Updates on treatment of *Staphylococcus aureus* / MRSA

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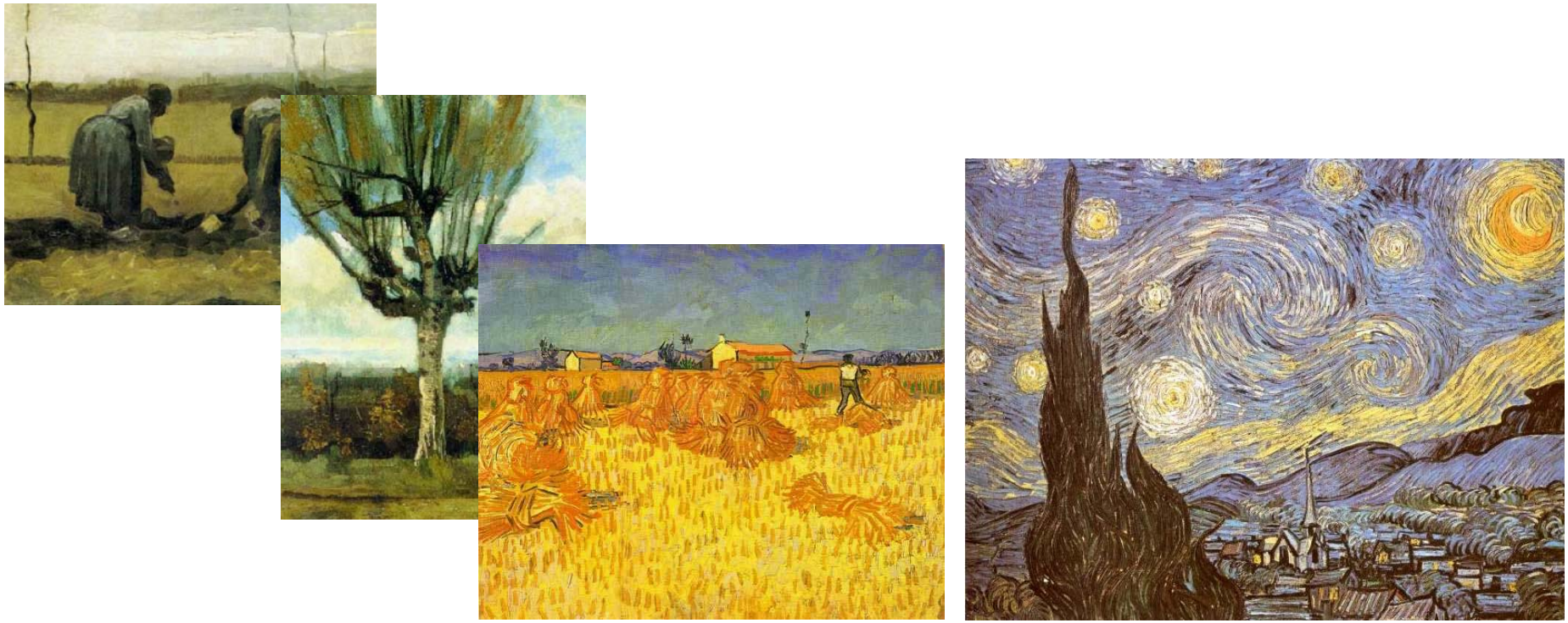
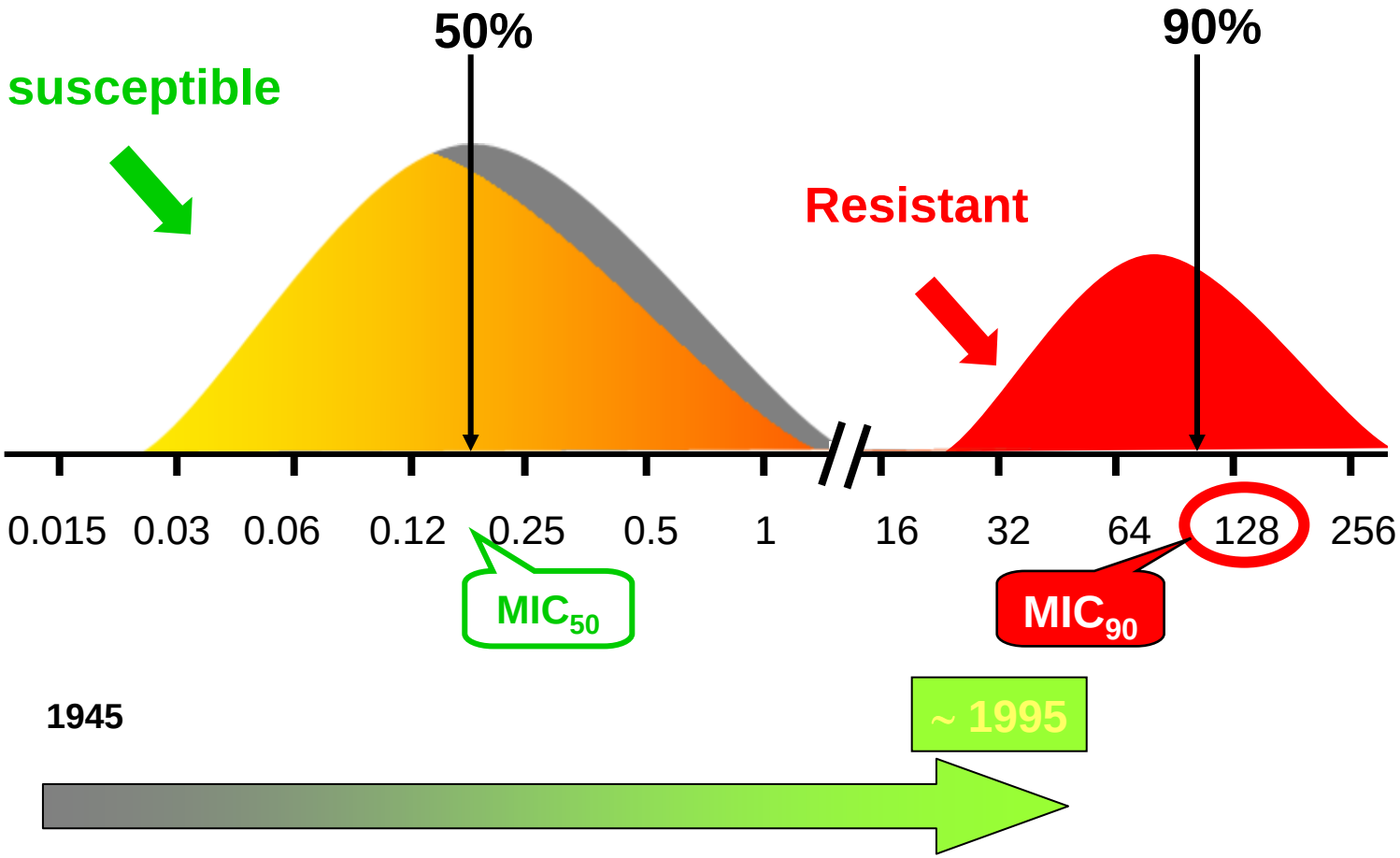
Tromsoe, Norway – 5 September 2009

