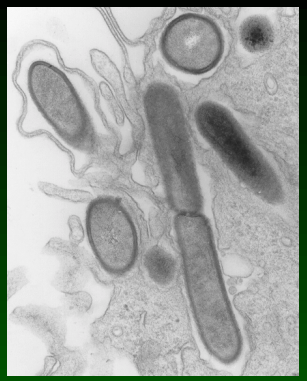
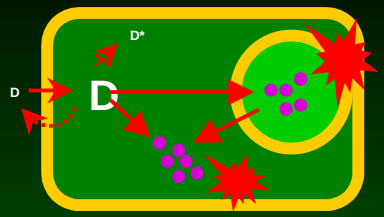


Intracellular antibiotics and Listeria monocytogenes



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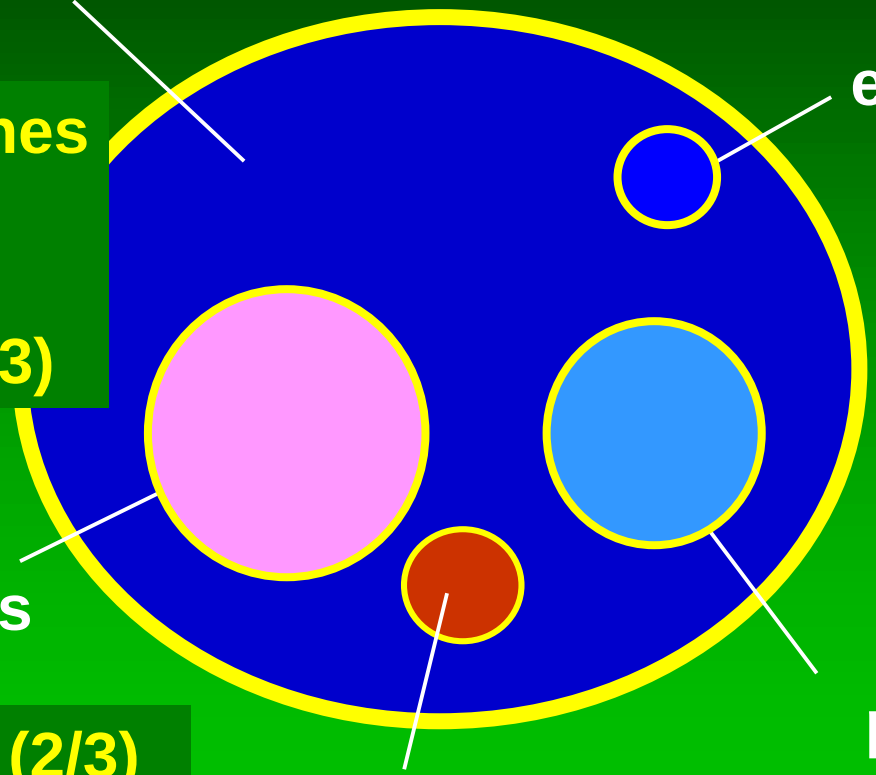
Brussels, Belgium

Presented at the 5th European Congress of Chemotherapy,
Rhodos, Greece, October 17th-20th, 2003

Why intracellular / intratissular antibiotics ?

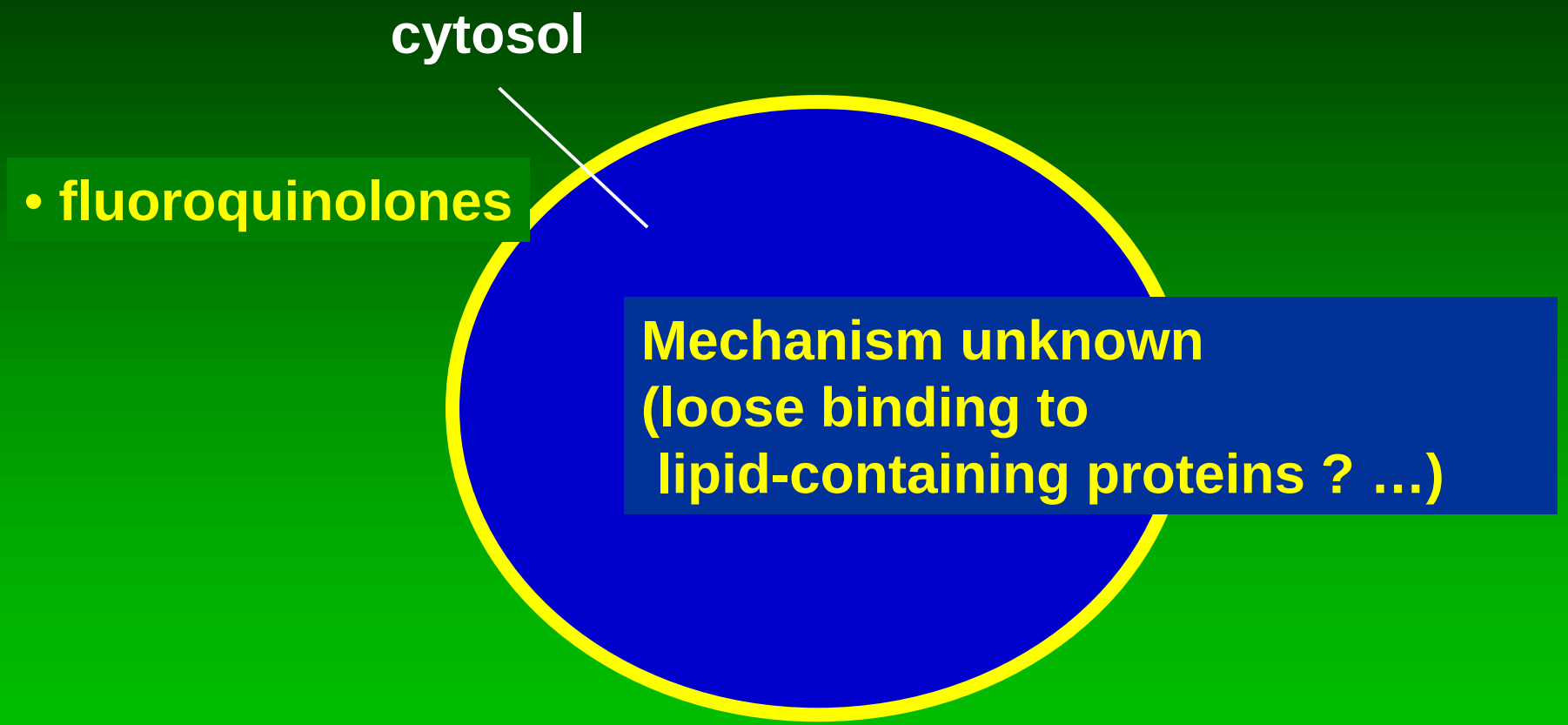
Subcellular localization ?



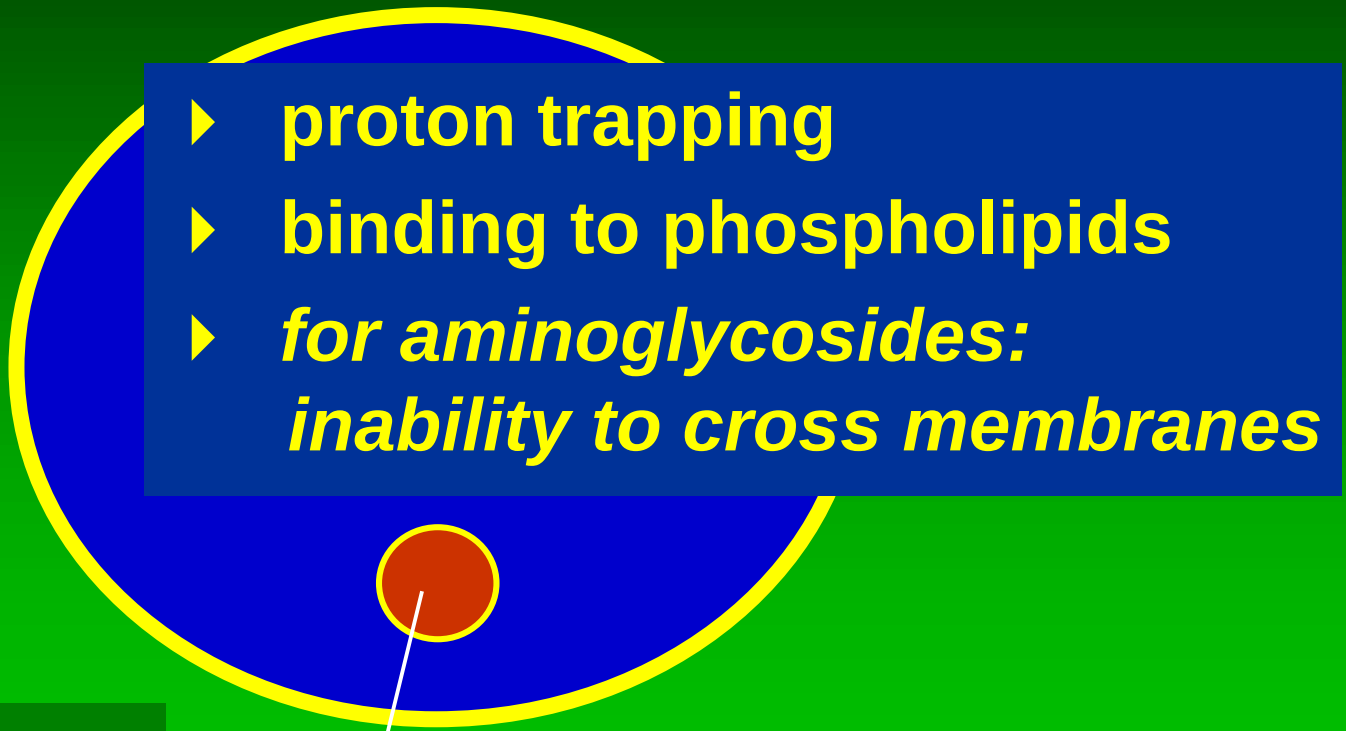
- fluoroquinolones
- beta-lactams
- ansamycins
- macrolides (1/3)

- macrolides (2/3)
- aminoglycosides

Mechanisms of localisation and accumulation ...



