

Pharmacodynamic evaluation of the bactericidal activity of telavancin (TLV) against extracellular and intracellular MSSA and MRSA

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S. aureus as an intracellular pathogen ...

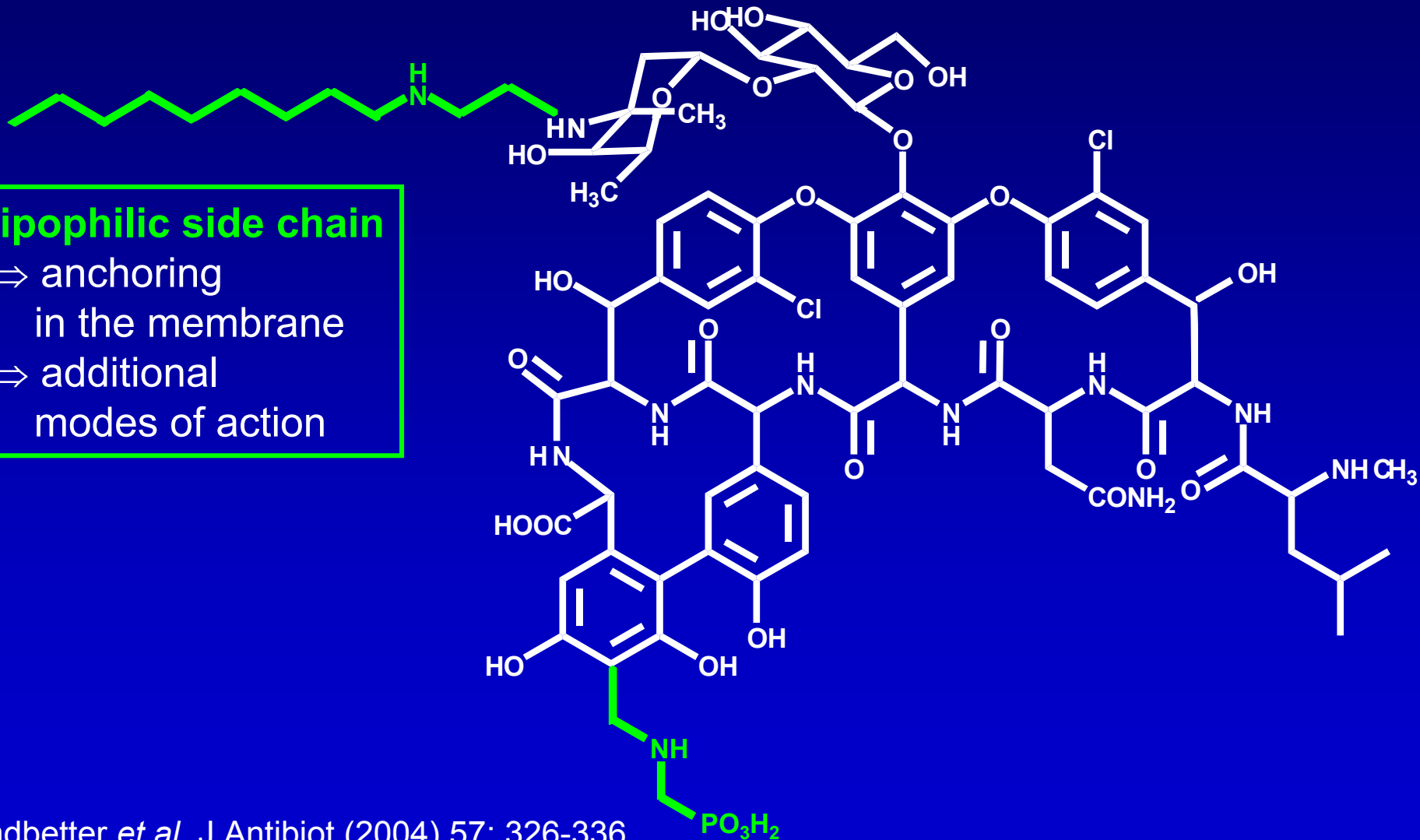
- professional phagocytes ~ reservoir
Gresham *et al.*, *J. Immunol.* (2000) 164:3713-22
- mammary epithelial cells ~ mastitis
Bayles *et al.*, *Infect. Immun.* (1998) 66:336-42
- aortic endothelial cells ~ CV diseases
Hamill *et al.*, *Infect. Immun.* (1986) 54:833
- osteoblasts ~ osteomyelitis
Ahmed *et al.*, *Infect. Immun.* (2001) 69:2872-77
- keratinocytes ~ skin infections
Mempel *et al.*, *Brit. J. Dermatol.* (2002) 146:943-51
- nasal epithelial cells ~ rhinosinusitis
Clément *et al.*, *J. Infect. Dis.* (2005) 192:1023-8

