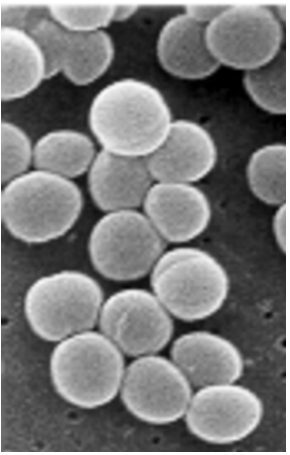

# Quinolones, macrolides, β-lactams, glycopeptides ... and a few others against resistant *S. aureus*


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Cellular and Molecular Pharmacology Unit
& Centre for Clinical Pharmacy

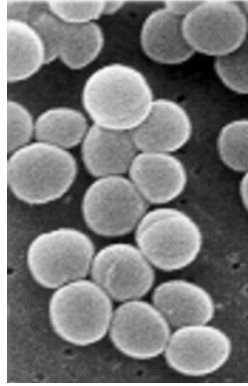
**Catholic University of Louvain,**
**Brussels, Belgium**

**www.facm.ucl.ac.be**


3rd International Symposium on
Resistant Gram-Positive Infections

Niagara-on-the-Lake
October 9-11, 2006

# Why do we need <u>new</u> antistaphylococcal agents ?



- rising resistance … reaching the limits of what we can give to patients …
- intrinsic PK/PD limitations of conventional glycopeptides towards *S. aureus* is severe infections
- difficulty in eradicating intracellular *S. aureus*… resulting in recurrences, relapses, and perhaps also favoring the selection/emergence of less susceptible oragnisms …

# Intracellular infection and recurrence/relapses

## In vivo importance assumed based on in vitro data

J Bone Joint Surg Br. 2003 Aug;85(6):918-21.

**Intracellular Staphylococcus aureus. A mechanism for the indolence of osteomyelitis.**

**Ellington JK, Harris M, Webb L, Smith B, Smith T, Tan K, Hudson M.**

Clin Infect Dis. 2001 Jun 1;32(11):1643-7. Epub 2001 Apr 30.

**Intracellular persistence of Staphylococcus aureus small-colony variants within keratinocytes: a cause for antibiotic treatment failure in a patient with darier's disease.**

**von Eiff C, Becker K, Metze D, Lubritz G, Hockmann J, Schwarz T, Peters G.**

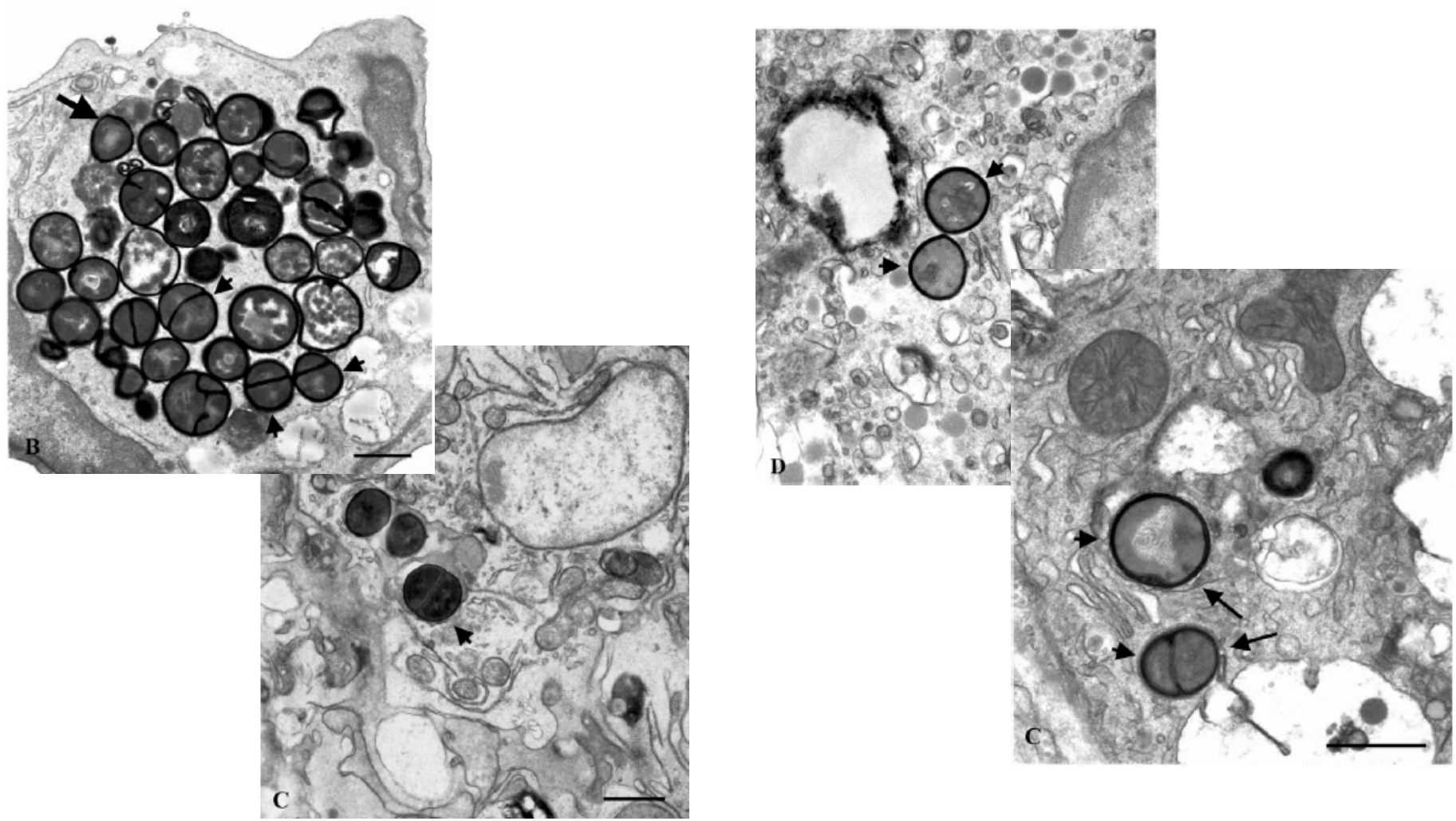
Infect Immun. 1986 Dec;54(3):833-6.

**Phagocytosis of Staphylococcus aureus by cultured bovine aortic endothelial cells: model for postadherence events in endovascular infections.**

**Hamill RJ, Vann JM, Proctor RA.**

# Intracellular infection and recurrence/relapses

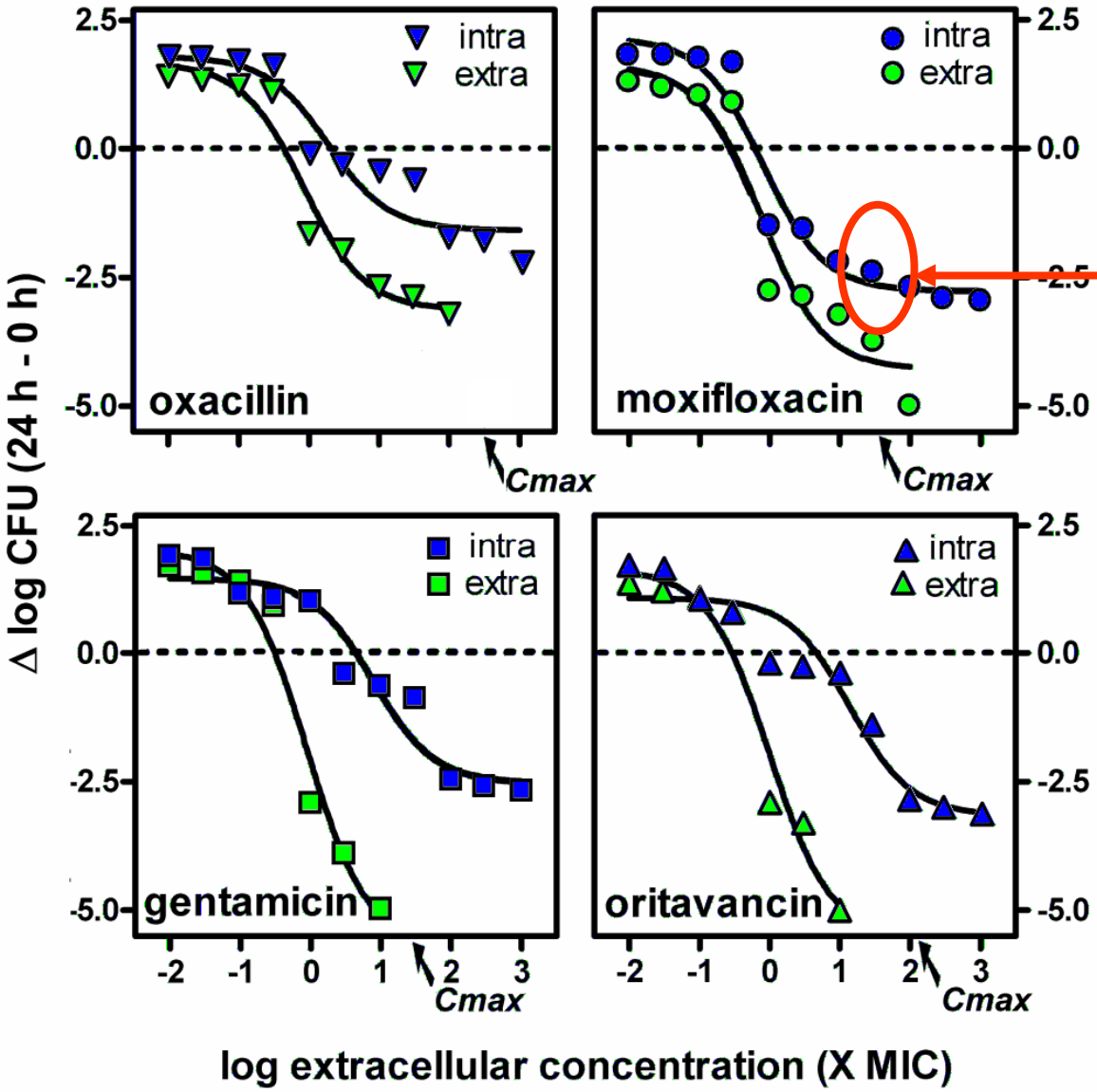
## Phagocytic and non phagocytic cells in mastitis




Brouillette *et al.,* Microb. Pathog. *(*2003) 35:159-68

# Quinolones ...

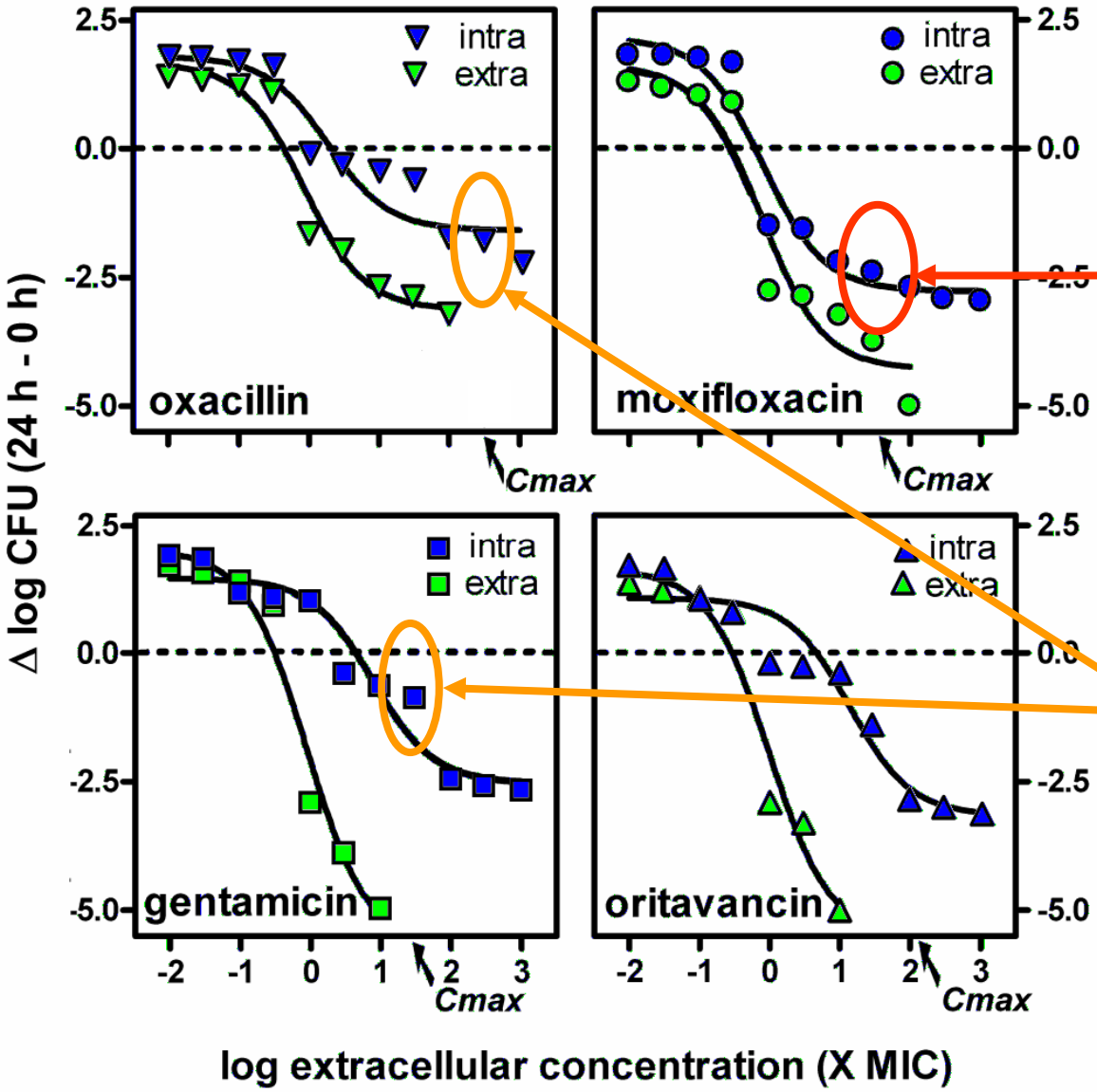
# Moxifloxacin is quite active against intracellular MSSA …




2.5 log decrease at $C_{max}$ (4.5 mg/L)

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

# Moxifloxacin is quite active against intracellular MSSA …




2.5 log decrease at $C_{max}$ (4.5 mg/L)

which is much better than oxacillin or gentamicin

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

# Quinolones and MRSA...

Distribution of fluoroquinolone MICs for 100 MRSA isolated in 2002

| Drug | No. of strains with indicated MIC (mg/l)[a] | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | ≥256 |
| NFLX | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 15 | 42 | 21 | 19 |
| ENX | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 1 | 12 | 73 | 11 |
| CPFX | 1 | 2 | 0 | 1 | 0 | 2 | 37 | 39 | 0 | 7 | 12 |
| TFLX | 4 | 0 | 1 | 32 | 27 | 18 | 2 | 0 | 17[b] | [c] | |
| FLRX | 0 | 3 | 1 | 0 | 0 | 0 | 20 | 54 | 4 | 1 | 18 |
| SPFX | 4 | 0 | 1 | 17 | 24 | 37 | 6 | 2 | 0 | 4 | 6 |
| LVFX | 3 | 1 | 0 | 1 | 25 | 50 | 4 | 4 | 3 | 0 | 10 |
| GFLX | 4 | 0 | 7 | 43 | 29 | 5 | 3 | 0 | 3 | 4 | 3 |
| MFLX | 4 | 1 | 32 | 42 | 4 | 7 | 0 | 0 | 8 | 2 | 0 |

*Abbreviation*: NFLX, norfloxacin; ENX, enoxacin; CPFX, ciprofloxacin; TFLX, tosufloxacin; FLRX, fleroxacin; SPFX, sparfloxacin; LVFX, levofloxacin; GFLX, gatifloxacin; MFLX, moxifloxacin.