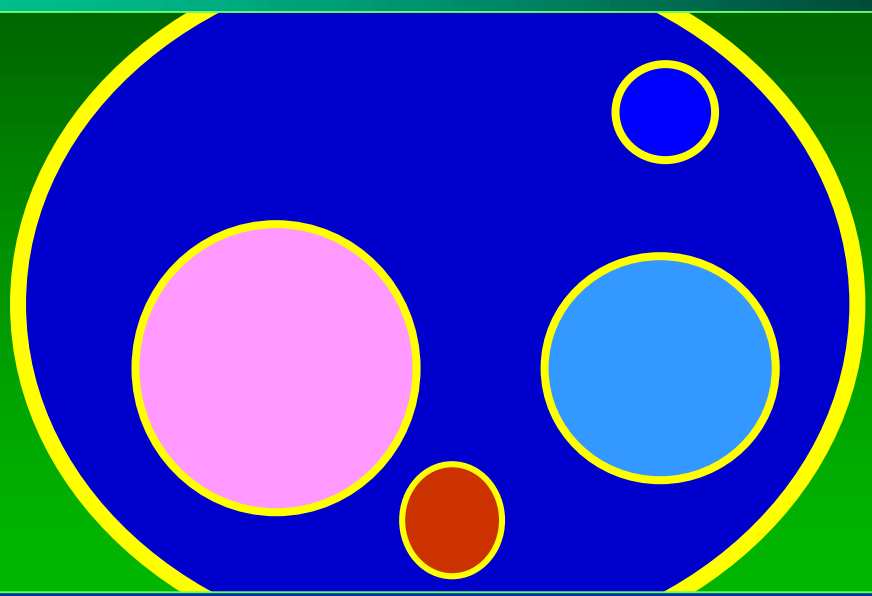
Mechanisms of localisation and accumulation ...



- macrolides
- aminoglycosides

Subcellular bioavailability of antibiotics ?

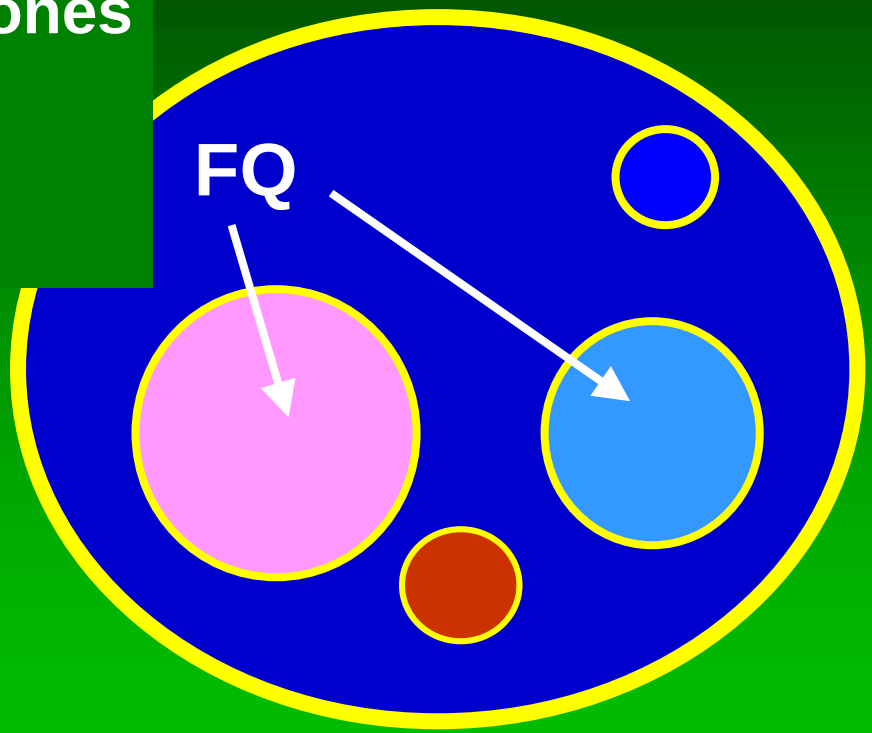
High **Fair** **Nil**



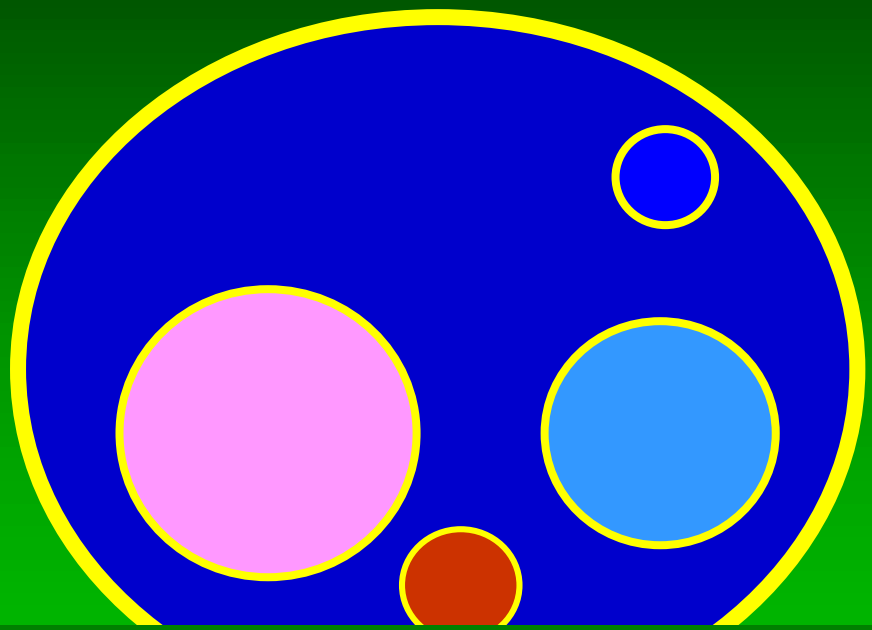
FQ / Ansamyc. / cytosol. ML **lysosom. ML / AG**

Subcellular bioavailability of antibiotics ?

Fluoroquinolones move easily across membranes



Subcellular bioavailability of antibiotics ?



aminoglycosides
and lysosomal macrolides
reamain largely if not totally sequestered
in an acidic environment ...

