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Oral presentation O147 – Sunday April 20th

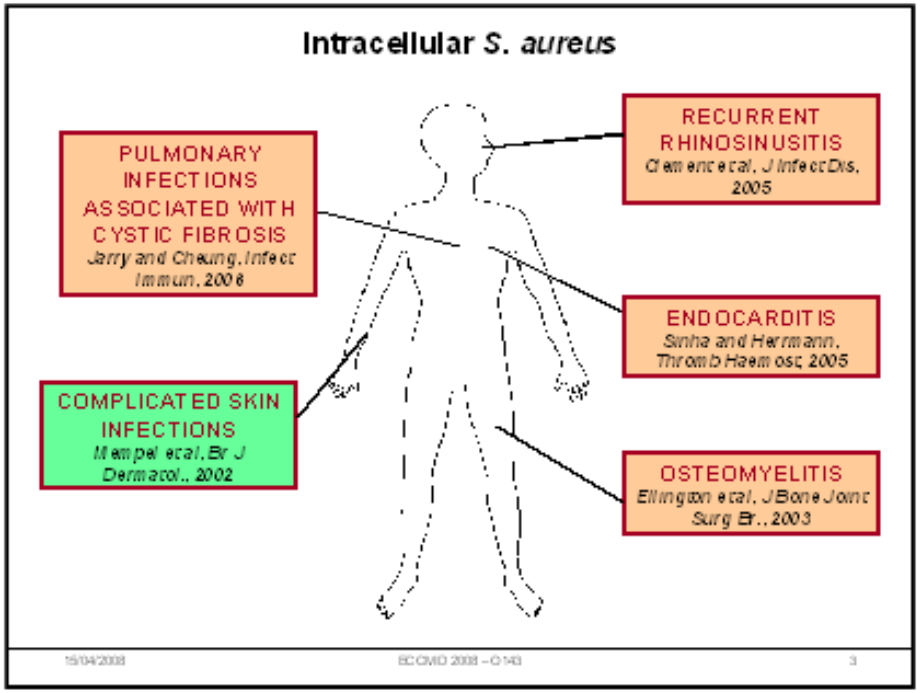
MDR1 (P-glycoprotein) and MRP1 (Multidrug resistance-related protein 1) eukaryotic efflux transporters do no affect the cellular accumulation and intracellular activity of tigecycline towards intraphagocytic *S. aureus*

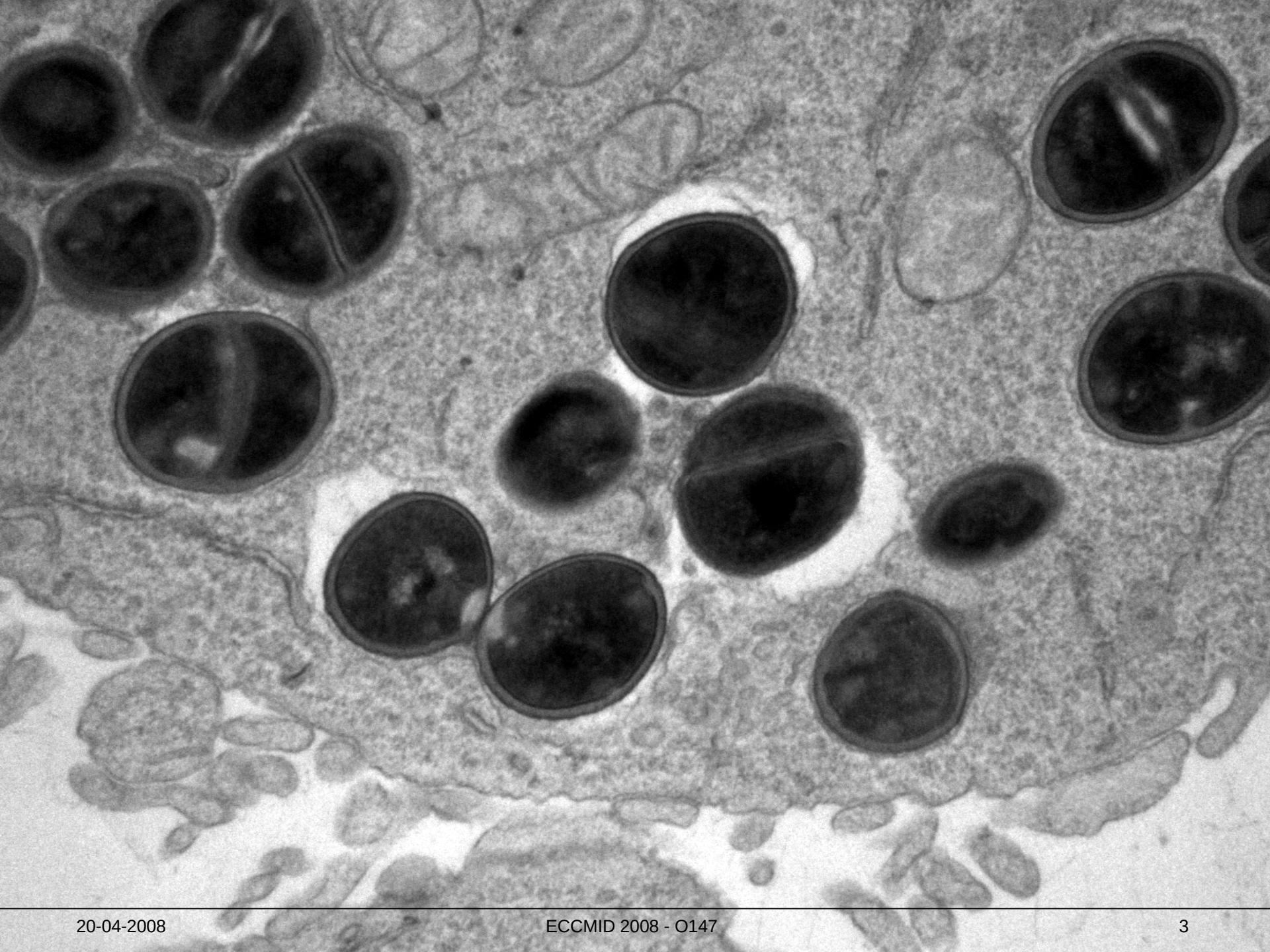
Sandrine Lemaire, Françoise Van Bambeke, M.-P. Mingeot-Leclercq and P.M. Tulkens