[a] The positions of breakpoints for resistance interpreted by the NCCLS are underlined. Breakpoints of MFLX and TFLX have not been established by the NCCLS.

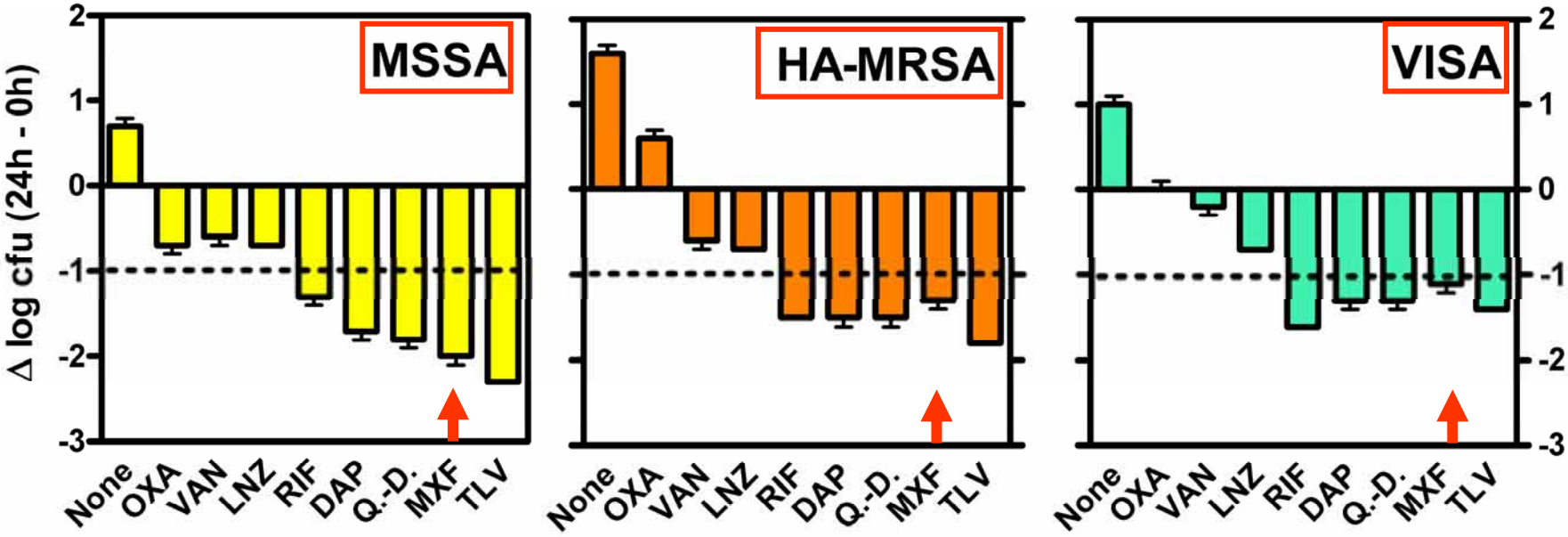
[b] MIC: ≥64 mg/l.

[c] Not determined.

Moxifloxacin has the lowest MICs amongst currently available quinolones, but resistance does exist !

Noguchi *et al.*, Int J Antimicrob Agents. (2005) 25:374-9.

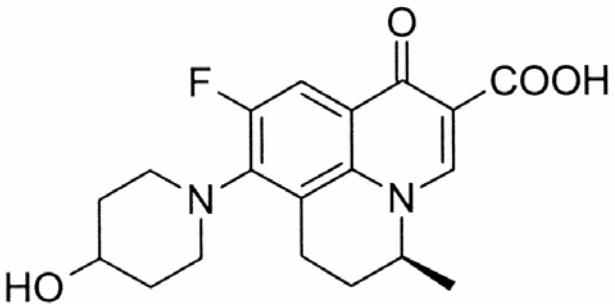
# Yet, moxifloxacin may be quite active against intracellular HA-MRSA and VISA …



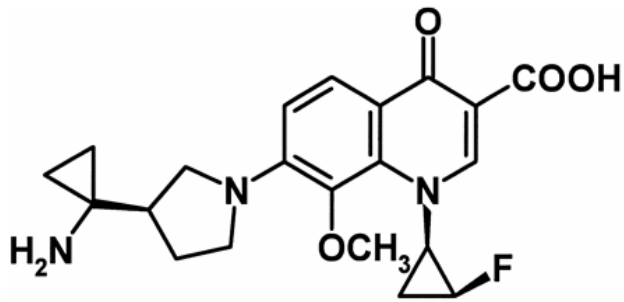

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

# Quinolones under development: can they be better ?

| quinolone | Range of MIC of MRSA | MIC 50 | MIC 90 |
|---|---|---|---|
| Moxifloxacin | 0.03-32 | 1-2 | 4-16 |
| WCK 771 | 0.015-4 | 0.5 | 1 |
| DX 619 | 0.008-2 | 0.125 | 1 |



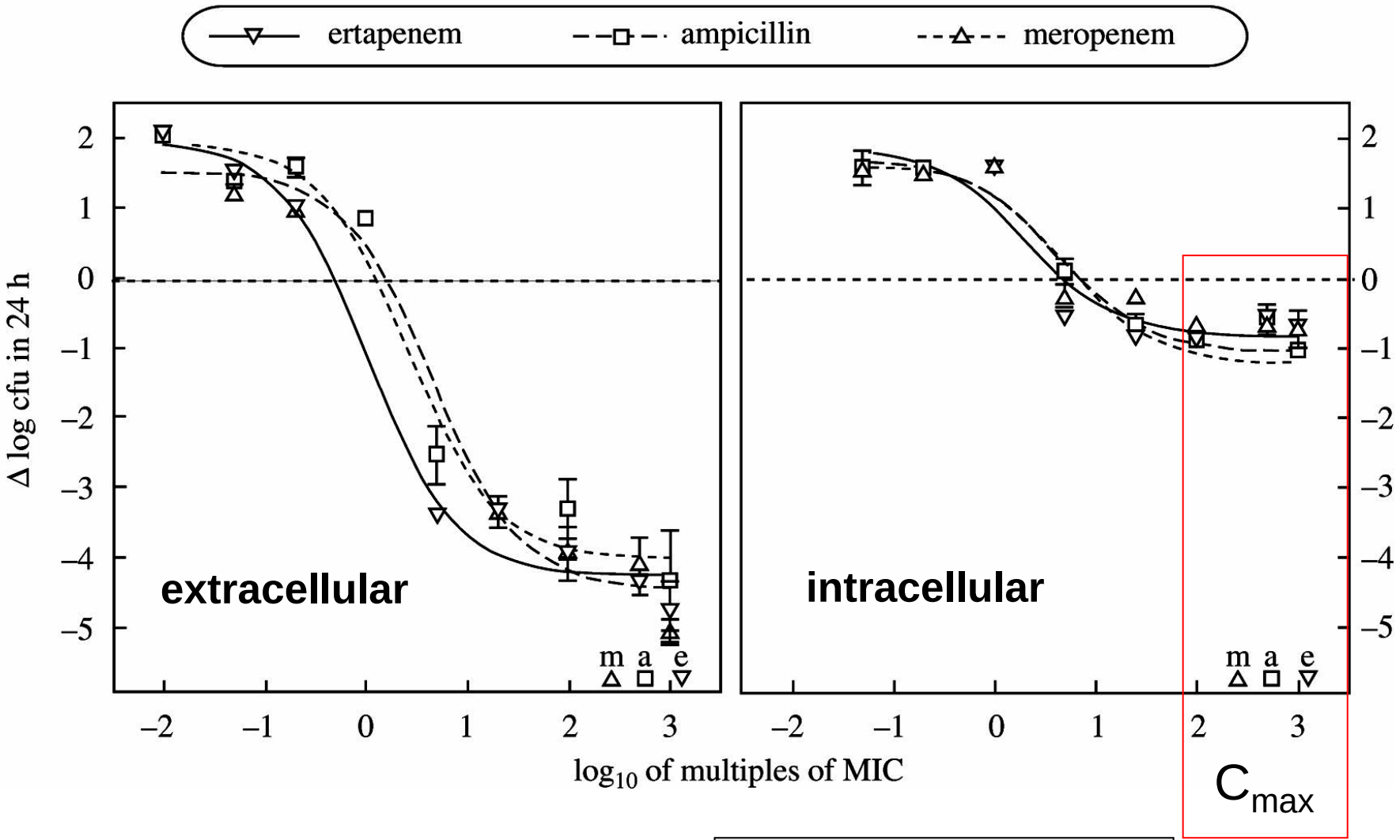

WCK 771,
a new quinolone in clinical trials




DK 619,
a new desquinolone in preclinical trials

Patel *et al.,* AAC (2004) 48:4754-4761;Bogdanovich *et al.,* AAC. (2005) 49:3325-33.

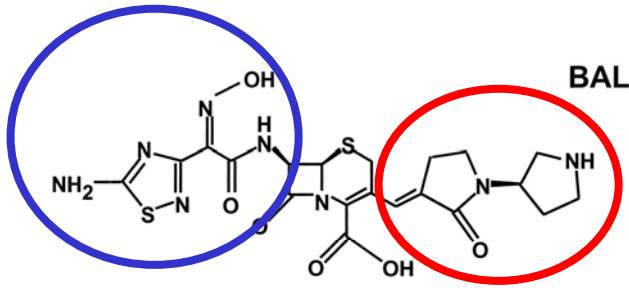
# β-lactams ...

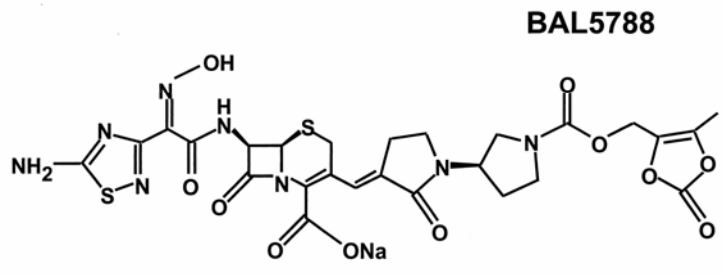



Lemaire et al., JAC 55:897-904, 2005

# Anti-MRSA cephalosporins: ceftobiprole…

- Highly resistant to beta-lactamases
- High affinity for PBP2a



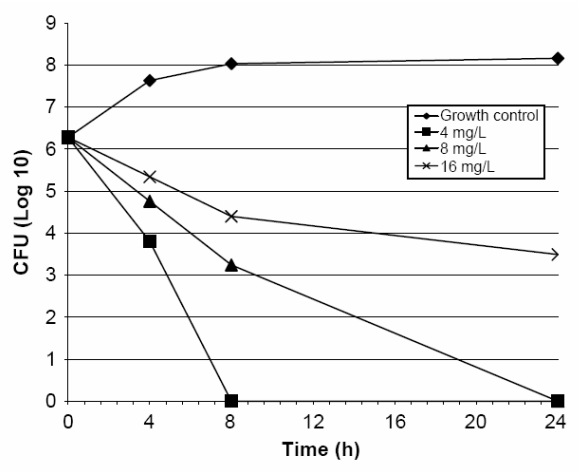

Ceftobiprole and its prodrug

- originally discovered by Roche in the late 90's
- activity against PBP2a is related to the hydrophobic side chain in C3 (conformational change)
- poor solubility necessitated the design of a pro-drug form

Entenza *et al*., Antimicrob Agents Chemother. (2002) 46:171-7.

# Anti-MRSA cephalosporins (ceftobiprole)…

- MIC range: 0.25-0.5 mg/L for MSSA
  0.25-2 mg/L for MRSA
  0.5-2 for SCV
- bactericidal
- synergistic with aminoglycosides

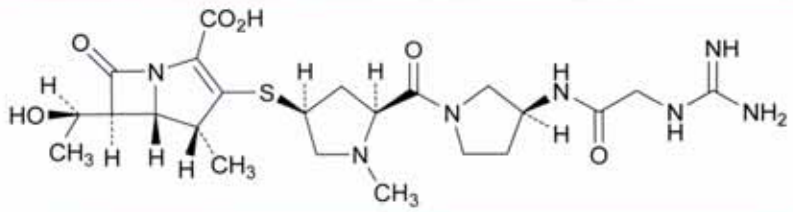



- FDA fast track designation for
  - the treatment of complicated skin and skin structure infections due to MRSA
  - a second indication in the treatment of hospital-acquired (nosocomial) pneumonia, including ventilator-associated pneumonia due to suspected or proven MRSA
- Excellent tissue penetration and powerful activity in models of
  - osteomyelitis
  - foreign-body infection
  - aortic valve endocarditis
- No available data on intracellular activity ...

# New carbapenems active on MRSA

Structure of CS-023 (RO4908463)

Roche



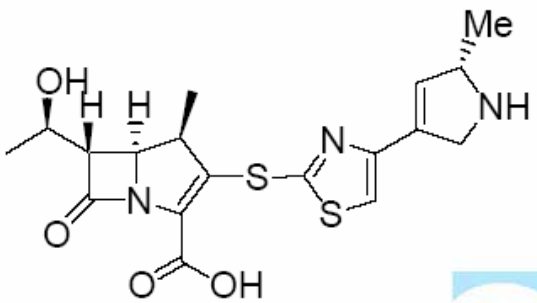
MIC range:

MSSA: 0.06-2 mg/L

MRSA: 0.25-32 mg/L !?!

