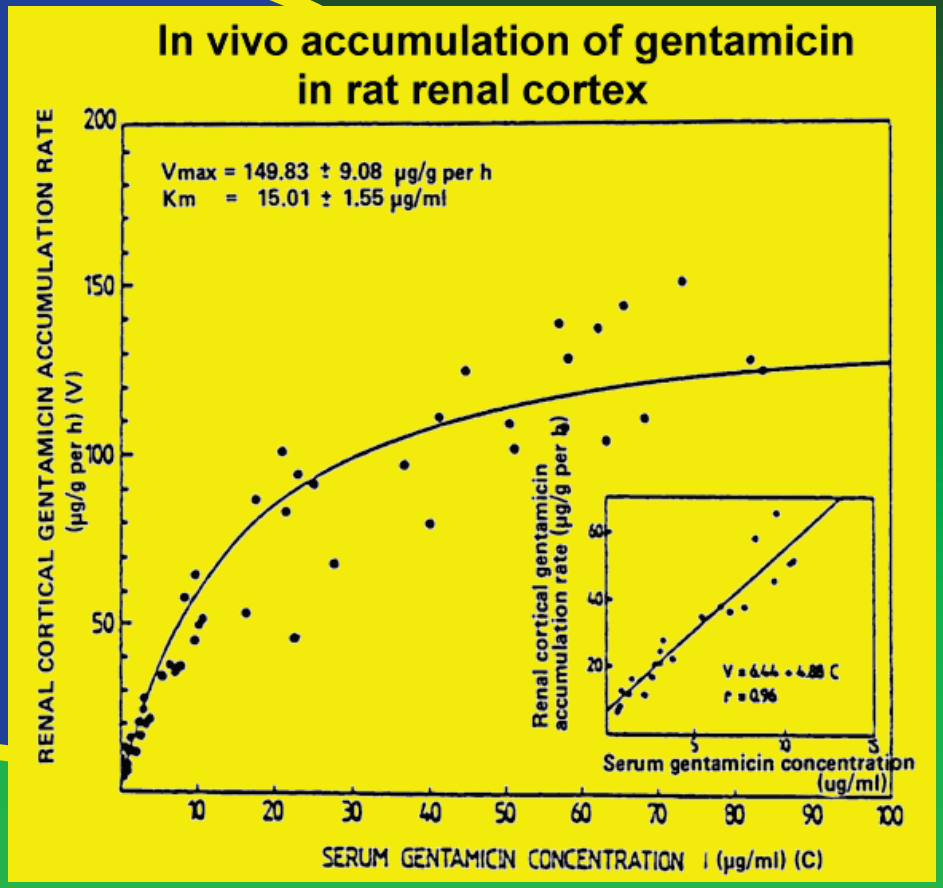
How do antibiotics penetrate in cells ?

receptor-mediated pinocytosis in kidney cortex



binding to

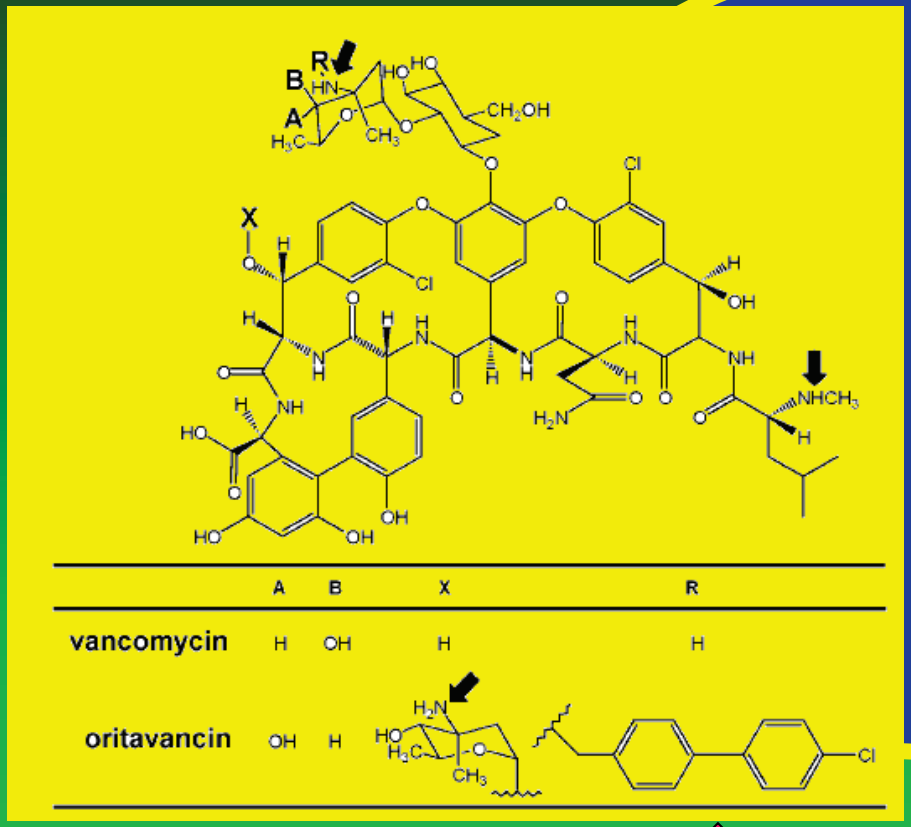
- **megalin**
  (Moeström et al., 1995)
- **acidic phospholipids**
  (Humes et al, 1983)



Giuliano *et al.*, J. Pharm. Exp. Ther., 1986

How do antibiotics penetrate in cells ?

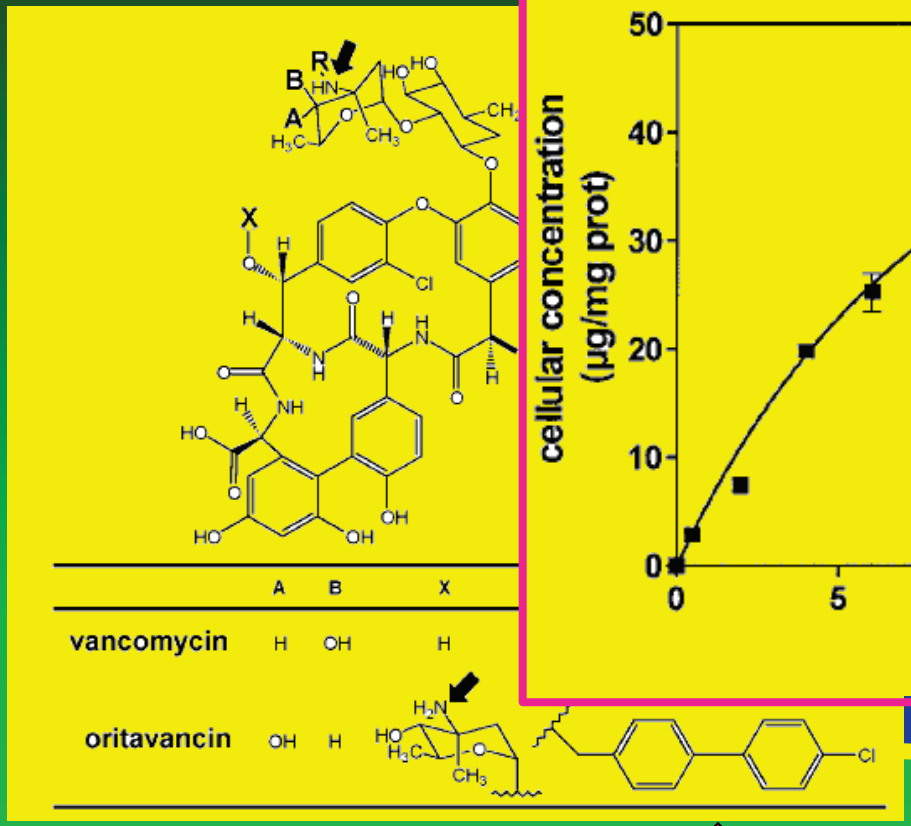
membrane binding and uptake of lipoglycopeptides

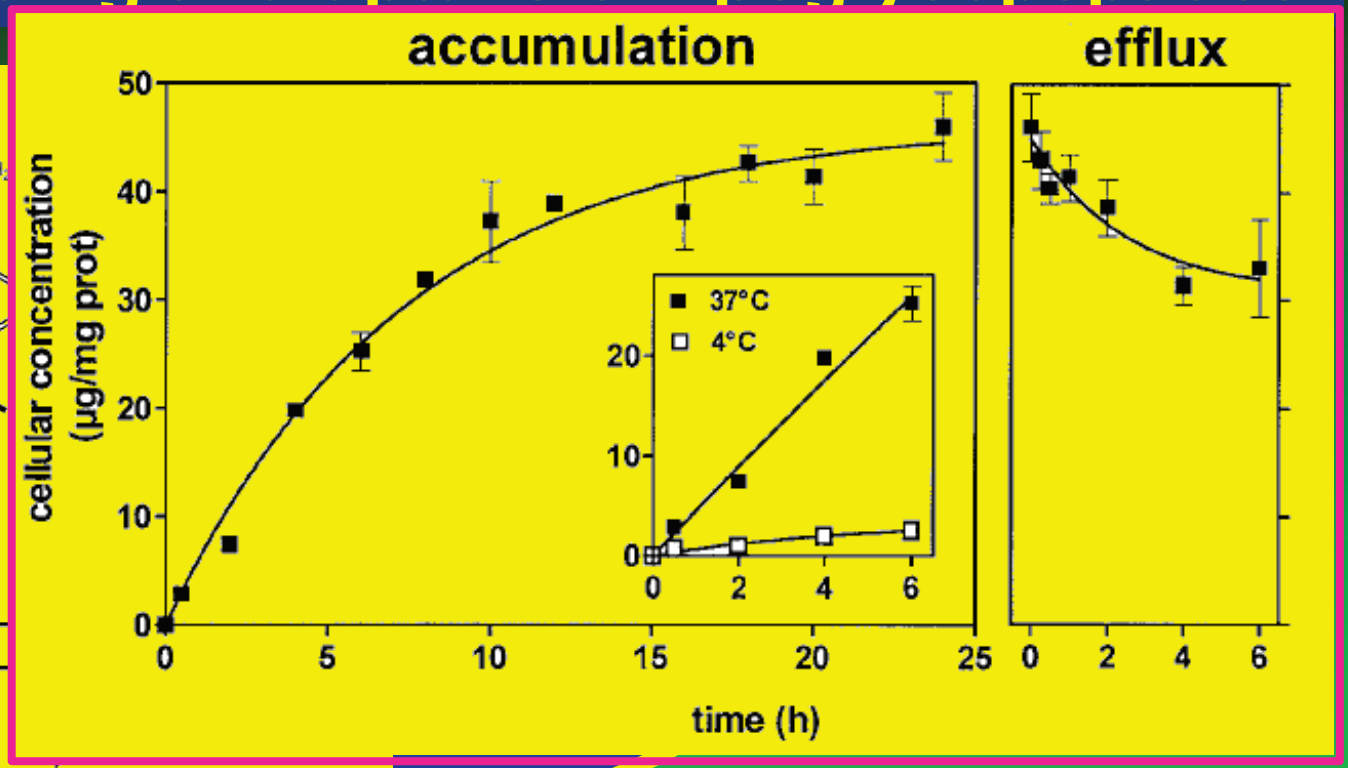


Vna Bambeke et al. Antimicrob Agents Chemother (2004) 48:2853-2860

How do antibiotics penetrate in cells ?

membrane binding and uptake of lipoglycopeptides





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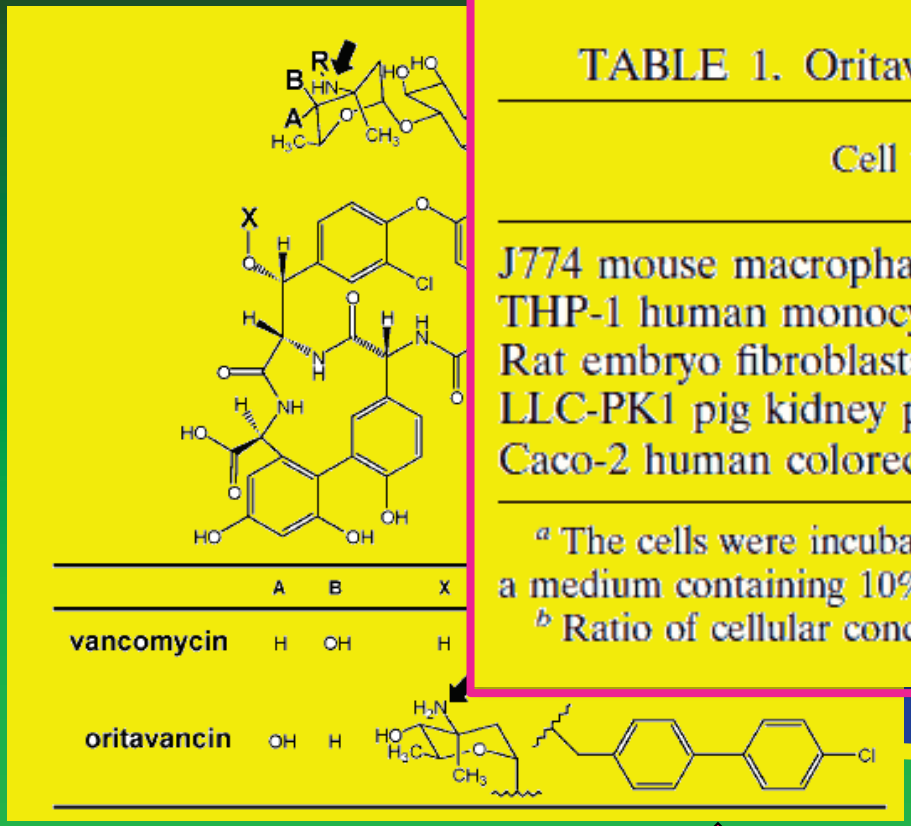


TABLE 1. Oritavancin accumulation by different cell types[a]

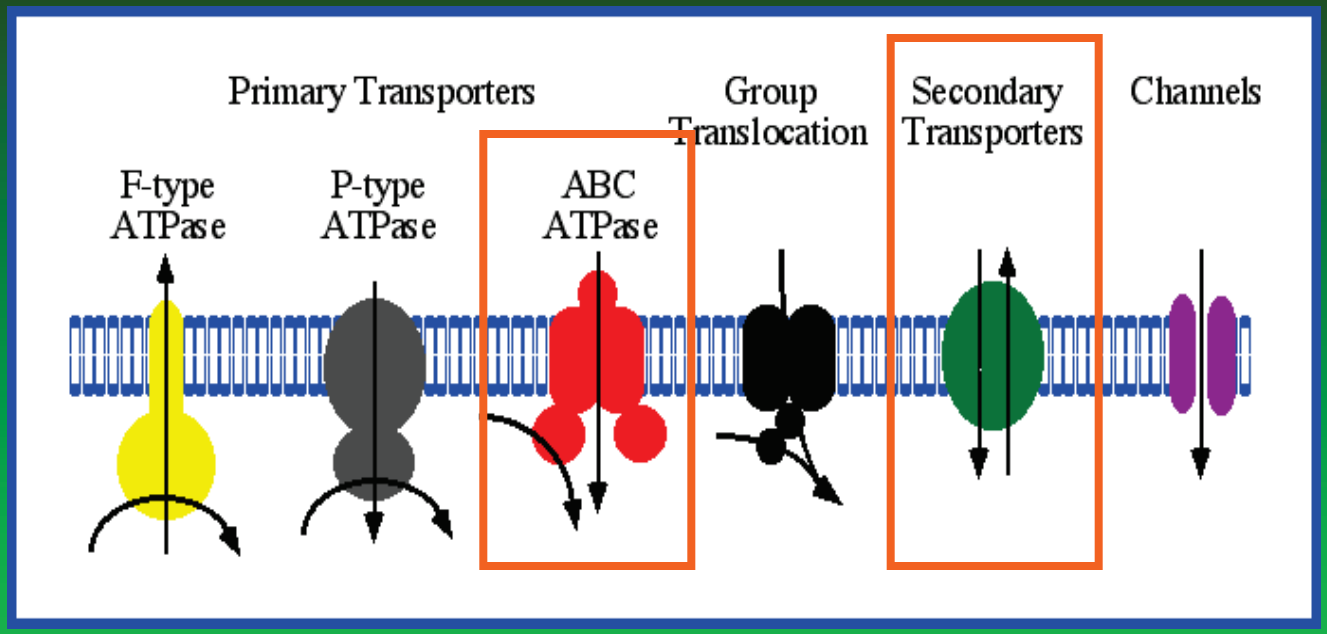
Cell type	Accumulation ratio[b] (no. of determinations)
J774 mouse macrophages	66.4 ± 11.8 (12)
THP-1 human monocytes	84.3 ± 7.0 (9)
Rat embryo fibroblasts	72.4 ± 9.4 (6)
LLC-PK1 pig kidney proximal tubular cells	37.8 ± 6.4 (3)
Caco-2 human colorectal cells	13.8 ± 0.4 (3)

[a] The cells were incubated for 2 h at 37°C with 25 mg of the drug per liter in a medium containing 10% FCS.
[b] Ratio of cellular concentration to extracellular concentration.

Vna Bambeke et al. Antimicrob Agents Chemother (2004) 48:2853-2860

Efflux

http://www.tcdb.org/

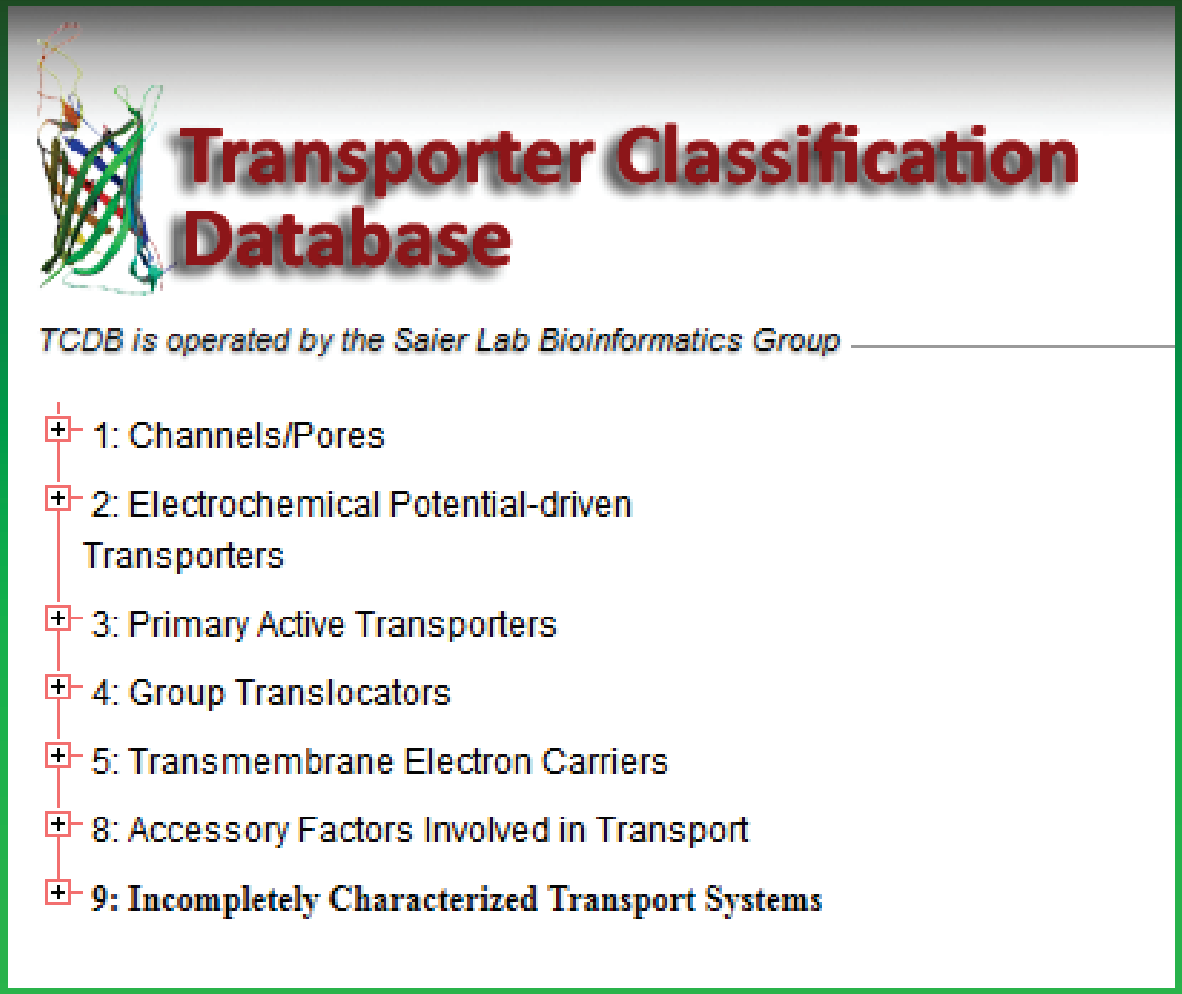


main drug transporters

Saier, 2000

Efflux

http://www.tcdb.org/



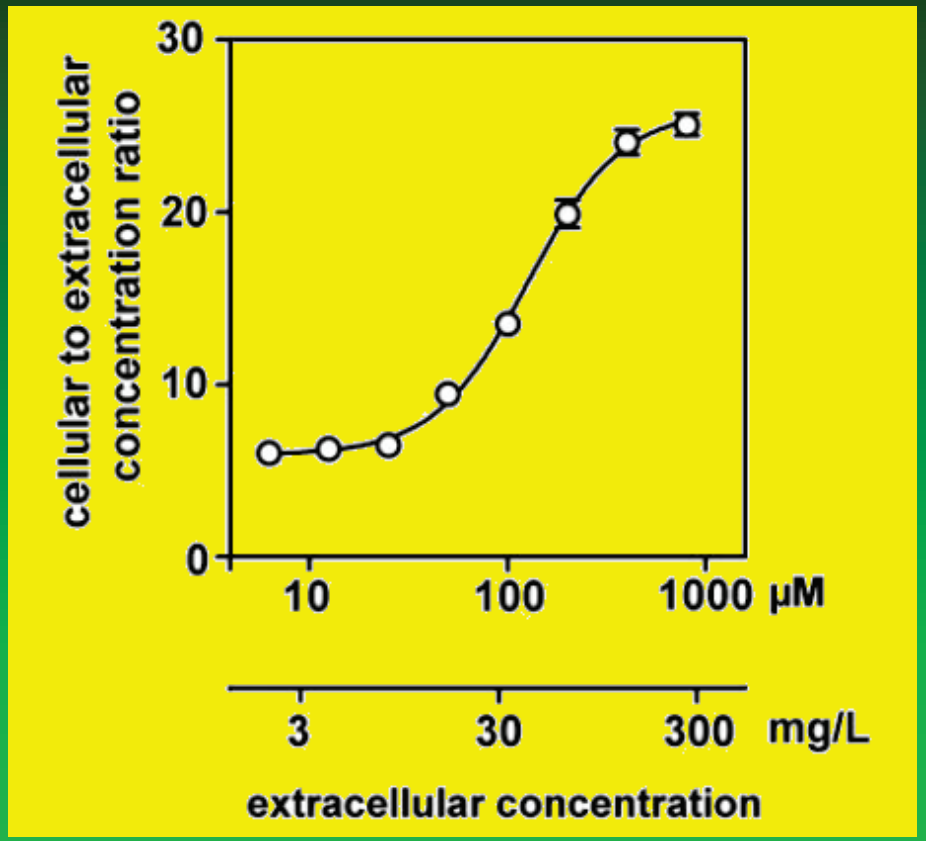
Saier, 2015

Some transporters involved in the efflux of antibiotics from eukaryotic cells

superfamily	transporter	physiol. substrates	antibiotics
ABC	MDR1	phospholipids	fluoroquinolones macrolides β-lactams tetracyclines streptogramins
	MRP1	phospholipids leukotrienes conjugates	fluroquinolones macrolides rifamycins
	MRP2 / 4	conjugates	fluoroquinolones β-lactams
MFS	NPT1	phosphates	β-lactams
OAT	OATP1	bile salts steroids	β-lactams