Unité de Pharmacologie cellulaire et moléculaire
Université catholique de Louvain
Brussels, Belgium

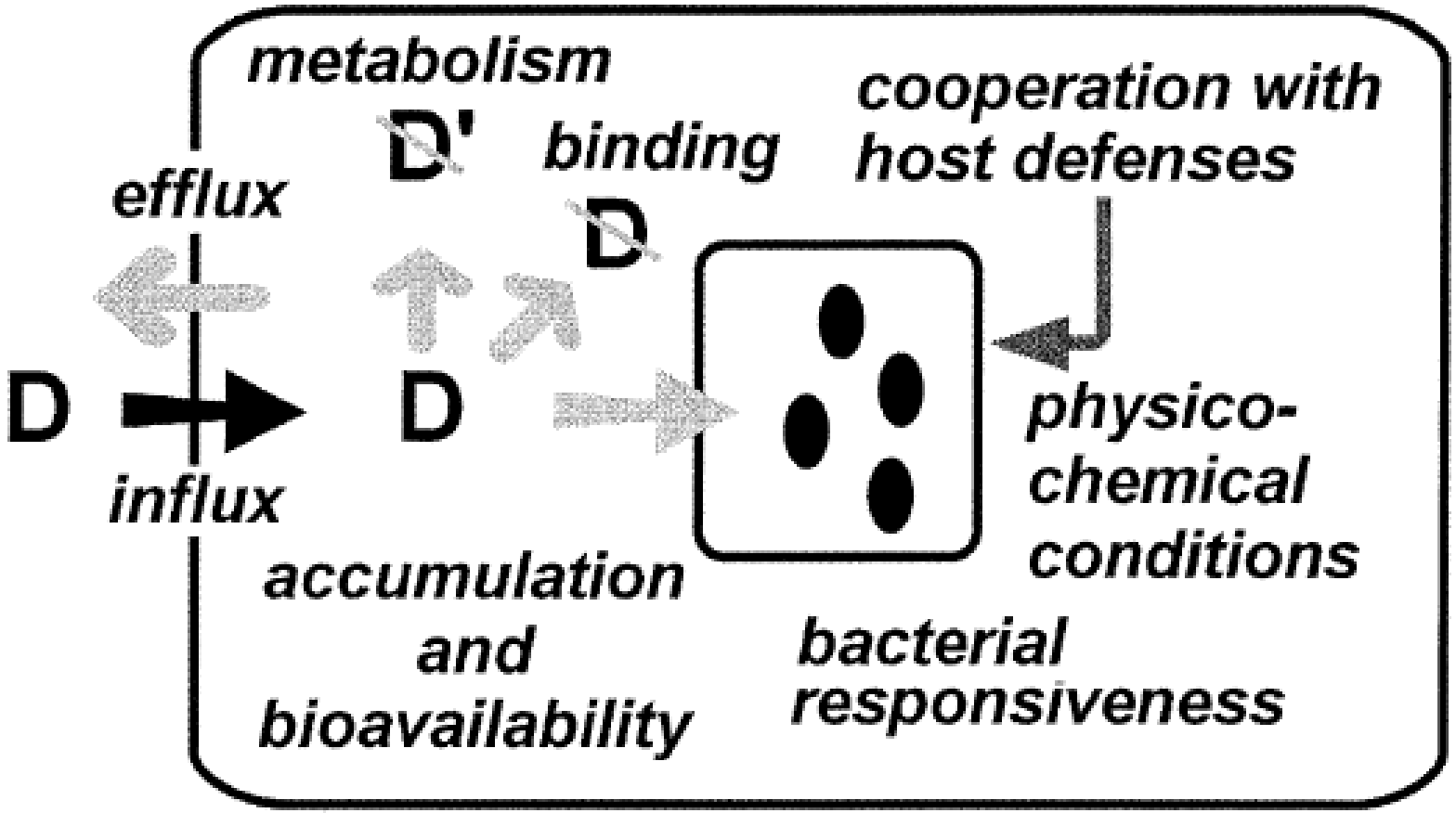
May I remind you that intracellular *S. aureus* is a reality …