new agents
bactericidal against
both extra- and intra-
cellular bacteria!



TELAVANCIN
in development for
Gram-positive infections

From vancomycin to telavancin



Leadbetter *et al.* J Antibiot (2004) 57: 326-336

Telavancin is bactericidal due to multiple modes of action

Antibacterial effects	Glycopeptide concentrations			
	Telavancin		Vancomycin	
	μM	μg/ml	μM	μg/ml
Inhibition of peptidoglycan synthesis	0.14	0.2	2.0	2.9
Membrane depolarization	10	18	> 44	> 64
Rapid onset bactericidal activity	10	18	> 44	> 64

adapted from Higgins *et al.* AAC (2005) 49:1127-34

Aim of the study

Pharmacodynamic comparison of the activity of telavancin

- against the $\left\{ \begin{array}{l} \text{extracellular forms} \\ \text{intracellular forms} \end{array} \right.$ \leftarrow culture medium
 \leftarrow J774 mouse macrophages
 \leftarrow THP-1 human macrophages
- of $\left\{ \begin{array}{l} \text{MSSA} \\ \text{MRSA} \end{array} \right.$ \leftarrow ATCC 25923 & ATCC 29213
 \leftarrow ATCC 33591 & ATCC 43300

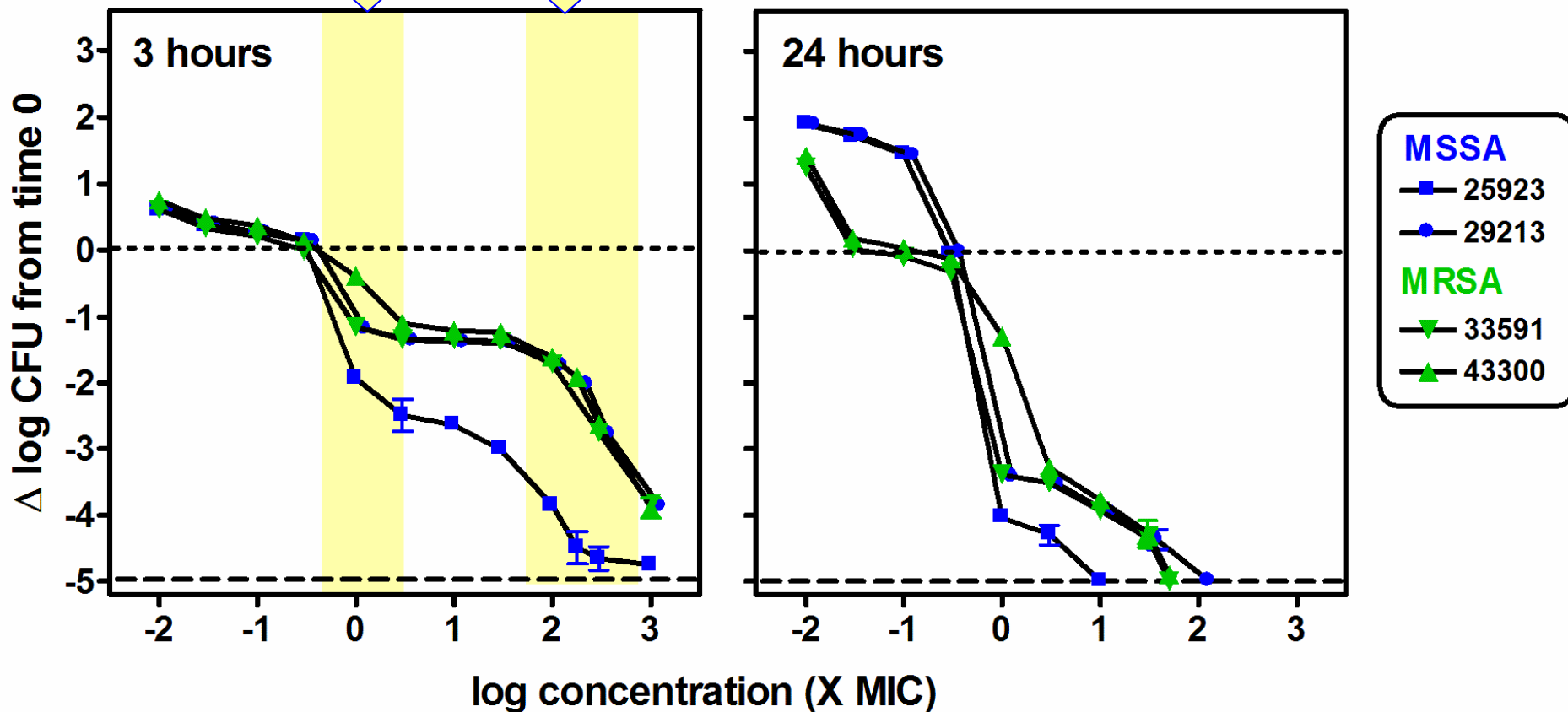
Full description of the intracellular models:

Seral *et al.*, AAC (2003) 47:2283-92

Barcia-Macay *et al.*, AAC (2006) 50:841-51

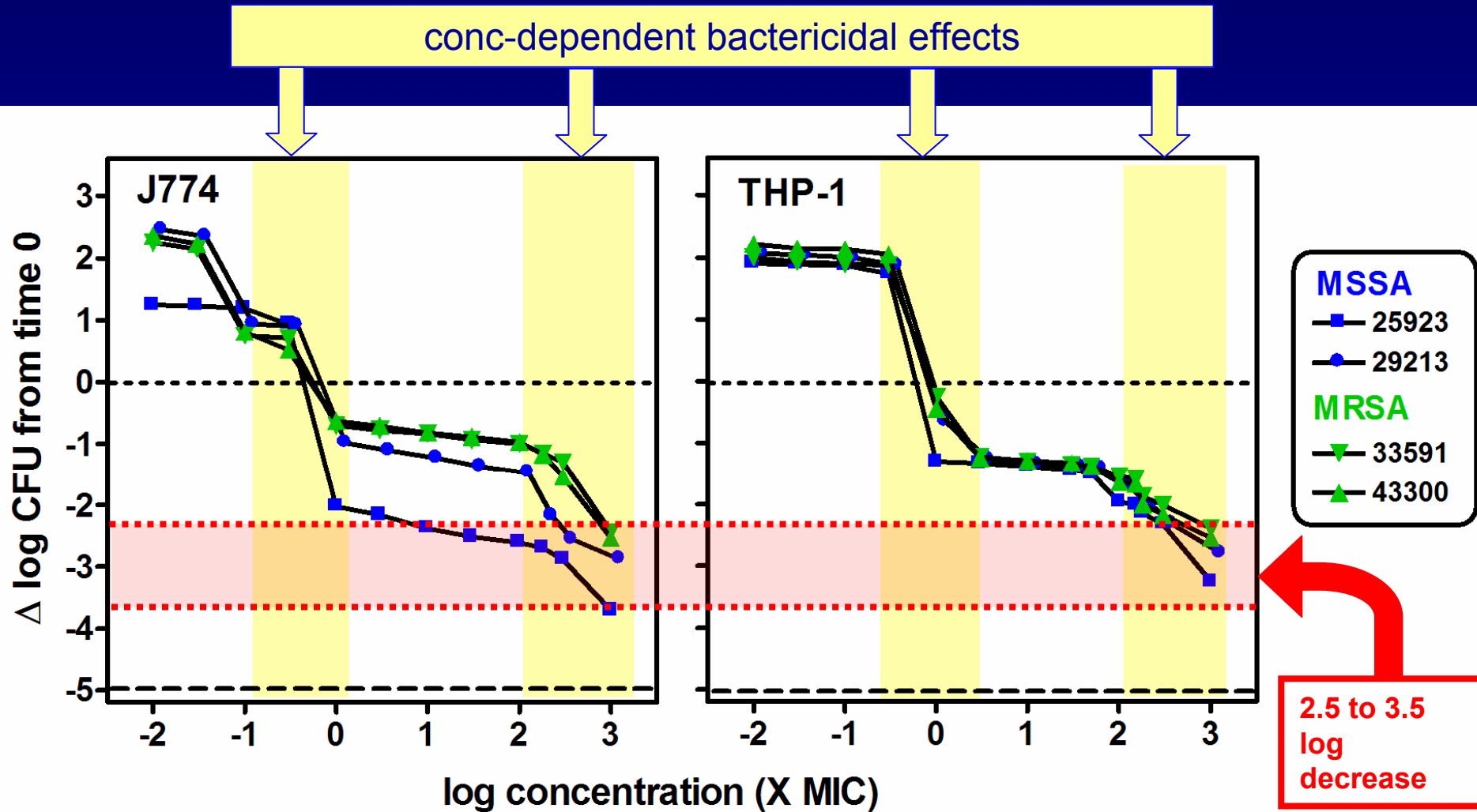
Extracellular activity

conc-dependent bactericidal effects



MIC = 0.5 $\mu\text{g/ml}$ for all strains

Intracellular activity



MIC = 0.5 $\mu\text{g/ml}$ for all strains

Bimodal curve : dual mode of action ?