Examples of efflux-mediated control of cellular accumulation

1. fluoroquinolones

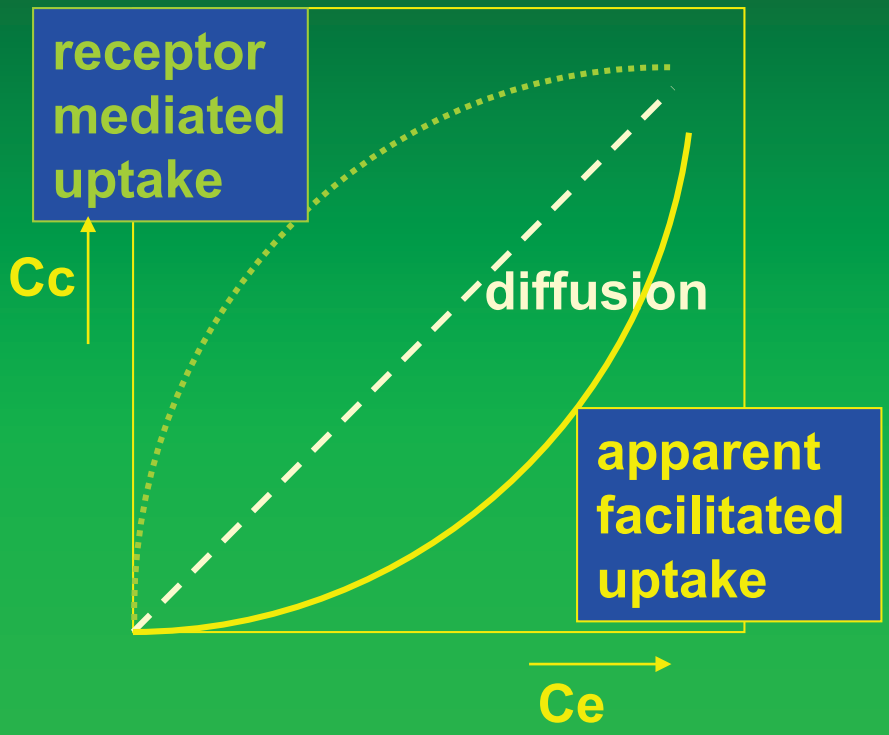


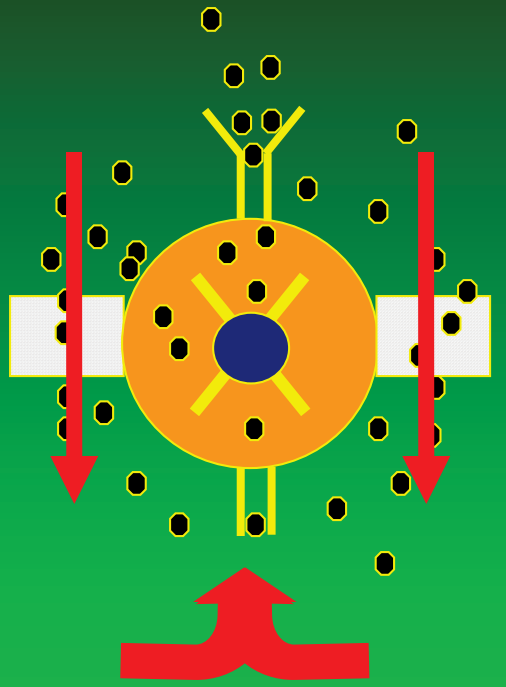
accumulation of ciprofloxacin in J774 macrophages

Michot et al. Antimicrob Agents Chemother (2004) 48:2673-2682

Evidencing active efflux ...

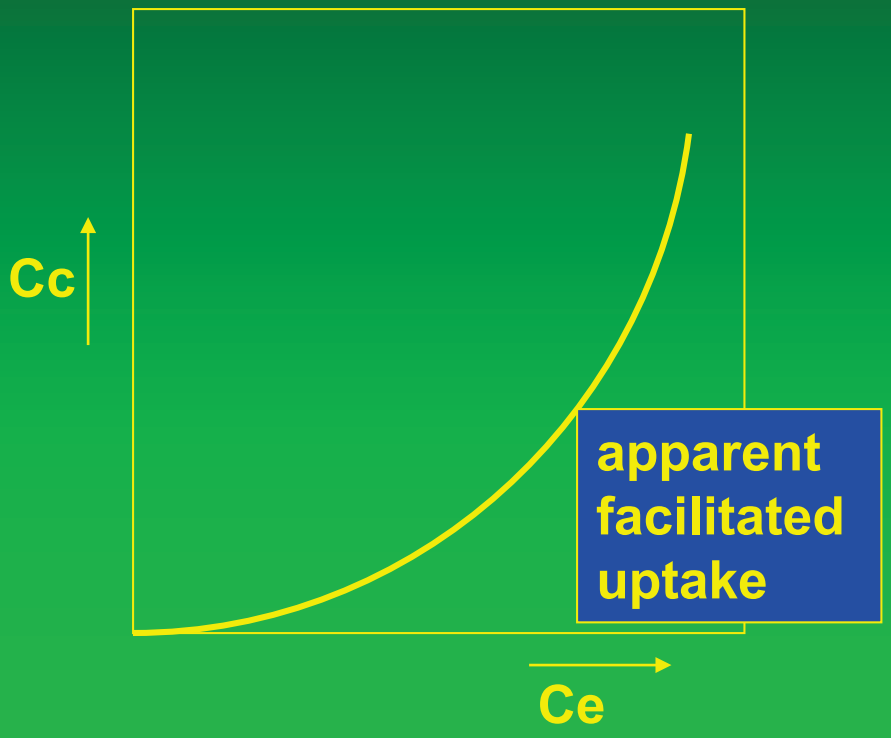
non linear accumulation kinetics ...

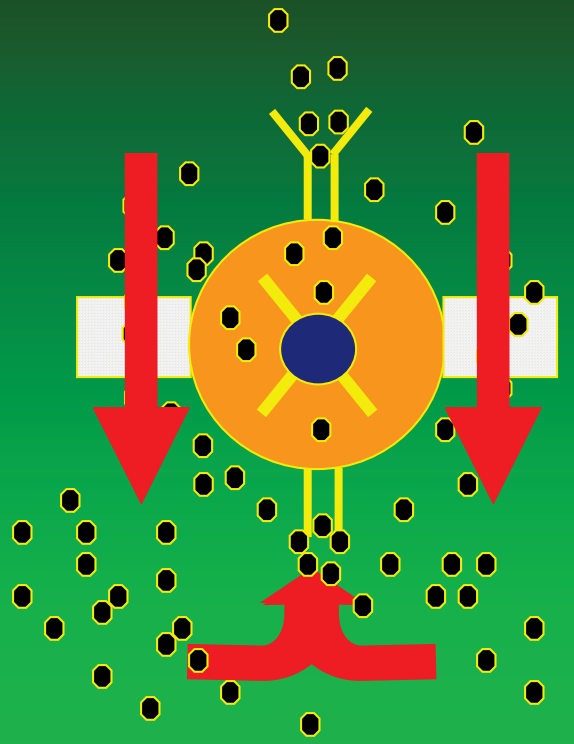




Evidencing active efflux ...

non linear accumulation kinetics ...





by saturation of efflux !

Influence of efflux inhibitors on fluoroquinolones and macrolide accumulation...

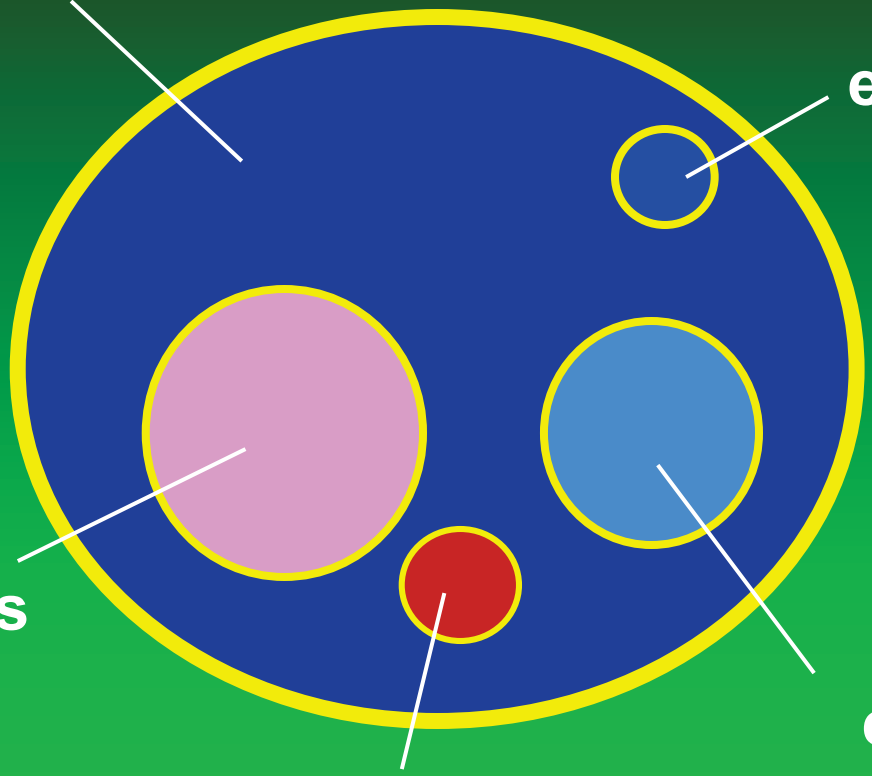
TABLE 1. Influence of efflux pump modulators on the accumulation of ciprofloxacin and azithromycin by J774 macrophages[a]

Modulator	Concn	Increase in accumulation (% of controls)	
		Ciprofloxacin[b]	Azithromycin[c]
Probenecid	2.5 mM	288 ± 4	101 ± 12
Gemfibrozil	200 μM	308 ± 3	101 ± 12
MK571	200 μM	392 ± 5	ND[d]
Verapamil	100 μM	136 ± 4	438 ± 45
Cyclosporin A	50 μM	236 ± 5	353 ± 77[e]
GF 120918	1 μM	116 ± 2	372 ± 61

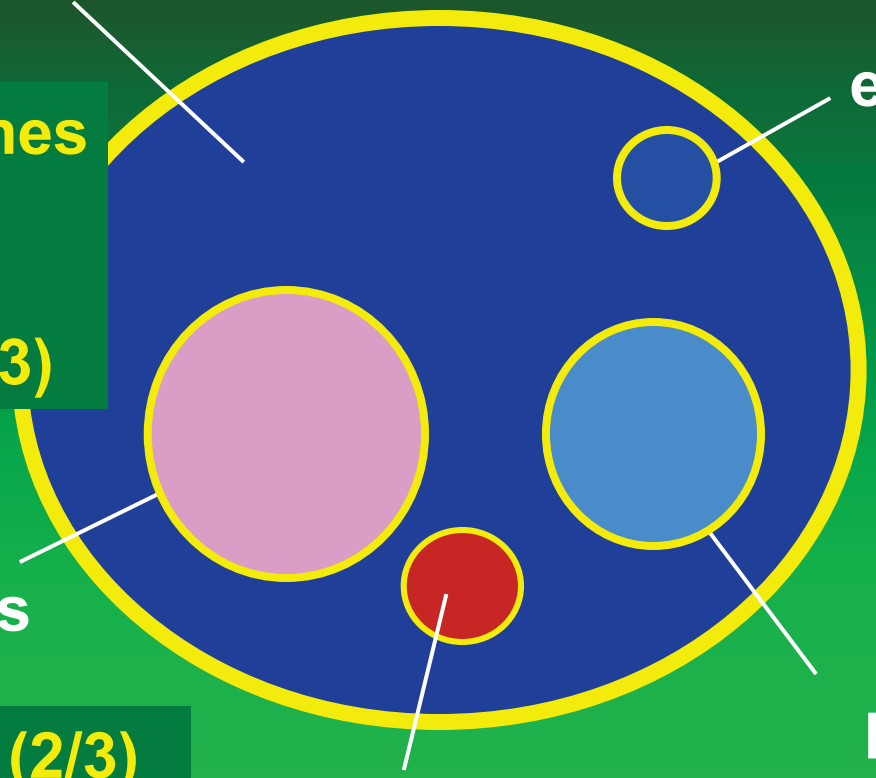
[a] Statistical analysis: for ciprofloxacin, all differences are significant; for azithromcyin, differences are significant for verapamil, cyclosporin A, and GF 120918 only (paired *t* test compared to controls).
[b] 17 mg/liter (50 μM); 2-h incubation.
[c] 5 mg/liter (6.8 μM); 3-h incubation (time to equilibrium).
[d] ND, not determined.
[e] 20 μM.

Michot et al. Antimicrob Agents Chemother (2004) 48:2673-2682

But once in cells, where are the drugs ?



Subcellular localization: a quick answer ?

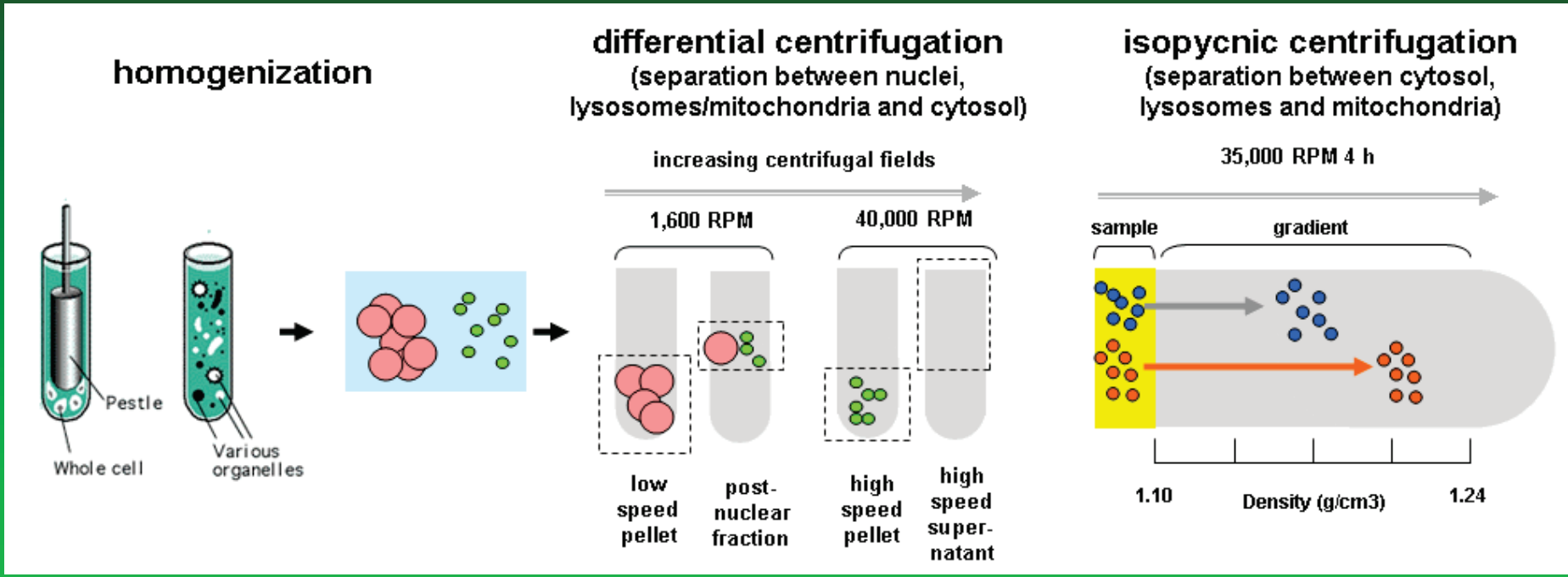


- fluoroquinolones
- beta-lactams
- ansamycins
- macrolides (1/3)

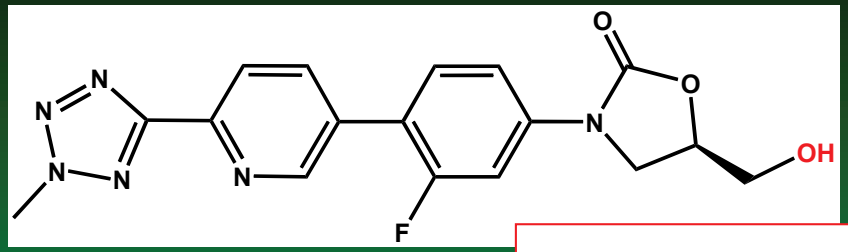
? phago-lysososomes

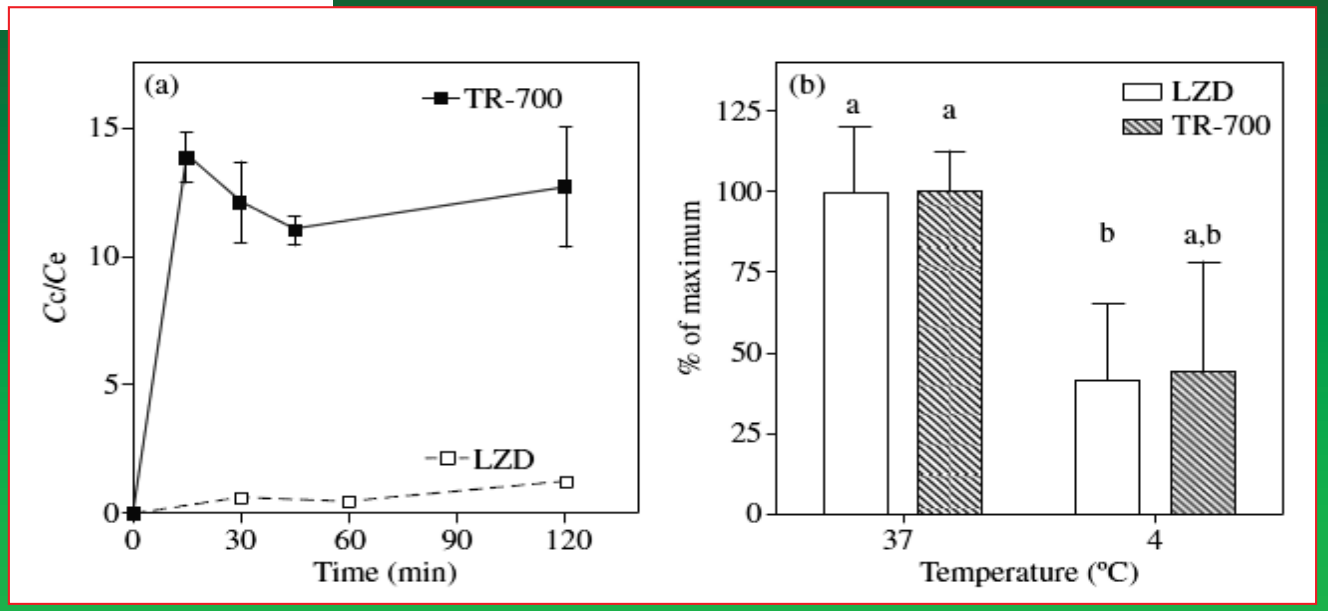
- macrolides (2/3)
- aminoglycosides

Subcellular localization is often studied by cell fractionation techniques



A recent example with two novel oxazolidinones: 1. tedizolid (accumulation)