and that tigecycline has indication for staphylococcal infections…

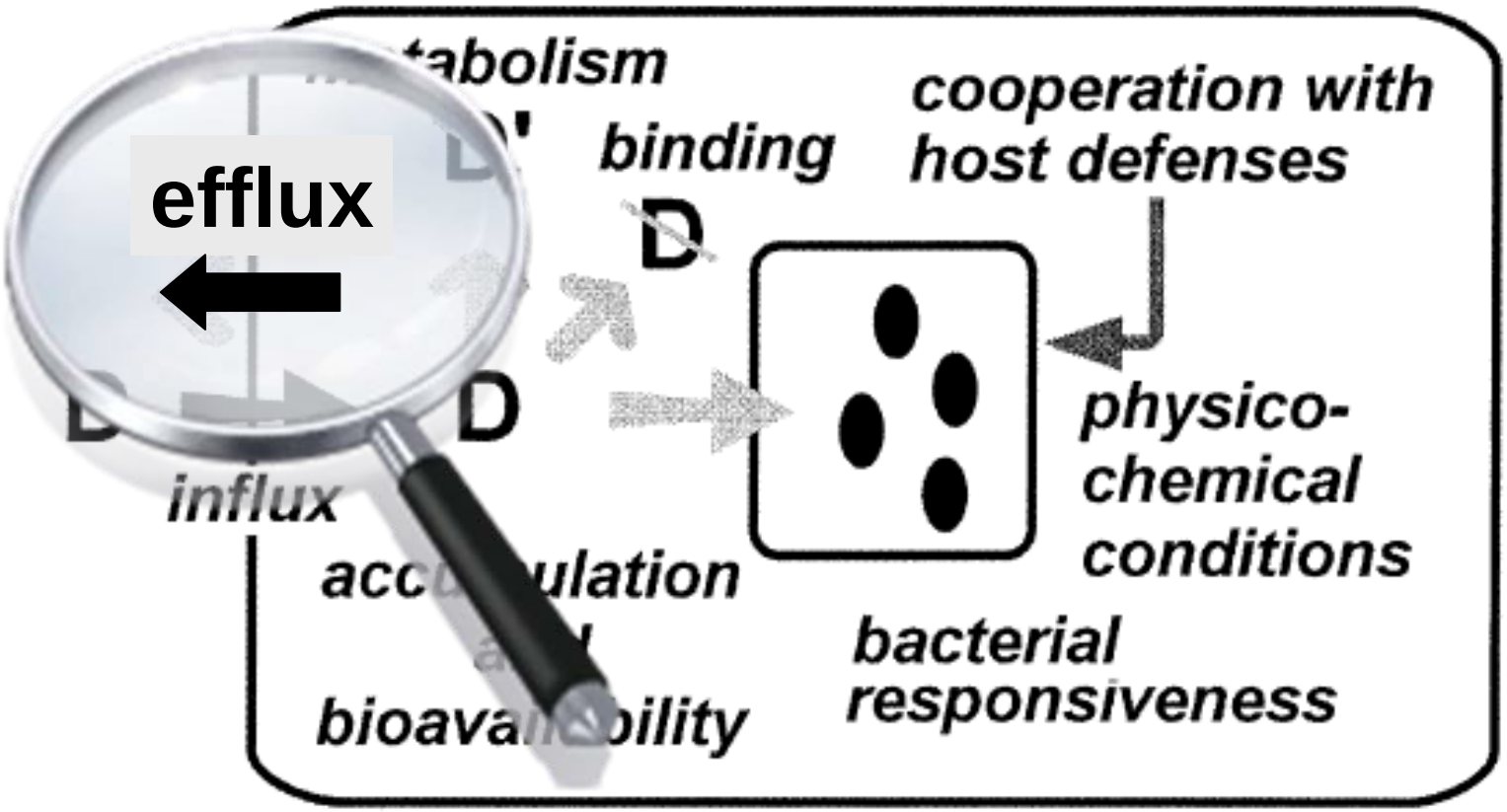




Factors modifying the activity of antibiotics against intracellular pathogens



Carryn et al., Infect Dis Clin N Am, 2003



Eukaryotic efflux transporters can modulate the cellular concentration and the intracellular activity of antibiotics