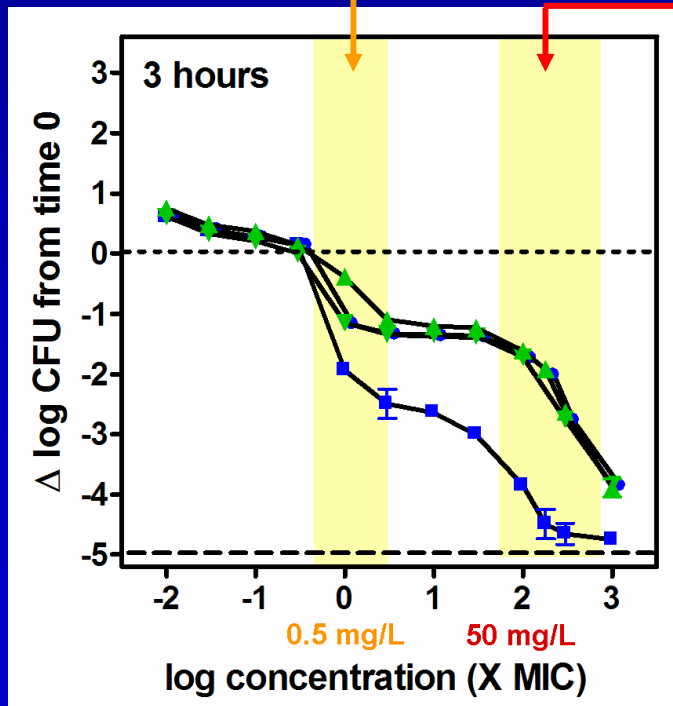
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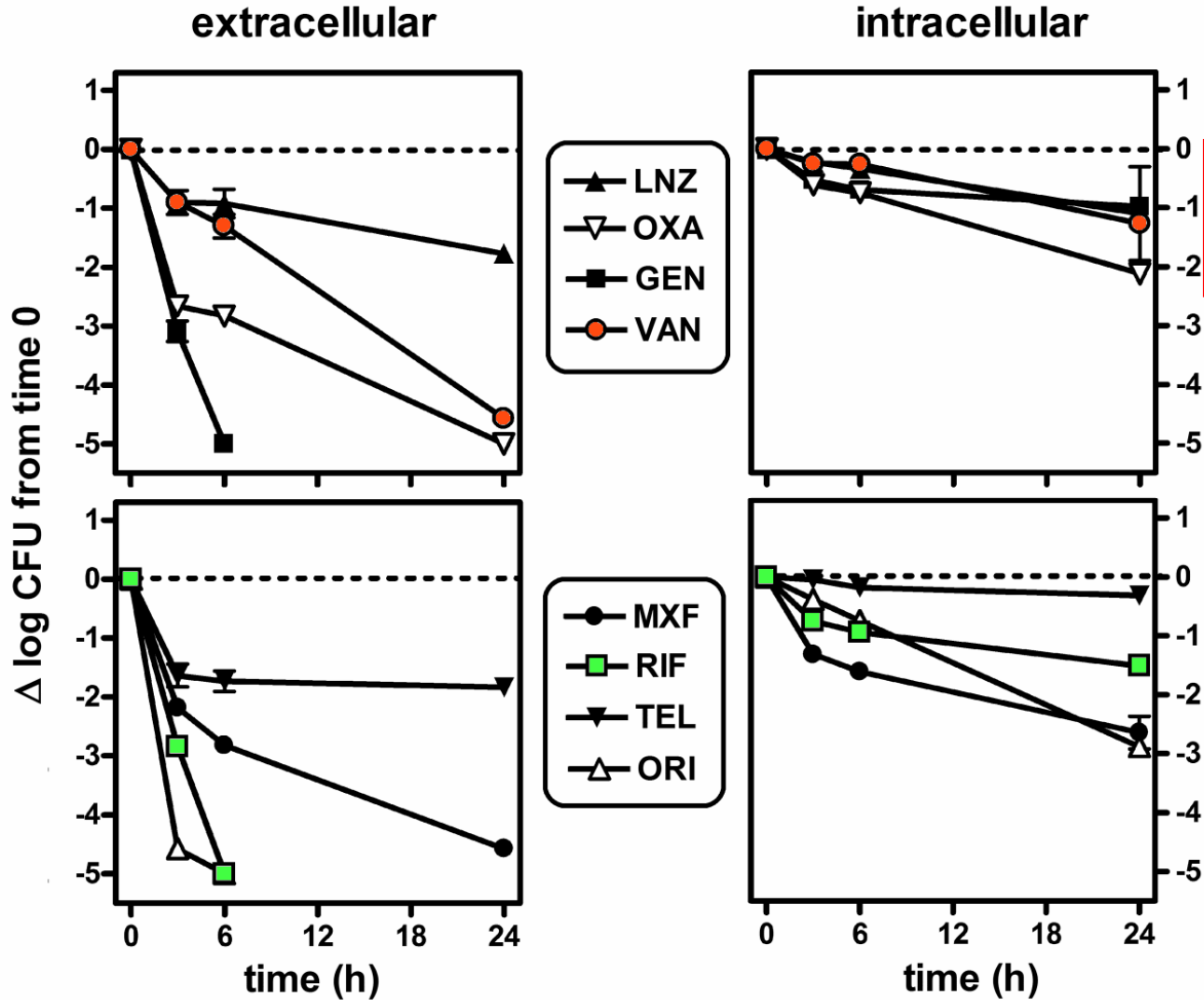
ECCMID 2006 – O356

04/04/06 4



As a comparison in the same model

(AAC 2006; 50(3):841-851) ...