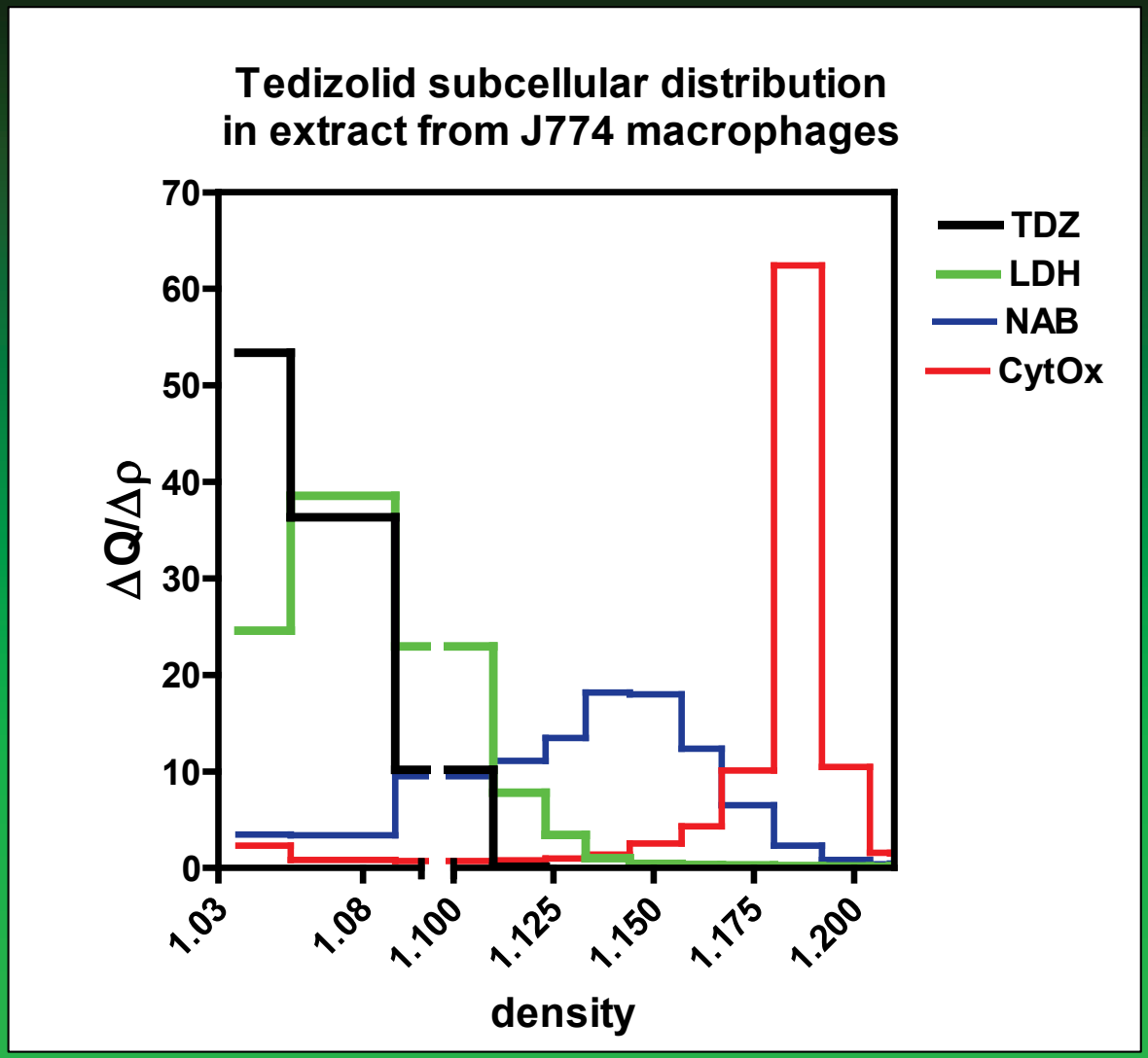




Comparative accumulation of linezolid (LZD) and of tedizolid (TR-700) in THP-1 macrophages
(a) Uptake kinetics
(b) Influence of the temperature (2 h incubation)

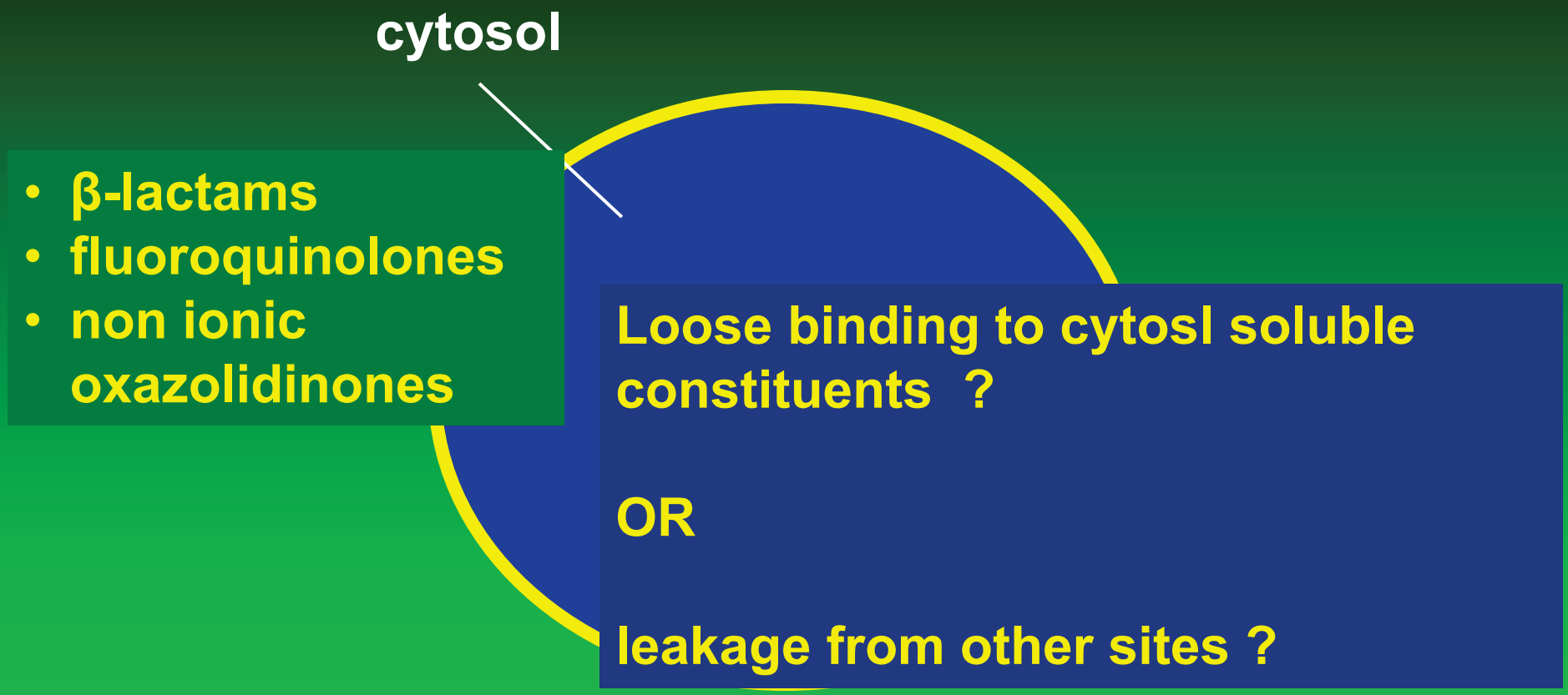
Lemaire et al. J Antimicrob Chemother (2009) 64:1035-1043

Subcellular localization of the accumulated tedizolid … or redistribution ?

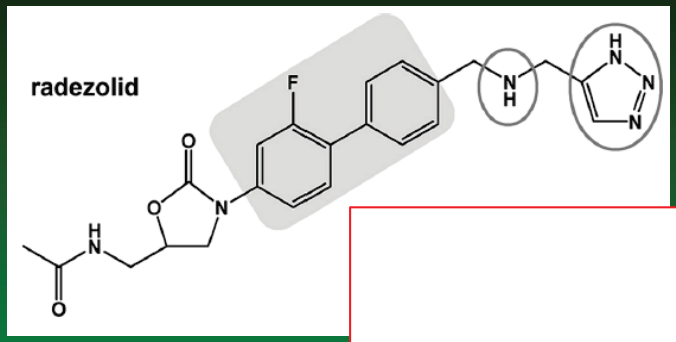


Das et al. Clin Infect Dis 2014;58 Suppl 1:S51-7.
Flanagan et al. Antimicrob Agents Chemother 2015;59:178-85

Mechanisms of localisation and accumulation in cytosol ...



Accumulation of radezolid



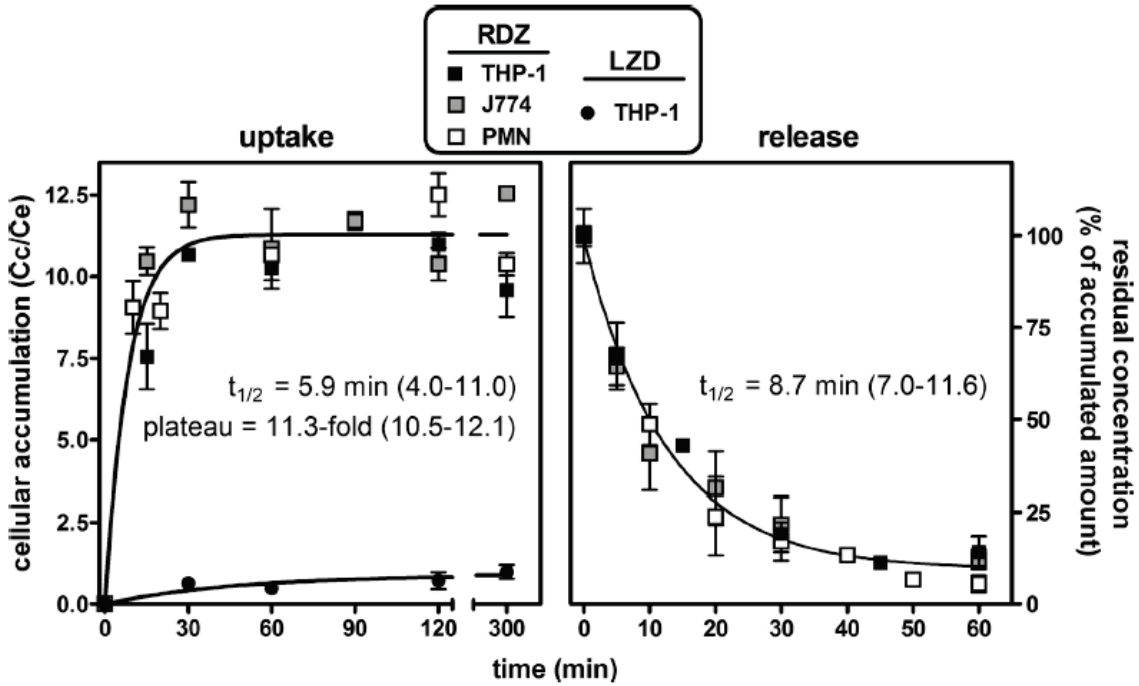


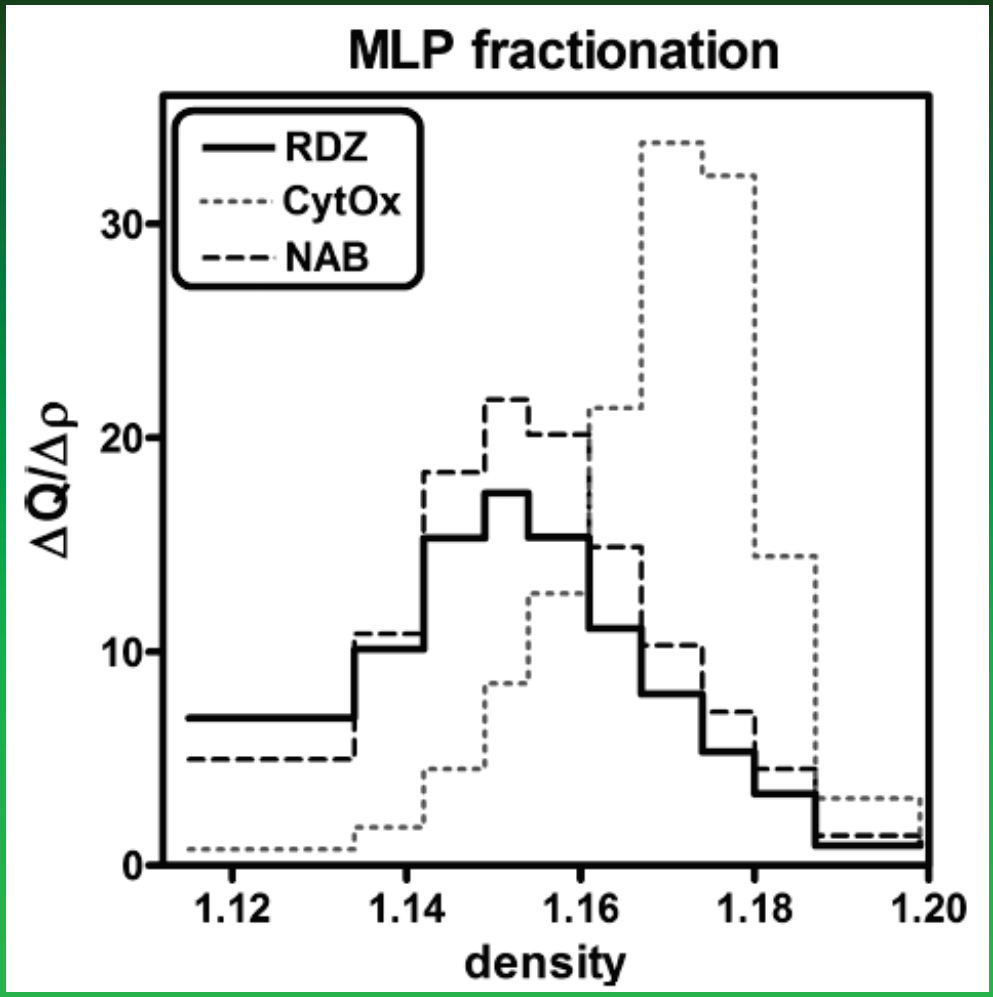
FIG. 2. Kinetics of radezolid uptake and release within THP-1 and J774 cell lines and PMNs. Left, uptake. Cells were incubated for up to 5 h in the presence of 4 mg/liter radezolid (RDZ) or 250 mg/liter linezolid (LZD). The ordinate shows the apparent cellular-to-extracellular concentration ratio. Data are fitted to one-phase exponential association (R^2 = 0.837 for RDZ, 0.824 for linezolid). Right, release. Cells were incubated with 4 mg/liter radezolid during 2 h before being transferred to drug-free medium. Values are expressed as the percentage of the accumulated amount at 2 h (time zero). Data are fitted to one-phase exponential decay (R^2 = 0.988). Results are given as means ± standard deviations (n = 3).

Lemaire et al. Antimicrob Agents Chemother (2010) 54:2540-2548

Subcellular localization of radezolid

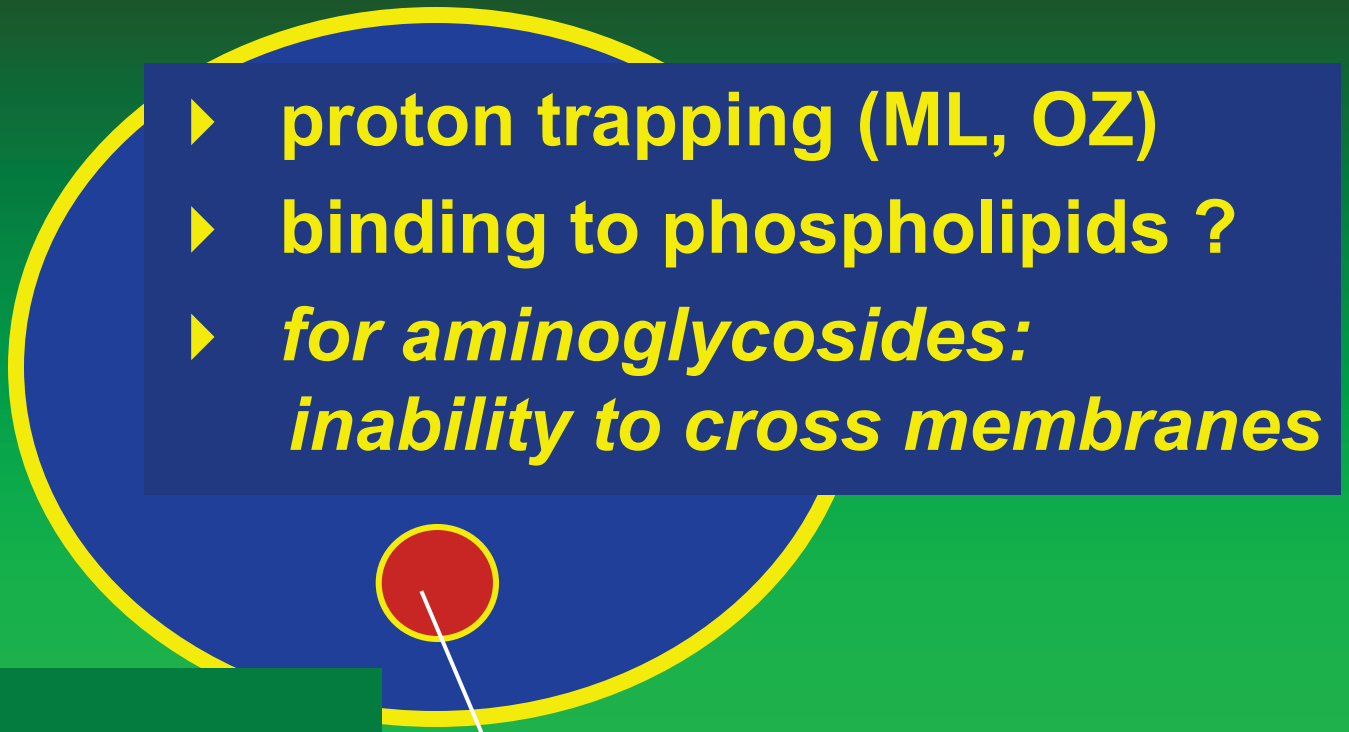
extract fractionation

tracer	% of total amount in the cell extract	
	S	MLP
Radezolid	58.2	41.8
NAB	10.6	89.4
CytOx	1.7	98.3
LDH	97.0	3.0