ICAAC 2006 E 0227-228

*PZ-601 is also known as SM-216601 and SMP-601



Protez pharmaceuticals

MIC range for MRSA:

PZ-601: 0.03-4 mg/L

IMI: 0.25- 32 mg/L

OXA: 4-128 mg/L

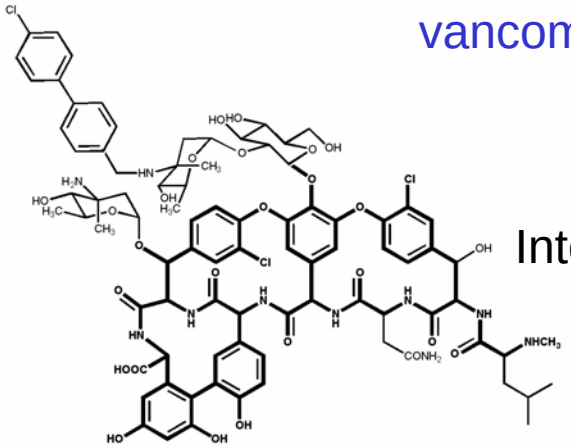
→ ongoing Phase I trials

ICAAC 2006 F1 230-231

# New glycopeptides (oritavancin,telavancin, dalbavancin)…

Hemi-synthetic derivatives derived from

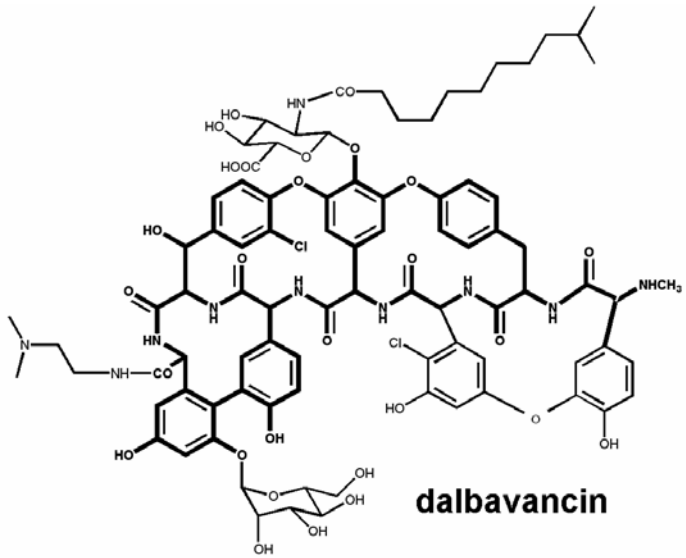
vancomycin



oritavancin

Phase III,
Intermune→ Targenta

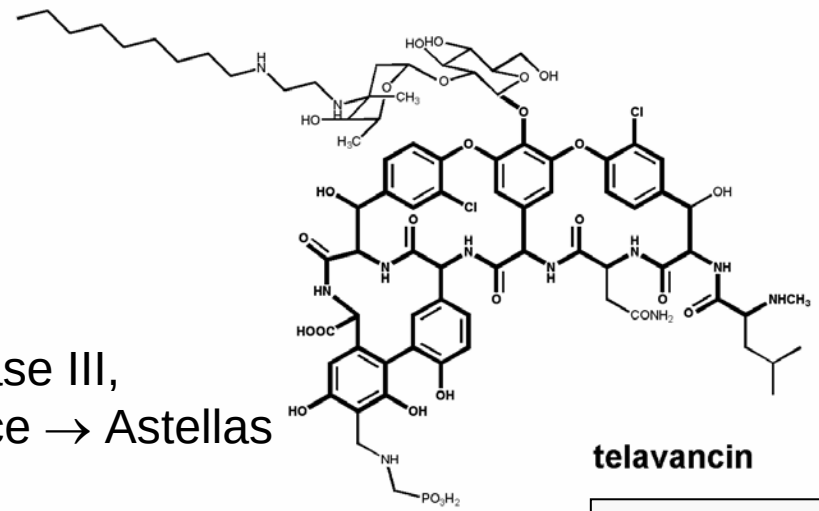
teicoplanin



dalbavancin

Awaiting FDA approval,
Vicuron → Pfizer

Phase III,
Theravance → Astellas

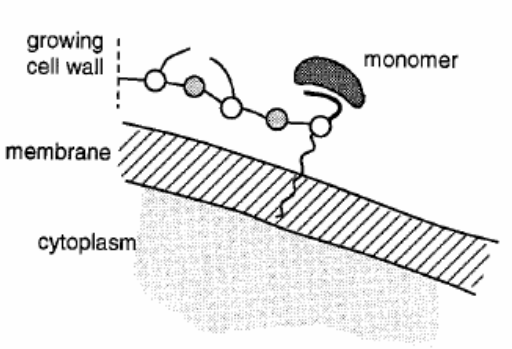


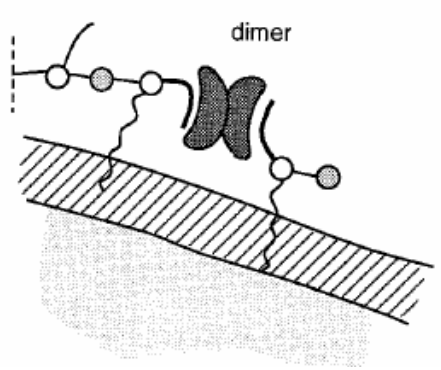
telavancin

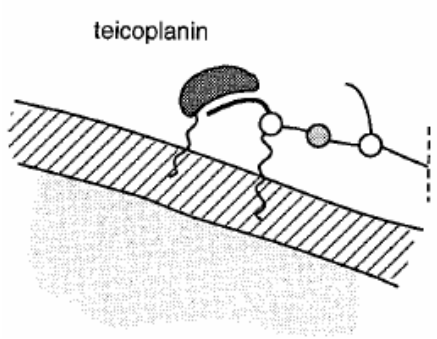
Van Bambeke, Current Opinion in Pharmacology (2004) 4:471-478

# Telavancin (and oritavancin) new modes of action …

- Possibility of dimerization
  - ➔ potential increase of intrinsic activity against D-Ala-D-Ala displaying organisms (MSSA, MRSA, VISA)
- Membrane destabilization effects…
  - ➔ strong <u>concentration-dependent</u> bactericidal effect (all strains ...) *

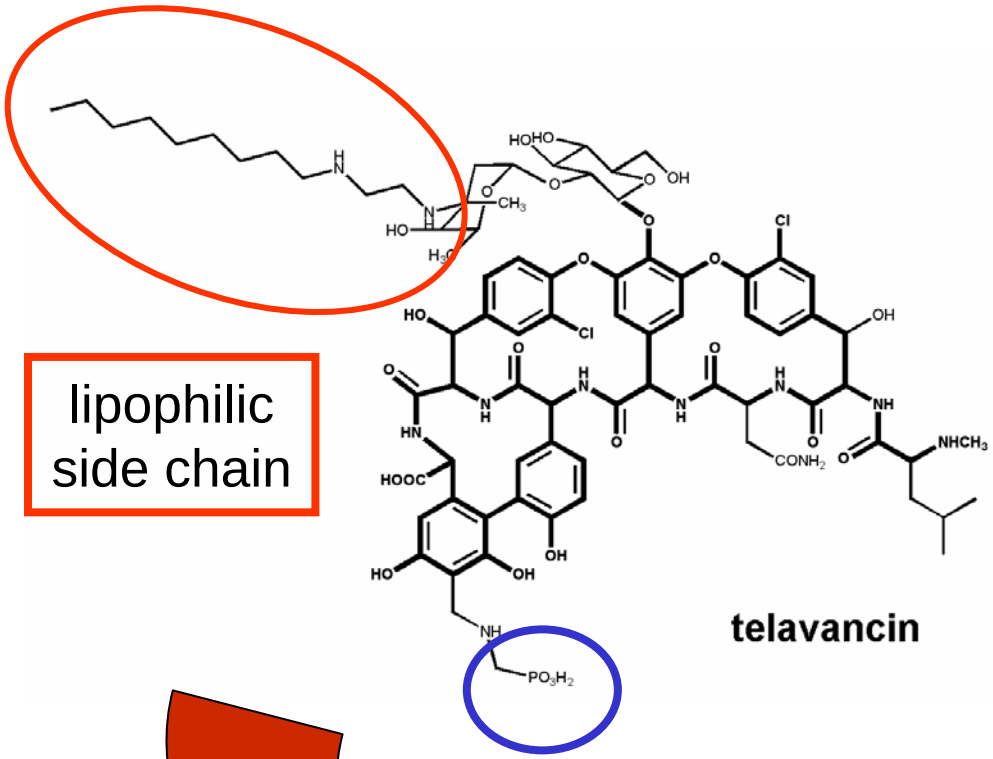


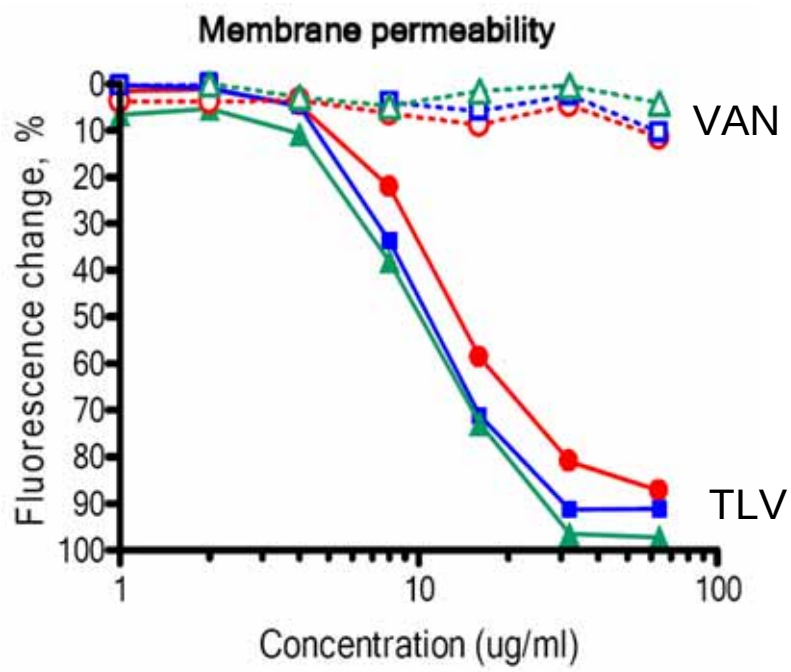

Beauregard et al., AAC 1995; 39:781-85

# Telavancin …




lipophilic side chain

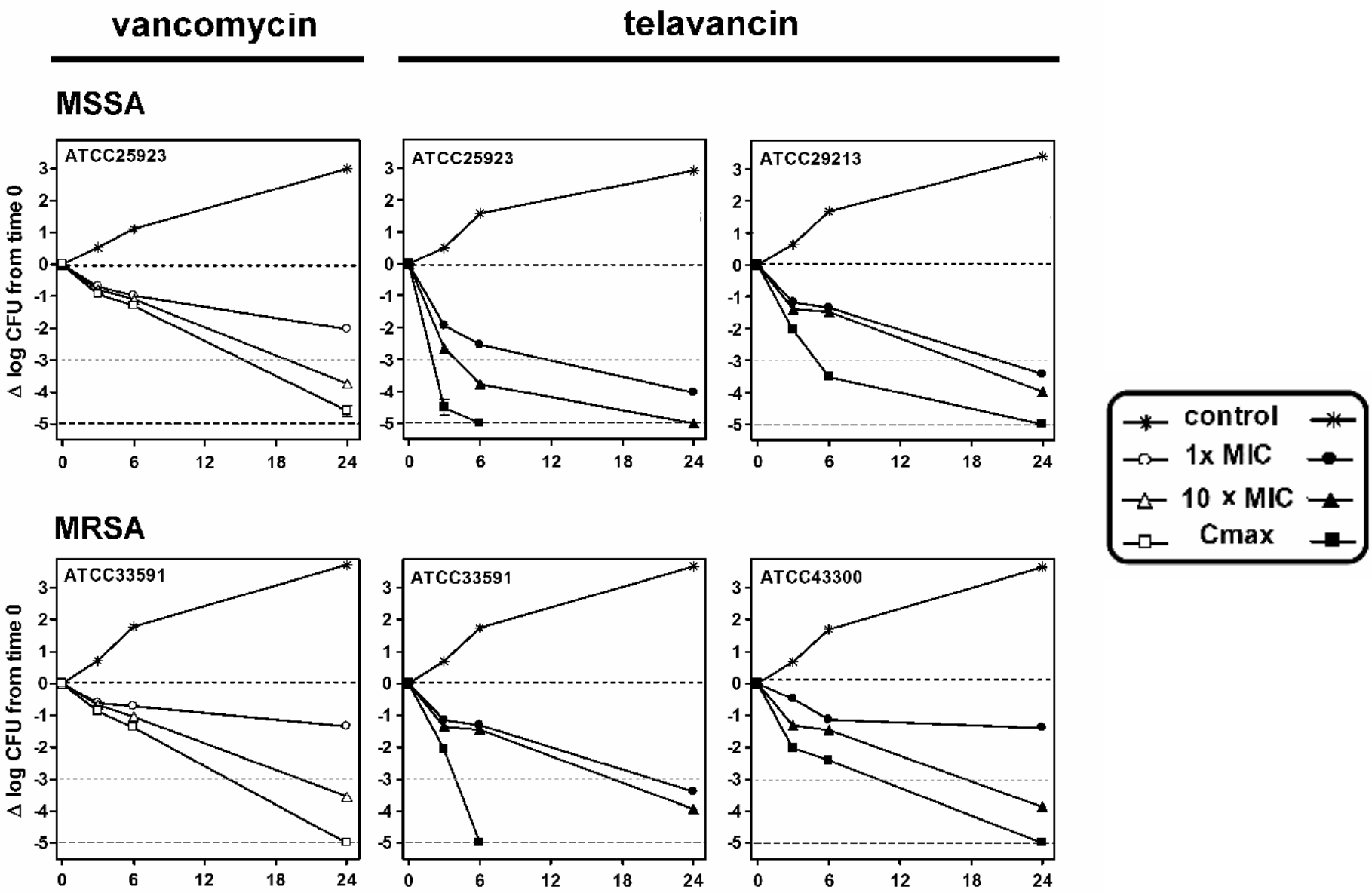
polar group




this causes increase in bacterial membrane permeability

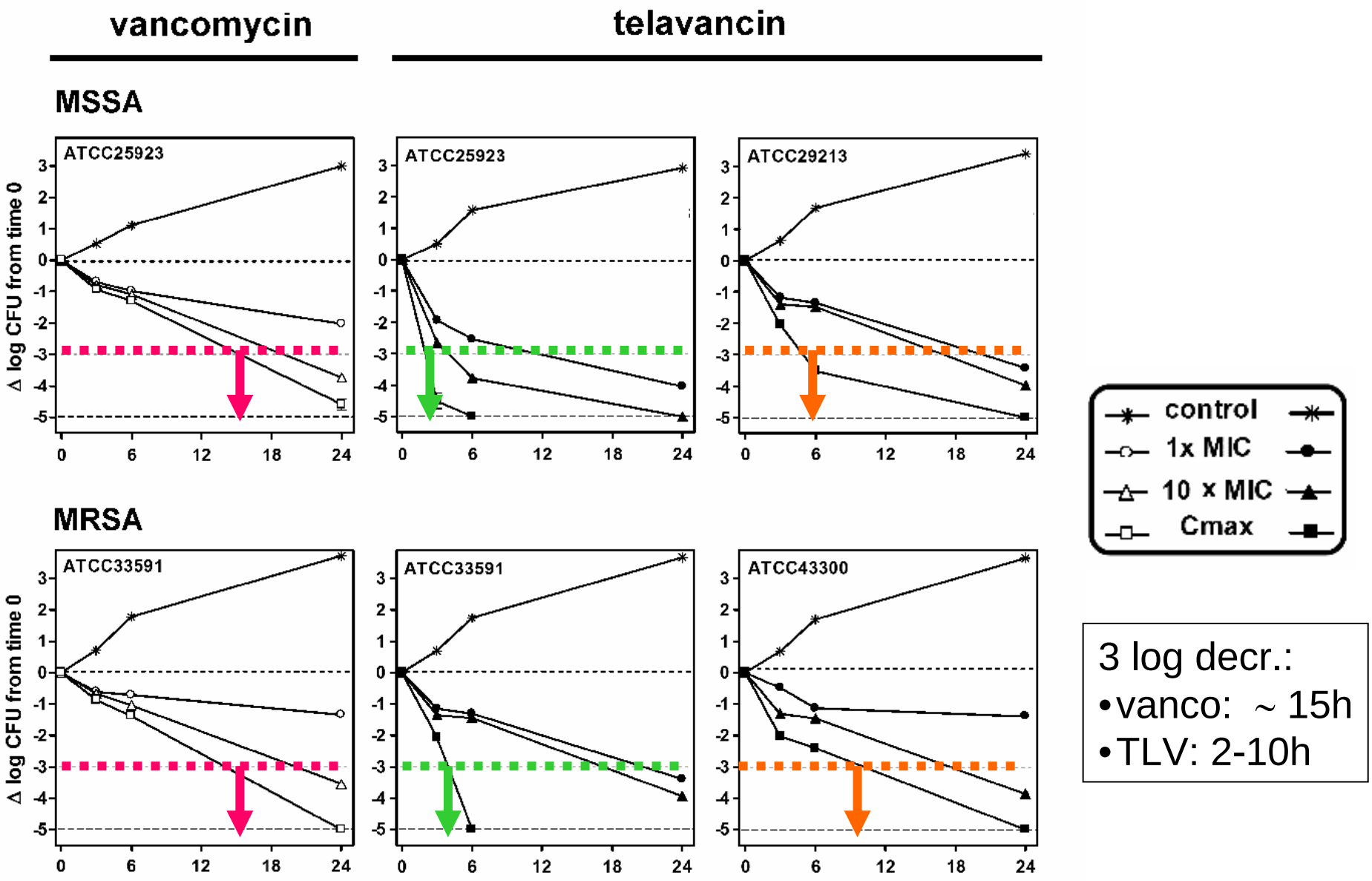
Higgins *et al*., Antimicrob Agents Chemother. (2005) 49:1127-34