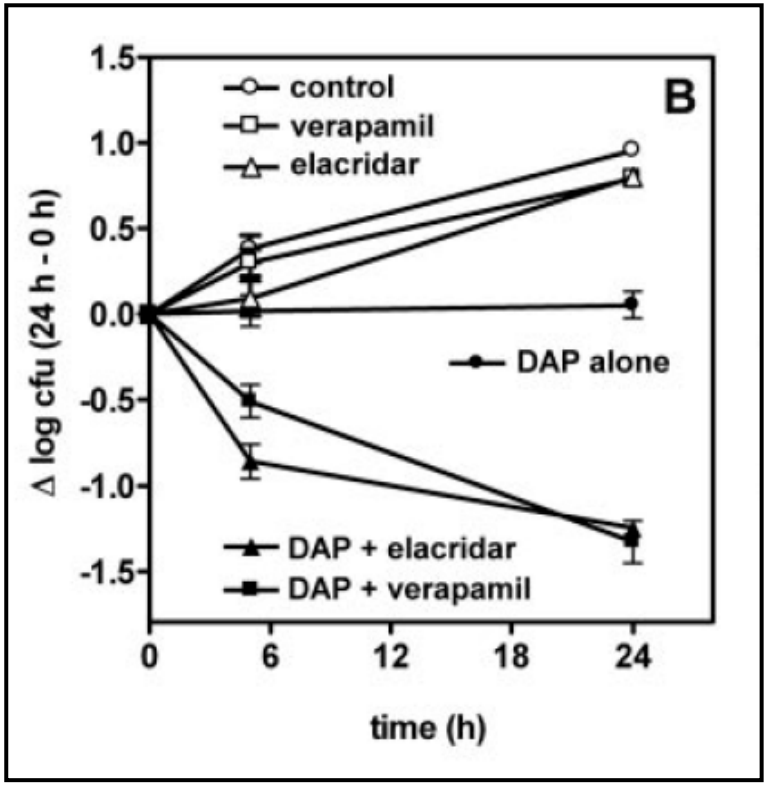
Carryn et al., Infect Dis Clin N Am, 2003

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2007, p. 2748–2757 Vol. 51, No. 8
0066-4804/07/$08.00+0 doi:10.1128/AAC.00090-07

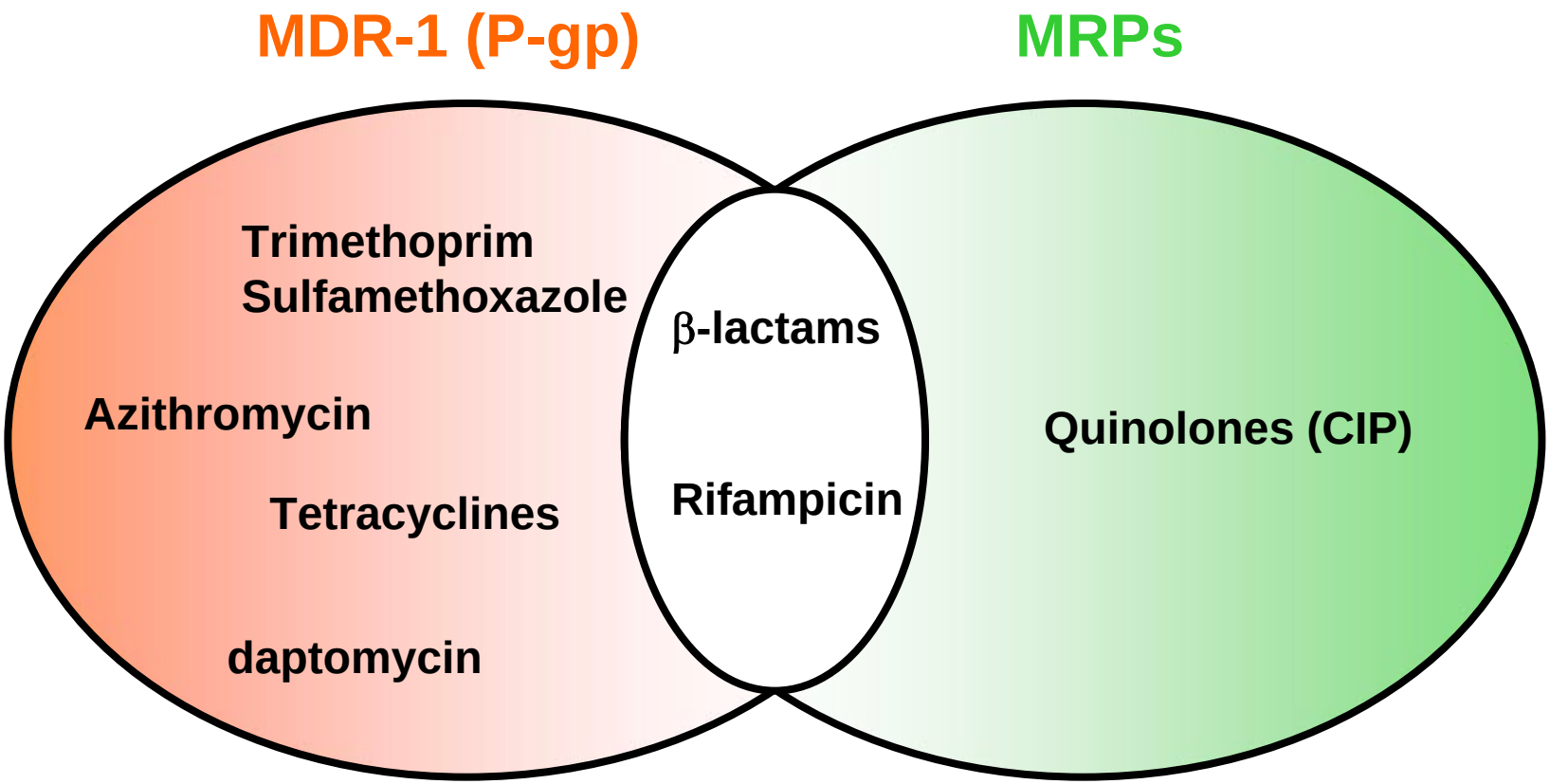
Modulation of the Cellular Accumulation and Intracellular Activity of Daptomycin towards Phagocytized *Staphylococcus aureus* by the P-Glycoprotein (MDR1) Efflux Transporter in Human THP-1 Macrophages and Madin-Darby Canine Kidney Cells[▽]