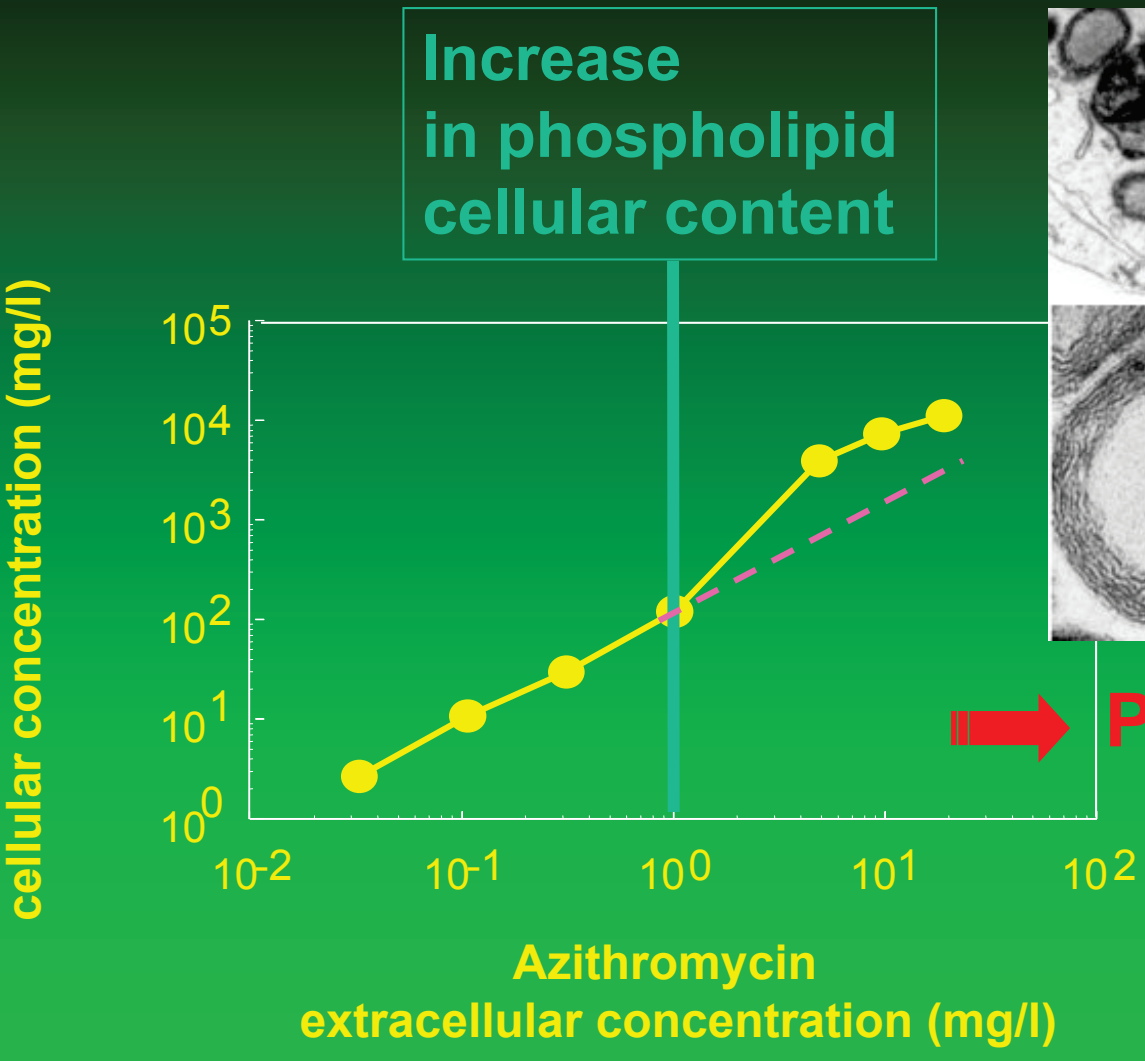
Lemaire et al. Antimicrob Agents Chemother (2010) 54:2540-2548

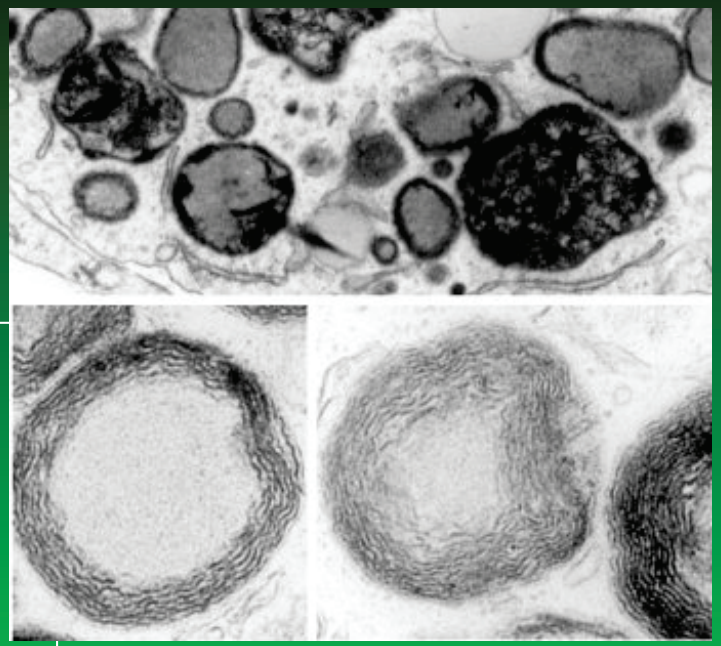
Mechanisms of localisation and accumulation ...



- macrolides
- aminoglycosides
- cationic oxazolidinones

Mechanisms of localisation and accumulation ...





Potential toxicity?

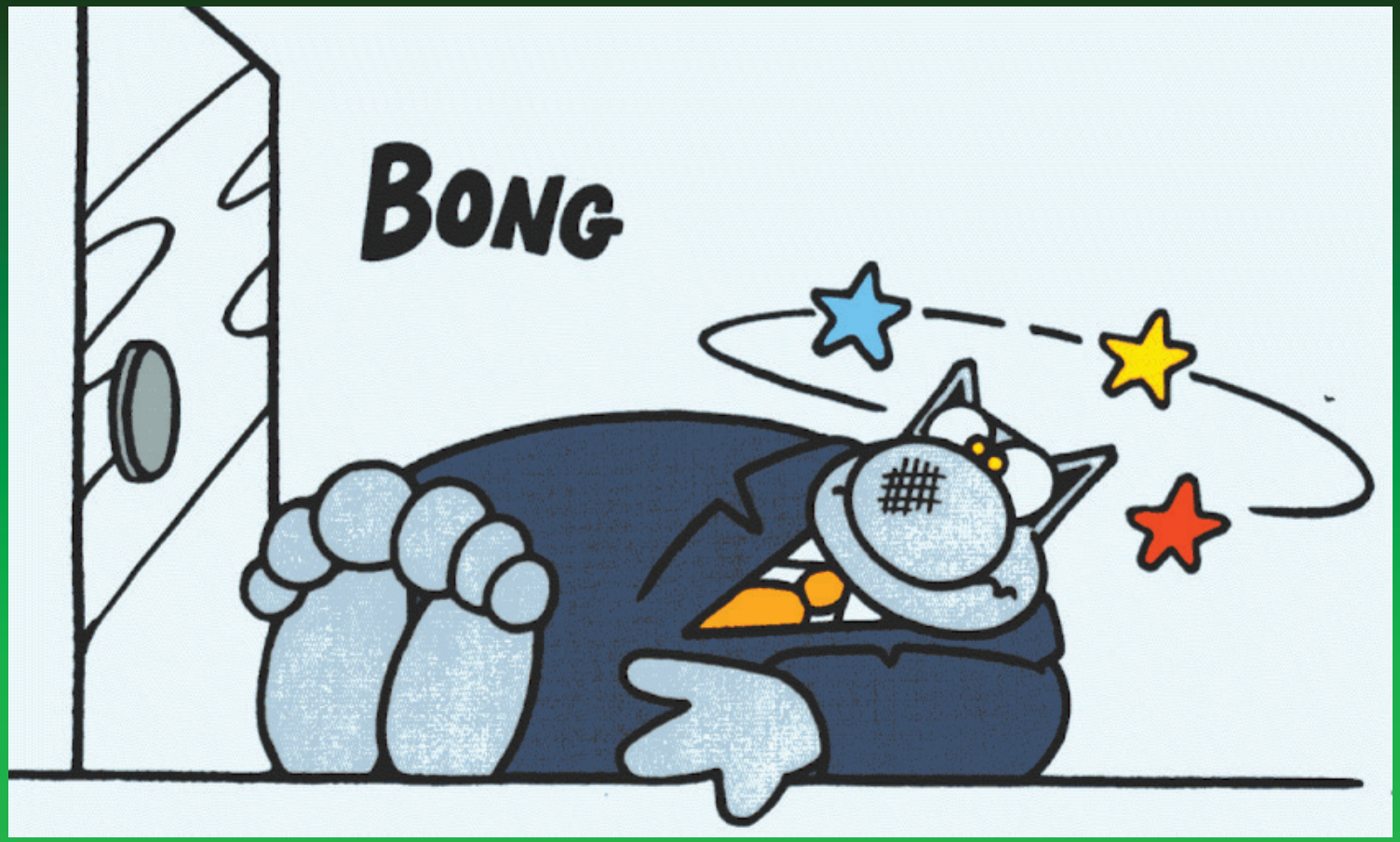
Van Bambeke et al.,JAC, 1998

So, what we know in a nutshell ...

Pharmacochemical class	Antibiotic	Accumulation level at equilibrium (C_C/C_E)[a]	Cellular concentration at equilibrium (mg/l)[b]	Time to equilibrium	Predominant subcellular localization
β-Lactams	All	< 1	~ 20 to 50	Fast	Cytosol
Macrolides	Erythromycin	4 to 10	~ 40 to 150	Moderate (a few hours)	2/3 Lysosomes 1/3 Cytosol
	Clarithromycin Roxithromycin Telithromycin	10 to 50	~ 20 to 400		
	Azithromycin	40 to 300	~ 16 to 120		
Fluoroquinolones	Ciprofloxacin Levofloxacin Grepafloxacin	4 to 10	~ 16 to 40	Fast (< 1 h) to very fast (< 5 min)	Cytosol
	Moxifloxacin Garenoxacin Gemifloxacin	10 to 20	~ 40 to 80		
Aminoglycosides	All	2 to 4 (after several days)	~ 40 to 80	Slow (several days)	Lysosomes
Lincosamides	Clindamycin	5 to 20	~ 50 to 200	Fast	Unknown
	Lincomycin	1 to 4	~ 15 to 60		
Tetracyclines	Probably all	1 to 4	~ 2 to 12	Unknown	Unknown
Ansamycins (rifamycins)	Rifampin	2 to 10	~ 36 to 180	Unknown	Unknown
	Rifapentine	60 to 80	~ 1200 to 1600	Unknown	
Glycopeptides	Vancomycin	8 (after 24 h)	~ 400	Slow (several hours)	Lysosomes (in kidney)
	Teicoplanin	60	~ 6000		Unknown
	Oritavancin	150 to 300 (after 24 h)	~ 3750 to 7500		Lysosomes
	Telavancin	50 (after 24 h)	~ 4500		Lysosomes
Oxazolidinones	Linezolid	~ 1	~ 20	Unknown	Unknown

Adapted from Van Bambeke et al., Curr. Opin. Drug Discov. Devel (2006) 9:218-230

But where does this lead us for activity ?



Ph. Geluck, with permission

* taken from a slide presented at ECCMID in 2002

Intracellular activity of antibiotics

- What has been know for long about pharmacokinetics…
- **What has surprised us …**
- Adding pharmacodynamics …
- A renewed model ?

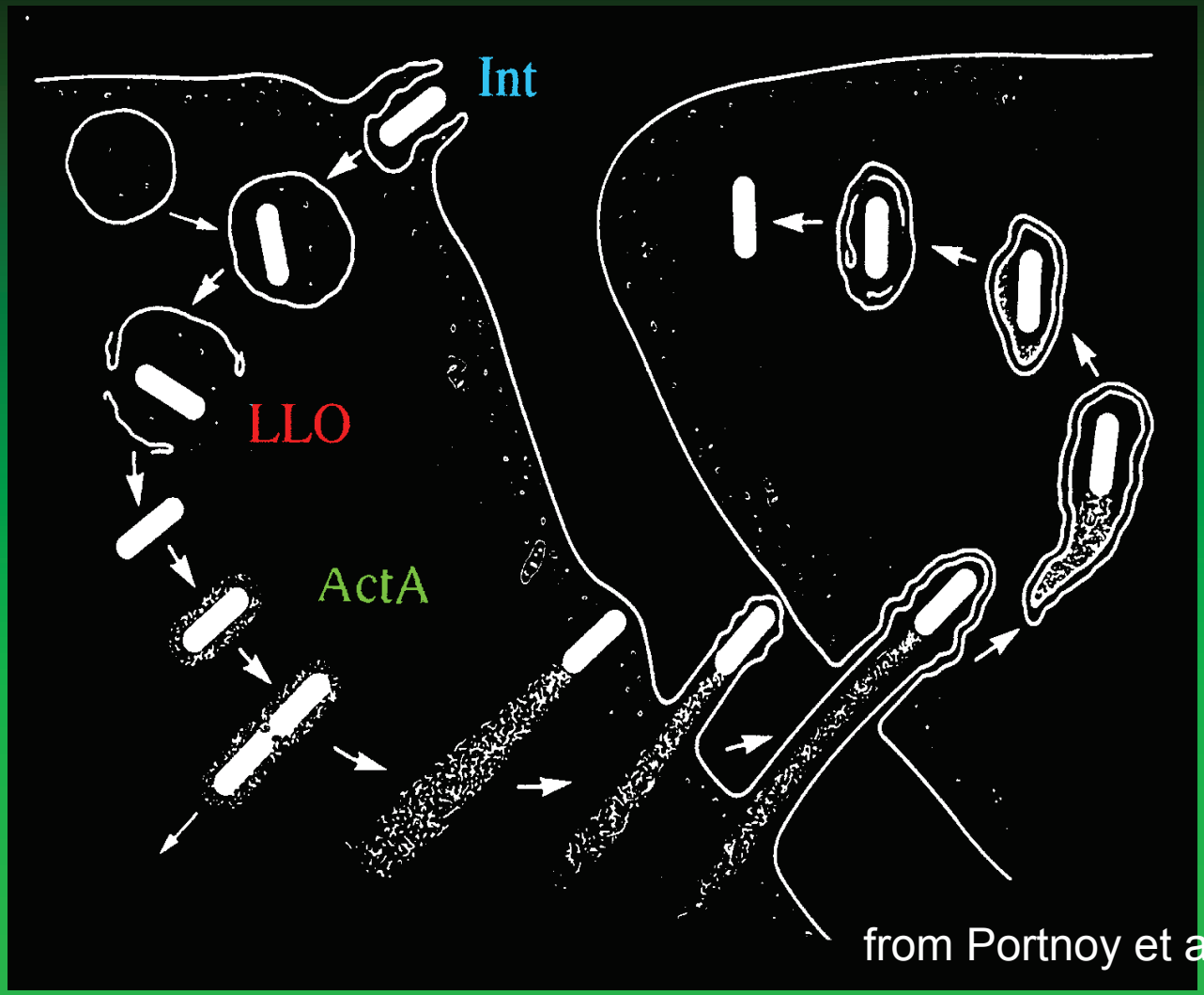
First Illustration: the Listeria story

antibiotics:

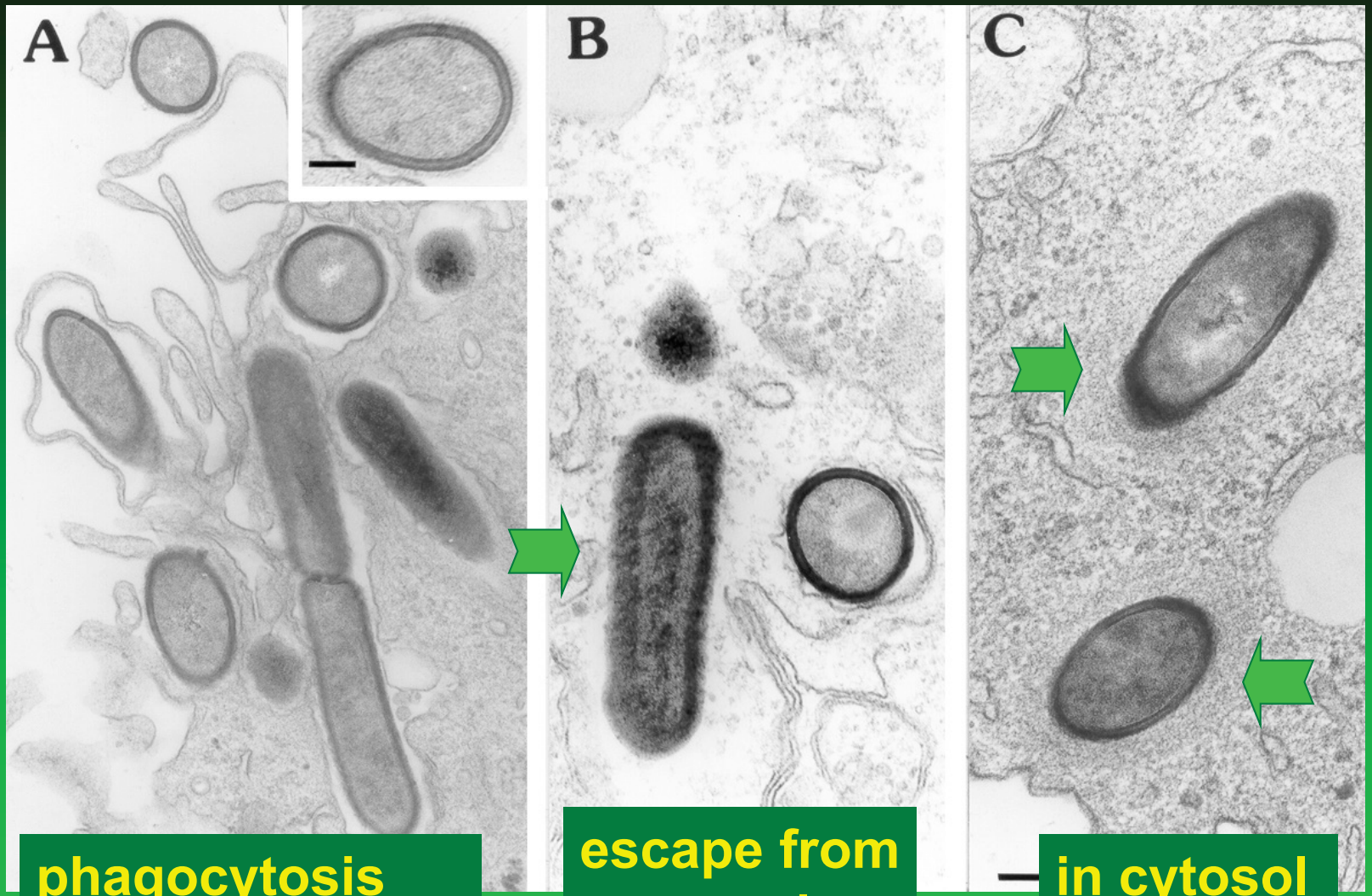
- **ampicillin**
- **azithromycin**
- **sparfloxacin**

Listeria monocytogenes
hly+

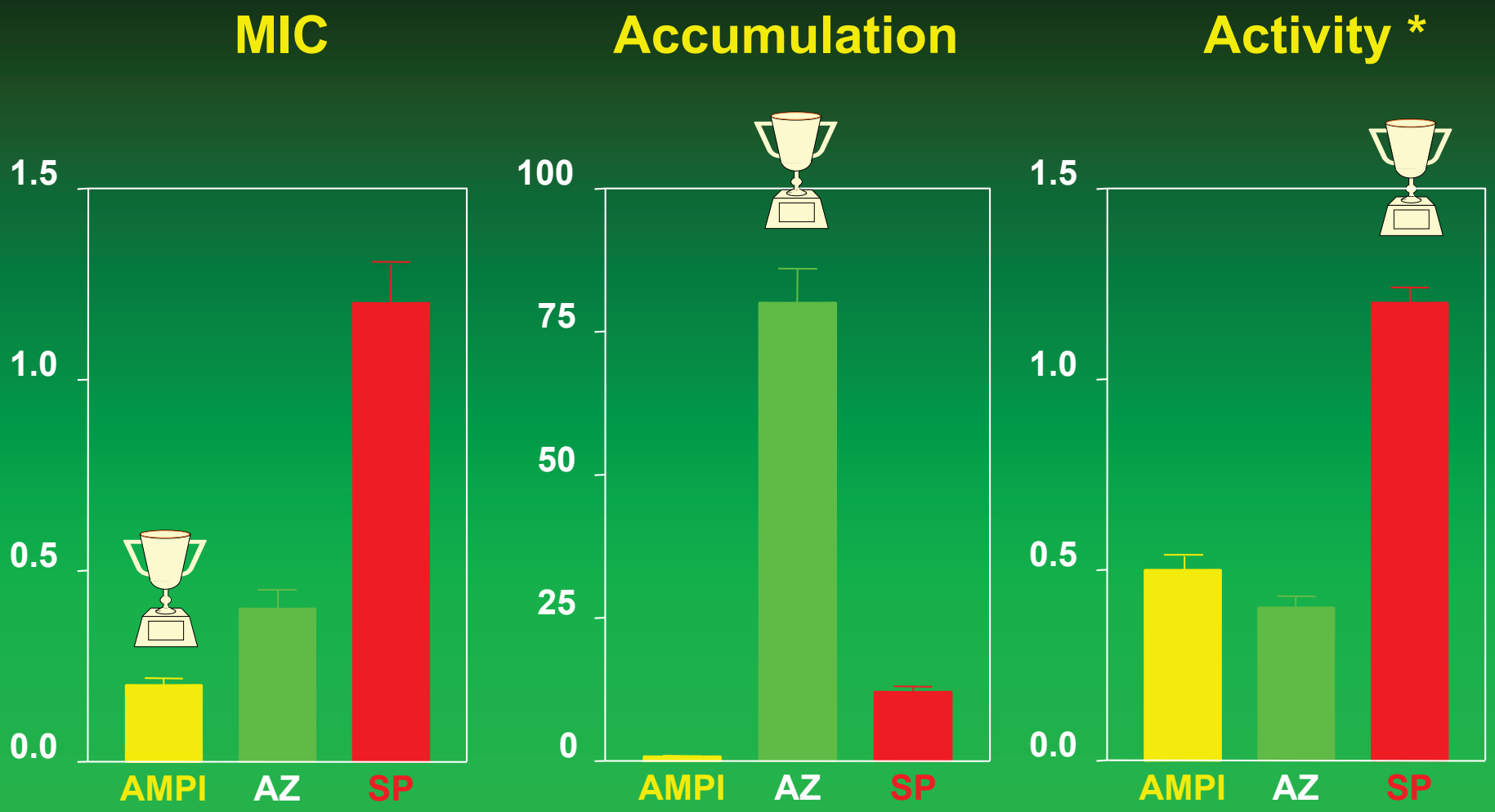
Intracellular infection cycle of *Listeria monocytogenes* hly^{+}



