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

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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
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 Cells³

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Active efflux of antibiotics

MDR-1 (P-gp)  MRPs

- Trimethoprim
- Sulfamethoxazole
- Azithromycin
- Tetracyclines
- daptomycin

- β-lactams
- Rifampicin
- Quinolones (CIP)

TIGECYCLINE ??
Aim of this work

role of MDR1 and MRP1 in the modulation of the cellular accumulation and activity of tigecycline
How to inhibit ABC-transporters?

VERAPAMIL, ELACRIDAR, …

MDR-1 (P-gp)

ATP    ADP

MRP

ATP    ADP

PROBENECID, MK571, …
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