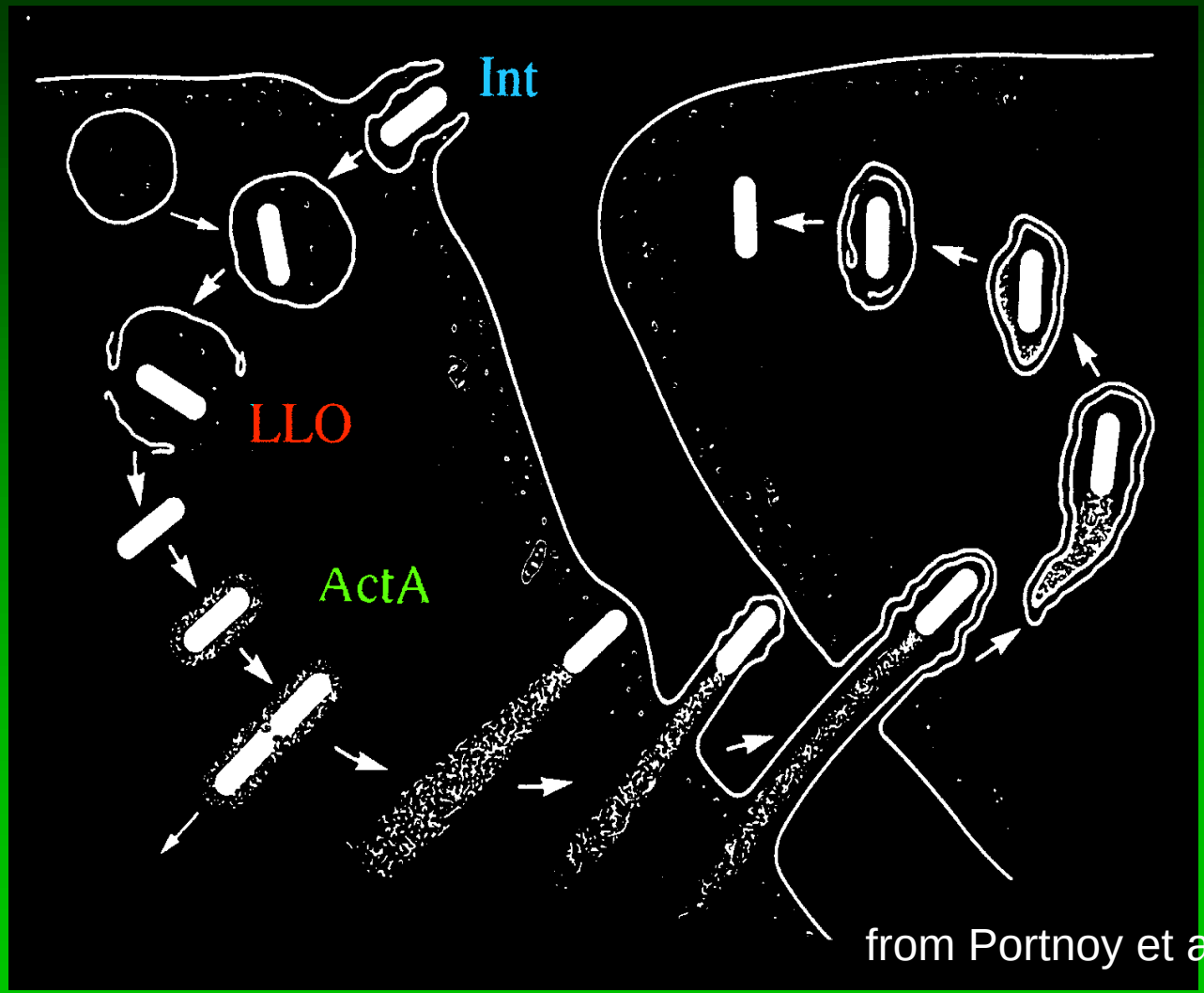
Illustration: the Listeria story

antibiotics:

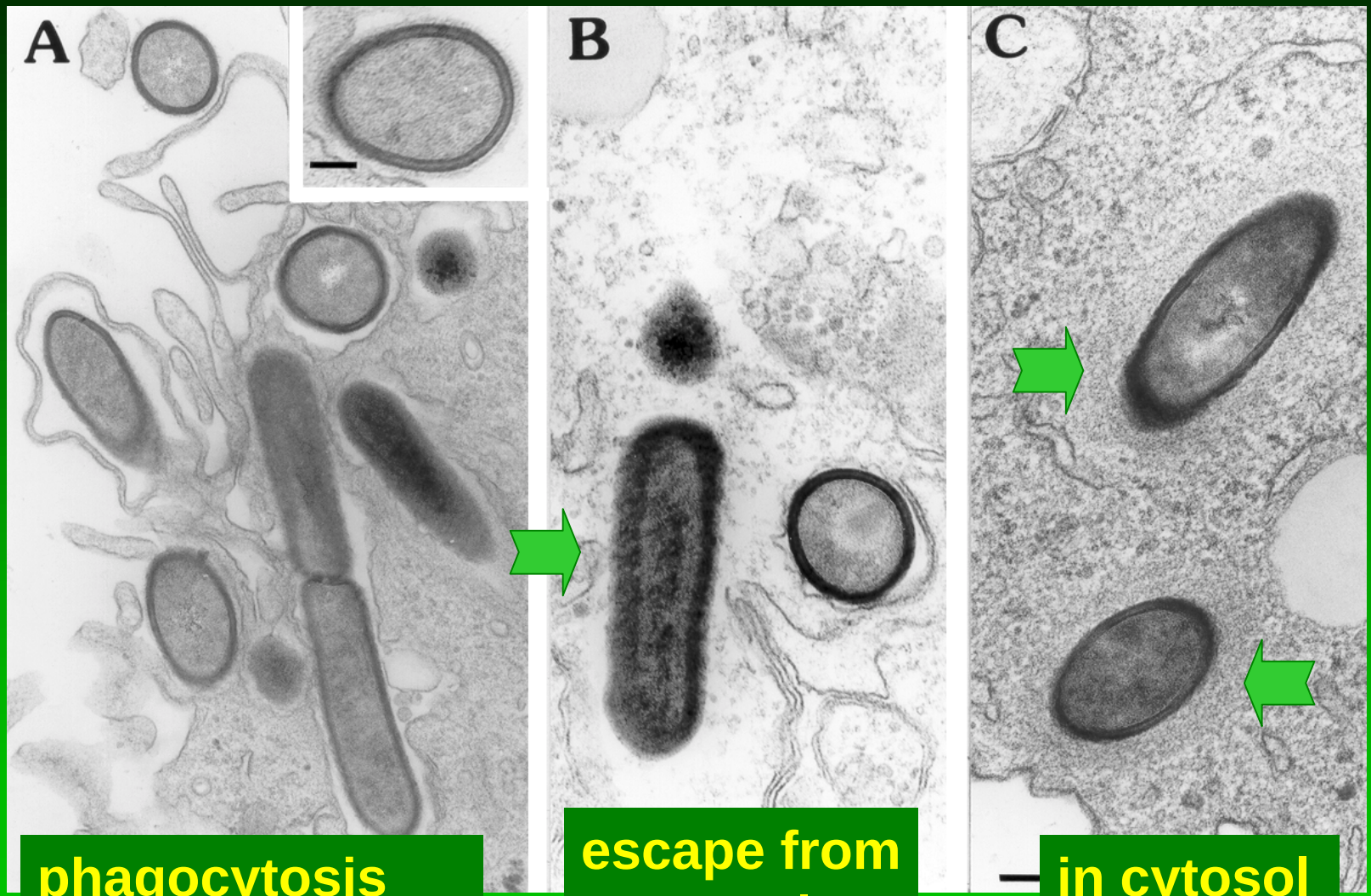
- **ampicillin/meropenem**
- **azithromycin**
- **sparfloxacin/moxifloxcin**
- **pivampicillin**

Listeria monocytogenes
hly+

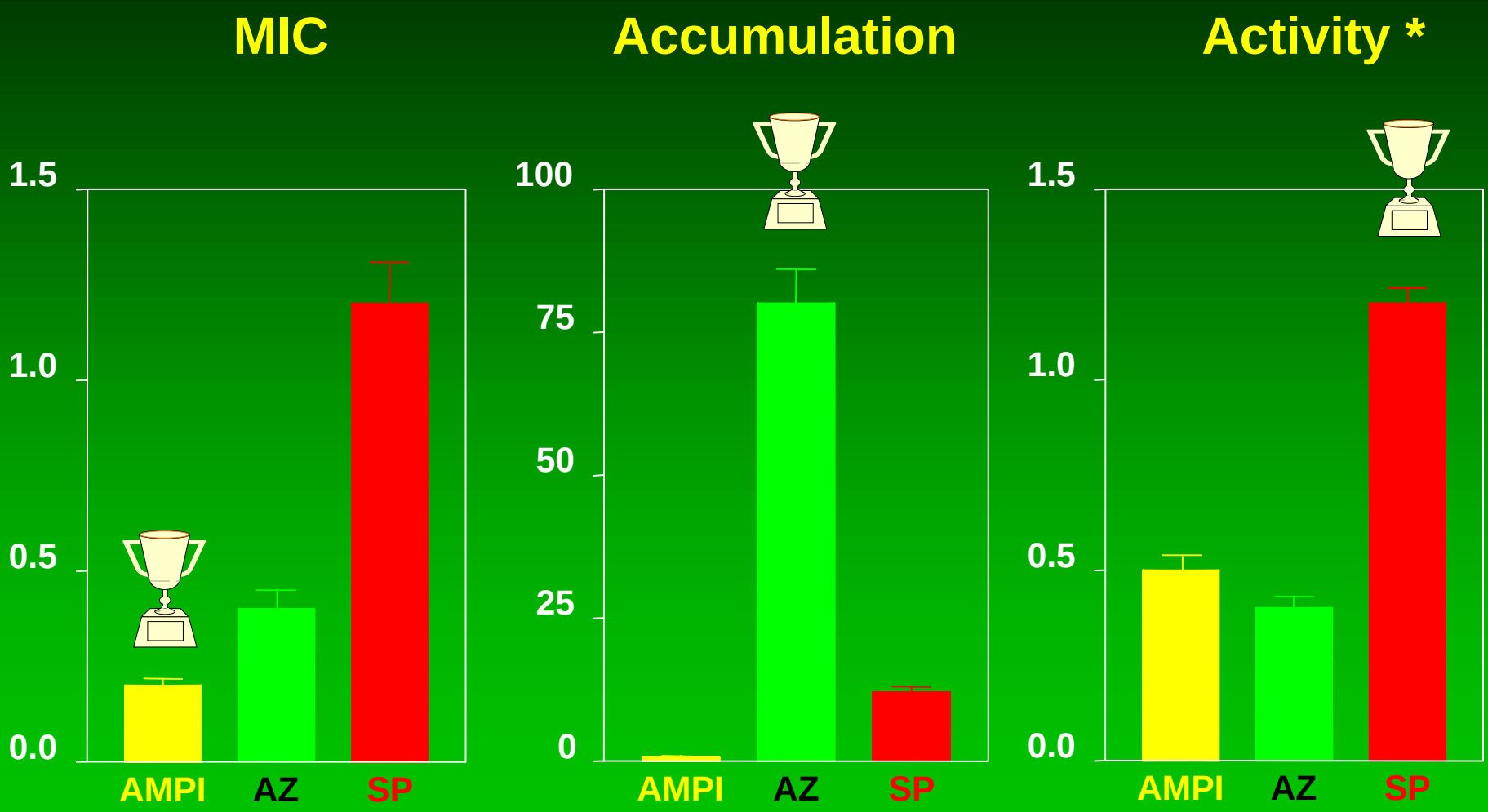
Intracellular infection cycle of *Listeria monocytogenes* hly^{+}



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



1st question: is there a simple relation between MIC, accumulation and intracellular activity (5 h model)



Ouadhriri et al., AAC,1999

* Δ log CFU 5h
Ce = 10 x MIC

Listeria m. and ampicillin

Ampicillin is poorly active against intracellular *Listeria m.* in spite of its favourable MIC;

➡ lack of accumulation ...