Following the intracellular fate of *Listeria m.* by EM

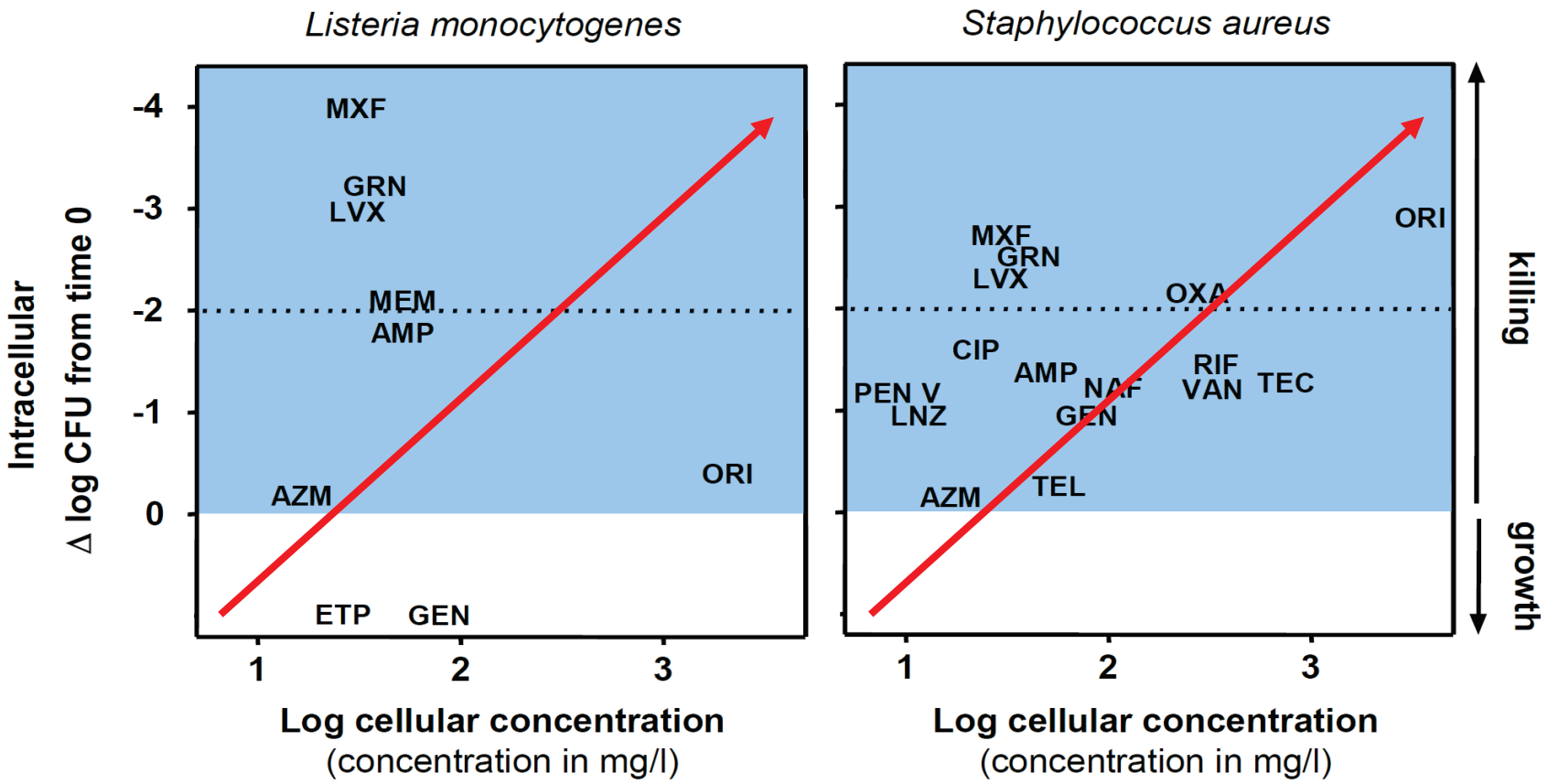


MIC, accumulation and activity against cytosolic *Listeria m.* ...



Ouadhriri et al., AAC,1999

To make a long story short: can we predict intracellular activity as a function of the accumulation



AMP=ampicillin; **AZM**=azithromycin; **CIP**=ciprofloxacin; **ETP**=ertapenem; **GEN**=gentamicin; **GRN**=garenoxacin; **LNZ**=linezolid; **LVX**=levofloxacin; **MEM**=meropenem; **MXF**=moxifloxacin; **NAF**=nafcillin; **ORI**=oritavancin; **OXA**=oxacillin; **PEN V**=penicillin V; **RIF**=rifampicin; **TEC**=teicoplanin; **TEL**=telithromycin; **VAN**=vancomycin

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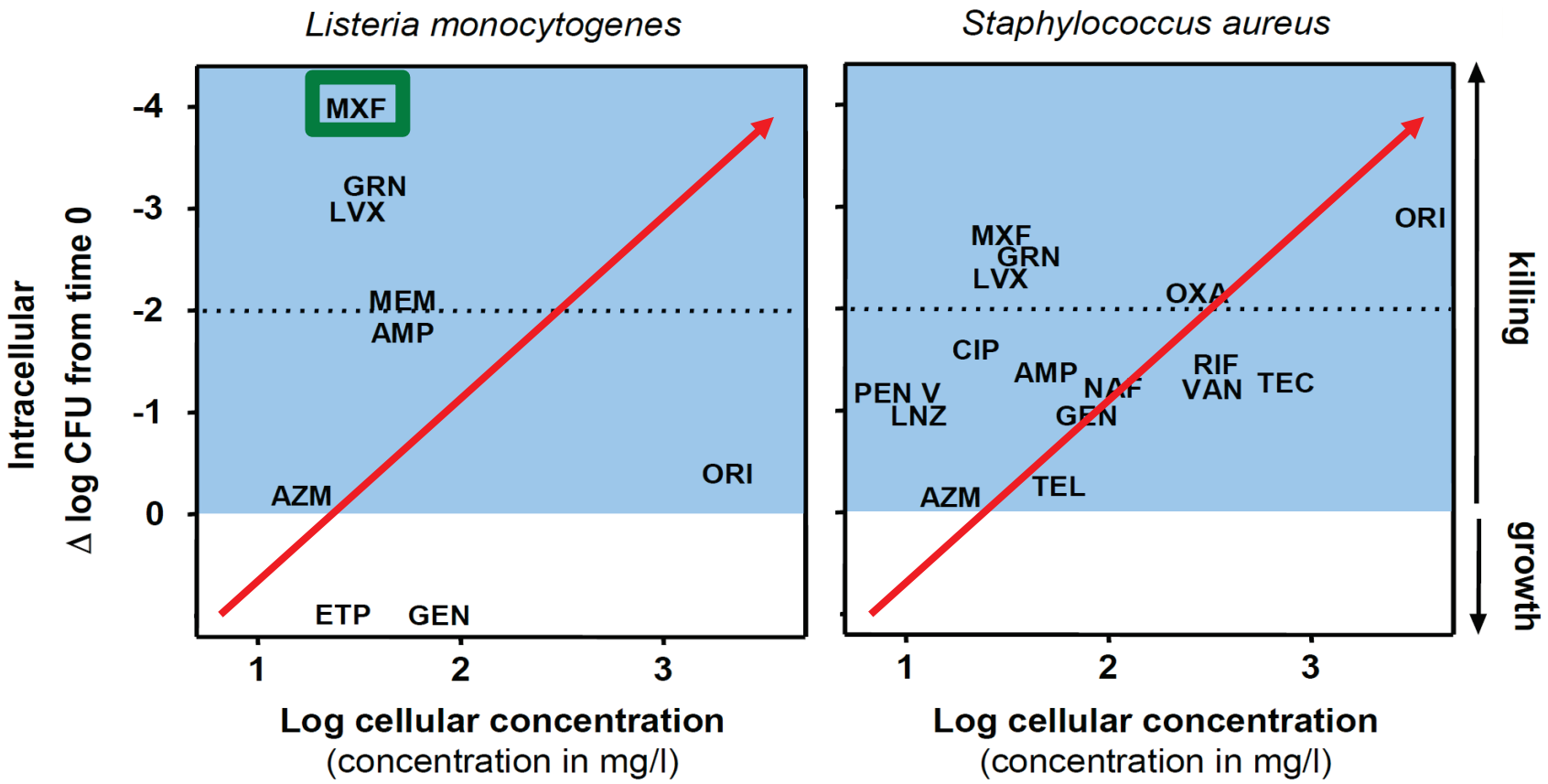

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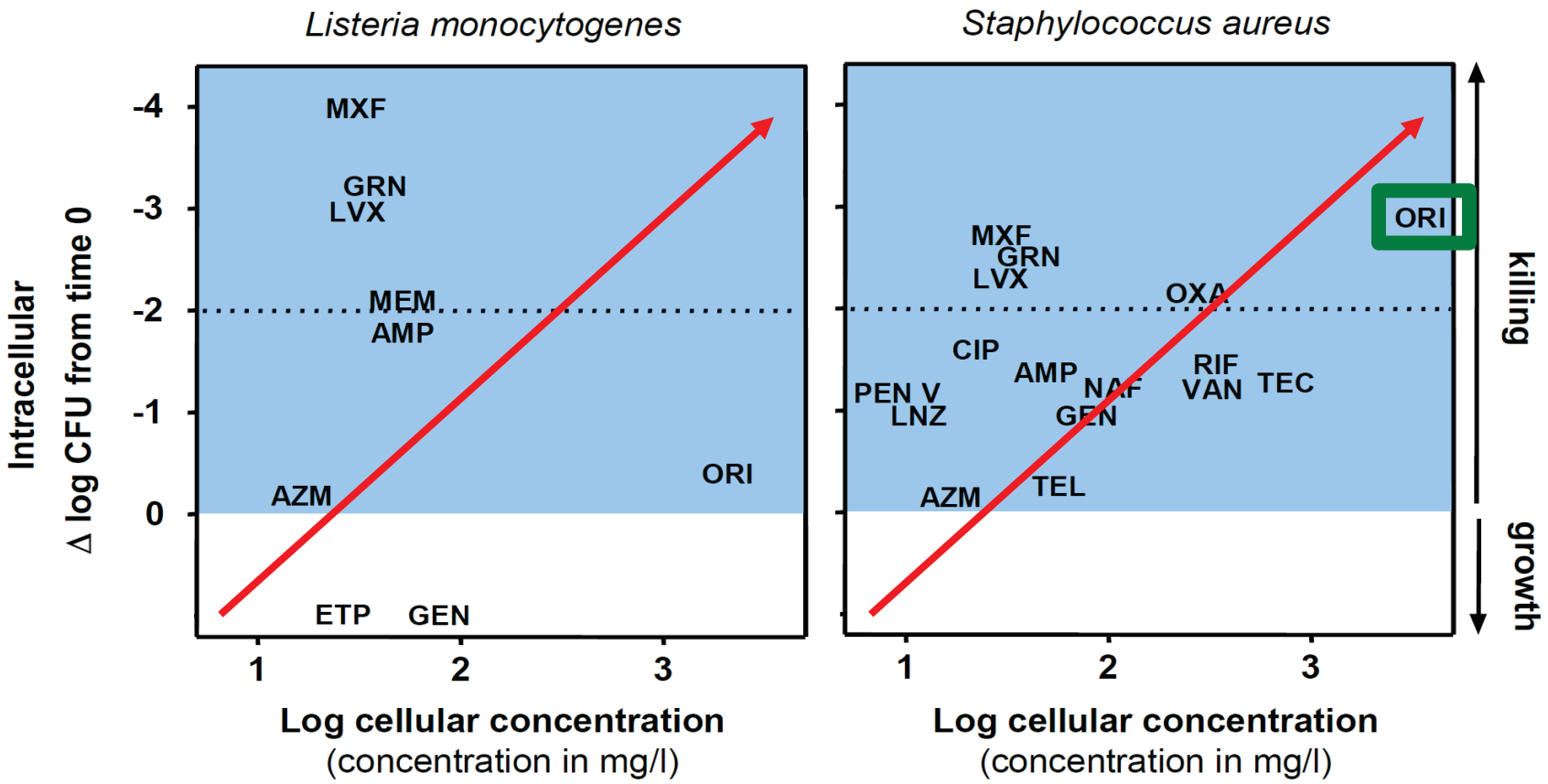

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Adapted from Van Bambeke et al., Curr. Opin. Drug Discov. Devel (2006) 9:218-230

Thus, there is now an obvious conclusion

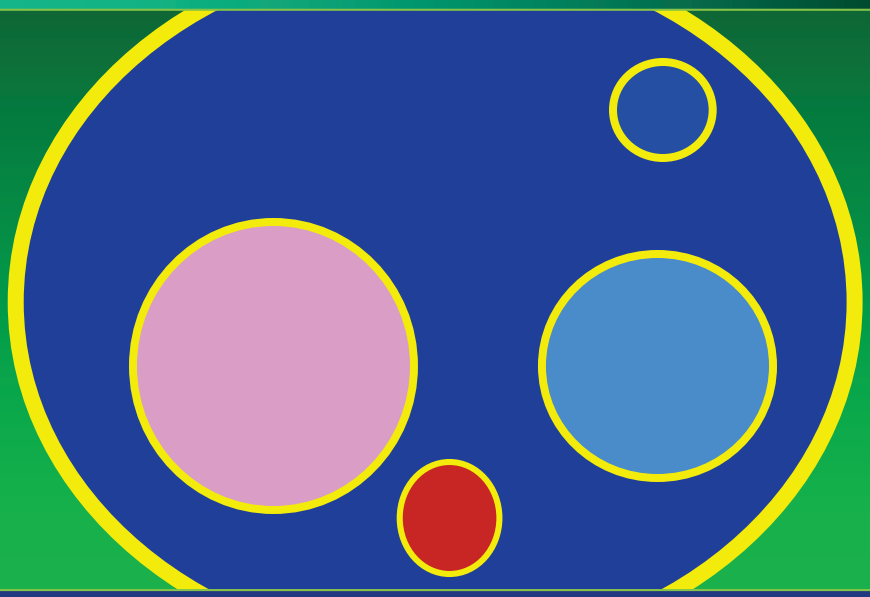
"Accumulation only" may not be the key property

One size does not fill all

Each class of antibiotic / bacteria combination may need to be examined separately

Subcellular bioavailability of antibiotics ?

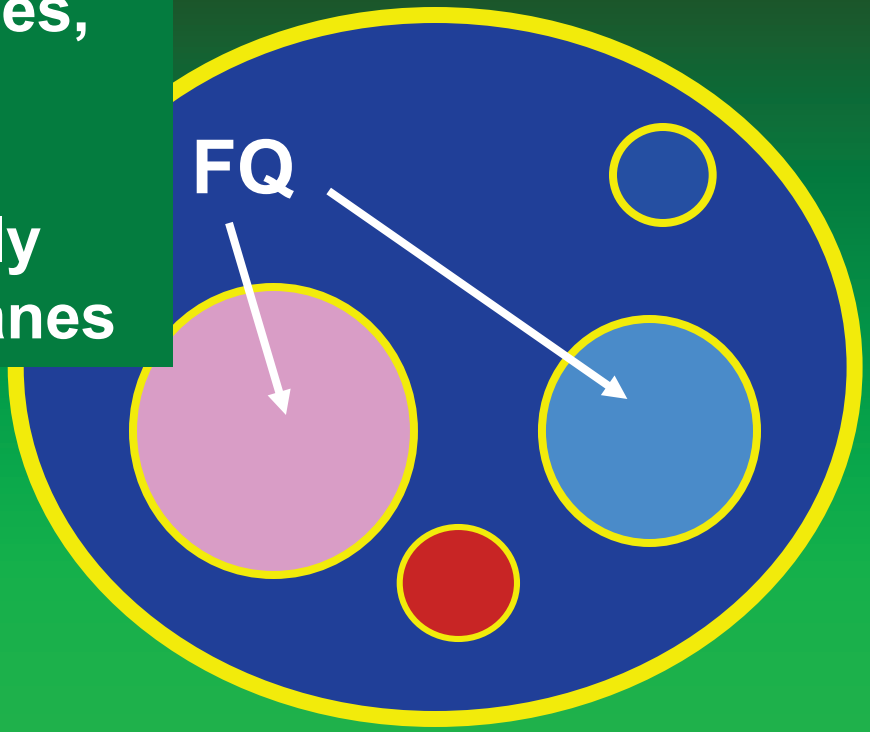
High **Fair** **Nil**



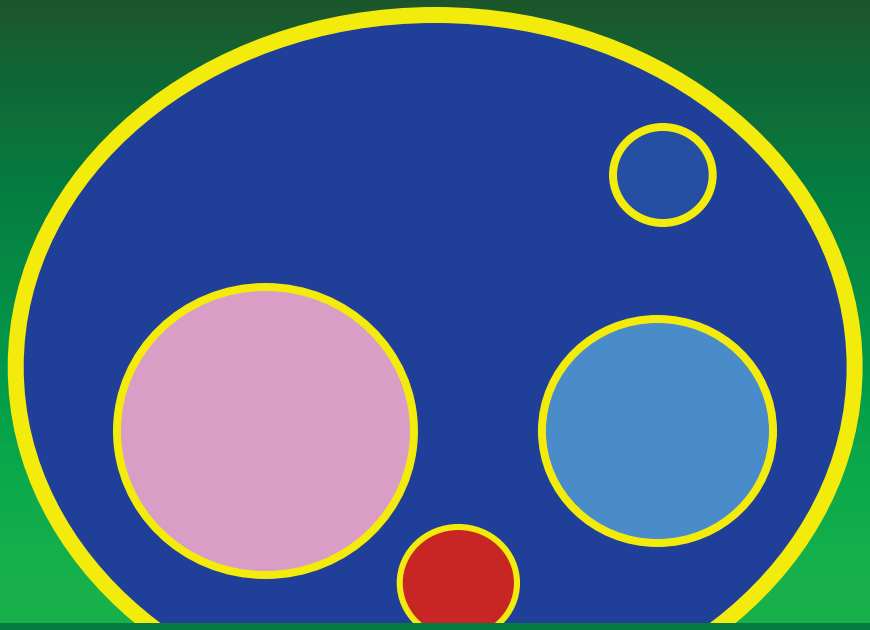
FQ / oxazolidinones / β-lactams **ML / AG**

Subcellular bioavailability of antibiotics ?

Fluoroquinolones, β-lactams, oxazolidinones may move easily across membranes



Subcellular bioavailability of antibiotics ?



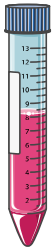
aminoglycosides, poorly diffusible drugs (oritavancin, e.g.) or subjected to proton-trapping sequestration (macrolides, e.g.) may remained confined therein ...

Intracellular activity of antibiotics

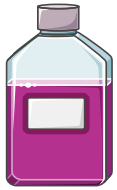
- What has been know for long about pharmacokinetics…
- What has surprised us …
- **Adding pharmacodynamics …**
- A renewed model ?

Second illustration: the 24h dose-effect model

1. Cell exposure to a <u>a wide range of extracellular concentrations of the antibiotic</u>



Opsonization (45', 37°c)
9 mL RPMI +
1 mL human serum



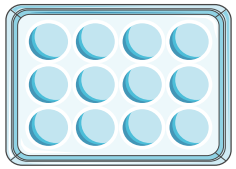
500,000 THP-1 cells/mL

4 cfu/cell (MOI = 4)

Phagocytosis (1 h)

Extracellular Wash
GEN 50 µg/mL
(45 min)

Typical post-phagocytosis inoculum:
5 to 7×10^5 CFU/mg prot.