# Time-kill of telavancin vs. vancomycin against MSSA and MRSA




Barcia-Macay *et al.,* JAC, in the press

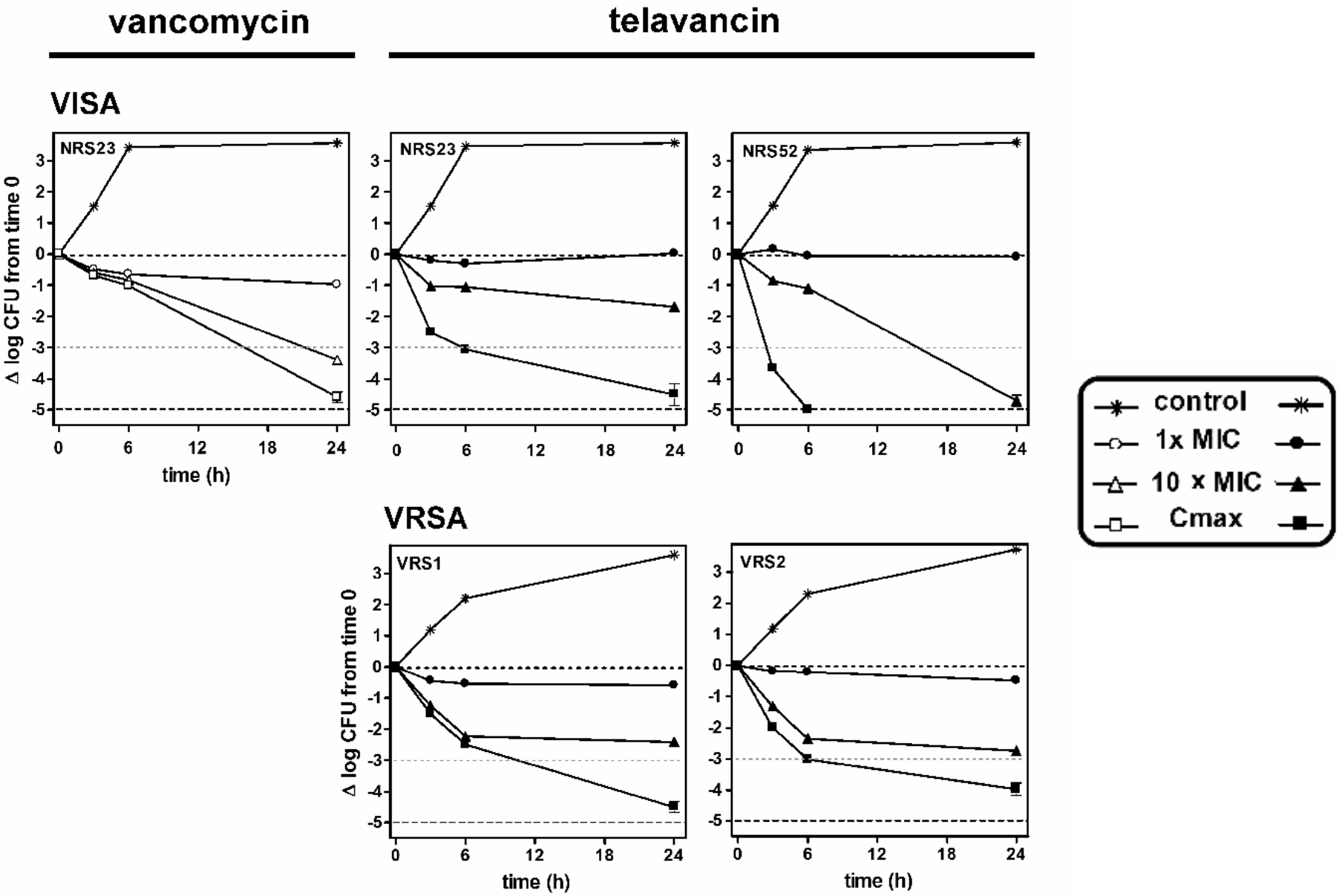
# Time-kill of telavancin vs. vancomycin against MSSA and MRSA




3 log decr.:
- vanco: ~ 15h
- TLV: 2-10h

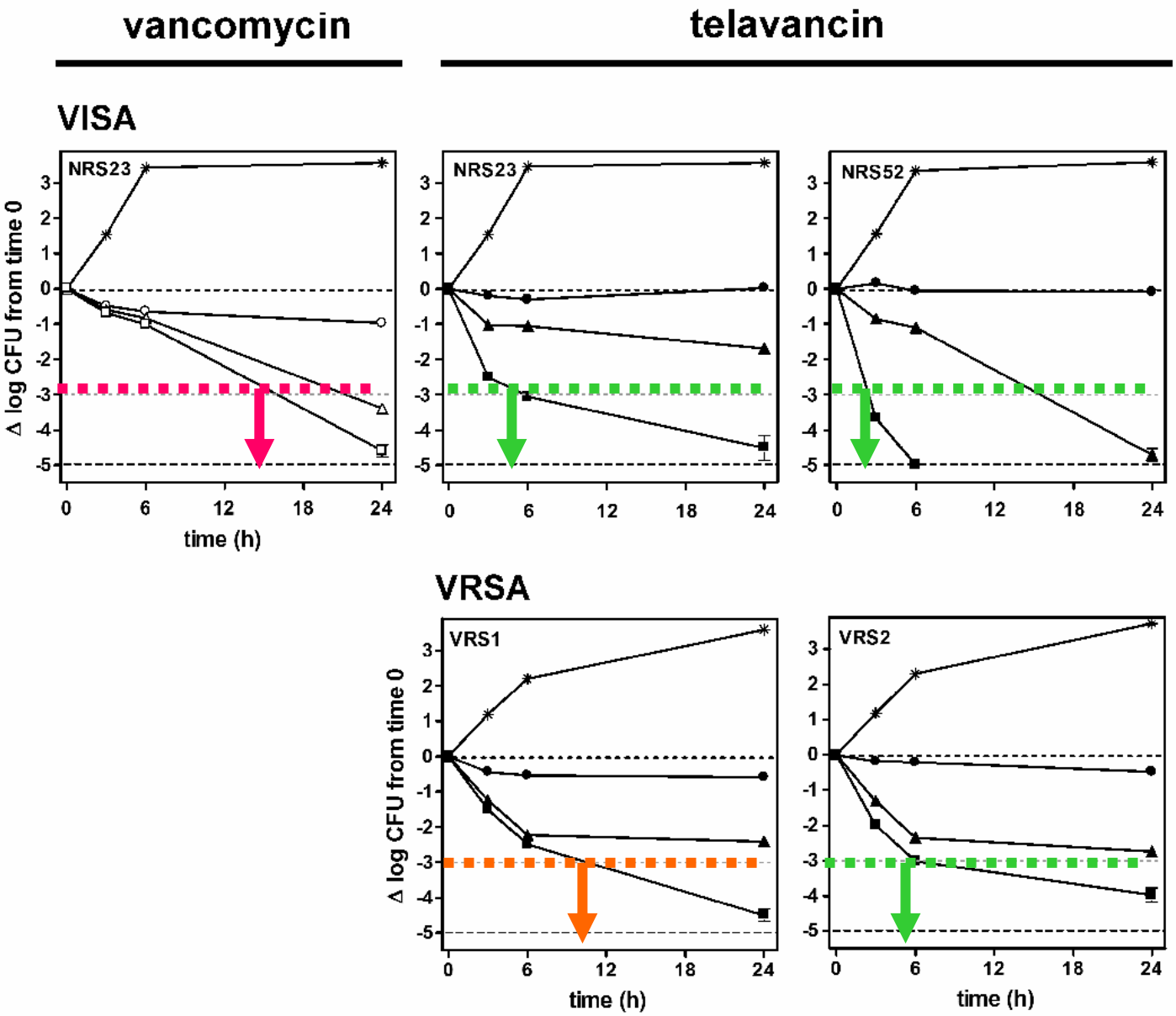
Barcia-Macay *et al.*, JAC, in the press

# Time-kill of telavancin vs. vancomycin against VISA and VRSA,




Barcia-Macay *et al.,* JAC, in the press

# Time-kill of telavancin vs. vancomycin against VISA and VRSA,

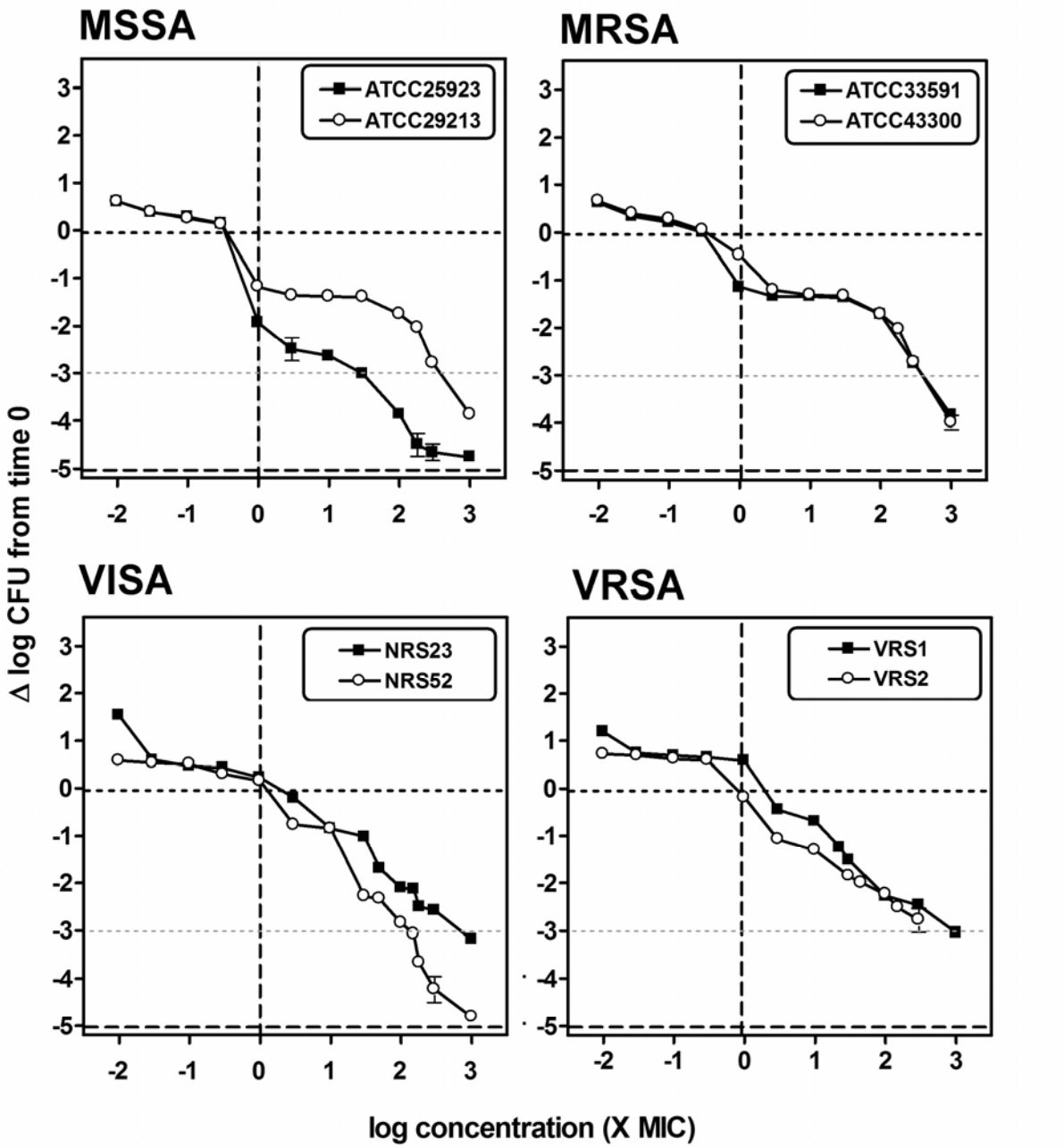



3 log decr.:
- vanco: ~ 15h
- TLV: 2-10h

Barcia-Macay *et al.*, JAC, in the press

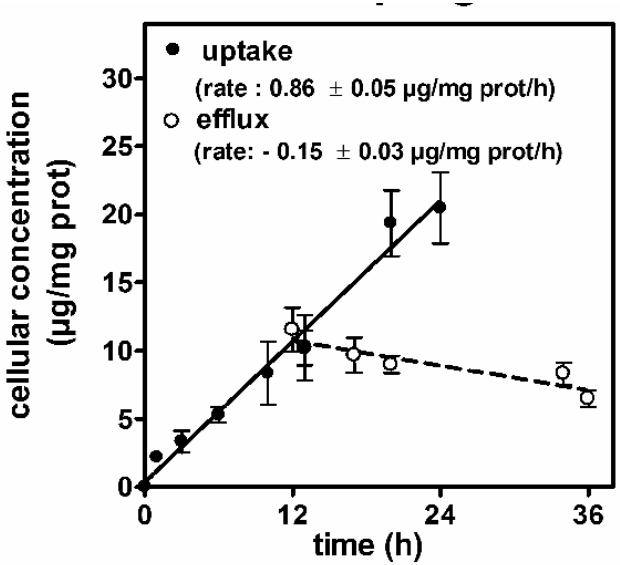
# Televancin dual mode of action ?