Why do you keep ampicillin ?

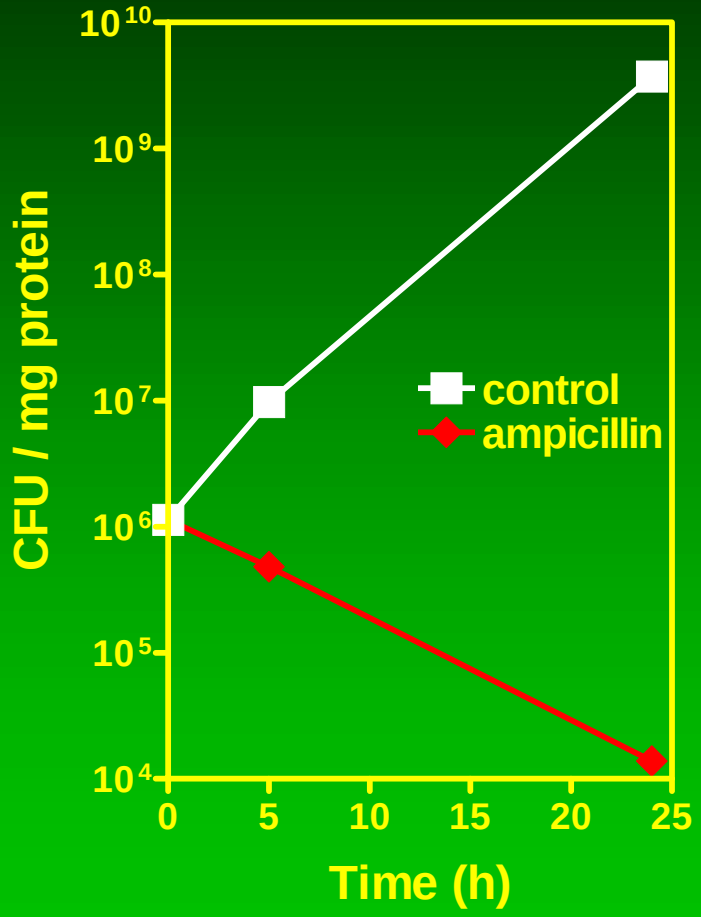
➔ extracellular bacteria

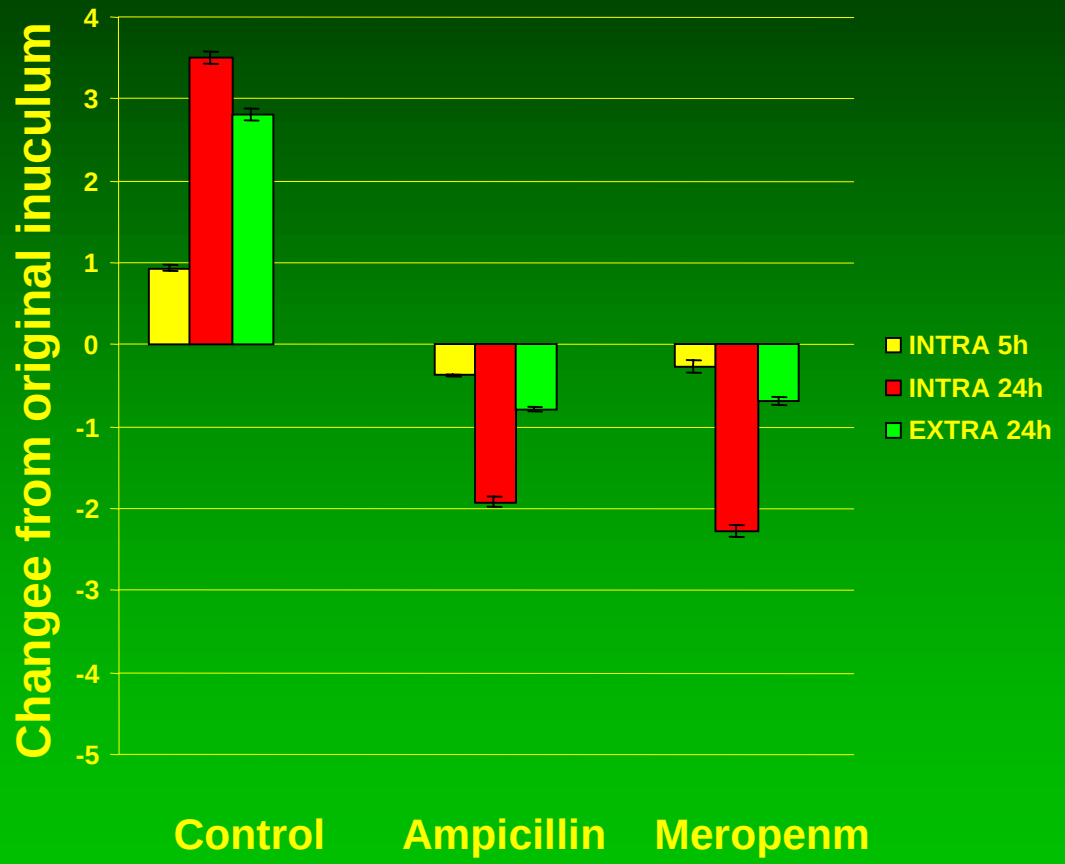
➔ get intracellular activity with very large doses ??

(but β-lactams are NOT dose-dependent…)

➔ **but may be you just have to wait ...**

β-lactams become bactericidal <u>intracellularly</u> after 24h





(Carryn et al., 2002, *JAC* 51:1051-52

Listeria m. and azithromycin

Azitromycin is also poorly active against intracellular *Listeria m.* in spite of its exceptionally large intracellular concentration

⇒ most azithromycin is trapped in lysosomes

⇒ azithromycin is poorly bactericidal

Is there a future for macrolides ?

Listeria m. and fluoroquinolones

In this pharmacological model *, sparfloxacin IS the most active in spite of a unfavourable MIC (1.4 µg/ml) and modest cellular accumulation (12 x)

Fluoroquinolones

⇒ have a large subcellular bioavailability

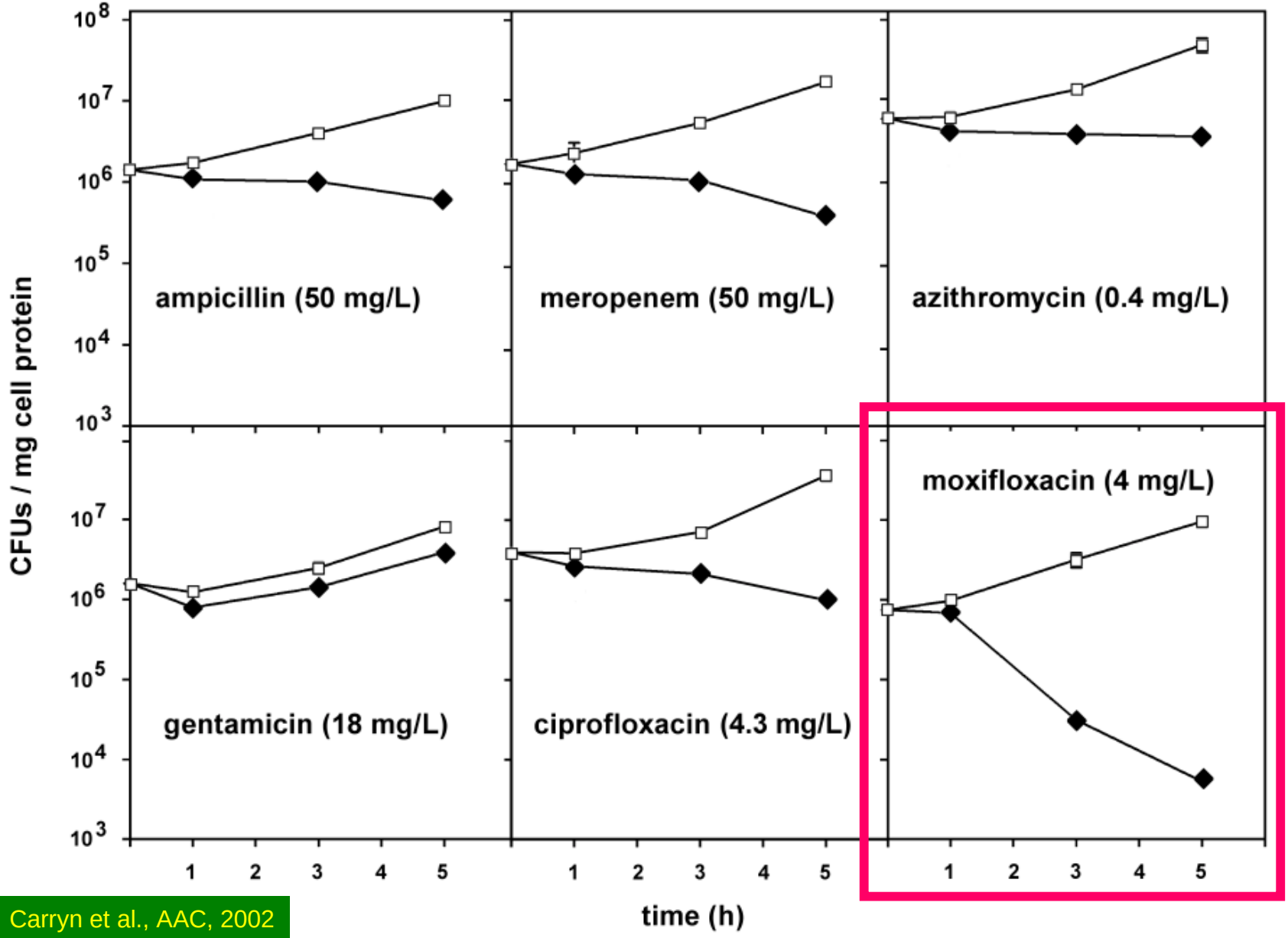
⇒ are highly bactericidal

Why don't you use fluoroquinolones today ?