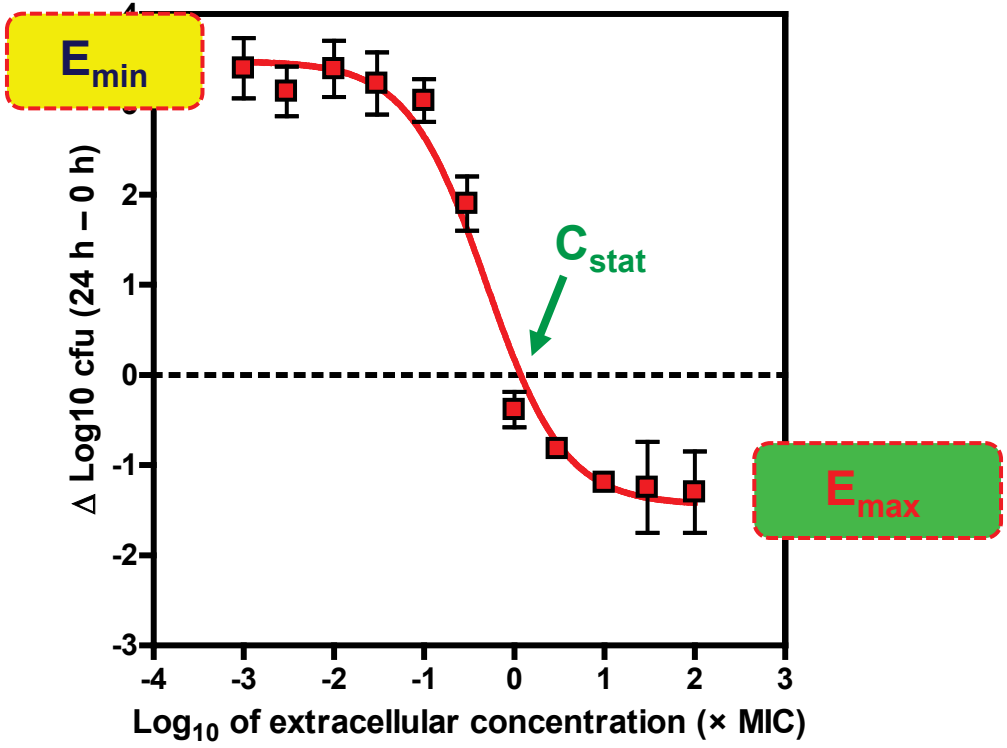
Incubation (with ATB)
(T0, T24 h)

- Cell washing, collection, and lysis
- Cell-associated CFUs counting
- Cell Protein content determination

This example is for S. aureus.
Similar design for other bacteria

Second illustration: the 24h dose-effect model

2. Analysis of the response



E_{min}: cfu increase (in log_{10} units) at 24 h from the corresponding initial inoculum as extrapolated for an infinitely low antibiotic concentration

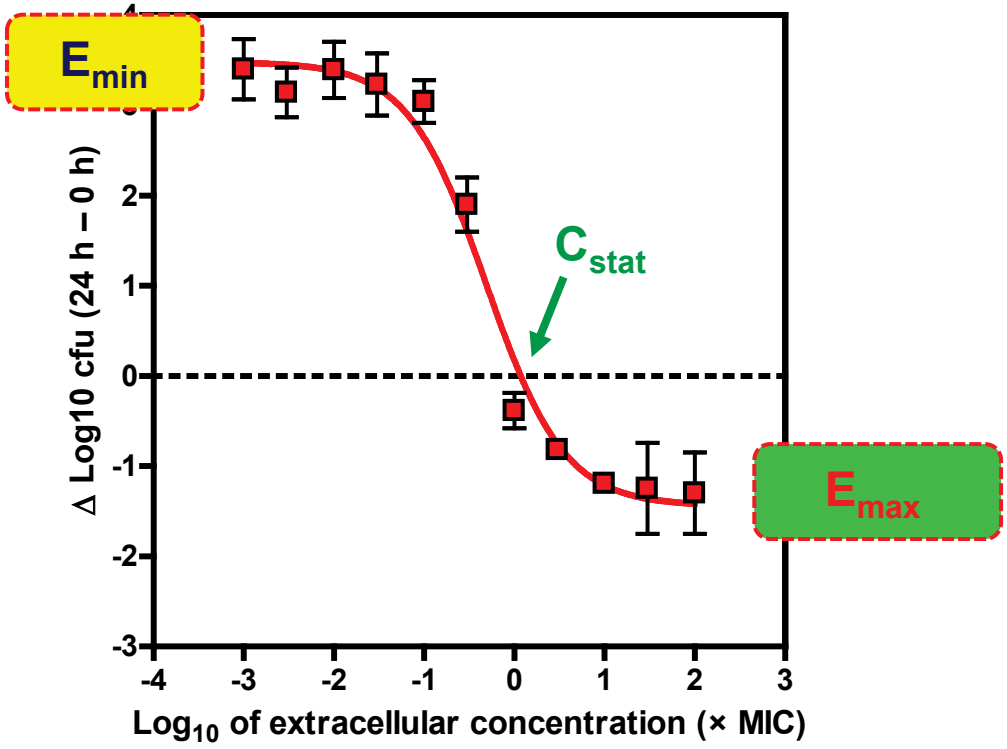
Static concentration (C_{stat}): extracellular concentration resulting in no apparent bacterial growth (number of cfu identical to the initial inoculum)

E_{max}: cfu decrease (in log_{10} units) at 24 h from the corresponding initial inoculum as extrapolated from infinitely large antibiotic concentration

Reference: Barcia-Macay M, Seral C, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activity of antibiotics against Staphylococcus aureus in a model of THP-1 macrophages. Antimicrobial Agents and Chemotherapy (2006) 50:841-851

Second illustration: the 24h dose-effect model

2. the analysis of the response



E_{min}: at 24 h f al inocu infinitely low antibiotic concentration

Bacteria !

Static concentration (C_{stat}): extrac ing in no (numb tial inoculum)

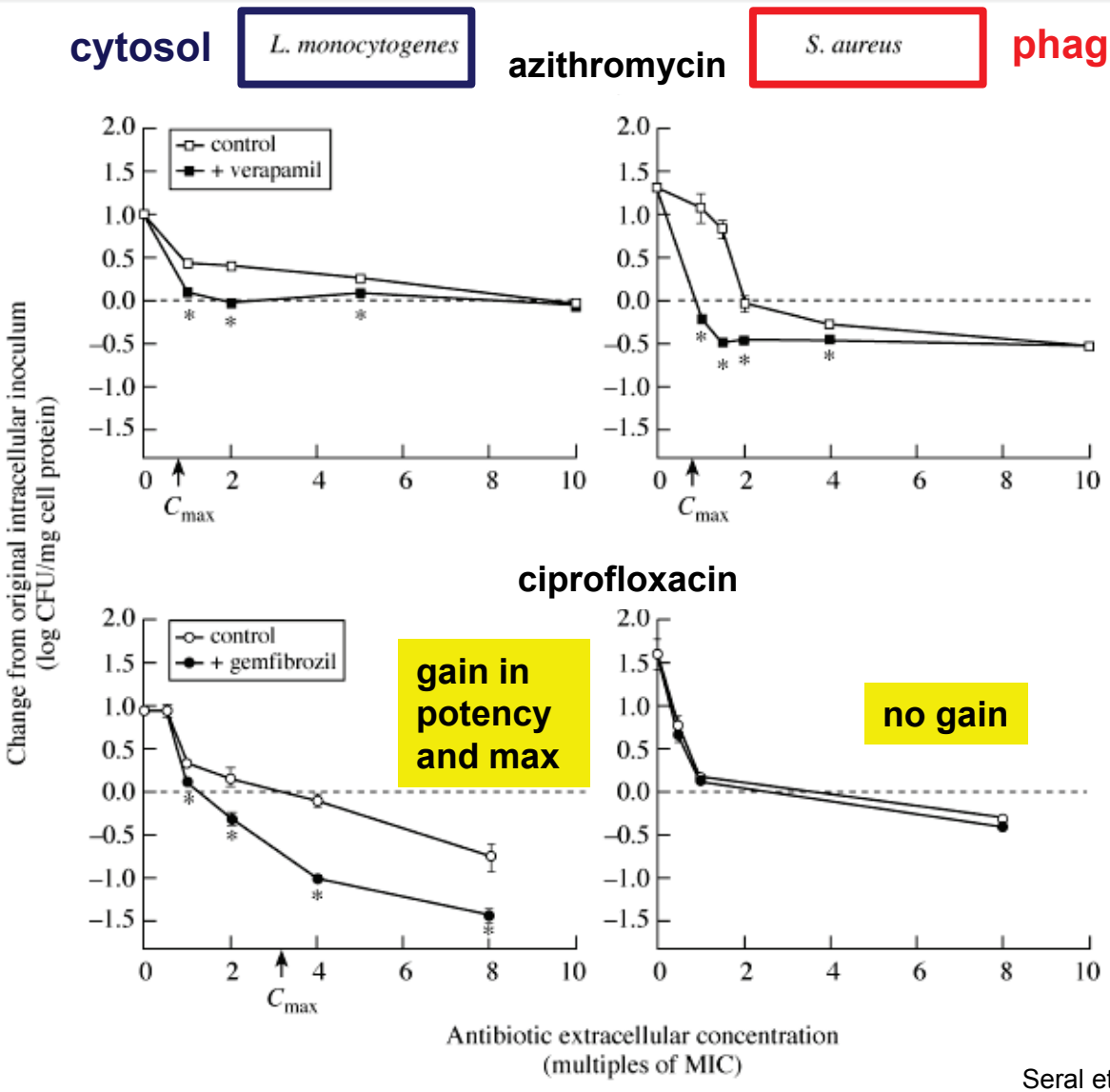
Potency !

E_{max}: cfu decrease (in log_{10} units) at 24 h from the corresponding initial concentration

Maximal effect

Reference: Barcia-Macay M, Seral C, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activity of antibiotics against Staphylococcus aureus in a model of THP-1 macrophages. Antimicrobial Agents and Chemotherapy (2006) 50:841-851

Question #1: does increased accumulation of a given antibiotic results in its increased potency and maximal activity ?



gain in potency but not in max. activity

the gain seems to depend on a common localization

Seral et al; J. Antimicrob Chemother (2003) 47:1047-1051

Question #2: does difference in accumulation of antibiotics of the same class results in commensurate differences in potency and maximal activity ?

International Journal of Antimicrobial Agents 38 (2011) 249–256

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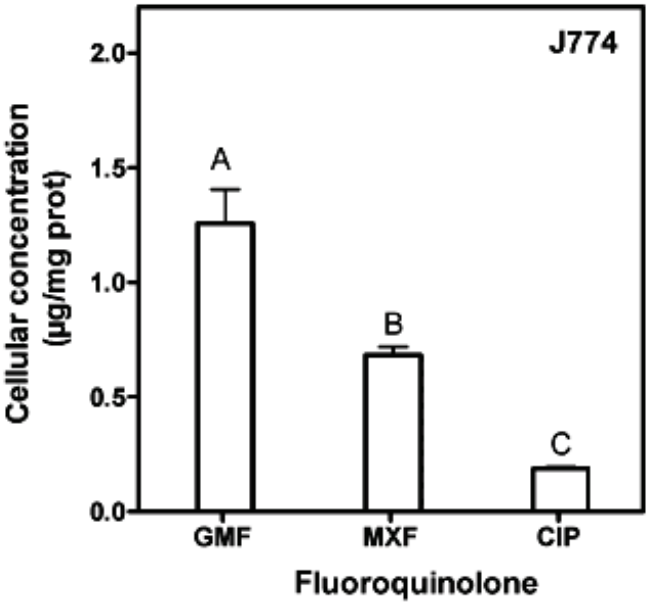
Cellular accumulation of fluoroquinolones is not predictive of their intracellular activity: studies with gemifloxacin, moxifloxacin and ciprofloxacin in a pharmacokinetic/pharmacodynamic model of uninfected and infected macrophages

Coralie M. Vallet, Béatrice Marquez [1], Eva Ngabirano, Sandrine Lemaire, Marie-Paule Mingeot-Leclercq, Paul M. Tulkens*, Françoise Van Bambeke

Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Avenue E. Mounier 73 bte B1.73.05, B-1200 Brussels, Belgium

Question #2: does difference in accumulation of antibiotics of the same class results in commensurate differences in potency and maximal activity ?

1. accumulation (Ce = 20 mg/L)



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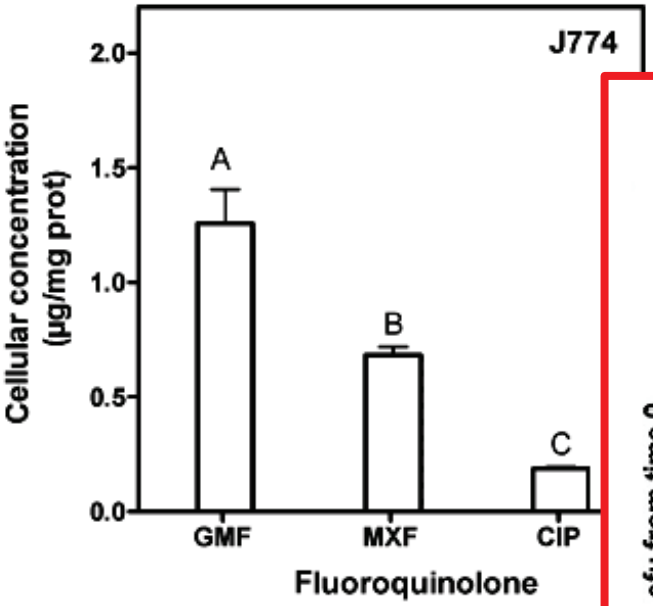
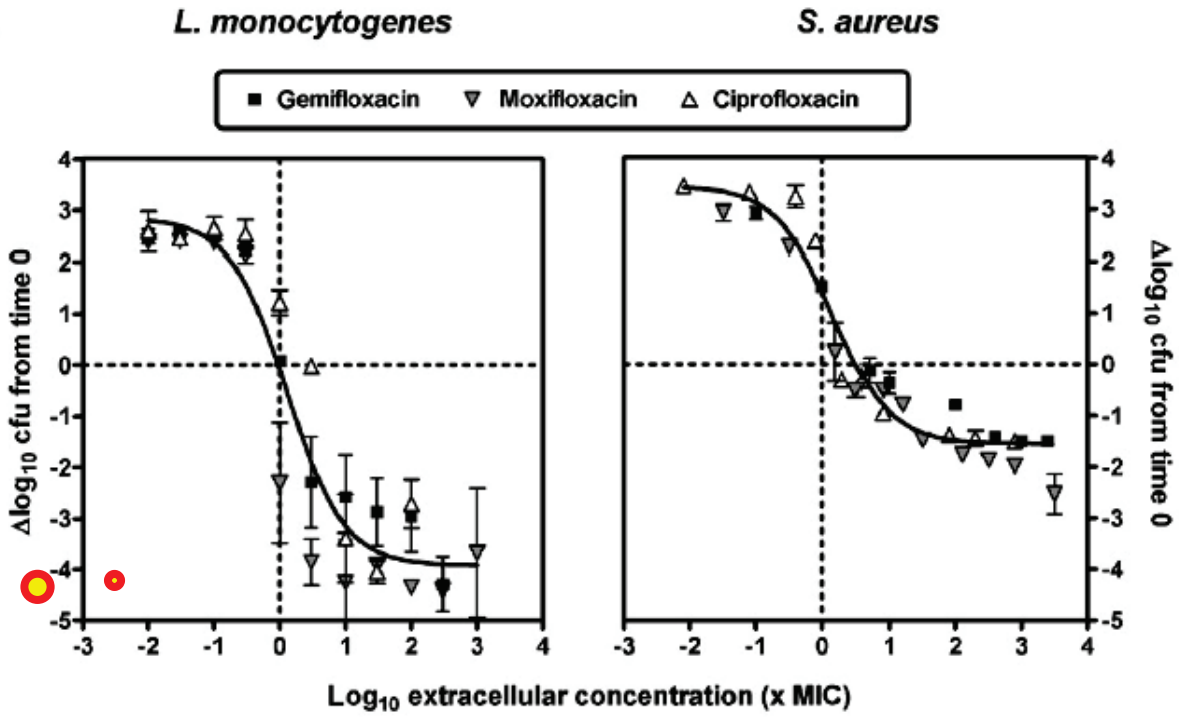


no difference in dose-effect relationship !

2. activity (MIC = 0.5 – 2 mg/L)



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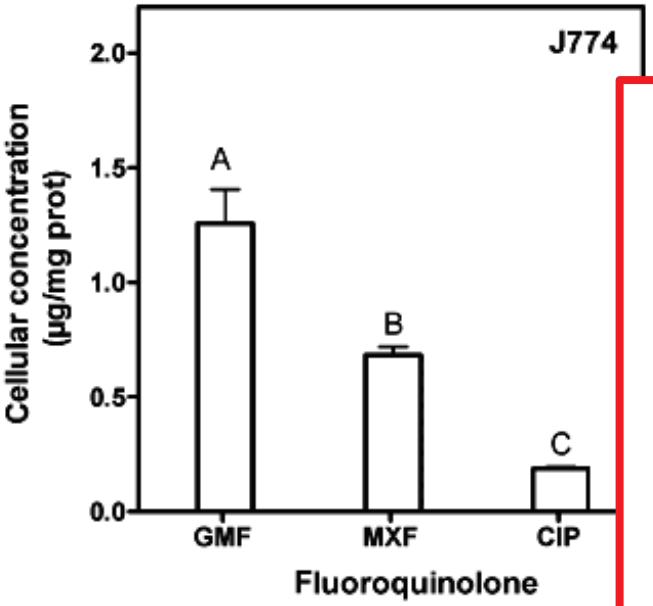
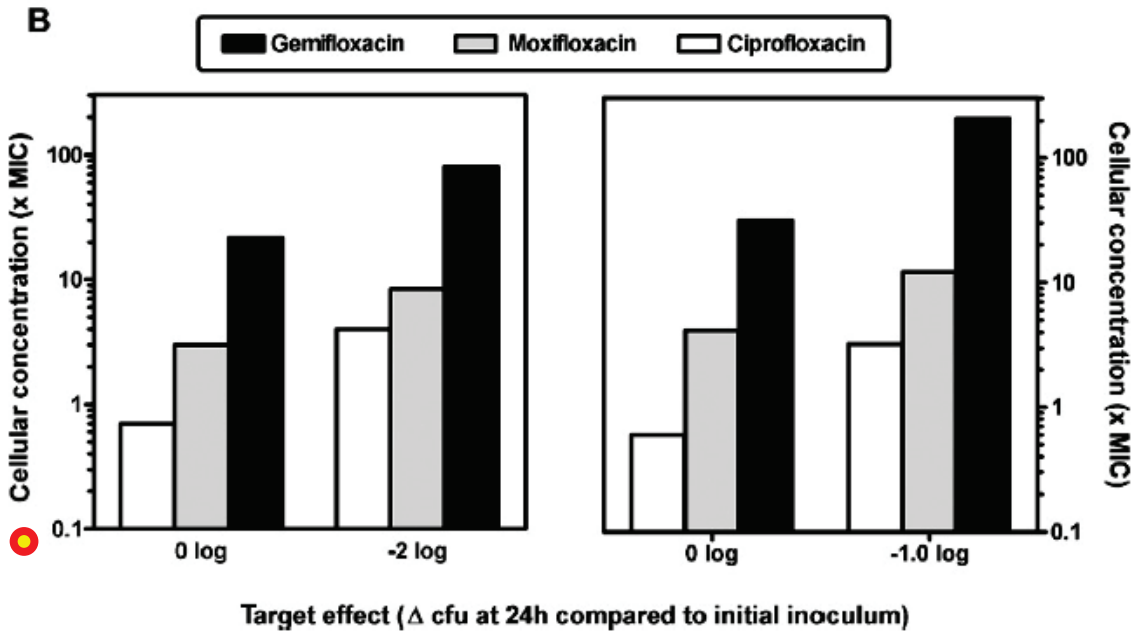
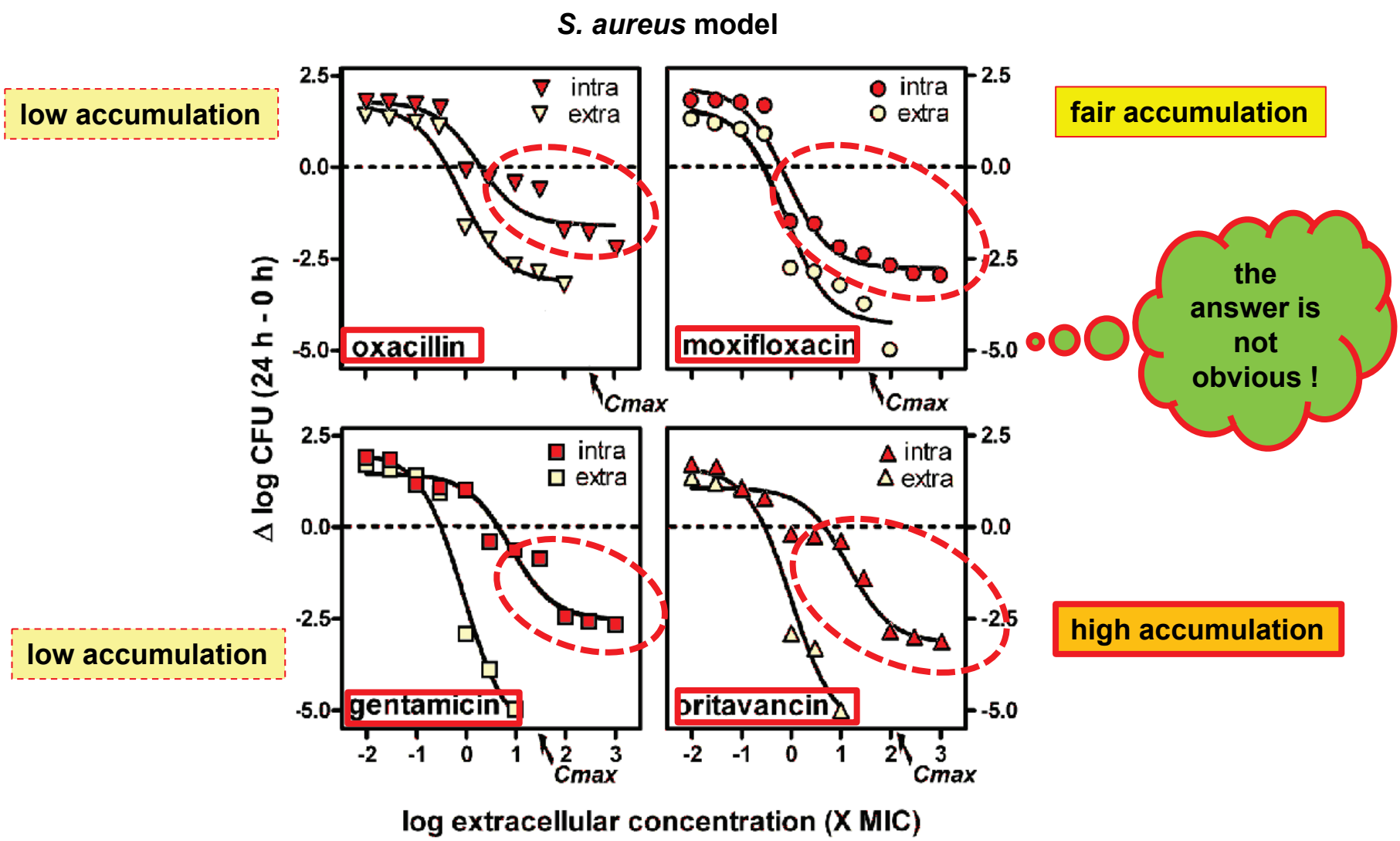