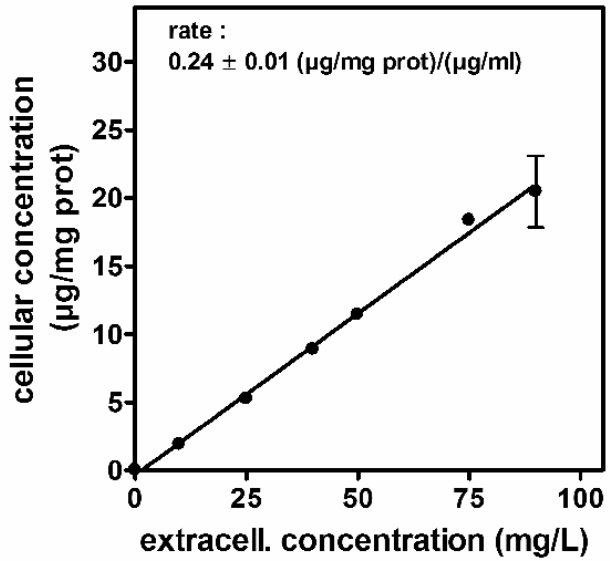
3 h kill curves

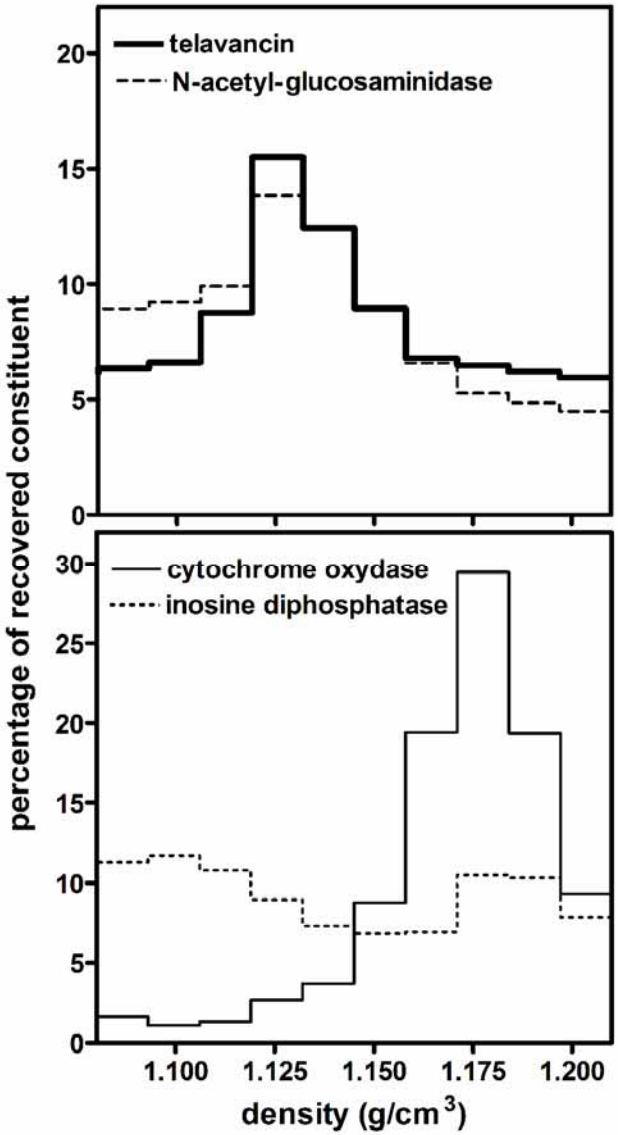



Barcia-Macay *et al.,* JAC, in the press

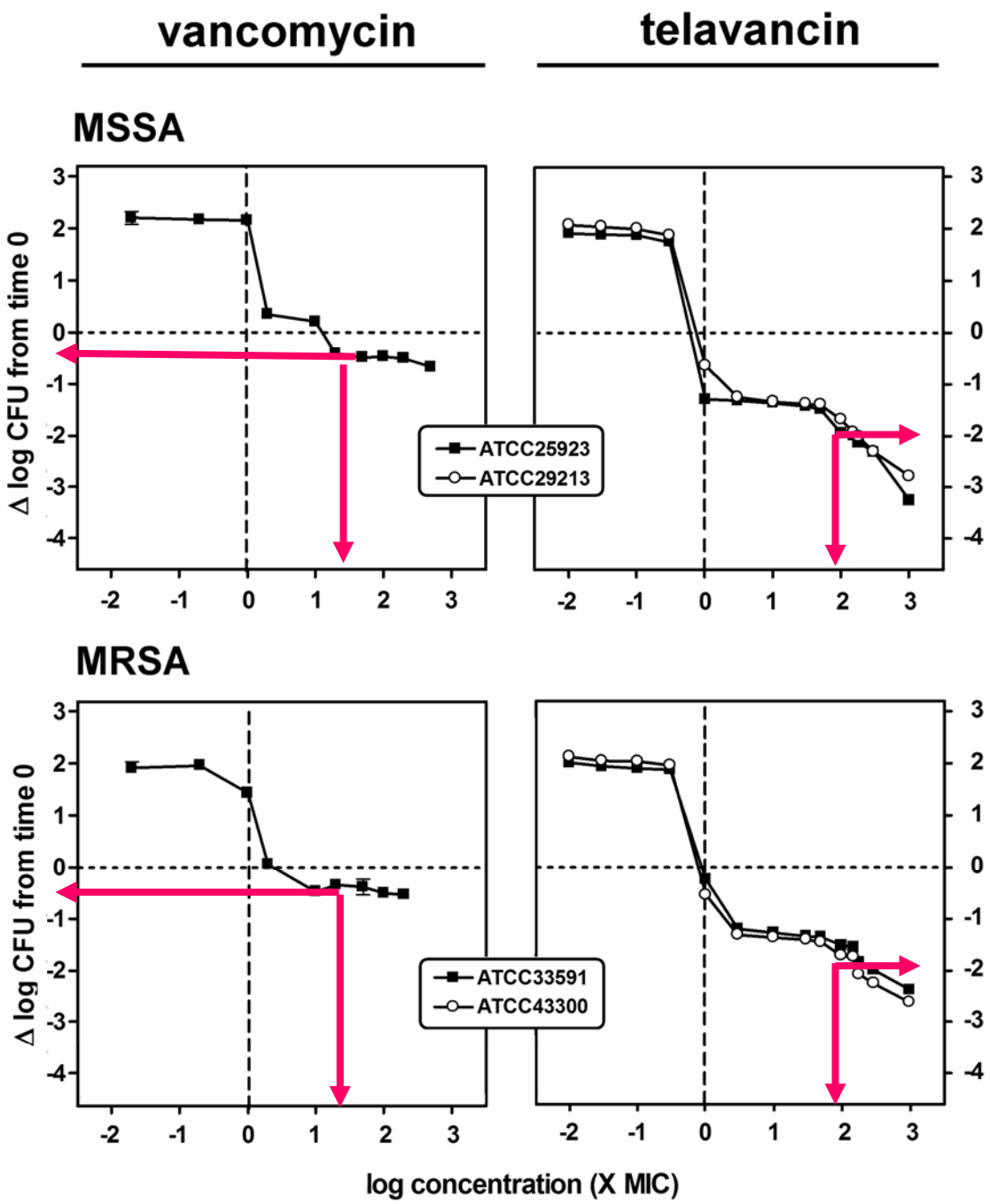
# Telavancin intracellular accumulation and subcellular disposition




Van Bambeke et al., unpublished




Intracellular activity of telavancin *vs.* vancomycin:

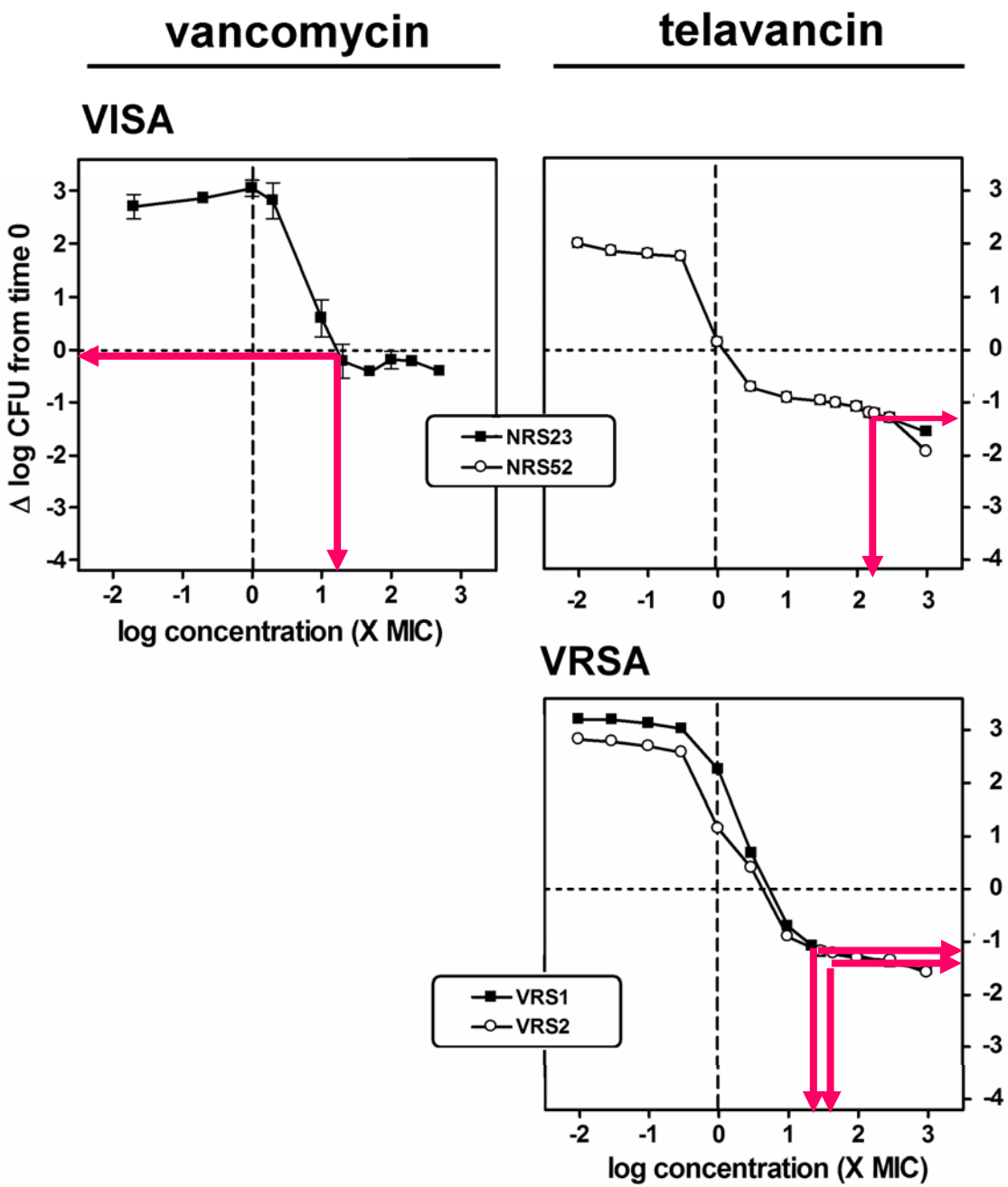
➔ MSSA

➔ MRSA

24h CFU ↘ at $C_{max}$:

- vanco: ~ 0.5 log
- TLV: ~ 2 log

Barcia-Macay *et al.,* JAC, in the press




Intracellular activity of telavancin *vs.* vancomycin:

➔ VISA

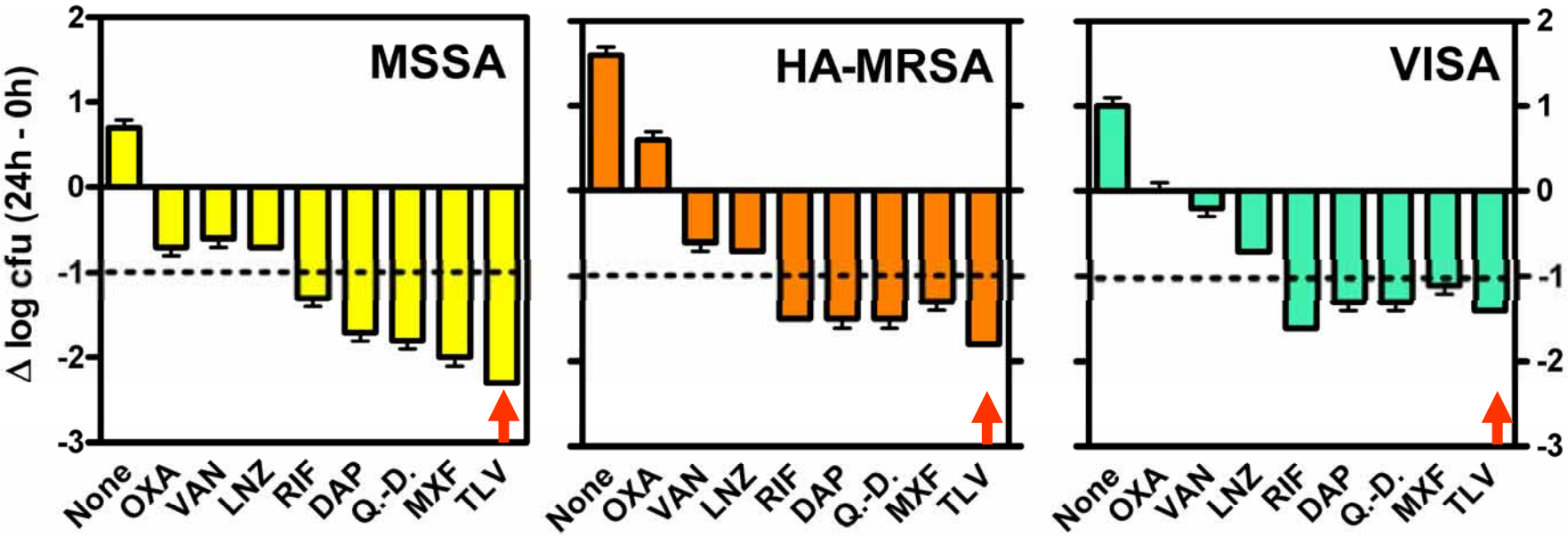
➔ VRSA

24h CFU ↘ at $C_{max}$:

- vanco: static
- TLV: ~ 1.2 log

Barcia-Macay *et al.,* JAC, in the press

# Telavancin intracellular activity in comparison with other drugs…




ISSSI 2006

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

# Microbiology, pharmacokinetics and clinical indications under investigation for the new glycopeptides

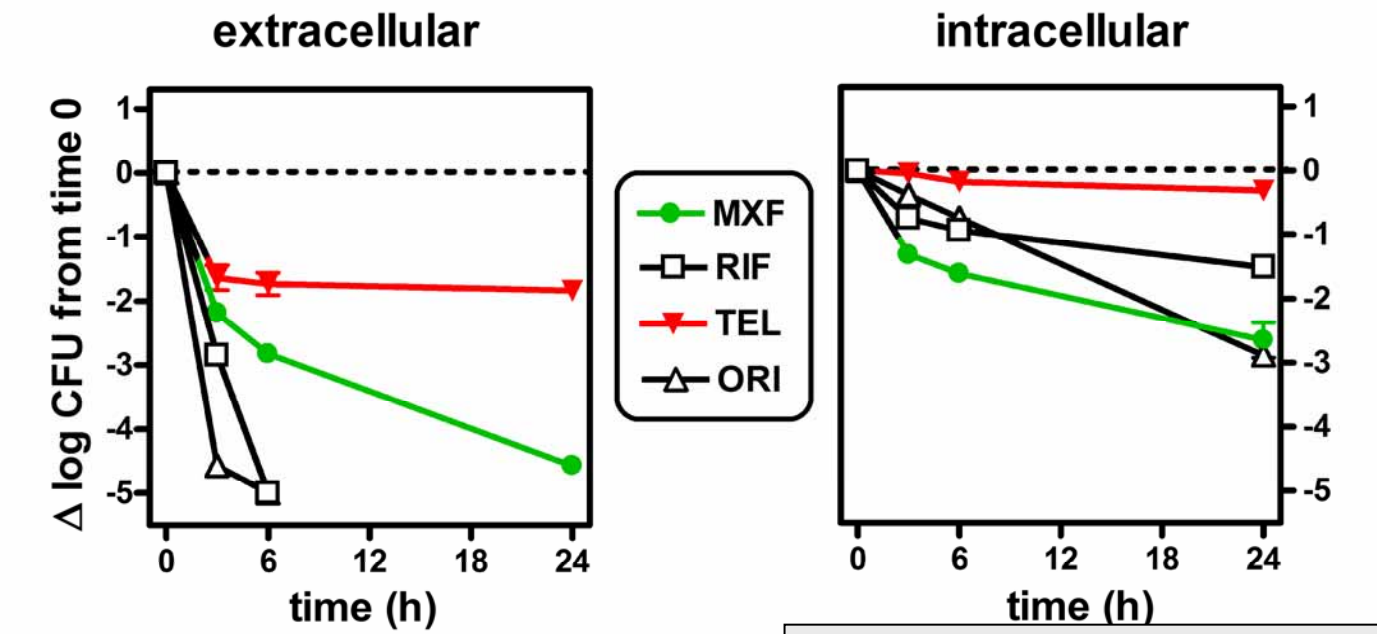
| | telavancin | oritavancin | dalbavancin |
|---|---|---|---|
| MIC MRSA<br>VISA<br>VRSA | 0.125-1<br>0.5-4<br>2 | 0.125-4<br>1-8<br>0.5 | 0.06-1<br>2<br>**inactive** |
| Half-life | 7 h → once-a-day ← | 18 h (β)<br>360 h(γ) | 140-300h → <u>once-a-week !!</u> |
| Tissular and cellular distribution | yes | yes | yes |
| Clinical efficacy | skin & soft tissue<br>HAP | skin & soft tissue | skin and soft tissue<br>catheter-related bloodstream infections |
| Activity in animal models | endocarditis<br>meningitis | endocarditis<br>meningitis<br>catheter infections | endocarditis<br>pneumonia<br>disseminated infections |

Van Bambeke, Curr. Opin. Invest. Drugs (2006) 7:740-749

# Macrolides ...

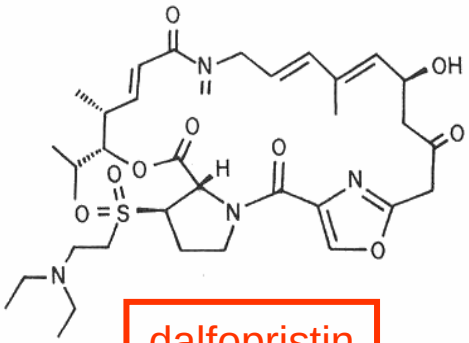
- Erythromycin, clarithromycin, azithromycin, ... Are no longer real options...
- Telithromycin, disregarding liver toxicity, is active only against inducible $MLS_B$-resistant strains...
- Extracellular and intracellular activities are essentially static...

**MSSA ATCC25923**

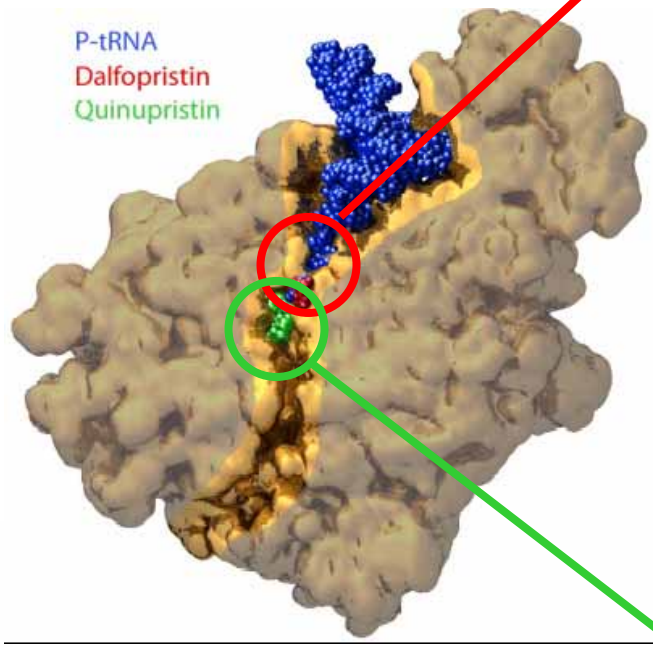



Barcia-Macay et al. AAC (2006) 50:841-851

# SYNERCID® = quinupristin + dalfopristin



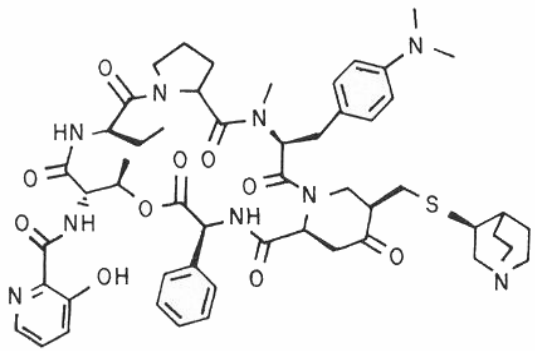
dalfopristin




**$S_A$ blocks peptide bound formation**

**SYNERGY**

quinupristin



**$S_B$ blocks the path of the nascent peptide**

Harms *et al,* BMB Biol (2004) 2:4

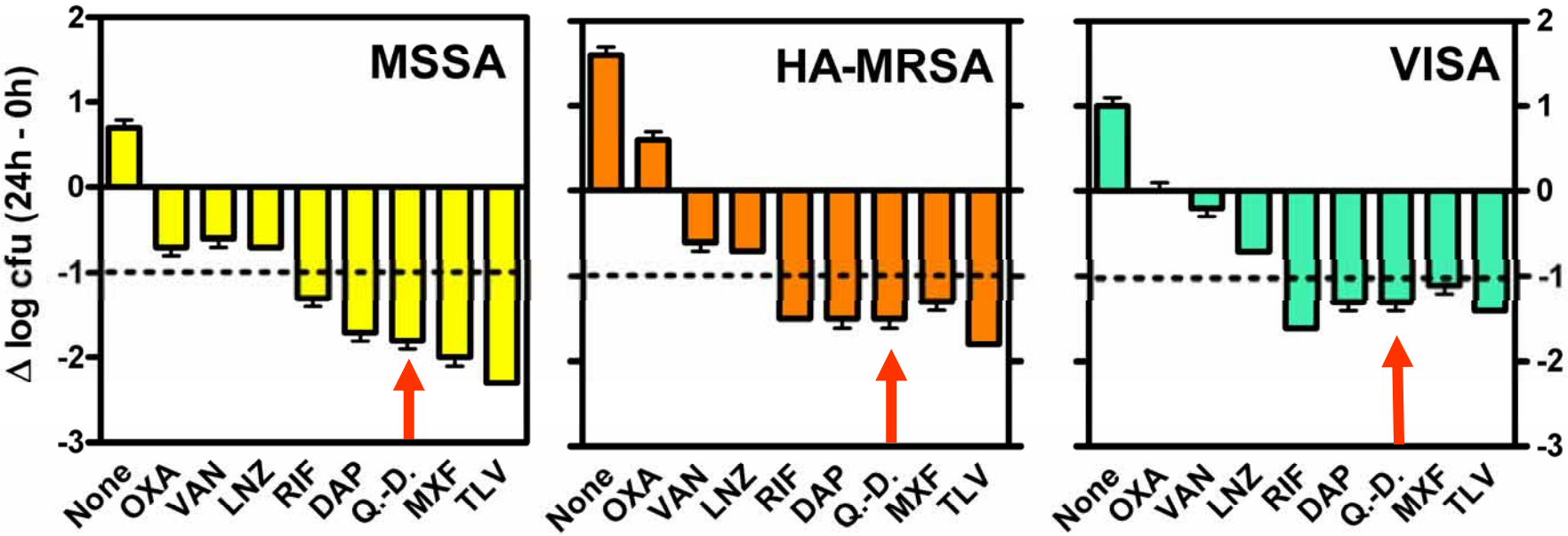
# SYNERCID®

- originally discovered and developped by Rhône-Poulenc (France)
- European (mutual recognition) and FDA approval in the late 90's for:
  - complicated skin and soft tissues infections by MSSA/strepto
  - bacteremia due to VR *E. faecium* (fast track at FDA)
  - efficacy also desmonstrated in nosocomial pneumonia (= vanco; lower success if MRSA in both groups)
- abandoned in early 2000's because of
  - side effects (rash; infusion-site inflammation; pain and edema; thrombophlebitis …) and inhibition of cytochrome P450 3A4
  - difficulties of production in large quantities
  - loss of interest after the merge of Rhône-Poulenc with Hoechst-Marion-Roussel to form AVENTIS…

- presently commercialized at a low scale by
  - Nordic Pharma in Europe
  - King Pharmaceuticals in the US

NORDIC PHARMA

# SYNERCID® does not behave too badly for intracellular *S. aureus*…




ISSSI 2006

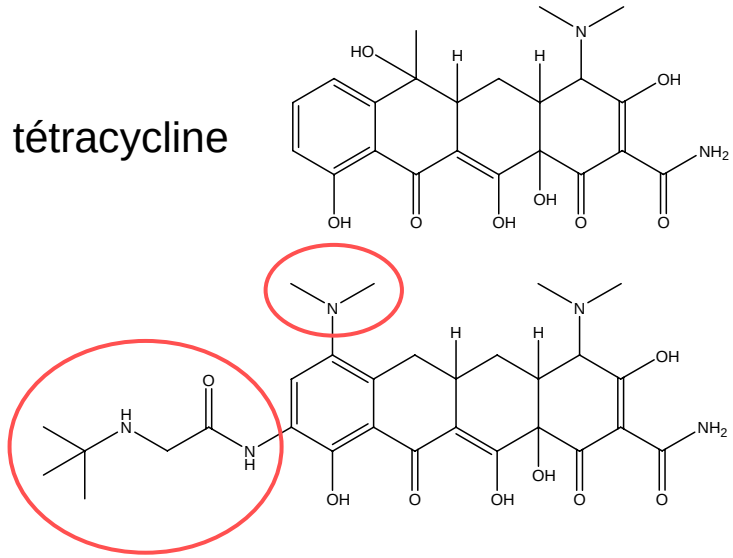
Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

# Tigecycline…

- truly made to resist efflux-mediated resistance in Gram(-) bacteria
- broad spectrum including MRSA (MIC < 2 mg/L) and VISA
- tet(M) [ribosomal protection] or tet(K) [efflux] have no discernible effect on MICs *(AAC 2006 Feb;50(2):505-10)*.
- large tissue accumulation (Vd=7-9L/kg)
  - ➔ low $C_{max}$ (1.5 mg/L; 70-80% protein-bound).
- approved by the FDA in June 2005 (and by the EME in April 2006) for
  - complicated skin infections, skin-structure infections (complicated skin and soft tissue infections);
  - intra-abdominal infections (complicated intra-abdominal infections)

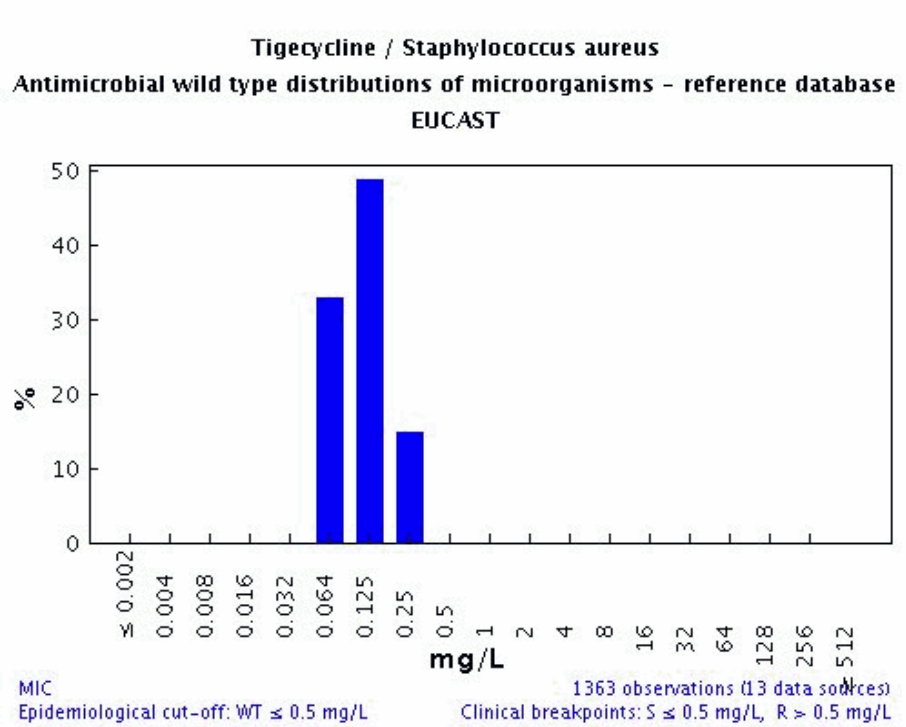
  both at 100 mg IV (initial) followed by 50 mg/12h IV
  - bkpt for *S. aureus* (FDA & EUCAST): S ≤ 0.5 mg/L