➔ too low intrinsic activity ** ...

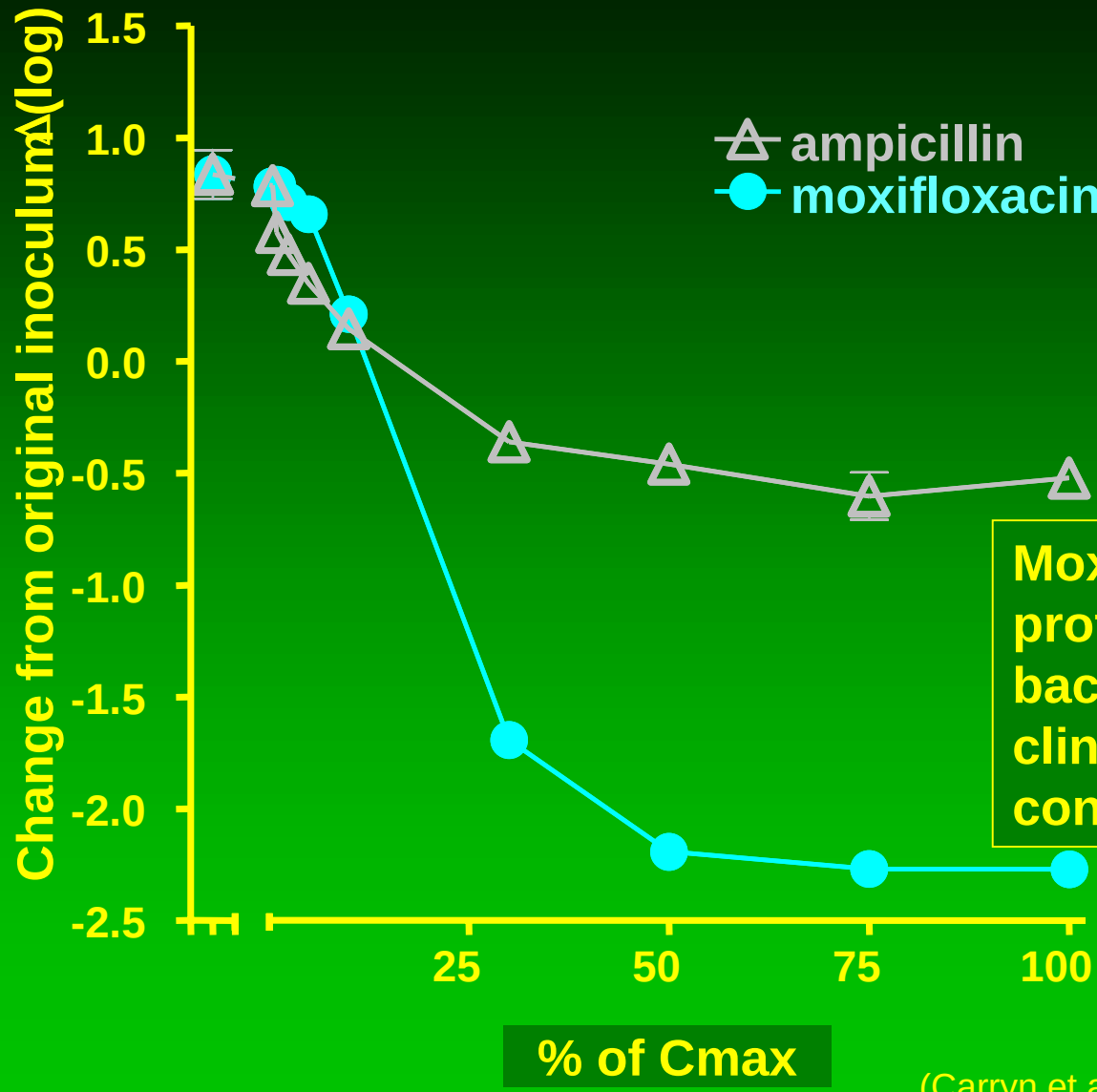
* all Ce = 10 X the MIC

But look at moxifloxacin (5h model) ...