Sandrine Lemaire, Françoise Van Bambeke, Marie-Paule Mingeot-Leclercq, and Paul M. Tulkens*

Unité de Pharmacologie Cellulaire et Moléculaire, Université Catholique de Louvain, B-1200 Brussels, Belgium

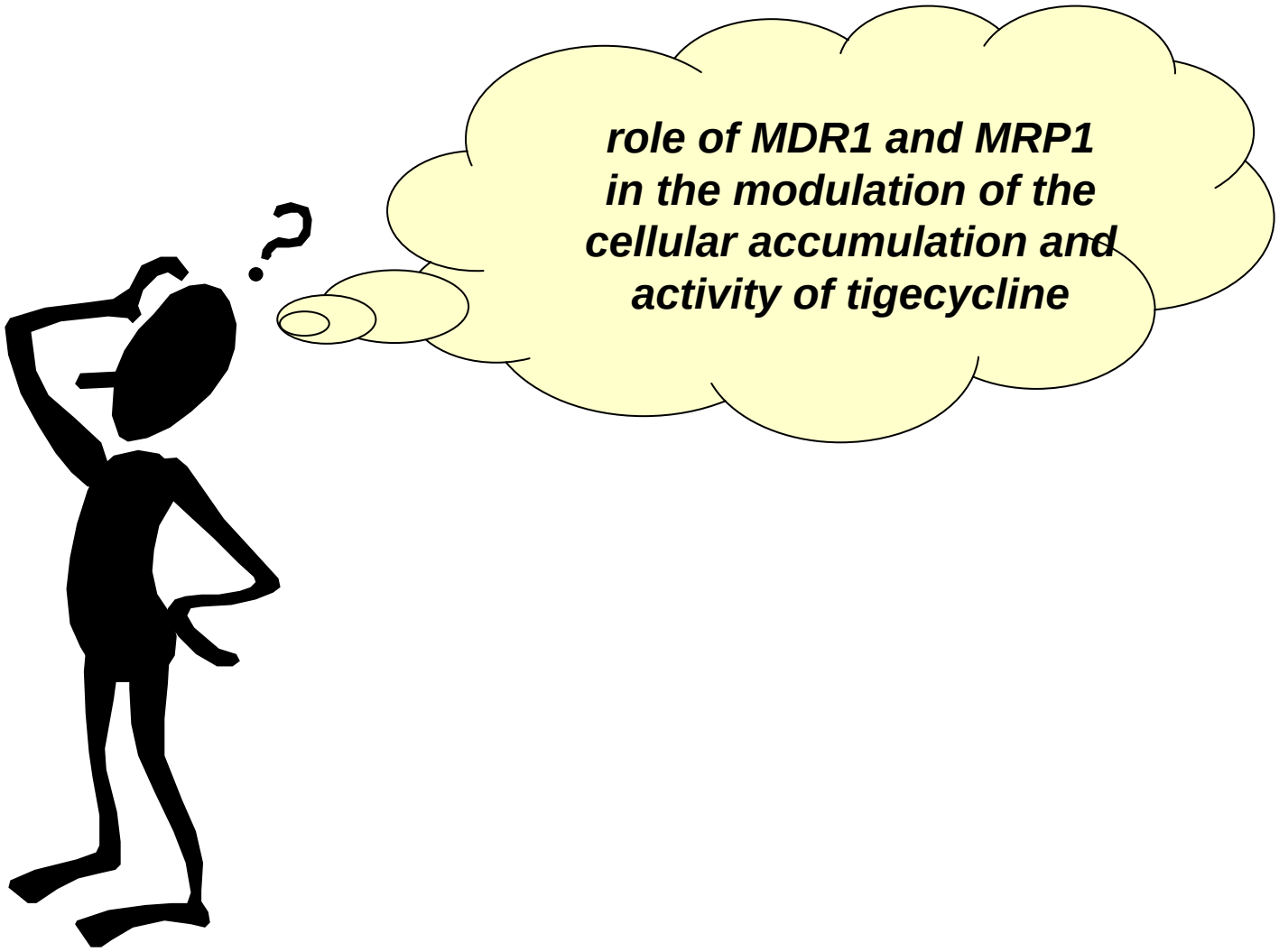


Active efflux of antibiotics

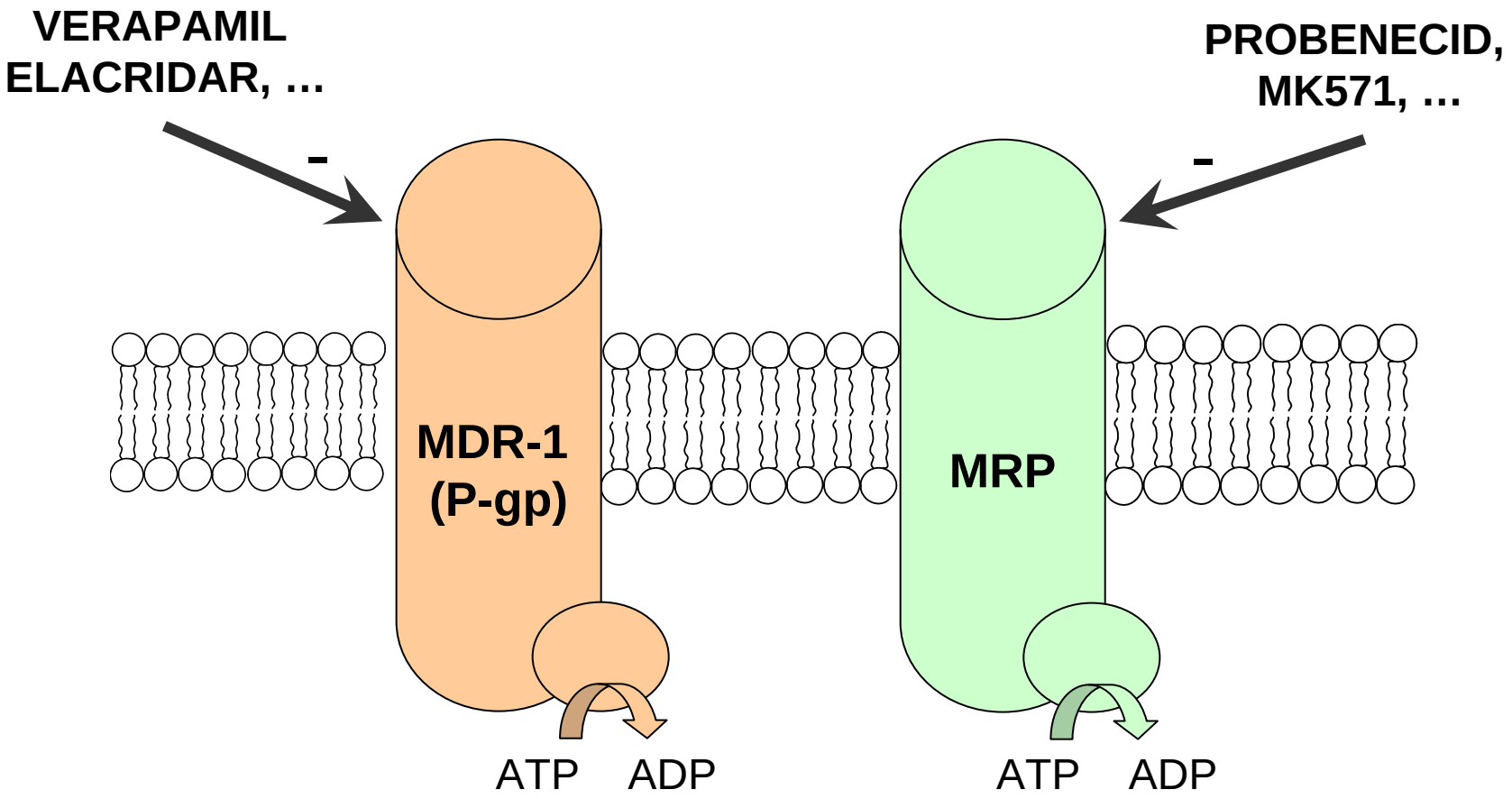


TIGECYCLINE ???