tétracycline

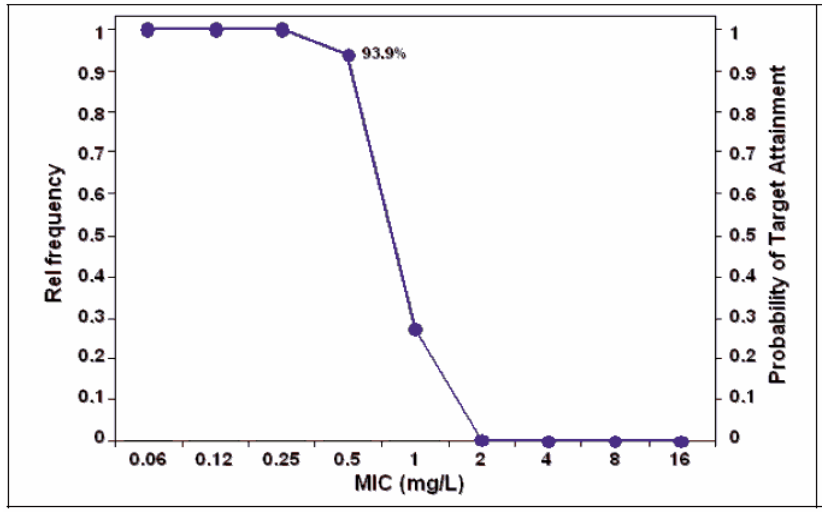


tigecycline

# Tigecycline… why a breakpoint ≤ 0.5 mg/L ?




Distributions of MIC as submitted to EUCAST

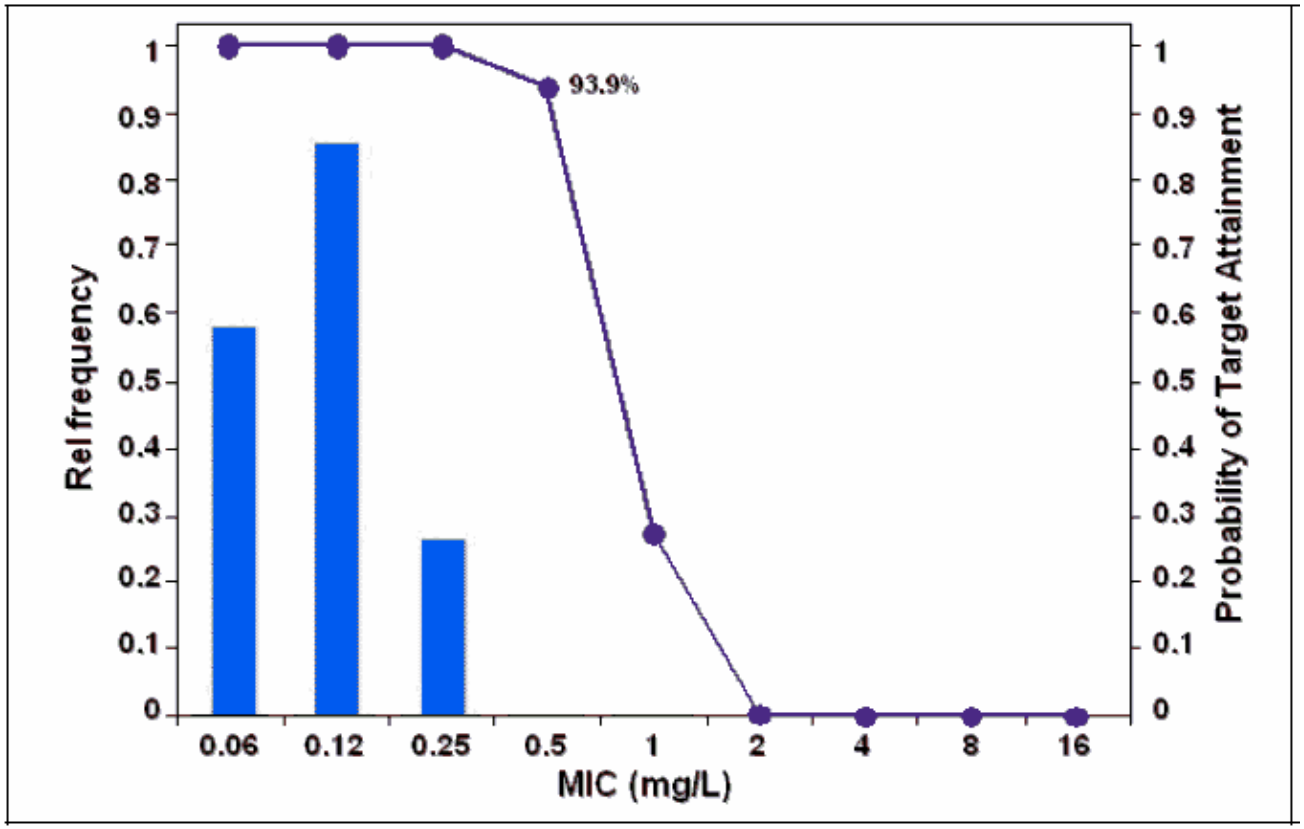



Probability of target attainment of a **suitable AUC/MIC ratio (≥ 7)** for the recommended dosage

http://217.70.33.99/Eucast2/SearchController/regShow.jsp?Id=7563

Wyeth: data on file

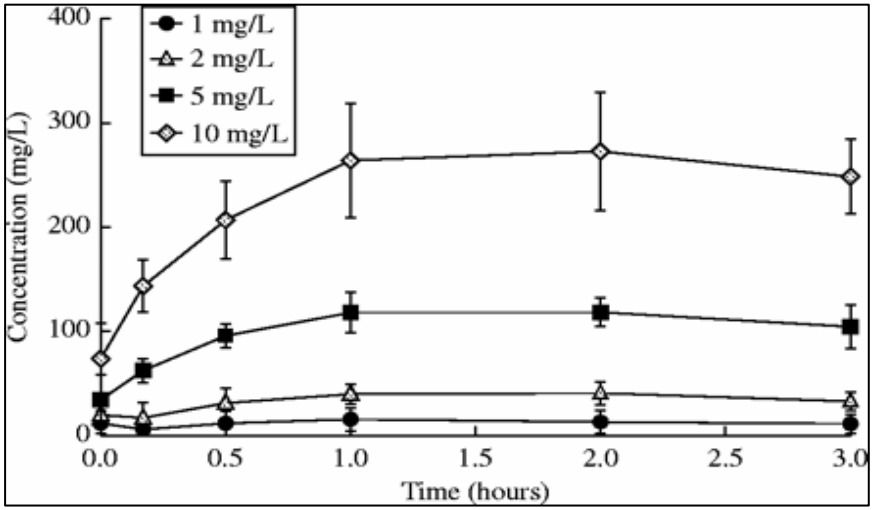
# Tigecycline… why a breakpoint ≤ 0.5 mg/L ?




Putting all together ….

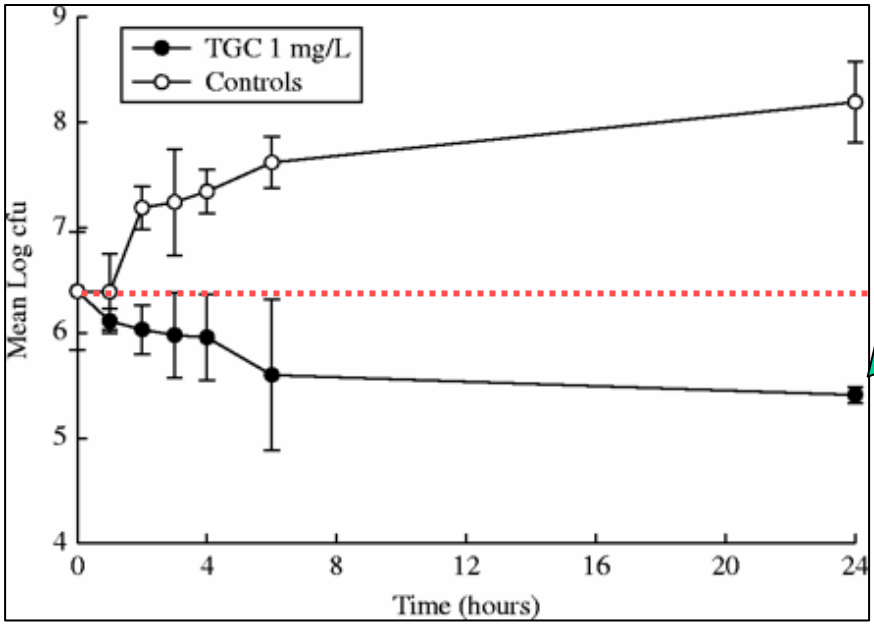
➔ you will be effective as long as the MIC remain ≤ 0.5 mg/L

# Tigecycline and intracellular *S. aureus*…



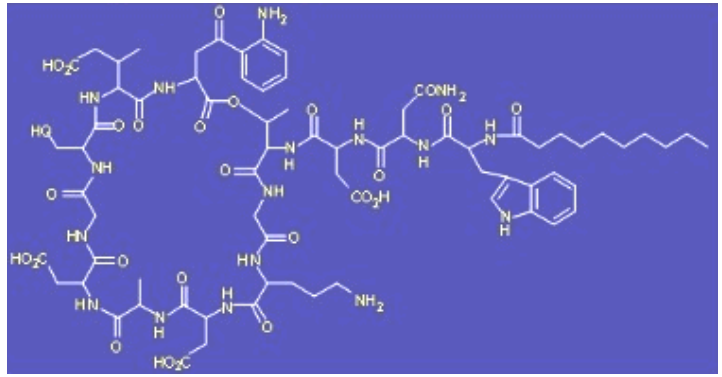

accumulation in PMN:
about 20-30 fold

Ong et al. J Antimicrob Chemother. 2005 Sep;56(3):498-501.

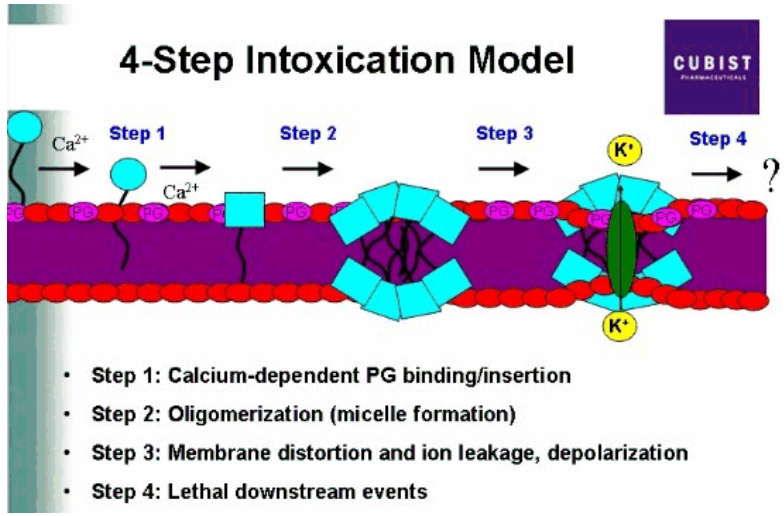



activity in PMN:
about 1 $\log_{10}$
at 1 mg/L
for S. aureus ATCC 29213
(MIC = 0.25 mg/L)

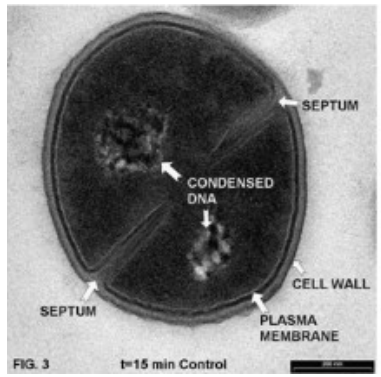
# Daptomycin …

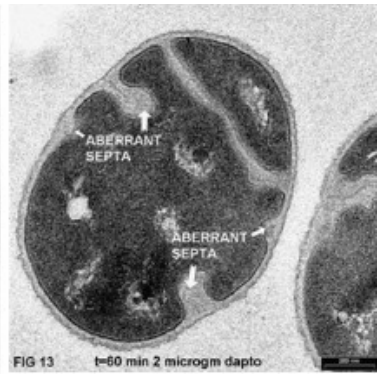


- very bactericidal towards Gram (+) organisms through membrane destabilization (no need of proteinaceous receptor!)
- BUT intrinsically inactive against Gram(-) due to LPS protection
- spare mammalian cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes)




- got a fast track registration in the US because of activity against vancomycin-resistant enterococci (VRE)



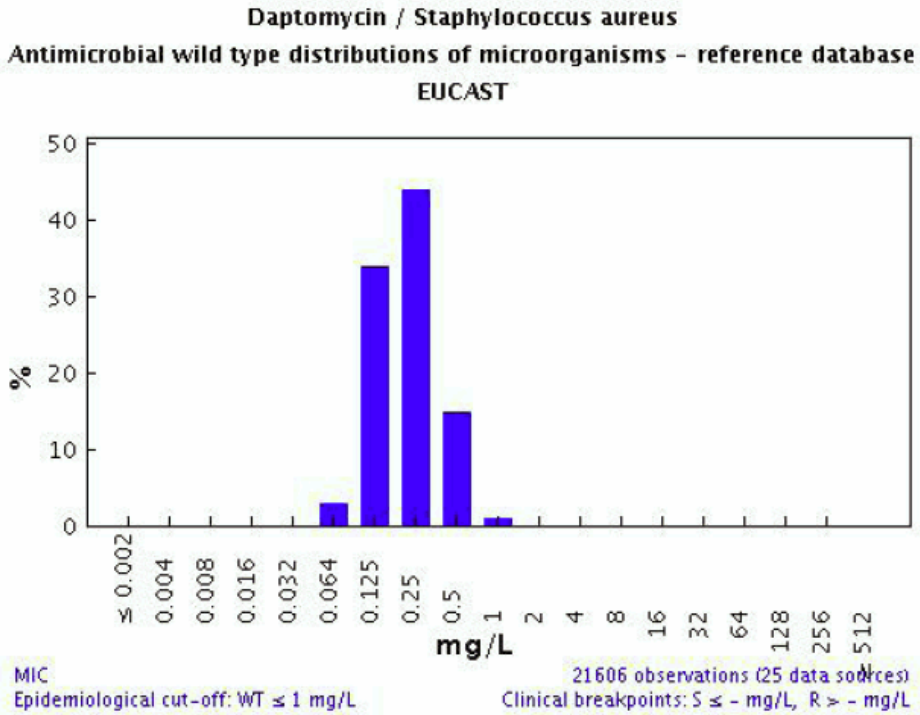



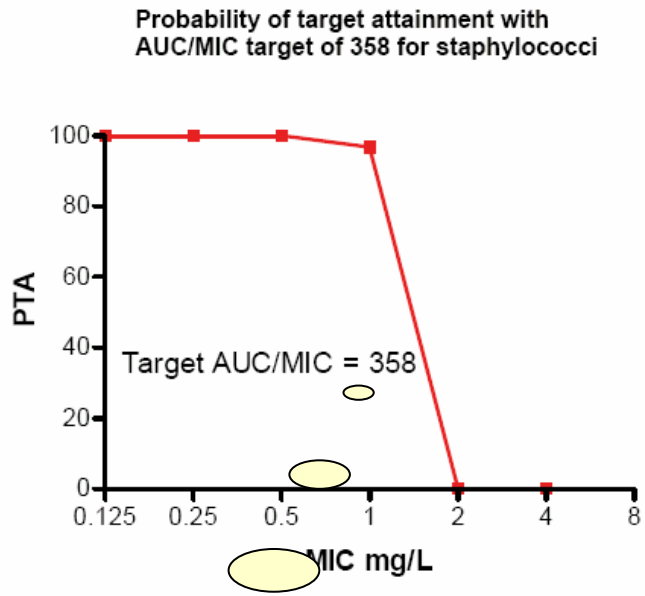

J. Silverman, 45thICAAC, 2005

# Setting Daptomycin breakpoint for *S. aureus*…



**Figure 1: Daptomycin MIC distribution and probability of target attainment for *S. aureus***




358 is the minimal value for efficacy based on animal and human data

# Is there a (real) place for daptomycin ?

- PK/PD-based breakpoint (as per EUCAST): 1 mg/L
- registered in USA/Europe for complicated skin and soft tissue infections
  (4 mg/kg administered once every 24 hours for 7-14 days)
- New registration in USA for bacteremia
- potential issues:
  - no clnical evidence of superiority to vancomycin for vancomycin-susceptible strains;
  - VISA strains tend to have MIC > 1 mg/L
  - poorly efficient in pneumonia (inactivated by surfactant)
  - safety concerns with higher dosages (myopathy);
  - price (about 3-4 x vancomycin …)

# MX-2401: a (close) cousin of daptomycin ?

**MX-2401: semi-synthetic derivative of amphomycin ...**

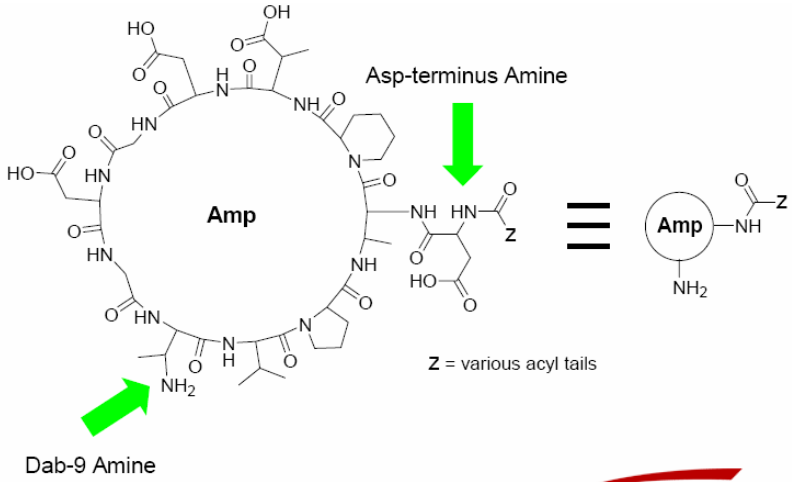



Figure 1: Amphomycin lipopeptide core.