Carryn et al., AAC, 2002

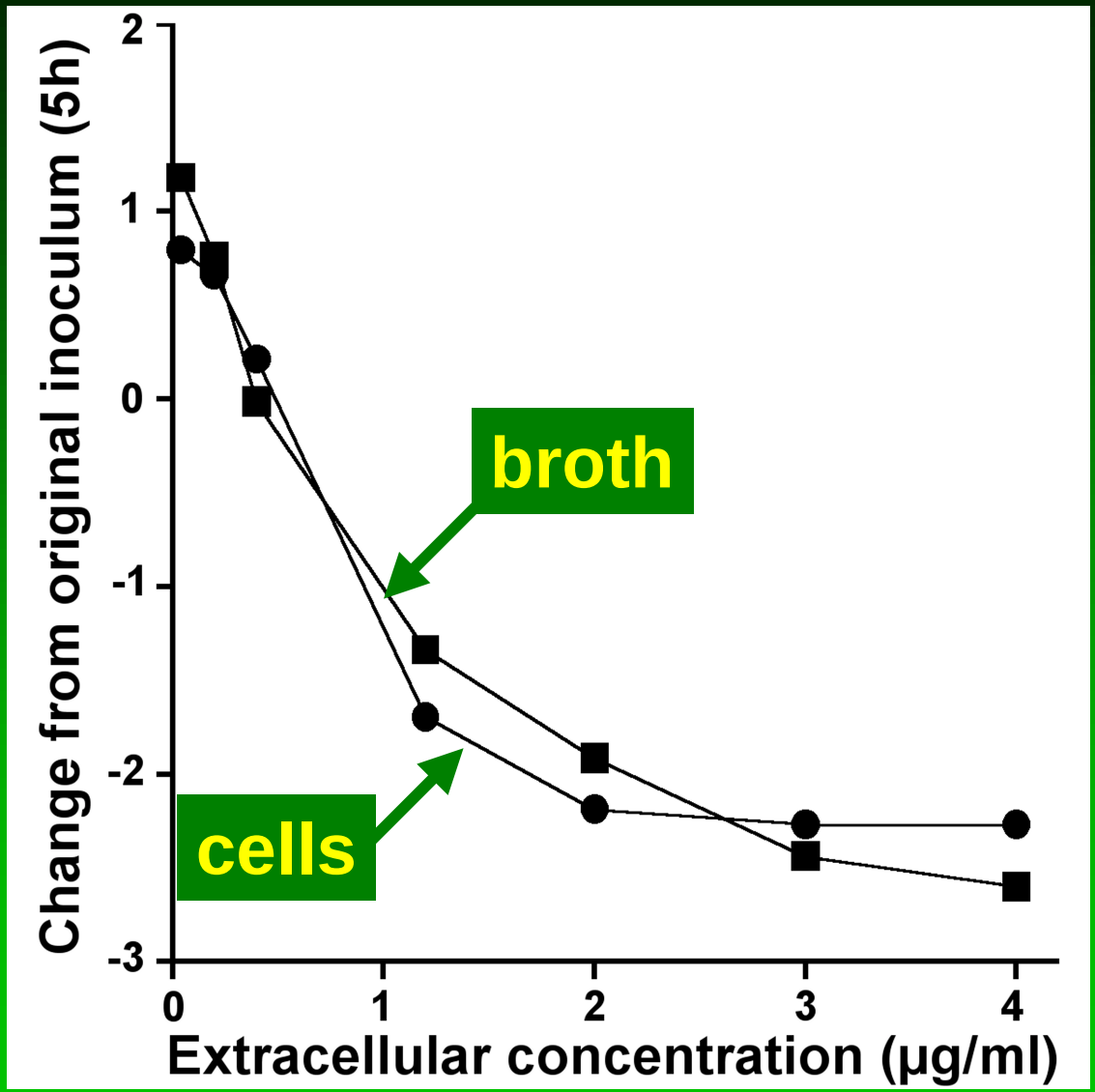
Comparative intracellular activities



Moxifloxacin is profoundly bactericidal at clinically achievable concentrations

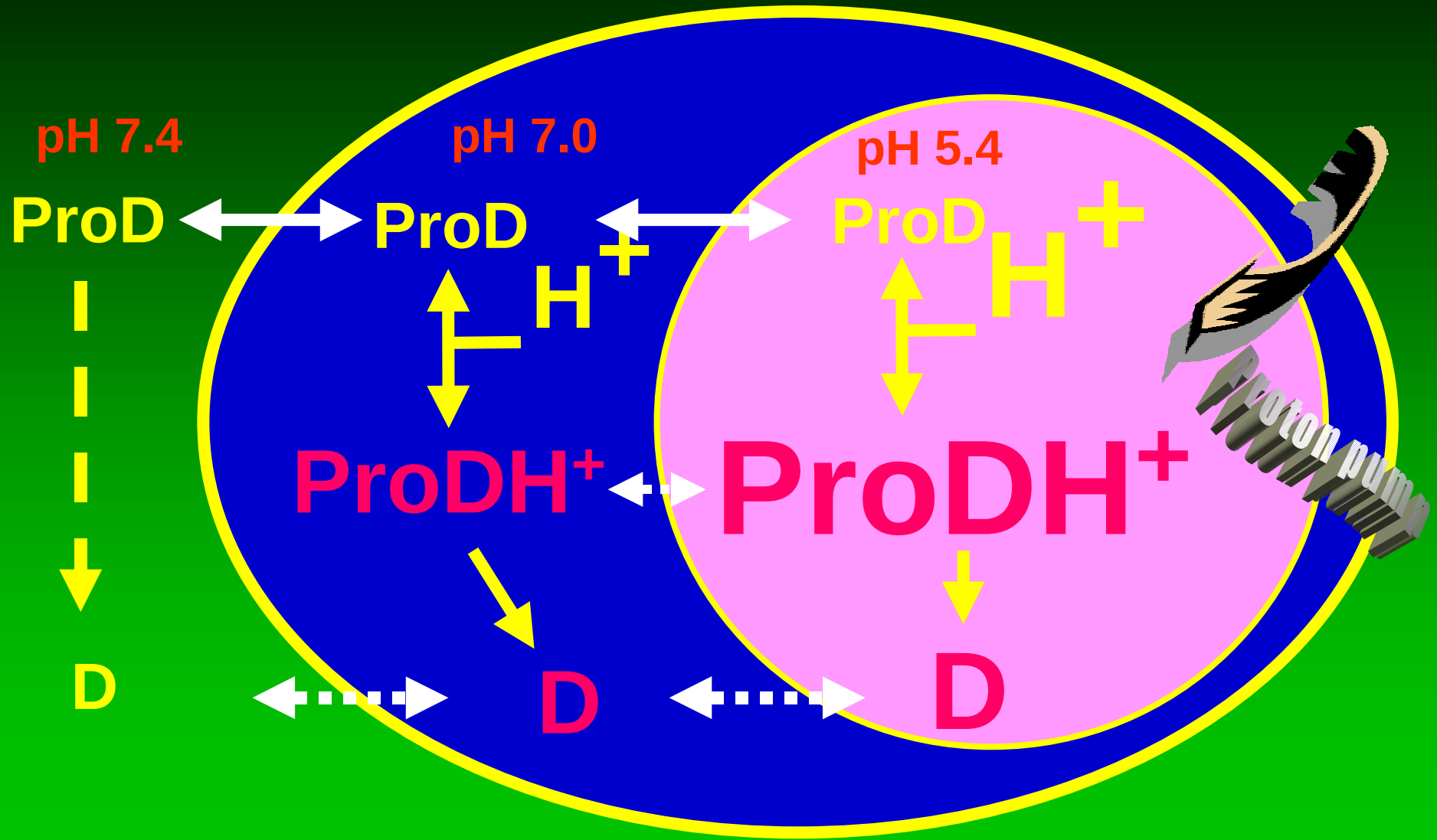
(Carryn et al., 2002, *AAC* 43:2095-103)

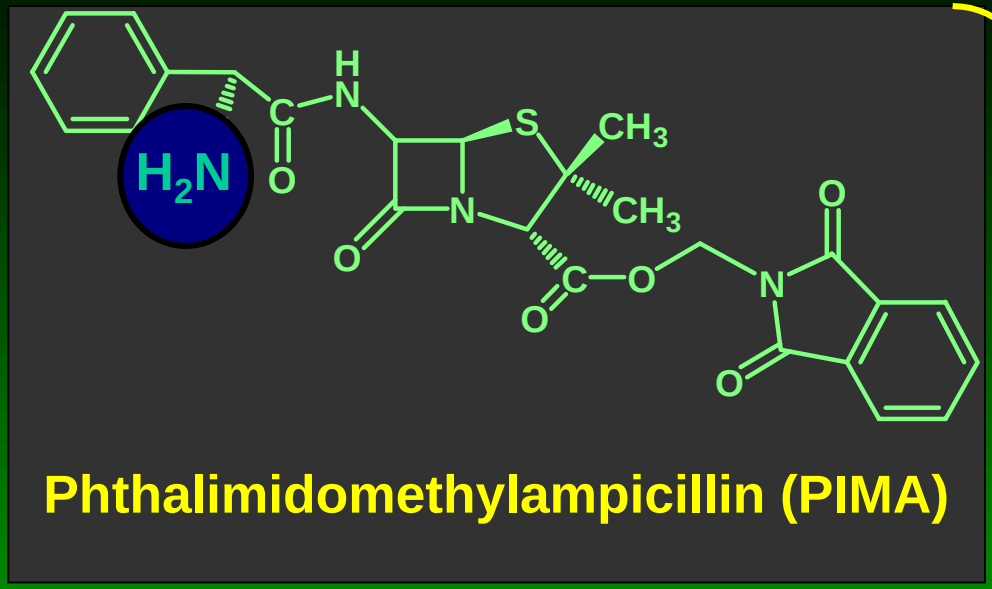
However, intracellular moxifloxacin is NOT more active intracellularly than extracellularly ...



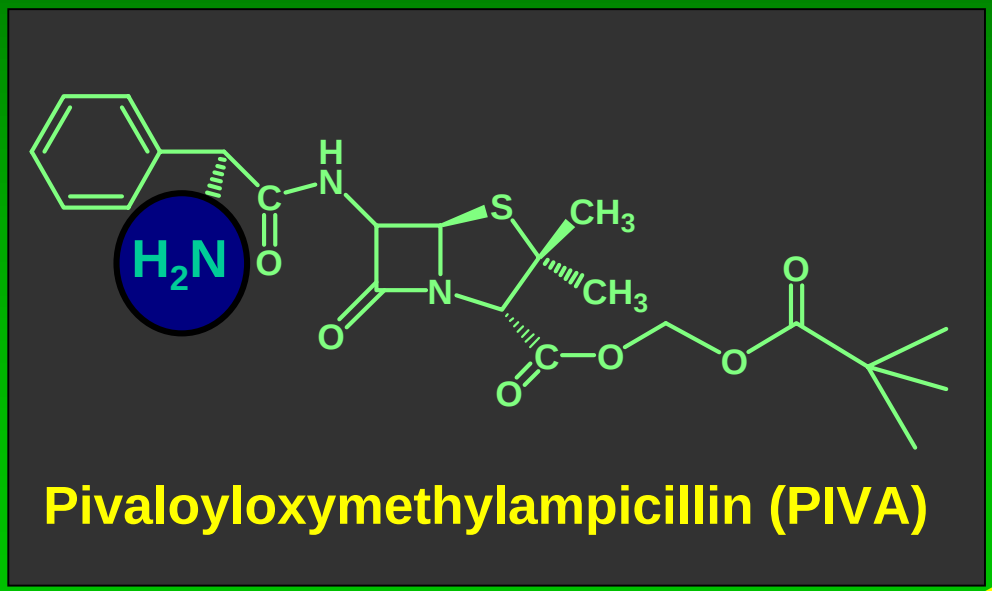
Carryn et al., AAC, 2002

A basic prodrug of a β-lactam ?





Phthalimidomethylampicillin (PIMA)



Pivaloyloxymethylampicillin (PIVA)