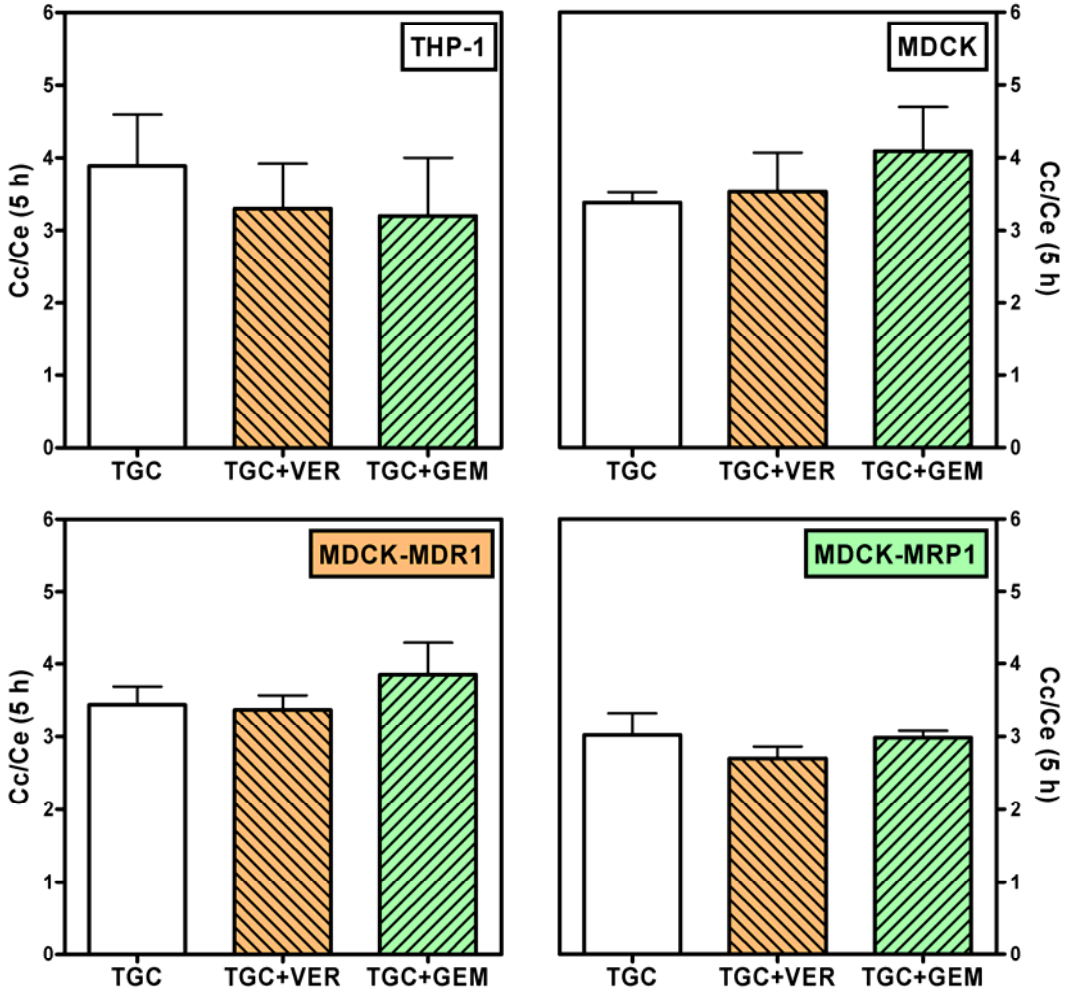
Aim of this work



How to inhibit ABC-transporters ?