Why do we need new antimicrobials ?



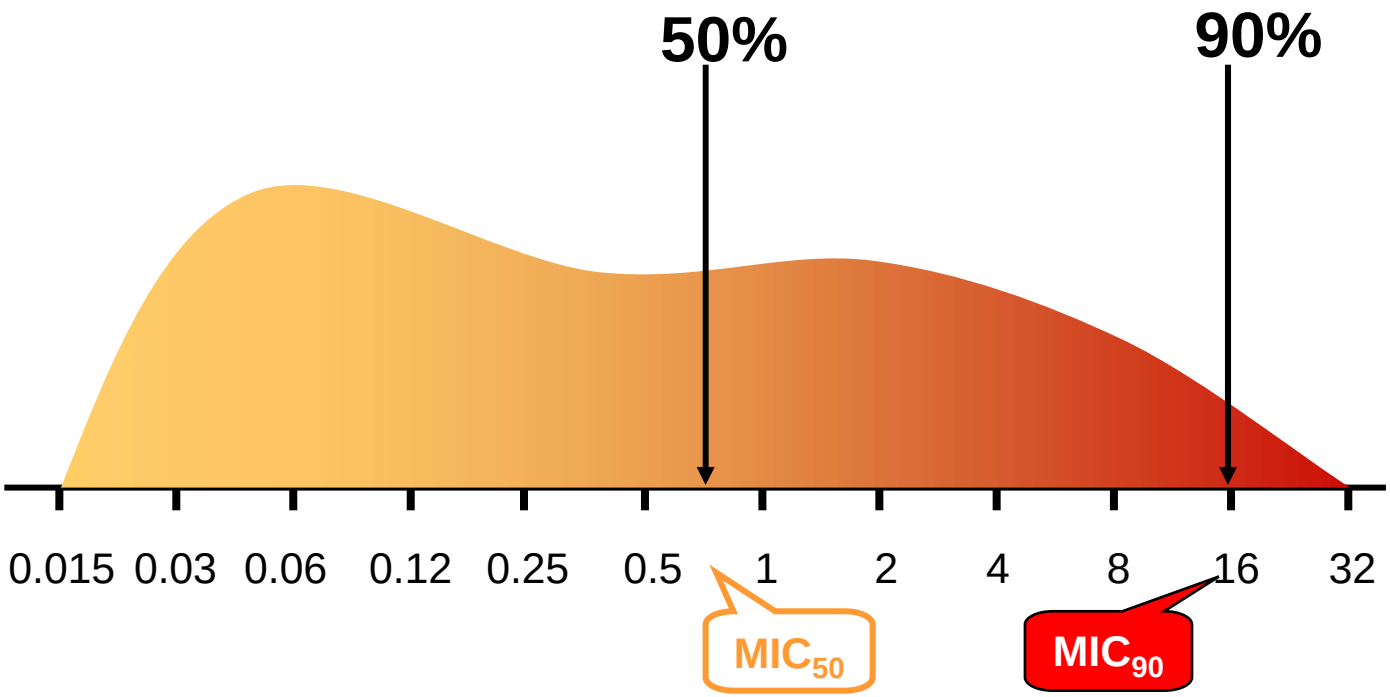
1945 **~ 1995** **2009**

Easy resistance …



A more difficult situation …

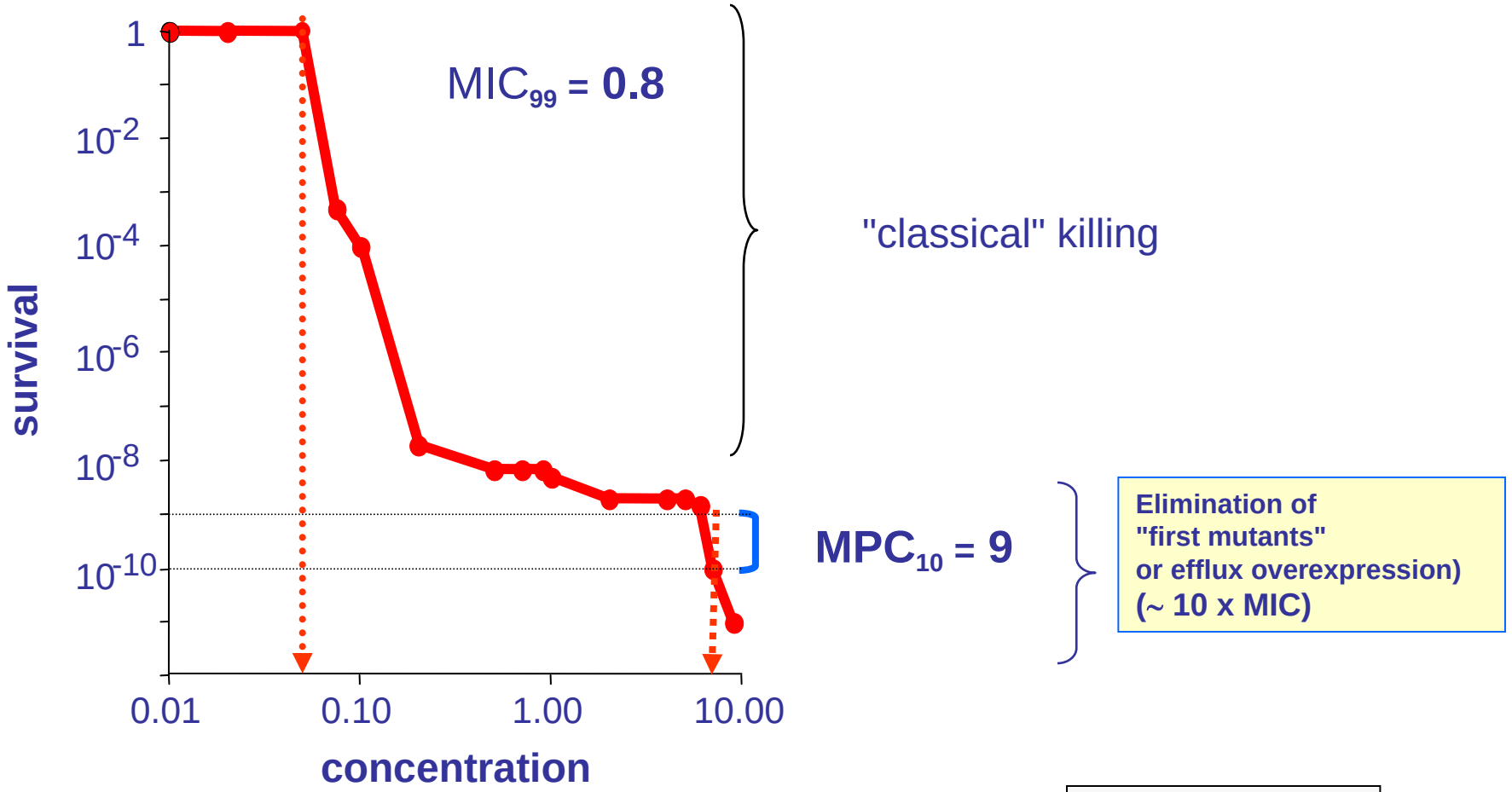
Multiplicity of mechanisms



2009

Populations of decreased susceptibility

- Well known for *S. pneumoniae* (and, more recently with *S. aureus* [VISA])
- Rediscovered under the the acronym "MPC" (***M**utation **P**revention **C**oncentration*) for fluoroquinolones with *Mycobacteriae* (and since then, with several other microrganisms)