you need more of the drug that accumulates more

3. intracellular concentration to obtain a given effect



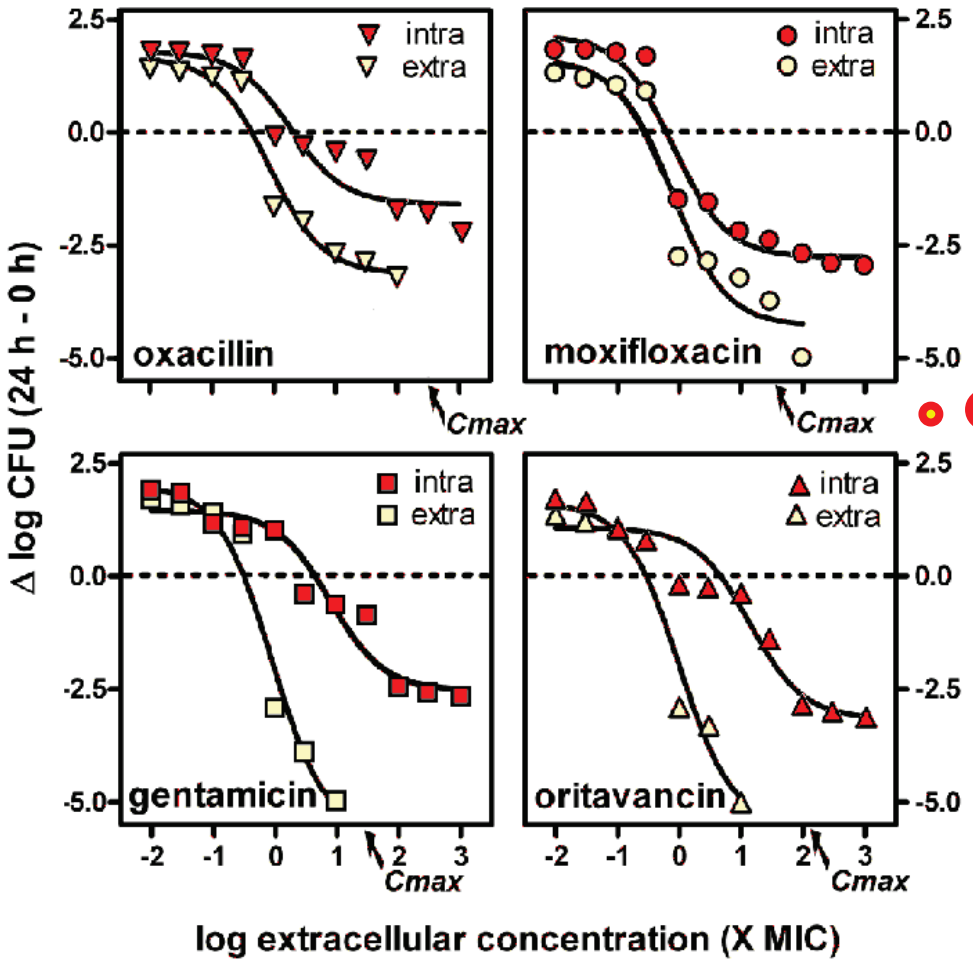
Question #3: are antibiotics that accumulate more effective (potency and maximal activity) than those which do not ?



Barcia-Macay et al. Antimicrob Agents Chemother (2006) 50:841-851

Question #4: why are antibiotics unable eradicate the intracellular bacteria (viz. low maximal efficacy) ?

***S. aureus* model (ATCC25223)**

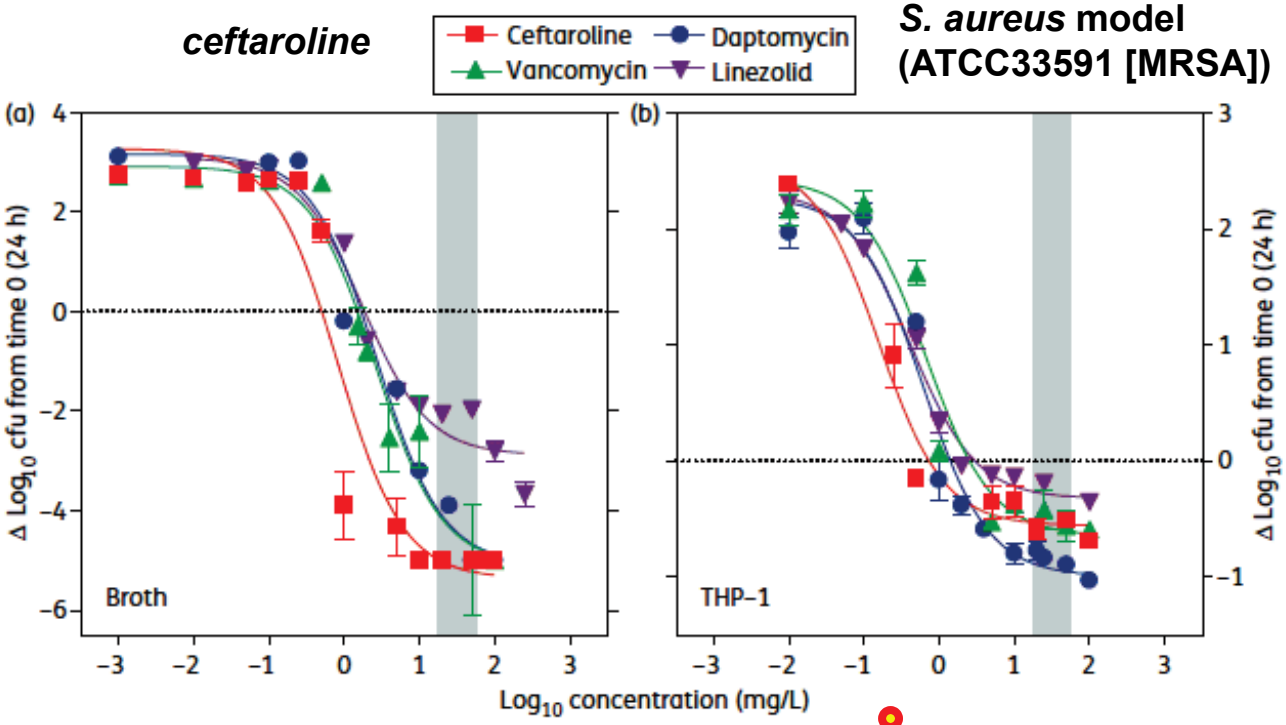


compare the extracellular and the intracellular E_{max}

Barcia-Macay et al. Antimicrob Agents Chemother (2006) 50:841-851

Question #4: why are antibiotics unable eradicate the intracellular bacteria (viz. low maximal efficacy) ?

ceftaroline



***S. aureus* model (ATCC33591 [MRSA])**

- 5 log !

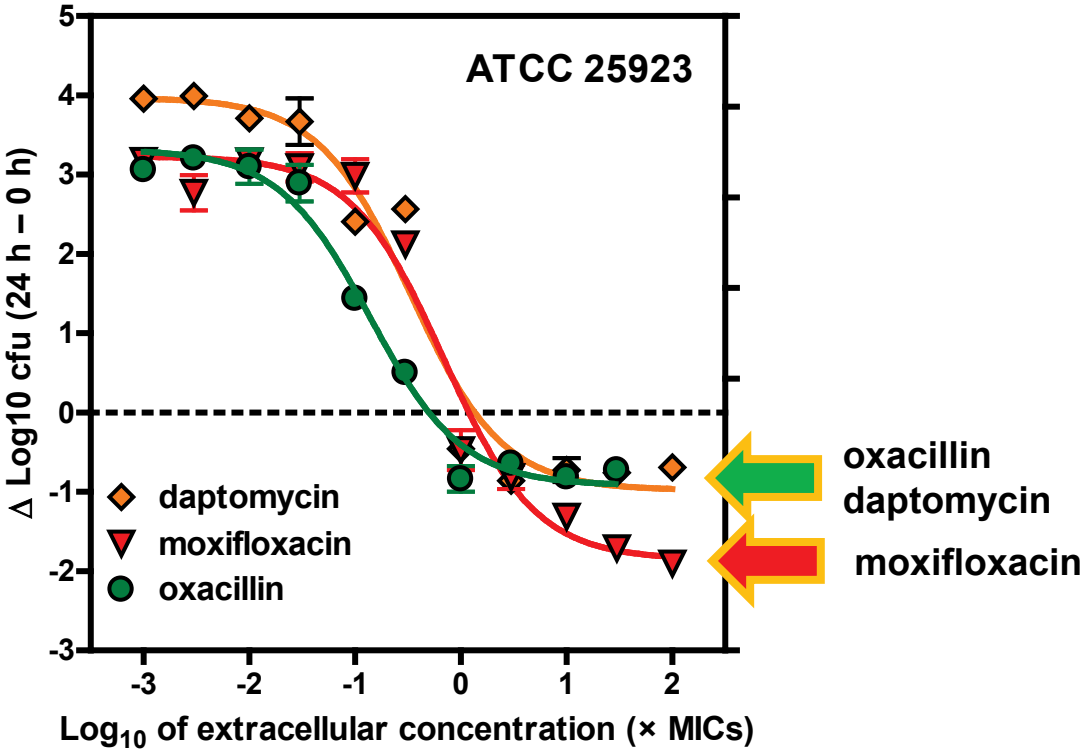
- 1 log !

Figure 1. Concentration-dependent activities of four antistaphylococcal antibiotics against extracellular [MHB broth pH 7.4 (a)] and intracellular [THP-1 monocytes (b)] forms of *S. aureus* strain ATCC 33591 (MRSA). For these experiments, broths or inf cells were incubated presence of increasing concentrations of antibiotic (total drug; abscissa). The ordinates show the change in the medium (broth) or per mg or cell protein (THP-1). Note that because of the marked difference in the amplitud broth versus bacteria in THP-1 cells, the scale extends from −6 to 4 in panel (a) and from −1 to 3 in pa showing the zero value (no apparent change from the initial, post-phagocytosis inoculum). All values are the SD bars are smaller than the size of the symbols). The lowest limit of detection corresponds to a cfu the original inoculum. The grey zone shows the range of maximal serum concentrations observed in h based on the following reported C_{max} values: ceftaroline, 21 mg/L; vancomycin, 20–50 mg/L; daptomycin, footnote c in Table 2).

compare the extracellular and the intracellular E_{max}

Melard et al. J Antimicrob Chemother (2013) 68: 648–658

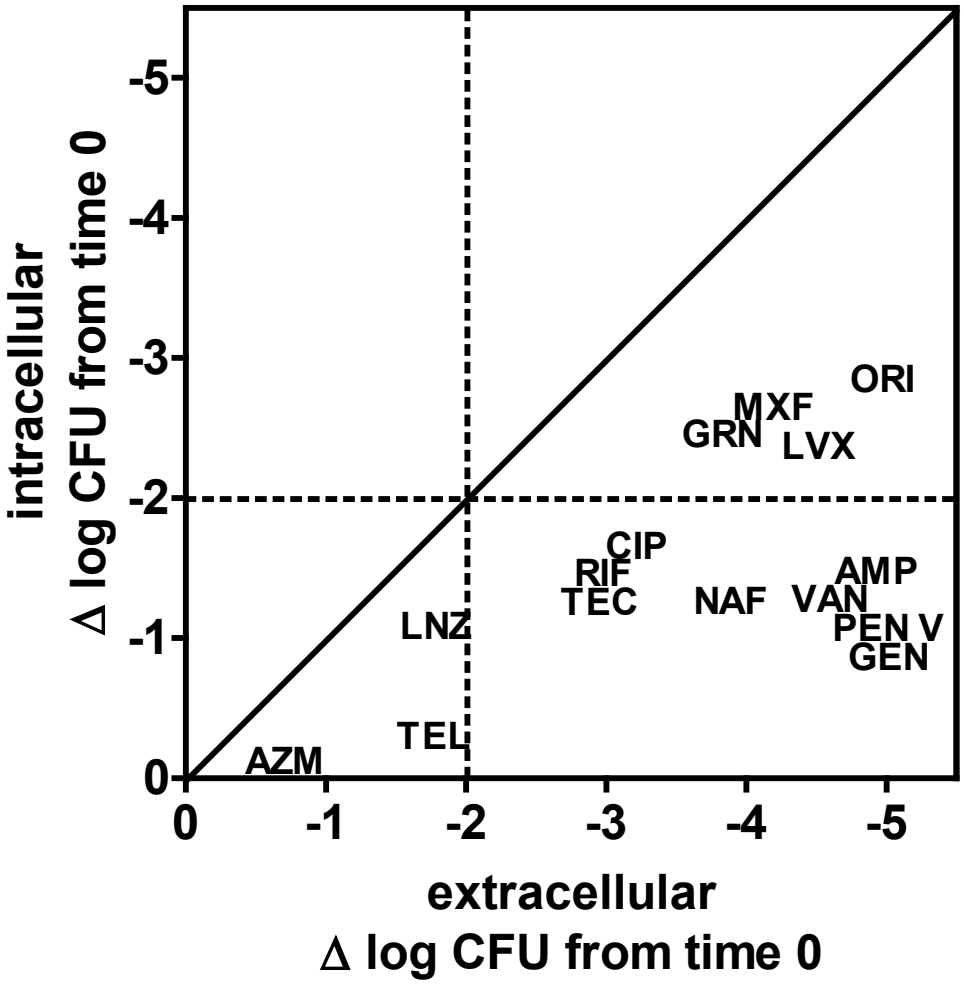
about question #4 (eradication): some do (slightly) better than others (viz. maximal efficacy) ?



Peyrussoon et al. Antimicrob Agents Chemother (2015) 59:5747-5760

about question #4 (eradication): some do (slightly) better than others (viz. maximal efficacy) but all do less than in broth …

a more systematic comparison with ATCC 25983 (*S. aureus*) and at human C_{max}



From high to low intracellular activity:

ORI = oritvancin
MXF =moxifloxacin
GRN = garenoxacin
LVX = levofloxacin
CIP = ciprofloxacin
AMP = ampicillin
RIF = rifampincin
TEC = teicoplann
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PEN V : penicillin V
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Adapted from Barcia-Macay et al. Antimicrob Agents Chemother (2006) 50:841-851

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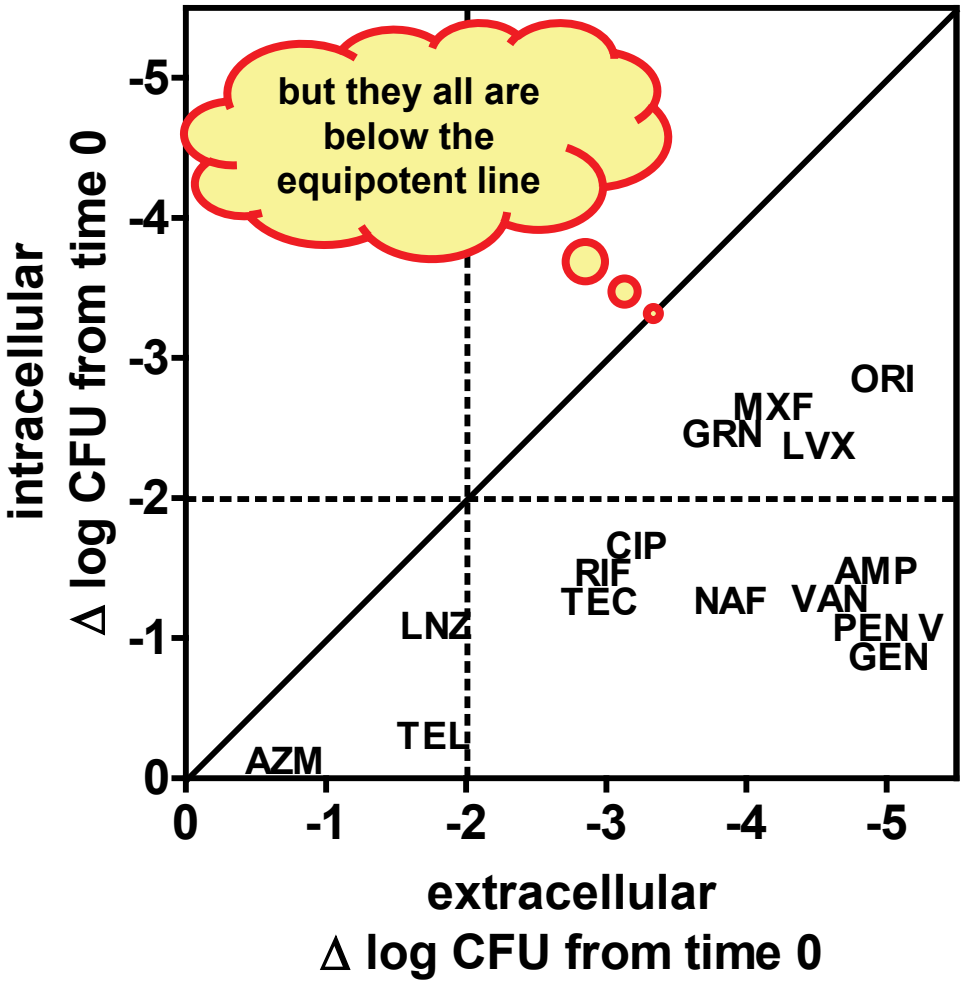

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Intracellular activity of antibiotics

- What has been know for long about pharmacokinetics…
- What has surprised us …
- Adding pharmacodynamics …
- **A renewed model ?**

The seven pillars of intracellular activity ?

1. Penetration

This is obvious:
no penetration = no activity
ex.: aminoglycosides in short term exposures

The seven pillars of intracellular activity ?

1. Penetration
2. No efflux

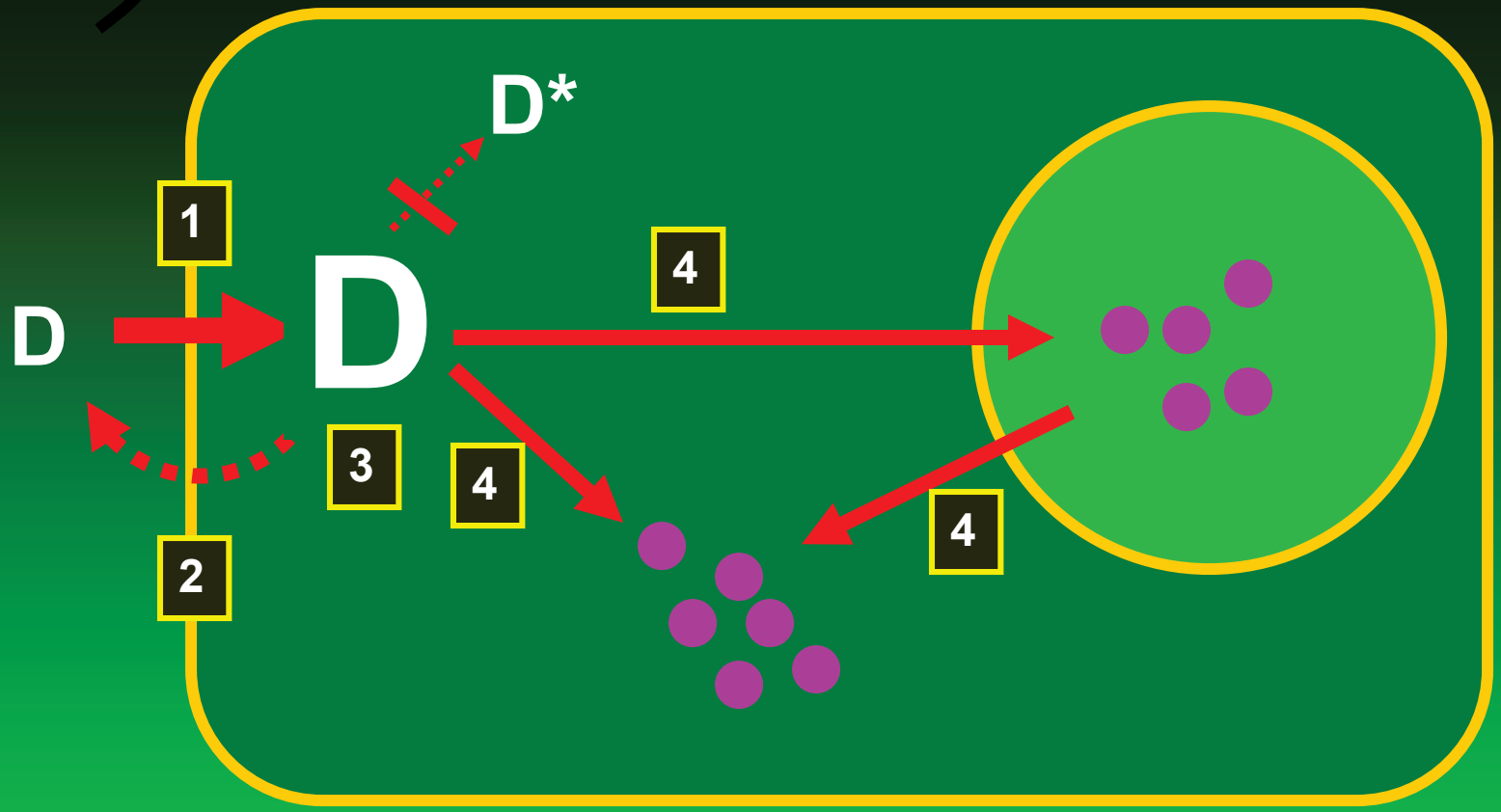
Also obvious:
efflux decreases the intracellular concentration
ex.: fluoroquinolones (MRP4), macrolides (Pgp)

The seven pillars of intracellular activity ?