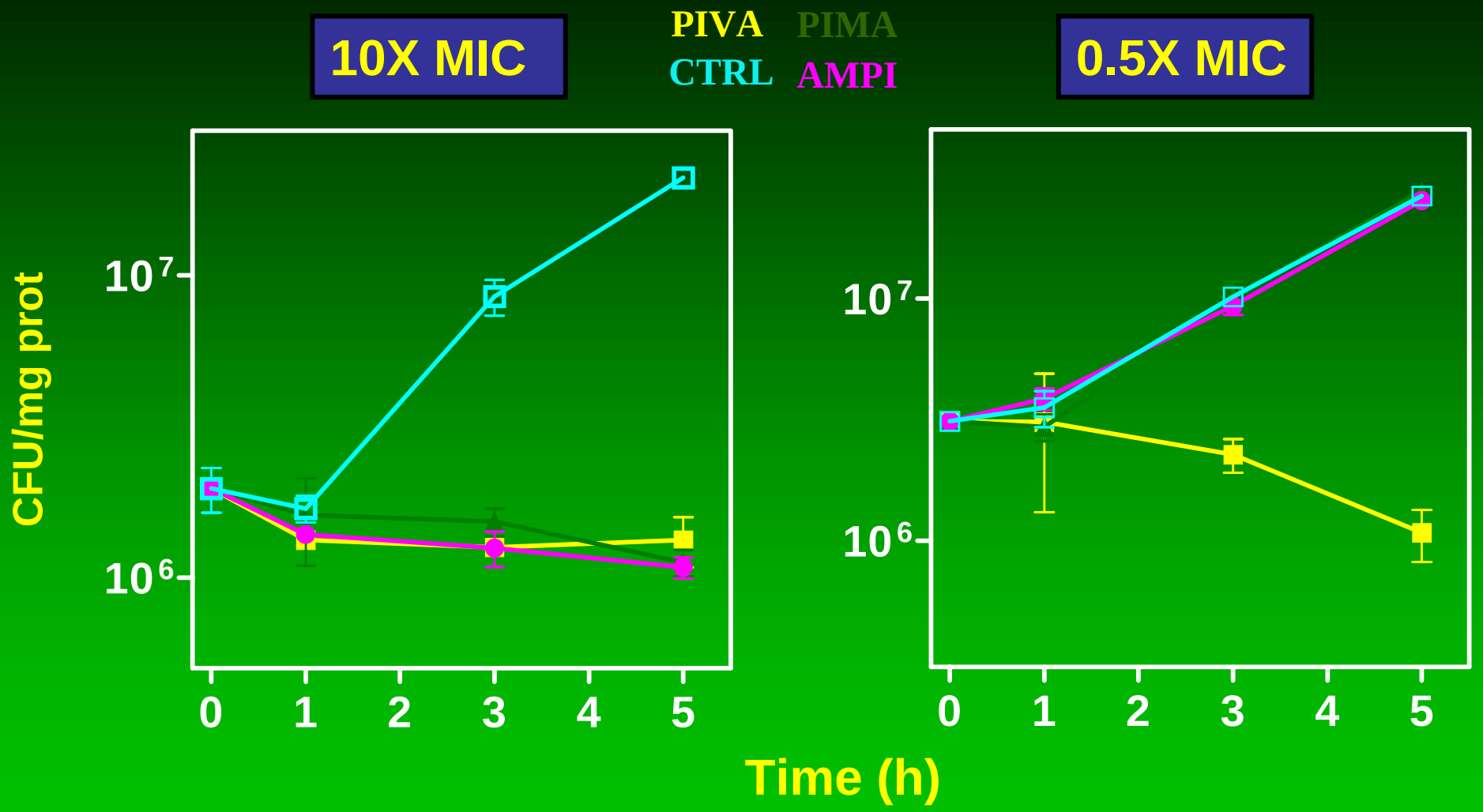
Basic compounds that

- **regenerate ampicillin**
- **accumulate in J774 macrophages**

Fan et al, Bioorg. Med. Chem. Let.1997

Paternotte et al, Biorg. Med. Chem. 2001

Intracellular activity for extracellular concentrations of ...

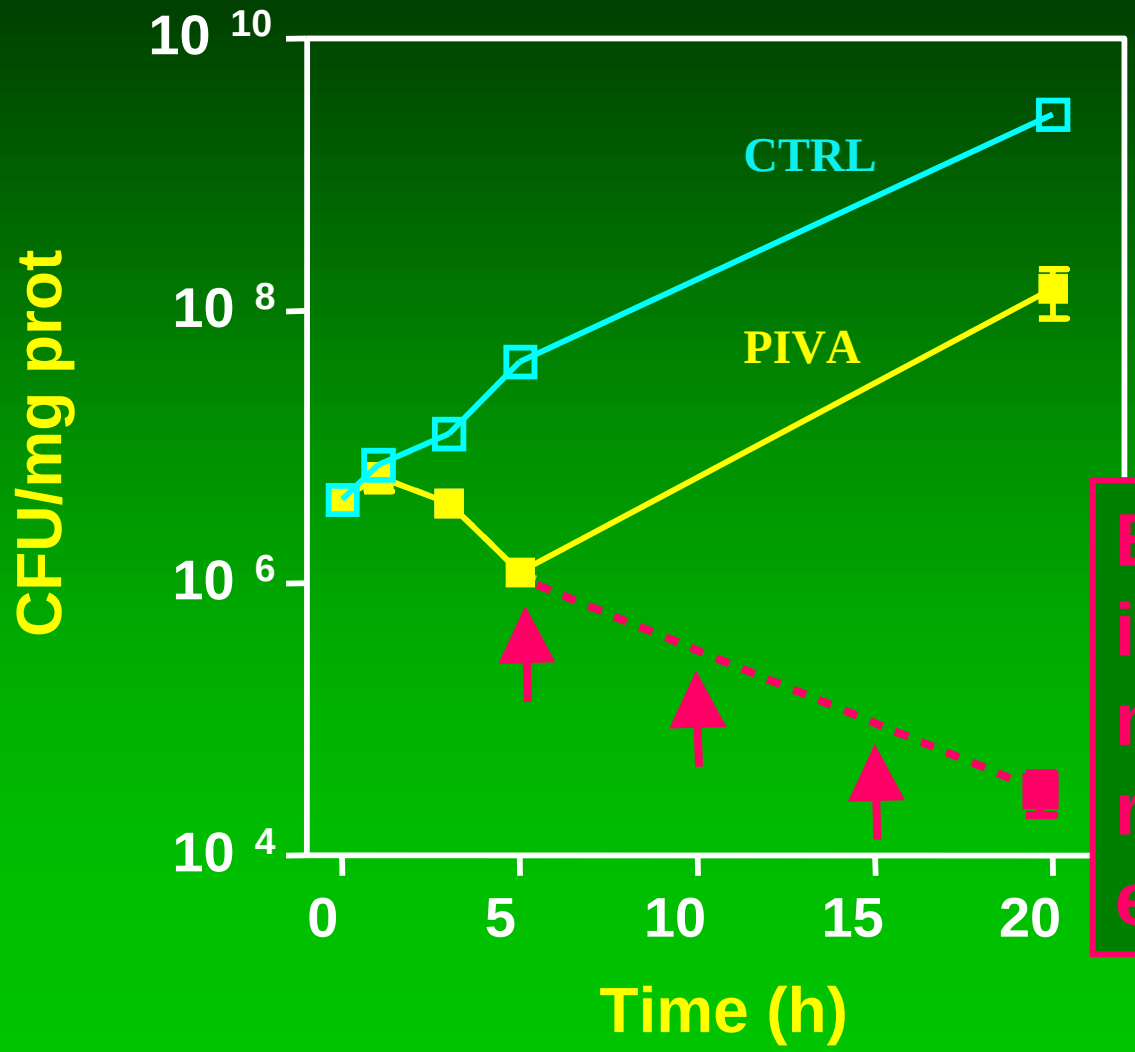


Same activity for PIVA, PIMA and AMPI

Only PIVA is active

Chanteux et al, JAC, 2003

At low extracellular concentration, PIVA loses its activity after 5 h if the medium is not renewed