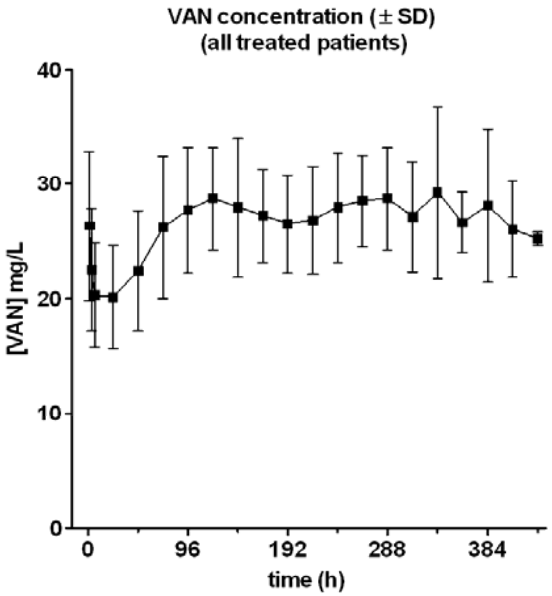


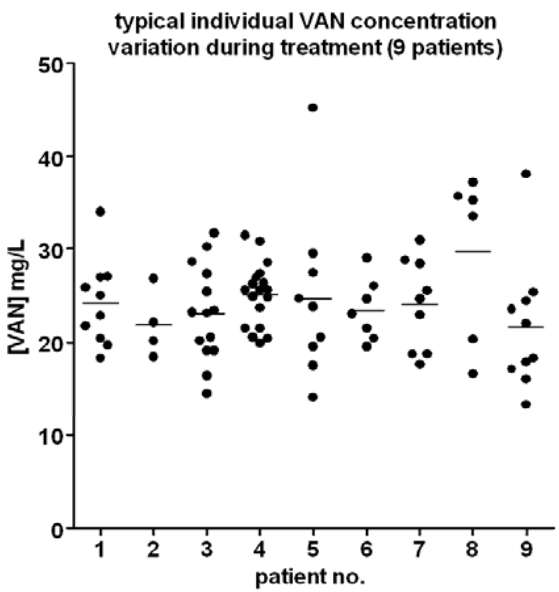
Dong *et al*; AAC 43:1756-1758

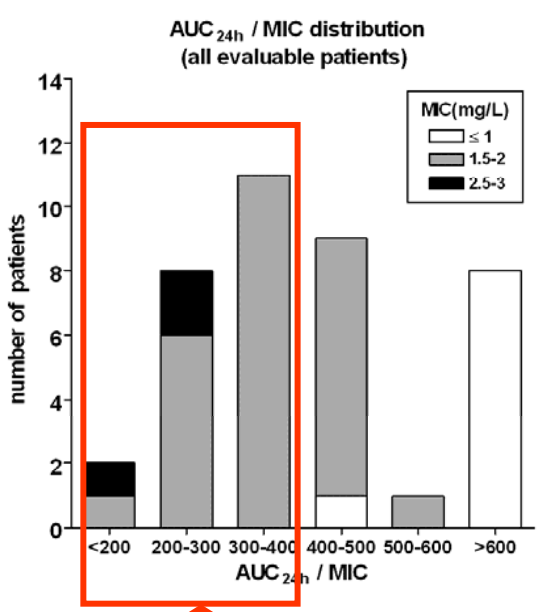
MIC creep

- Suggested to take place with vancomycin
- Viable according to reports (local or technique variations ?)
- Significance to be established, but …

Patients with documented Staphylococcal infection and treated with vancomycin by continuous infusion



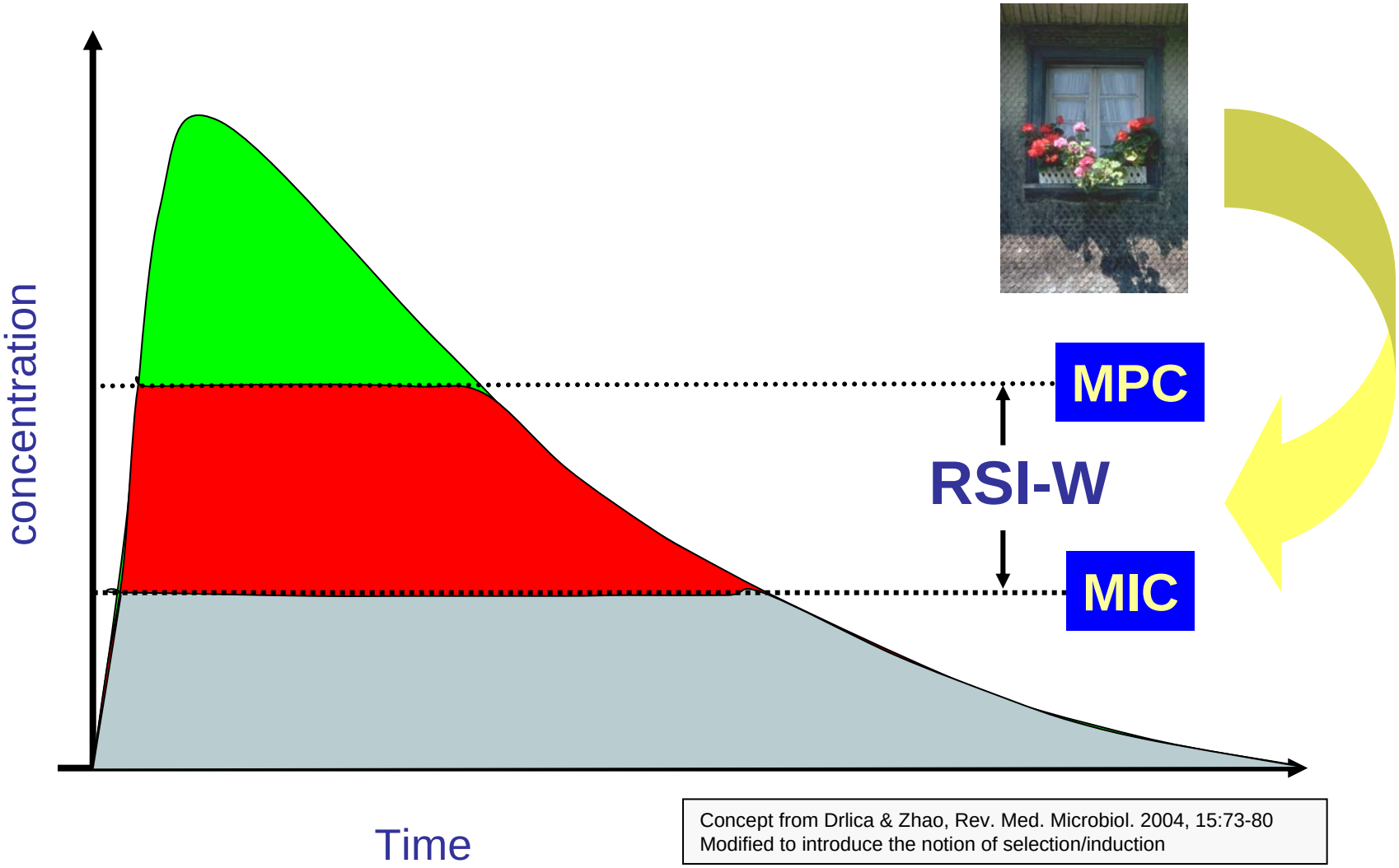




Ampe et al. ECCMID 2009

This where we start seeing failures…

The concept of "Resistance/Selection/Induction Window"



Concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80
Modified to introduce the notion of selection/induction

New antibiotics … a risky business…

- Registered in the EU (EMEA) and the U.S.A. (FDA)

- Daptomycin - http://www.emea.europa.eu/humandocs/Humans/EPAR/cubicin/cubicin.htm
- Tigecycline - http://www.emea.europa.eu/humandocs/Humans/EPAR/tygacil/tygacil.htm

- Registration pending in the US but EMEA status uncertain

- Telavancin (Theravance / Astellas; may become available in the U.S.A.)