1. Penetration
2. No efflux
3. Accumulation

Much less obvious …
no simple correlation accumulation-activity
ex.: fluoroquinolones, macrolides, β-lactams…

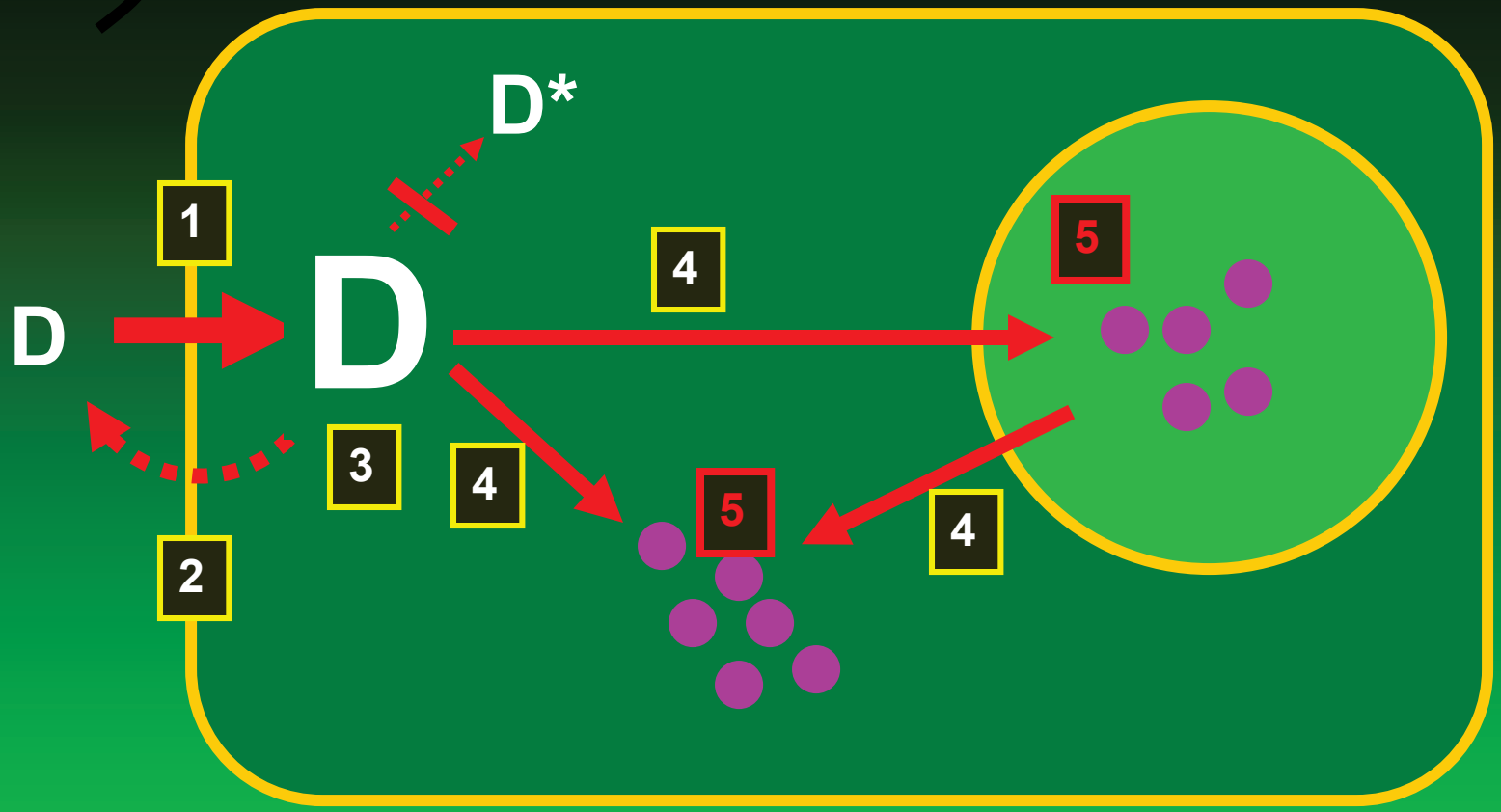
The seven pillars of intracellular activity ?



1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability

This is probably the most critical property
ex.: fluoroquinolones, oxazolidinones *vs* macrolides and aminoglycosides

The seven pillars of intracellular activity ?



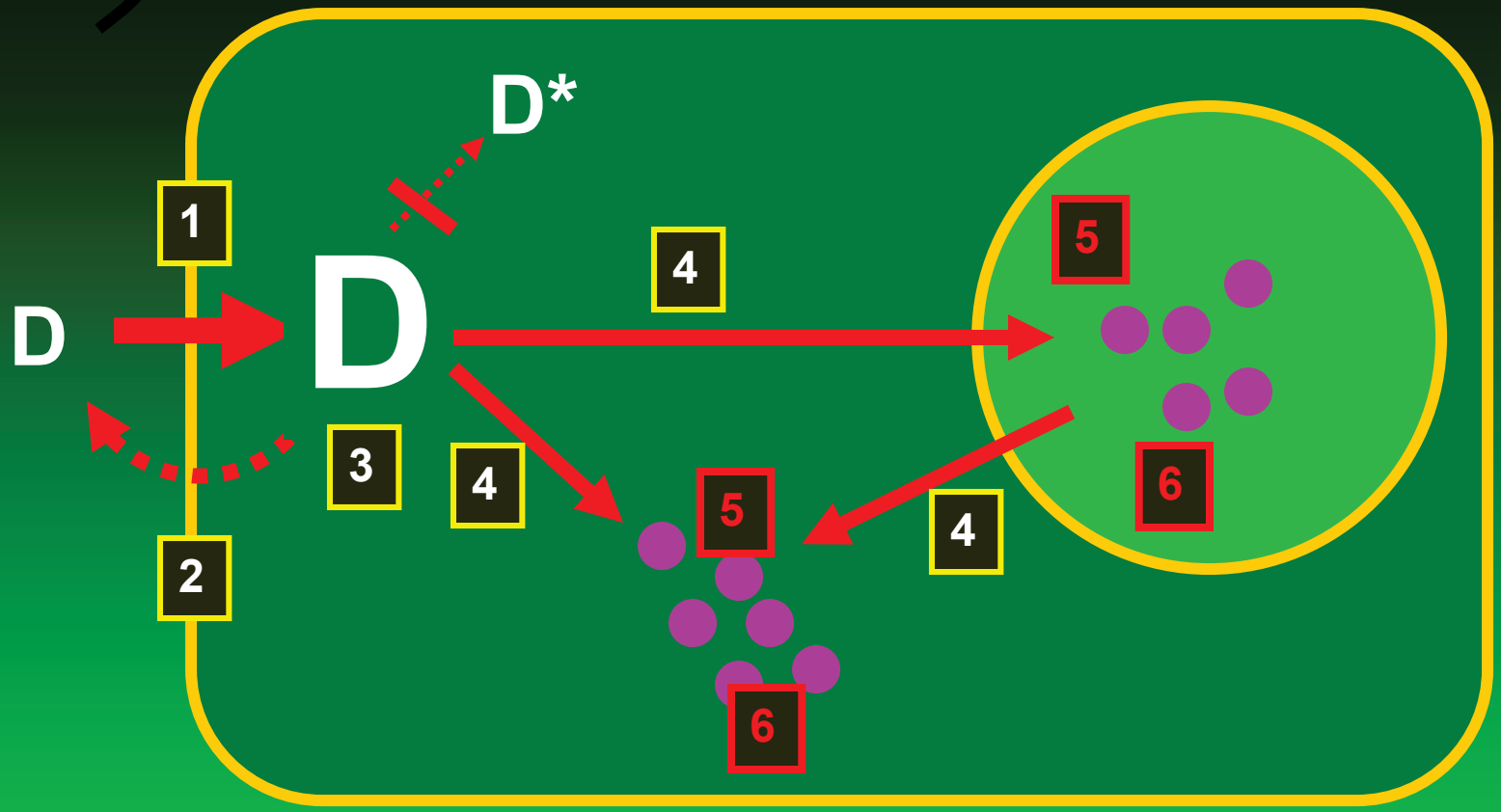
Interesting aspect but could vary for drugs and bugs …

- **one + example: intracellular MRSA and conventional β-lactams… (not shown in this lecture)**

4. Subcell. bioavailability

5. Expression of activity

The seven pillars of intracellular activity ?



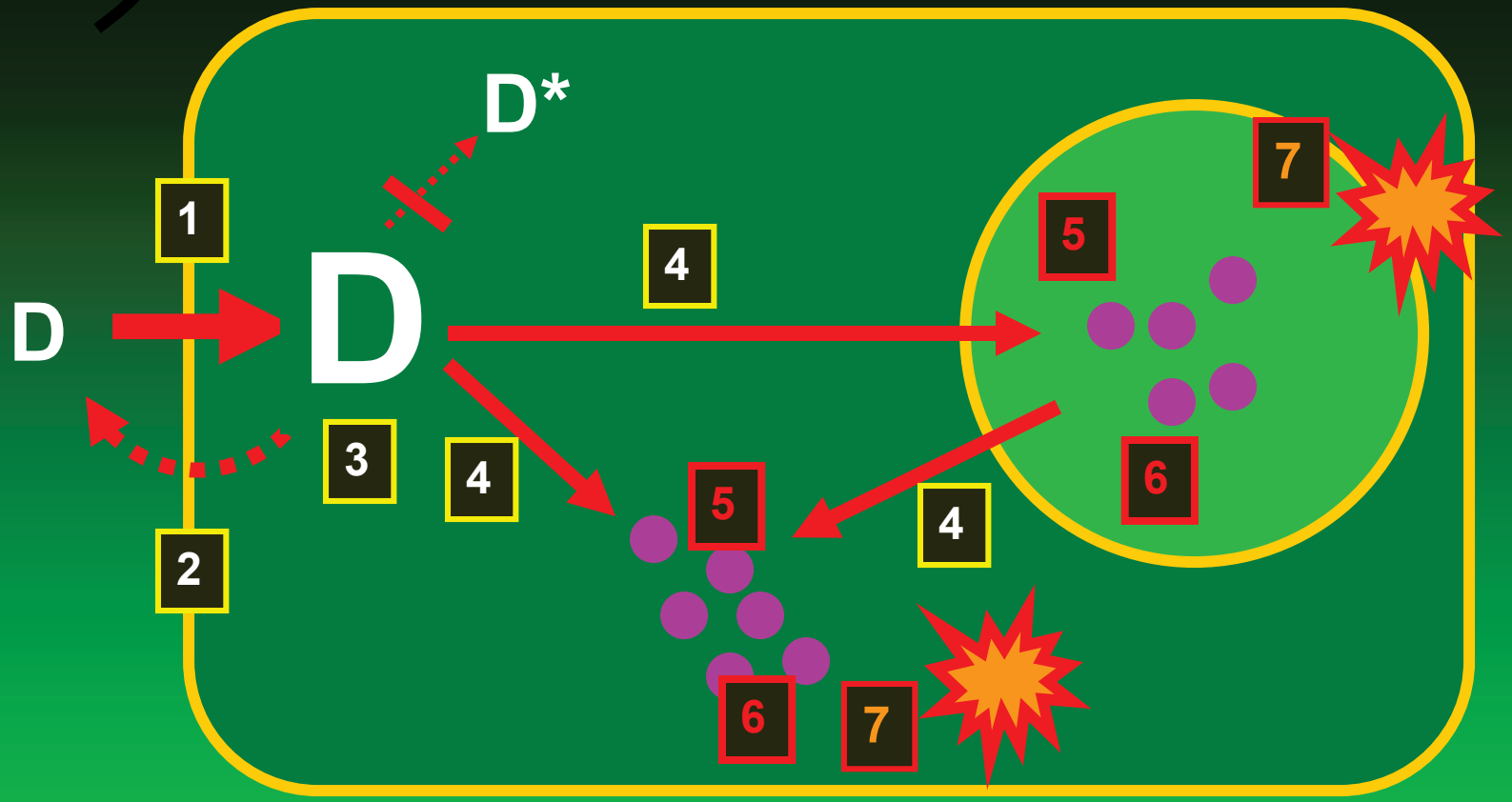
Probably critical to explain the non-eradication or part of the intracellular inoculum…
→ future therapeutic targets ?

4. Subcell. bioavailability

5. Expression of activity

6. Bacterial responsiveness (population)

The seven pillars of intracellular activity ?

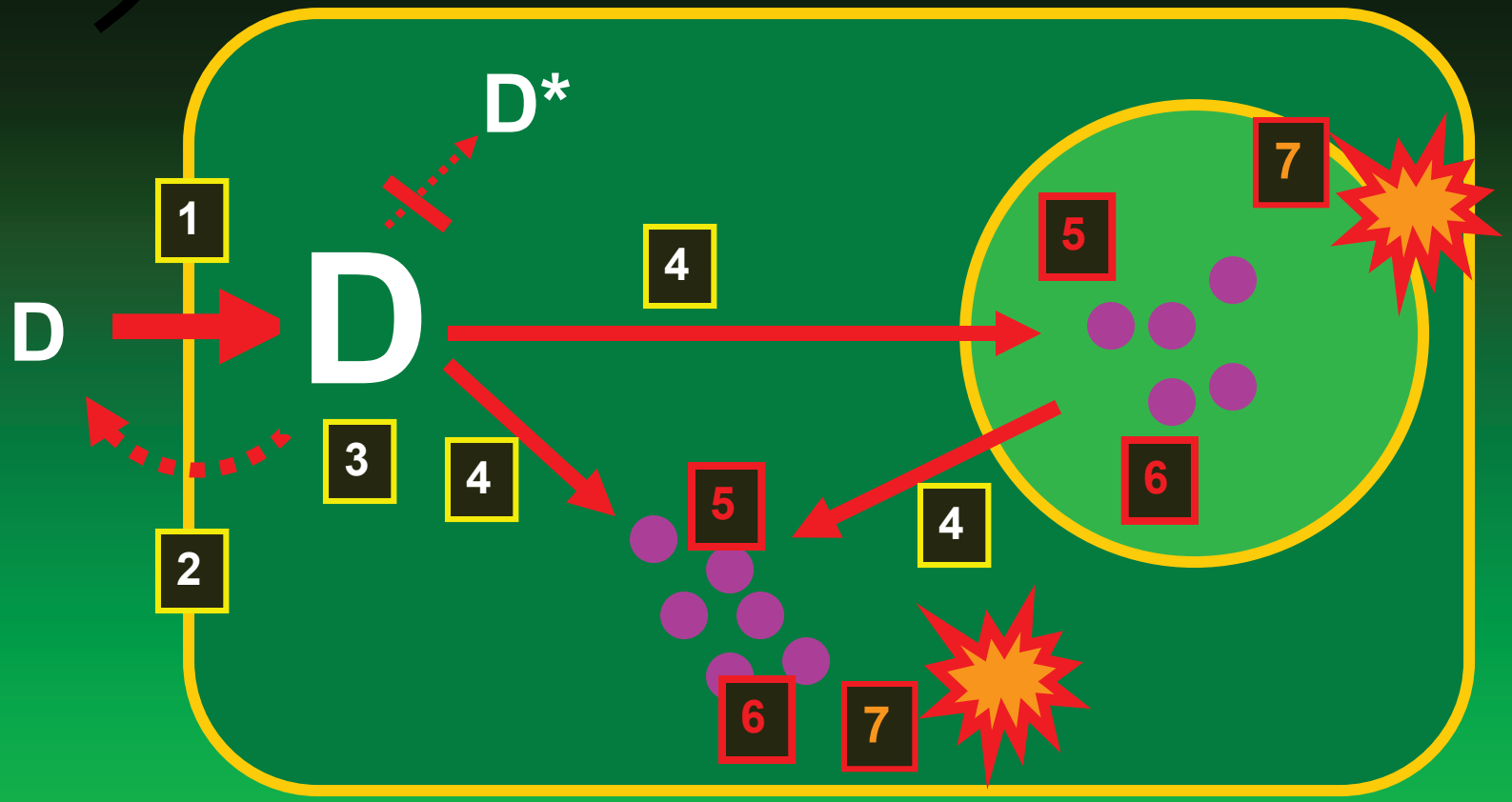


1. Penetration
2. No efflux
3. Accumula
4. Subcell.

Not addressed here but probably very important

5. Expression of activity
6. Bacterial responsiveness and pharmacodynamics
7. Cooper. with host def.

The seven pillars of intracellular activity ?



1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability

5. Expression of activity
6. Bacterial responsiveness and pharmacodynamics
7. Cooper. with host def.

So, it a nutshell…

from ancient

to contemporary

but still a lot of unknowns…

But this work would not have been possible without

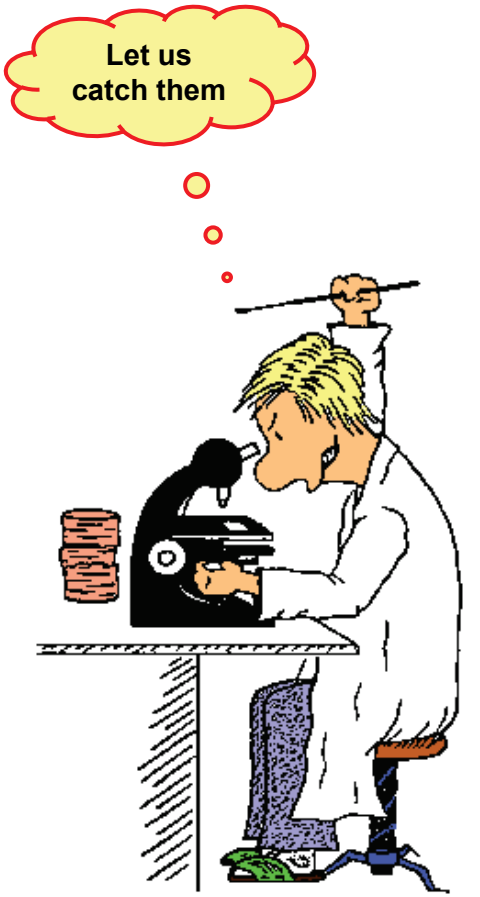
The drugs…

- **β-lactams**: penicillin V, oxacillin, cloxacililn, ceftaroline*, ceftobiprole* (+ avibactam*)
- **aminoglycosides:** gentamicin, amikacin
- **lincosamides:** clindamycin, pirlimycin
- **fluoroquinolones:** ciprofloxacin, pefloxacin, lomefloxacin, sparfloxacin, moxifloxacin,, garenoxacin*, gemifloxacin, finafloxacin*, delafloxacin*
- **oxazolidinones**: linezolid, radezolid*, tedizolid*
- **glycopeptides**: vancomycin, telavancin*, oritavancin*,
- **macrolides:** clarithromycin, azithromycin, solithromycin*,
- **other classes**: daptomycin, GSK 1322322*, gepoditacin*, Debio1452*
- etc…

* new molecules studied at preclinical level

The people…

- M.B. Carlier *,**
- A. Zenebergh **
- B. Scorneaux *
- Y. Ouadrhiri *
- S. Caryn *,**
- C. Seral **
- M. Barcia-Macay *
- H.A. Nguyen **
- J.M. Michot *
- B. Marquez **
- C. Vallet *
- S. Lemaire *,**
- A. Melard
- J. Buyck **
- D. Das **
- F. Peyrusson *
- **F. Van Bambeke (current head of the group)**
- …



* doctoral fellow; ** post-doctoral fellow