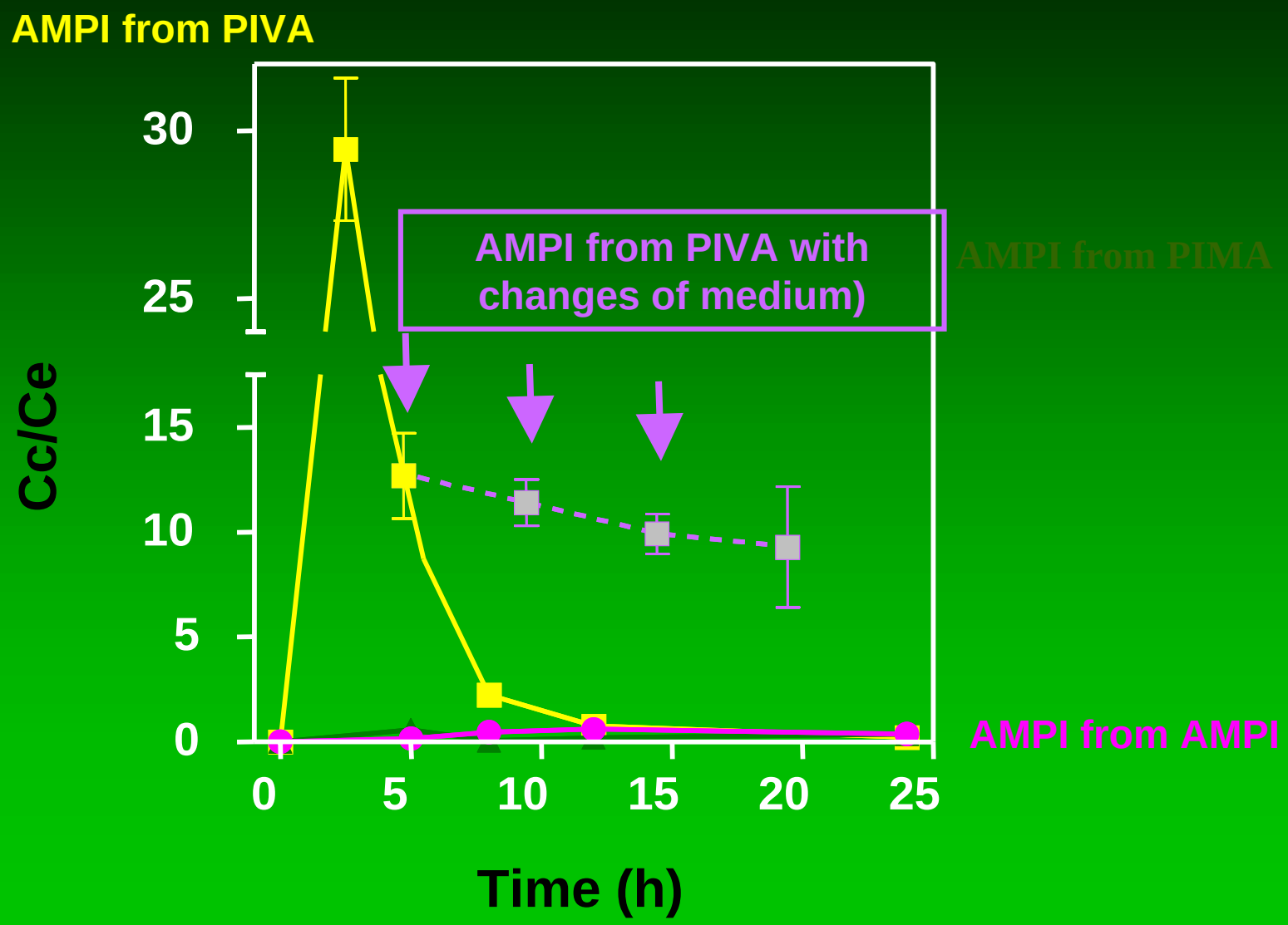
Extracellular concentration

0.5X MIC

But maintains it if the medium is renewed every 5 h

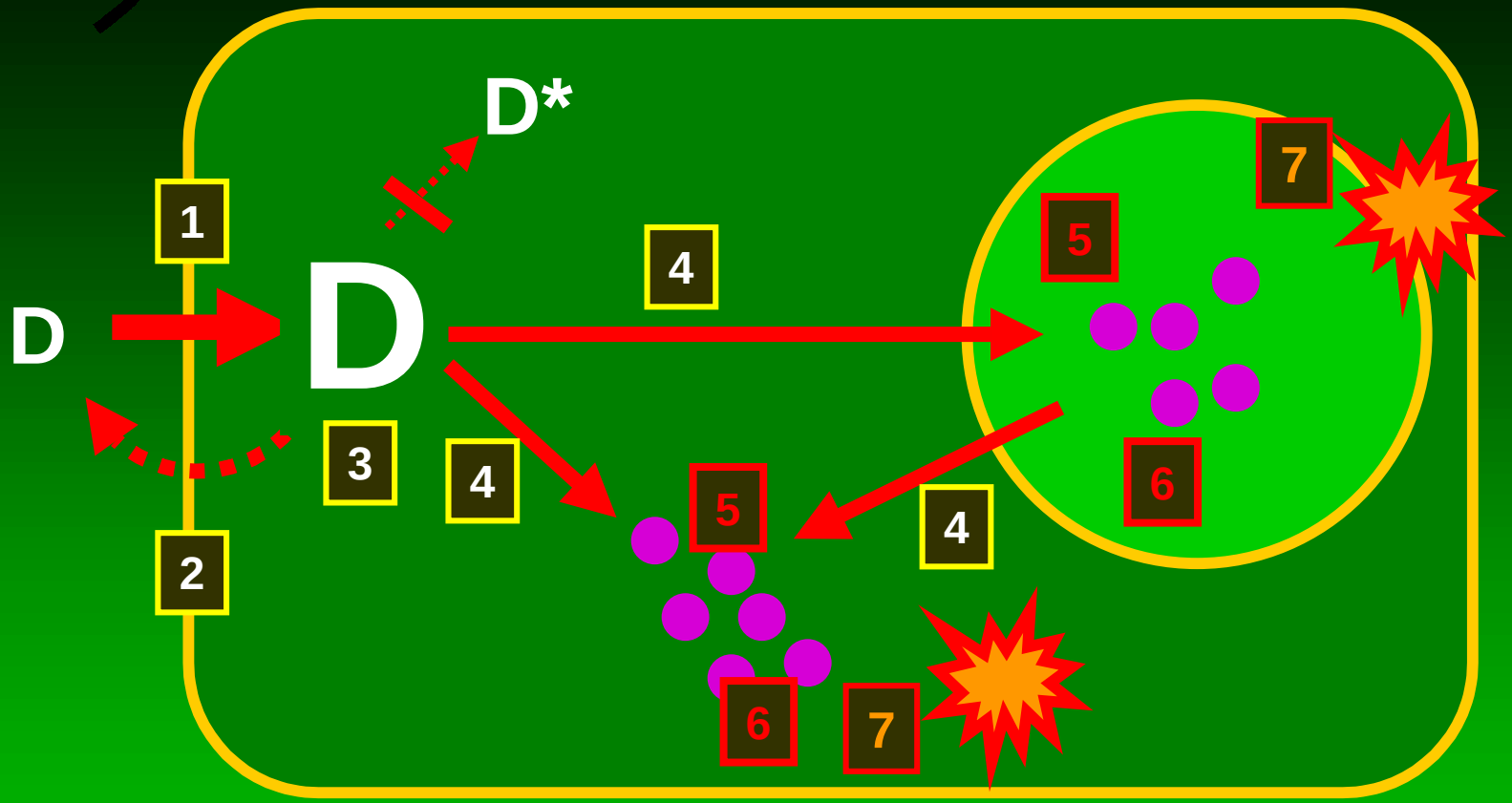
Chanteux et al, JAC, 2003

PIVA releases large amount of intracellular ampicillin



Chanteux et al, JAC, 2003

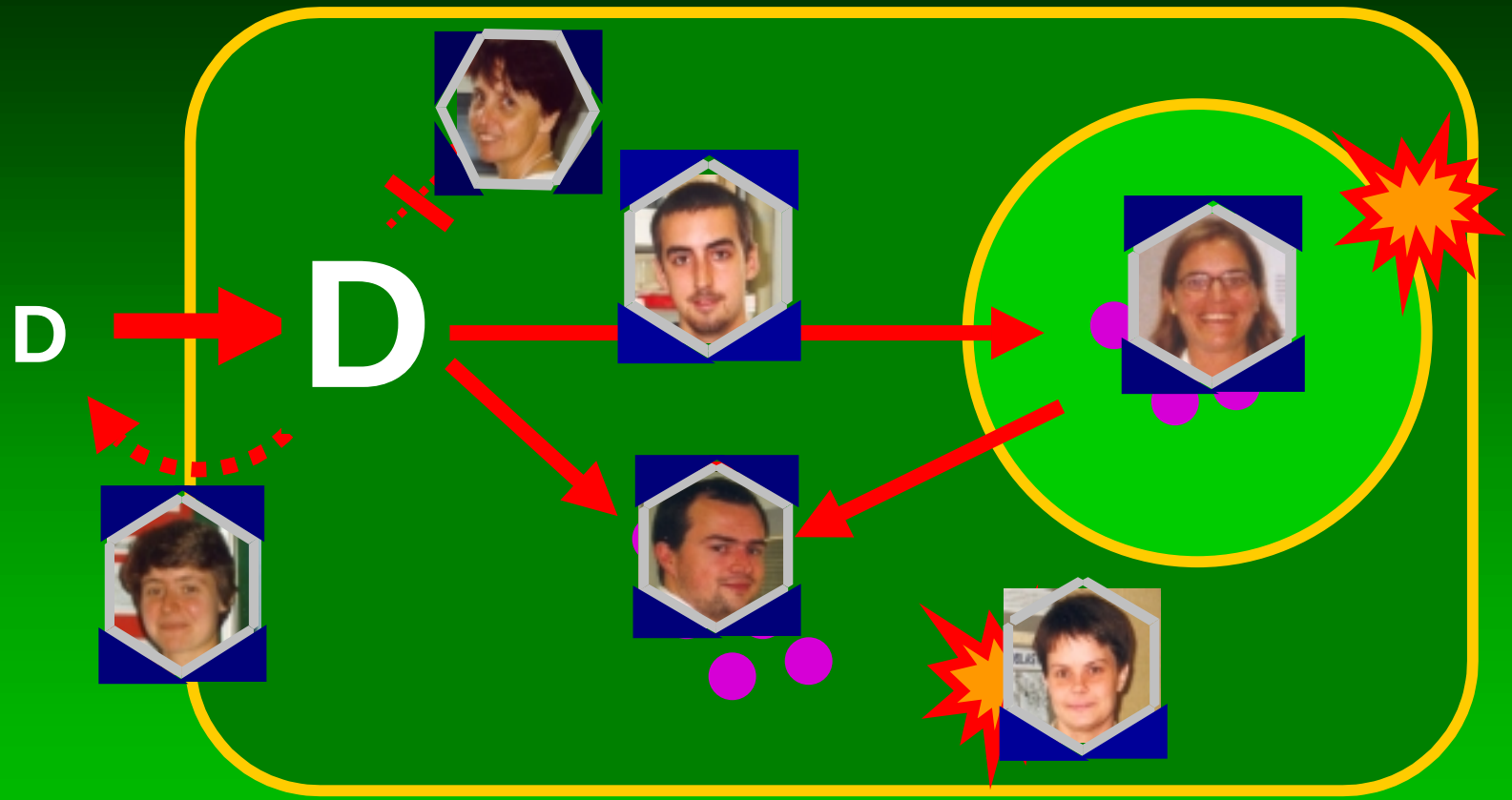
The seven pillars of intracellular / intratissular activity ?



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

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

The 6 pillars of intracellular / intratissular accumulation and activity of antibiotics...



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Hugues Chanteux, Donatienne Tyteca, Marie-Paule Mingeot-Leclercq ...