- Registration postponed in the US and EMEA status uncertain

- Ceftobiprole (Basilea / Johnson & Johnson; available in Canada, Switzerland and Ukraine)

- Withdrawn from both FDA and EMEA

- Oritavancin (The Medicines Company; uncertain status)

- Rejected by EMEA

- Gemifloxacin (Oscient Pharm. In the US; but under chapter 11)

- Rejected by the FDA

- Iclaprim

- Development on hold…

- Dalbavancin (Pfizer)

"Consistent with Basilea's earlier press releases, an FDA "Warning Letter" issued in August 20008 asserts that there was a failure to ensure proper monitoring of the studies as well as deficiencies in study conduct…"
(Basilea Press Release August 18th, 2009)

Daptomycin: historical landmarks….

1987 **1993** **1997**

Discovery of daptomycin as a novel anti-Gram + lipopeptide

In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.
Eliopoulos *et al*, **1986** Antimicrob. Agents Chemother. 30, 532-5

Development halted

- lack of efficacy
- toxicity

"Lilly was not satisfied with the overall clinical results observed with the twice-daily dosing regimen utilized in these studies"

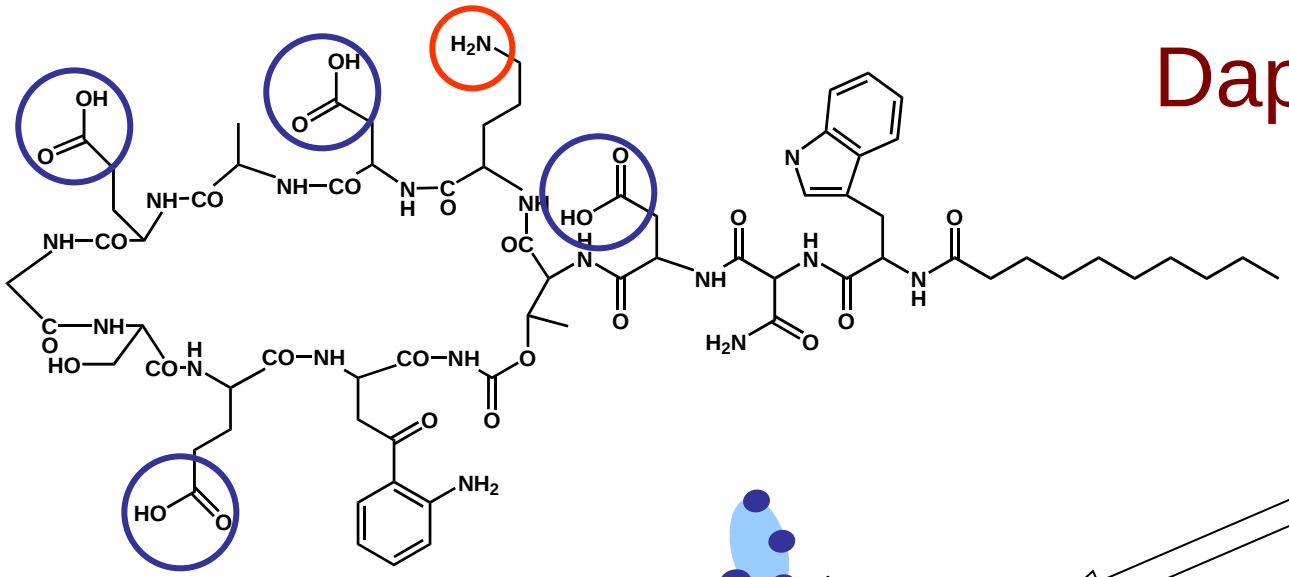
Taking over by CUBIST

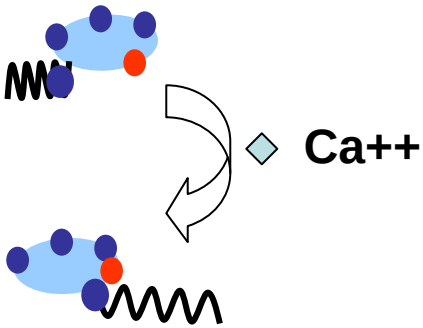
or *"pharmacodynamics in action ….."*

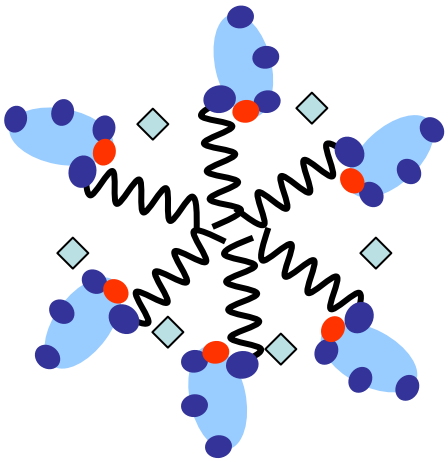
Once-daily dosing in dogs optimizes daptomycin safety.
Oleson *et al*, **2000**, AAC. 44:2948-53.