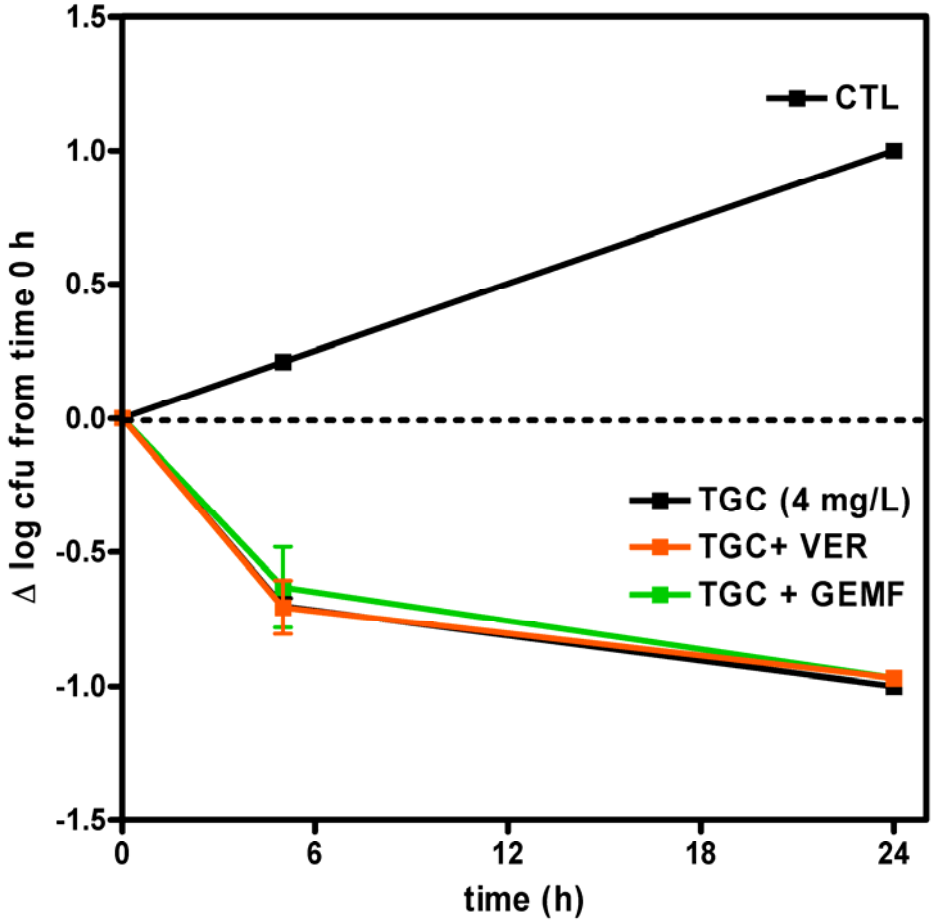


A) Cellular accumulation of tigecycline



Tigecycline accumulates 3-4 times in all cell lines, disregarding of the level of expression of MDR1 or MRP1 transporters

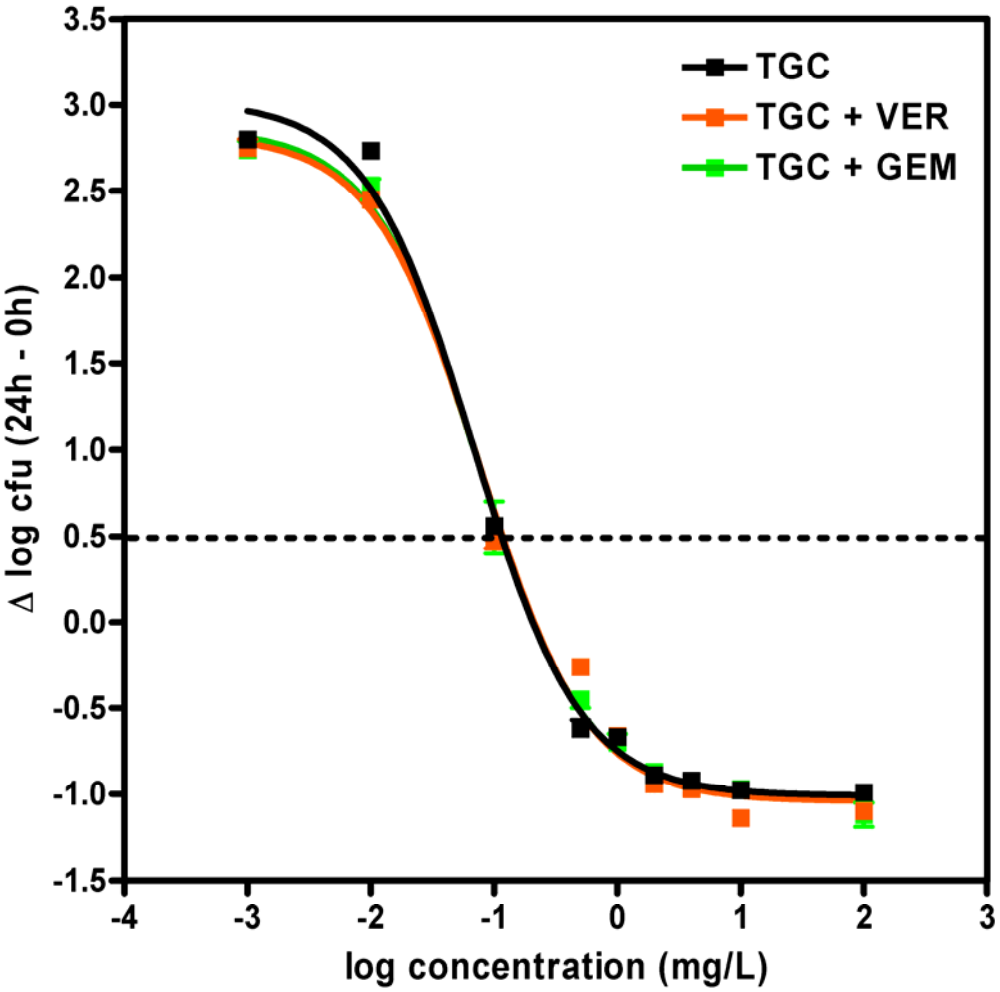
B) Activity of tigecycline against intracellular forms of *S. aureus*



- Tigecycline exerts quickly intracellular activity against *S. aureus*

- The pharmacological response of tigecycline is not modified in the presence of efflux pumps inhibitors

B) Activity of tigecycline against intracellular forms of *S. aureus*



• Against intracellular *S. aureus*, tigecycline exerts a concentration-dependent activity with:

- static dose: ~ 0.1 mg/L
- maximal effect: ~ - 1 log cfu

• The pharmacological response of tigecycline is not modified in the presence of efflux pumps inhibitors

Conclusion

- Tigecycline is substrate of **neither** MDR1 **nor** MRP-1 efflux transporters, two well recognized multidrug efflux pumps

- **Lack or low recognition** by efflux transporters appears as an asset for antibiotics when dealing with intracellular infections