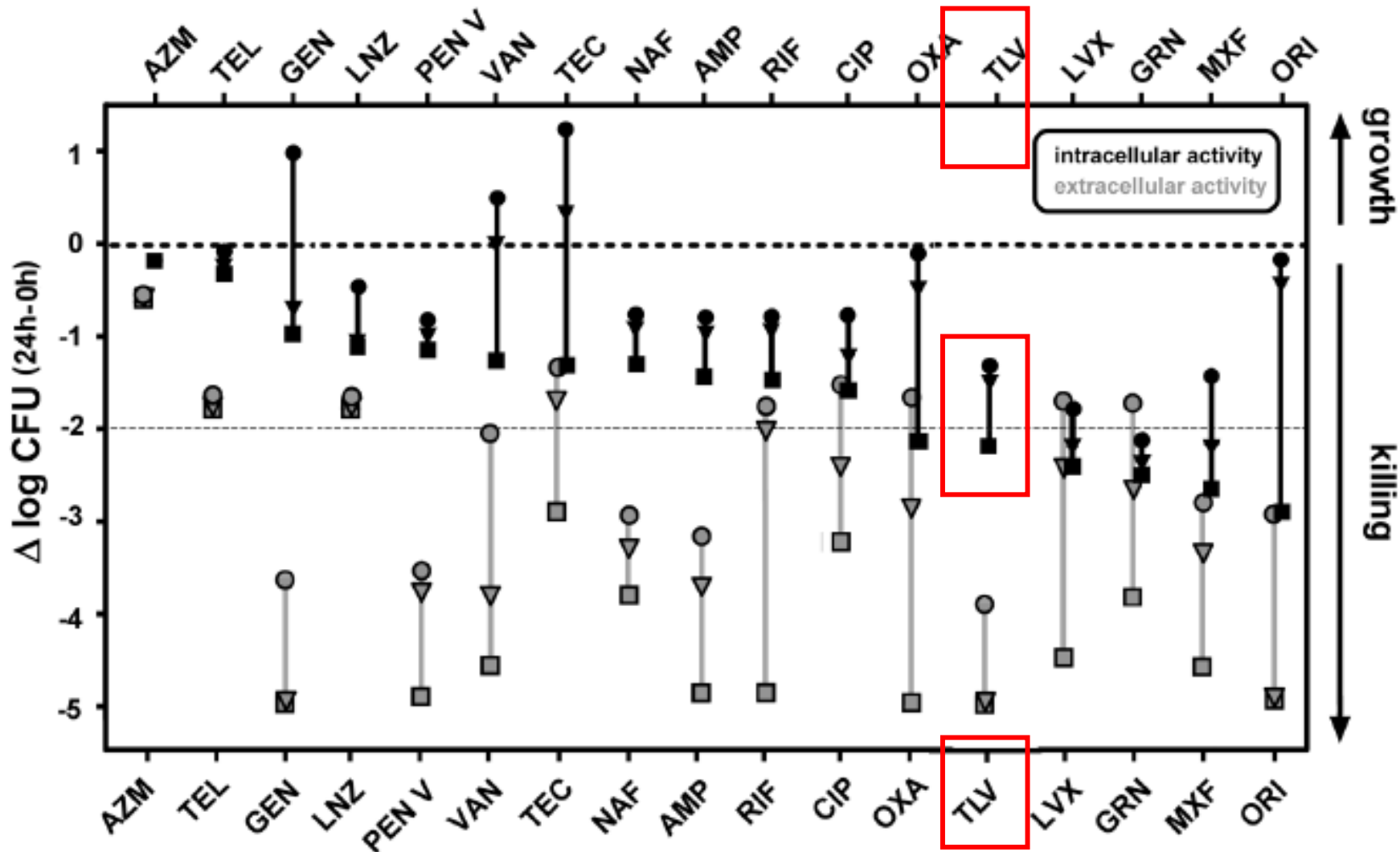


vancomycin:
1.2 log decr.

rifampin:
1.5 log decr.

As further comparison in the same model

(Data on file)



Conclusions

Telavancin shows towards both MSSA and MRSA

■ Extracellularly:

- at 3 h : concentration-dependent bactericidal effect
- at 24 h : sterilization of the culture ...

■ Intracellularly:

- at 24 h :
 - concentration-dependent bactericidal effect;
 - in both J774 (murine) and THP1 (human) macrophages
- 2.5-3.5 \log_{10} reduction in cell-associated CFU, which is among the largest observed so far for registered antibiotics

(see Barcia-Macay et al., Antimicrob. Agents Chemother. (2006) 50(3):841-851)

General Conclusions

- Telavancin is a lipoglycopeptide that shows activity towards cell-associated *S. aureus* that is clearly faster and superior to vancomycin.
- The data, therefore, supports the use of telavancin in infections where intracellular *S. aureus* may play an important role in the pathogenicity and persistence of the infection.
- The fact that intracellular activity is, nevertheless, weaker than the extracellular one (as for all other antibiotics examined so far) remains unexplained.