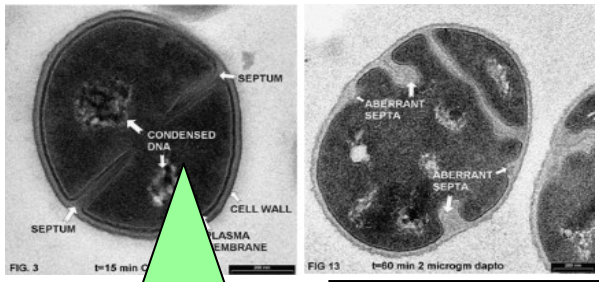
Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha *et al*, **2003,** AAC 47:1598-603

Daptomycin …

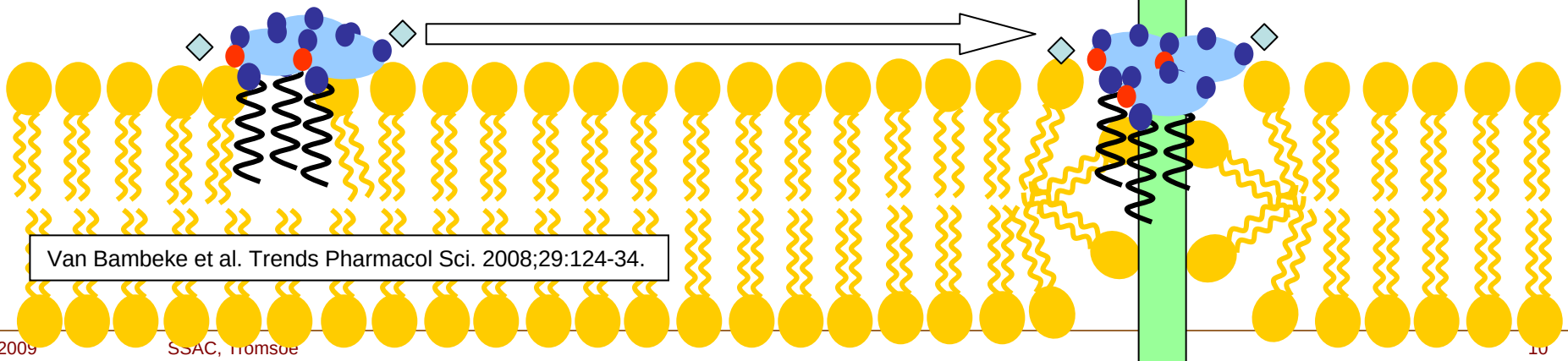








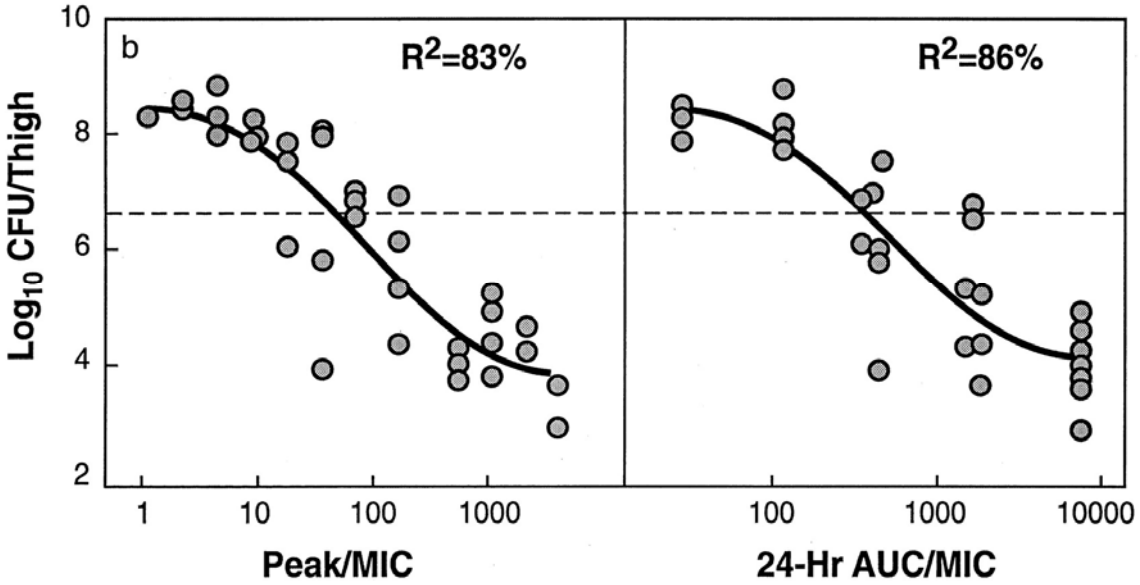
J. Silverman, 45thICAAC, 2005



Van Bambeke et al. Trends Pharmacol Sci. 2008;29:124-34.

PK/PD of daptomycin - animal models

Mouse thigh - *S. aureus*



Efficacy for
- Peak/MIC > 60-100
- AUC/MIC > 400-550 (total concentr.)