MIGENIX

MIC for MRSA: 0.25 mg/L

*In vitro* demonstration of efficacy in models of infections (including pneumonia) by *S. aureus* and *S. pneumoniae*

NO surfactant effect ?

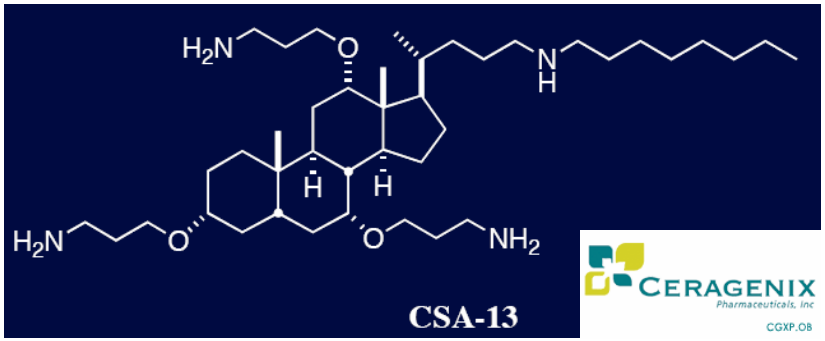
Target indications: cSSTI
pneumonia

MIGENIX has an agreement with the Government of Canada under the Technology Partnership's Canada program which is funding 26% of eligible costs (up to $9.3 million) for the development of MX-2401.

ICAAC 2006 F1 1879

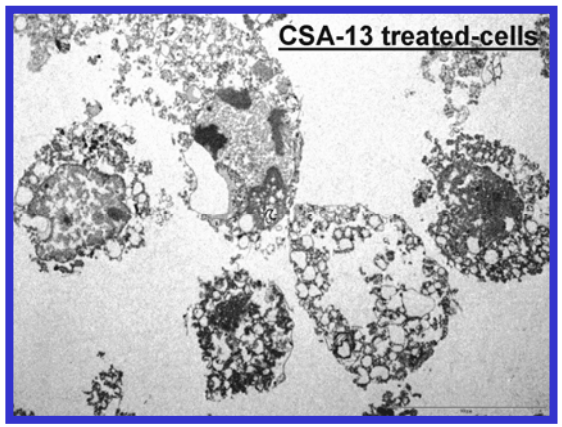
# Another membrane-active agent ...

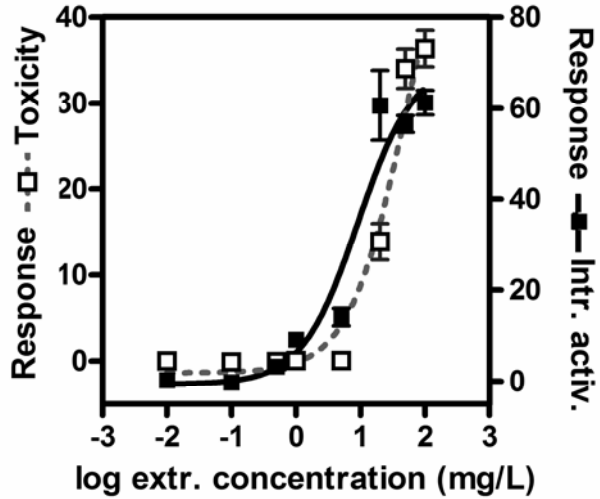
CSA-13




MIC range for MRSA: 1 mg/L
VISA: 1 mg/L
VRSA: 1 mg/L

Highly bactericidal,
but as toxic for eucaryotic
as for procaryotic membrane ….




Also active in biofilms;
will be further developped for topical applications

Lemaire et al., ICAAC 2006 A 0633

# New diaminopyridines active on MRSA

Iclaprim (AR-100): hospital use – cSSTI (Phase II/III)


ARPIDA

MIC for MRSA:

Iclaprim: 0.06 mg/L

AR-709: 0.25-1 mg/L

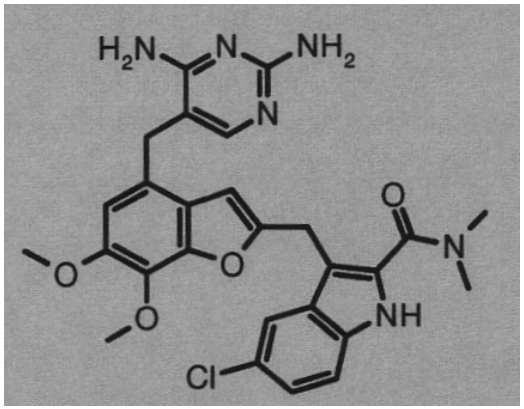
TMP: 1- >16 mg/L

active on TMP-resistant strains

**Table. 4: Binding affinities of AR-709 and TMP**

| DHFR Enzyme | Ka ($\times 10^7$ $M^{-1}$) | |
|---|---|---|
| | AR-709 | TMP |
| **Binary complex with NADPH** | | |
| *S. pneumoniae* ATCC 49619 wild-type, $TMP^S$ | >684 | 6.41 |
| *S. pneumoniae* I100L $TMP^R$ | 92 | 0.364 |
| *S. aureus* NCTC 8325 wild-type, $TMP^S$ | 109 | 0.317 |
| *S. aureus* F98Y $TMP^R$ | 2.5 | 0.093 |

AR-709: community use ?



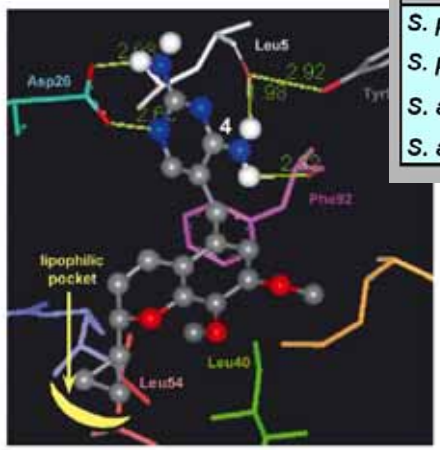


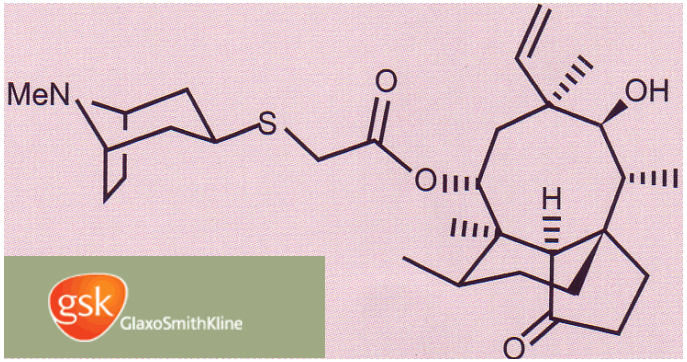

Figure 3. X-ray of co-crystallized Iclaprim in a resistant *S. aureus* DHFR (Phe98 to Tyr98). The distance to Leu5 and Phe92 carbonyls indicate that hydrogen bonds are possible with the 4-amino group. The cyclopropyl group occupies a lipophilic pocket influencing the binding properties of Iclaprim (Roche, unpublished results).

ICAAC 2006 F1 1959

Schneider *et al,* Bioor. Med.Chem. Letters (2003) 13:4217-21

# Revamping older drugs (and rediscovering targets...)

Retapamulin




MIC for MRSA:
0.12 mg/L

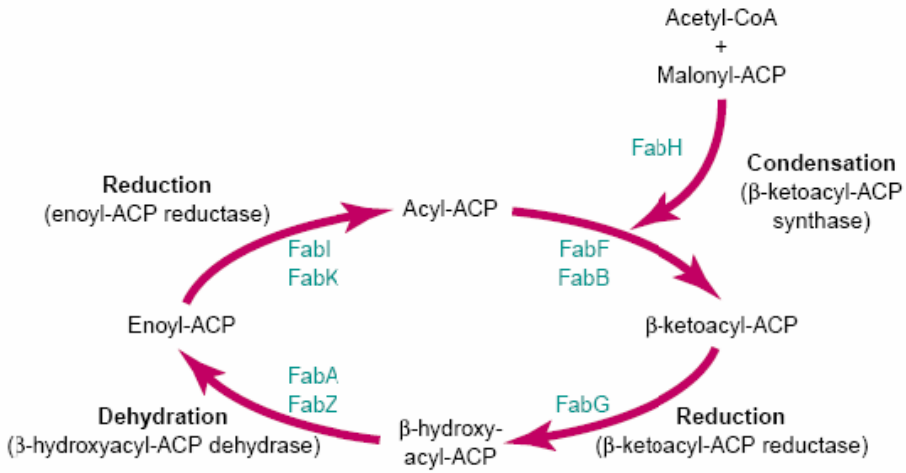
ICAAC 2006 F1 1861

Topic application for cSSTI; accepted for review by the US Food and Drug Administration in February 2006

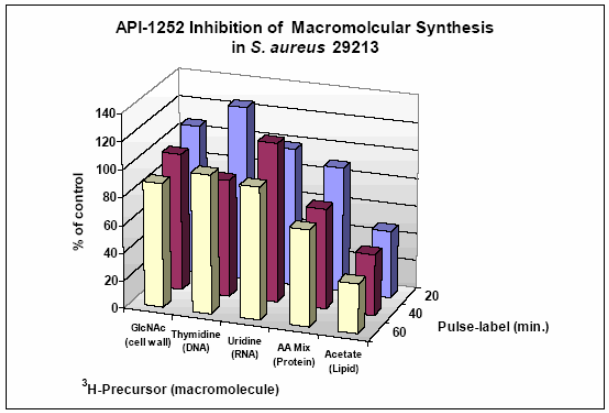
Retapamulin binds to the bacterial ribosome with high affinity, inhibits ribosomal peptidyl transferase activity, and partially inhibits the binding of the initiator tRNA substrate to the ribosomal P-site.
Taken together, these data distinguish the retapamulin mode of action from that of other classes of antibiotics. This unique mode of action may explain the lack of clinically relevant, target specific cross-resistance of retapamulin with antibacterials in current use.

Yan *et al,* AAC (2006) Epub ahead of print

# New target : FabI



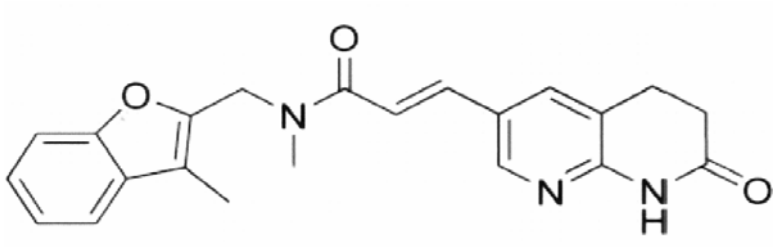

- FabI (enoyl-ACP reductase) catalyzes the final step in FASII chain elongation cycle
- Different than the mammalian system (FASI)
- FabI is essential for bacterial growth and survival




- Primary mechanism of action of API-1252 is via inhibition of lipid biosynthesis
- Selective for inhibition of acetate incorporation
  - 52% inhibition at 20 minutes and 75% inhibition at 60 minutes

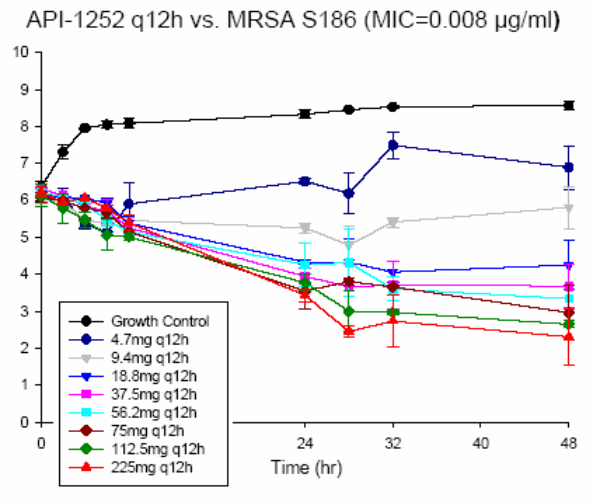
# New target : FabI

API-1252 Affinium Pharmaceuticals

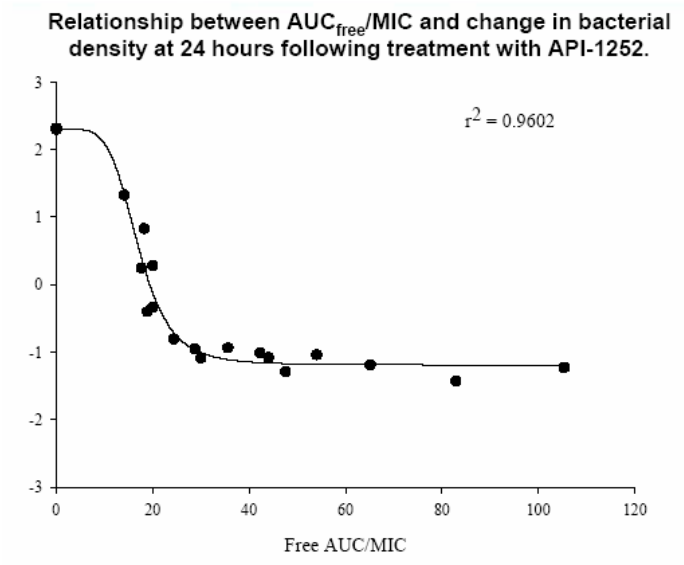


MIC range for MRSA: < 0.002-0.016 mg/L
VISA: 0.03-0.06 mg/L
VRSA: < 0.008-0.25 mg/L

Time- and concentration-dependent in *in vitro* pharmacodynamic models




AUC-dependent *in vivo*




ICAAC 2006 F1 754-759

# Will this be successful ?