Safdar *et al.*, AAC (2004) 48:63

PK/PD of daptomycin - application to humans

dose and route of administration	compartment	AUC	AUC/MIC (1 mg/L)
4 mg/kg iv (registered dose)	serum	417	417
	inflamm. exsudate	318	318
6 mg/kg iv	serum	747	747

Dose adjustment if creatinine clearance < 30 ml/min

EUCAST breakpoint:
1 mg/L

Wise *et al.*, AAC (2002) 46:31-3
Dvorchik *et al.*, AAC (2003) 47:1318-23

Launching daptomycin…

1987 1993 1997 **2003-2006**

Registration

FDA : 2003

Europe : 2006

Indications in Europe

- **complicated skin and soft tissues infections with Gram (+)**

Efficacy up to an MIC of 1 mg/L

- **bacteremia**
- **endocarditis**
- **complicated urinary tract infections**

Lack of efficacy :

- **pneumonia (neutralization by the surfactant)**
- **VISA strains (no access to target)**

Only available as intravenous form !

Carpenter & Chambers CID (2004) 38: 994-1000

Daptomycin: where are we in EU ?

European Medicines Agency

emea

4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Daptomycin: were are going to ?

1987 1993 1997 **2003-2006** 2009…

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.[32]

To minimize the risk, three steps are advised:

first to explore the potential for higher dosage, guaranteeing levels above a 'mutant prevention concentration';

secondly, to recognize patients where surgical debridement is warranted;

and thirdly, to prevent cross-infection with resistant organisms.

Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

Livermore DM. J Antimicrob Chemother. 2008;62 Suppl 3:iii41-iii49.

Tigecycline: historical landmarks …

1993 **1999**

Disvovery of glycylcyclines as a novel class of antibiotics

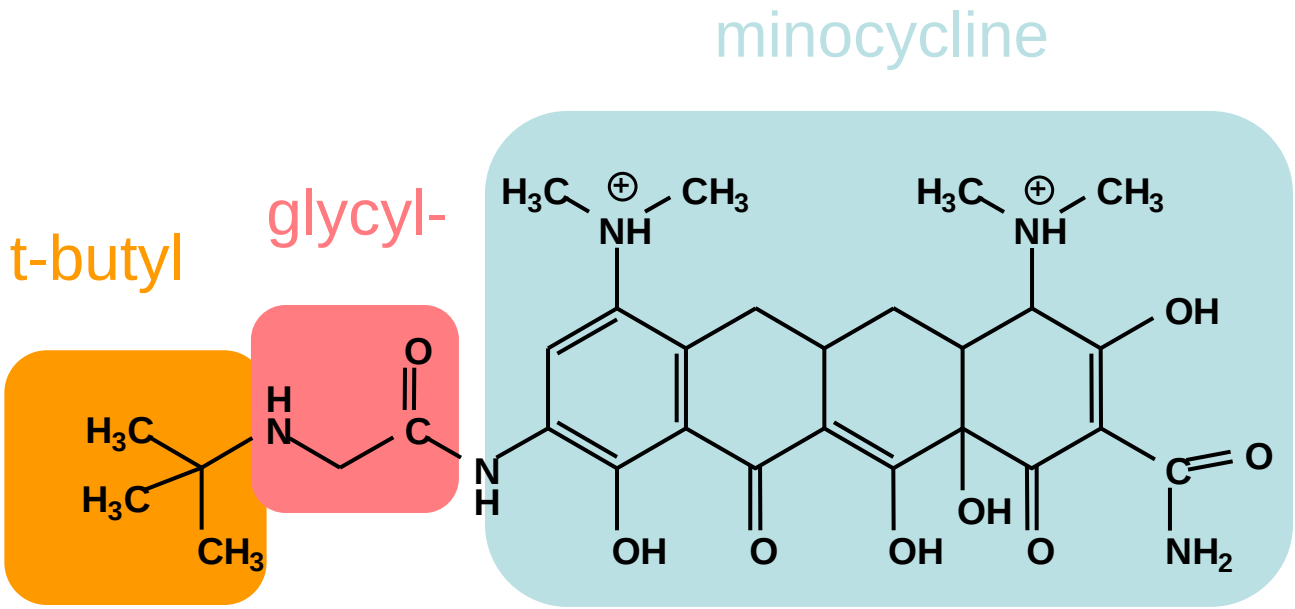
In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

Tufts UNIVERSITY

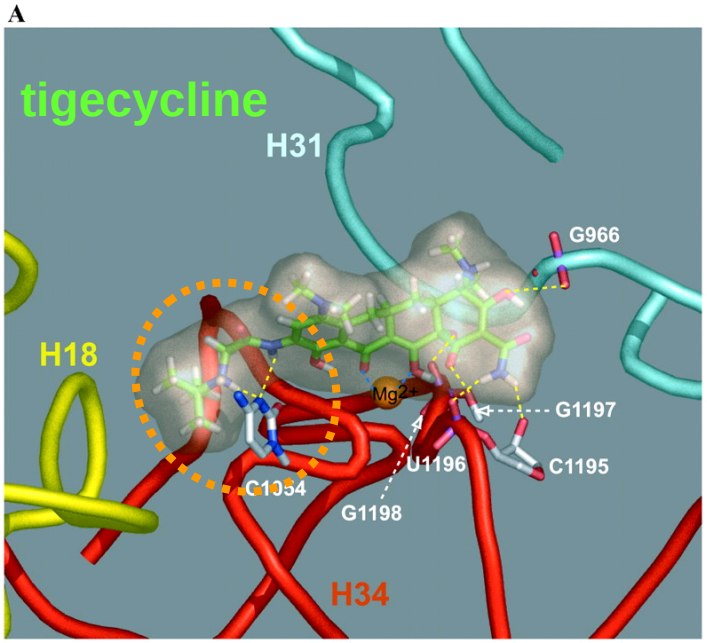
Demonstration of the spectrm of activity and candidate selection

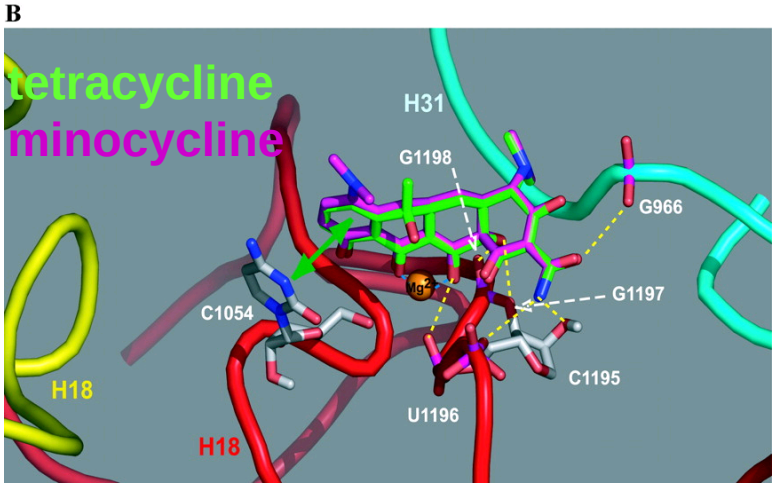
***In vitro* and *in vivo* antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).**
Petersen *et al.* **(1999)** Antimicrob Agents Chemother. 43:738-44.

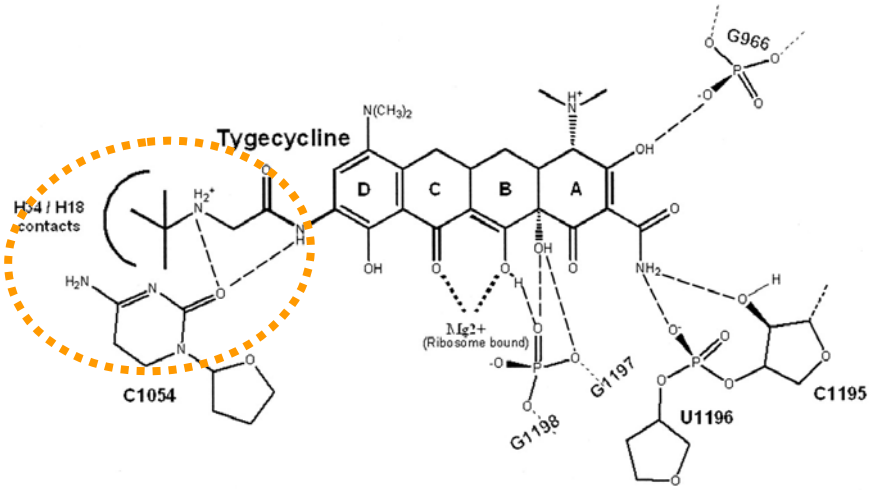
Tigecycline: chemical structure



Mode of action of tigecycline







- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps;
- But remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in *P. aeruginosa*)

Olson *et al.*, AAC (2006) 50:2156-66

Tetra- and glycyl-cyclines: activity and resistance

species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

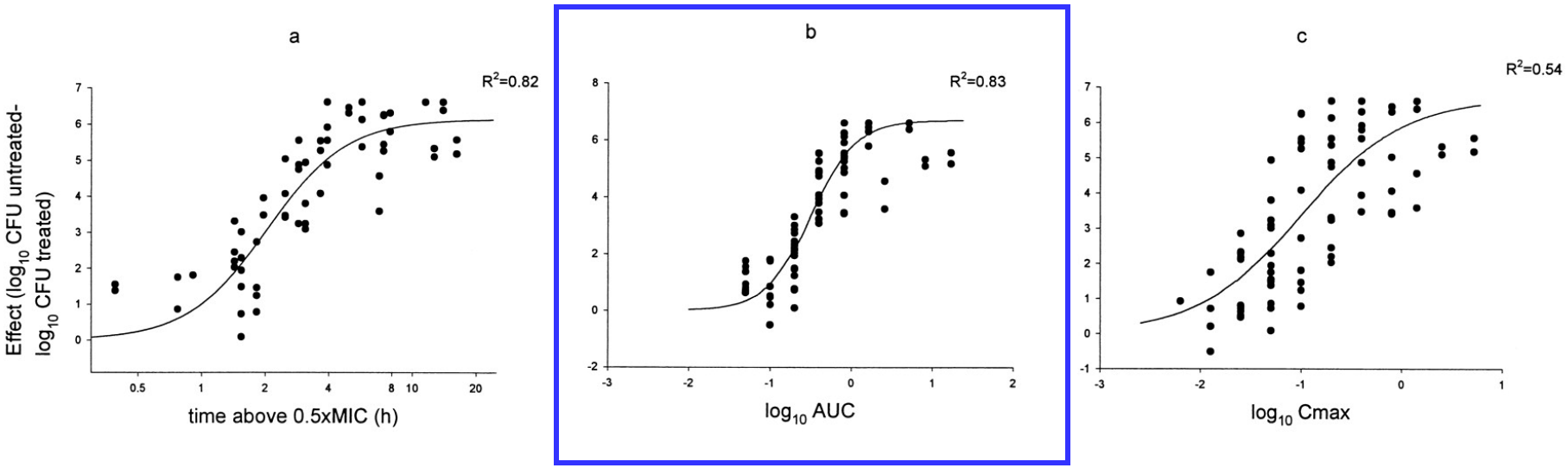
Tigecycline: pharmacokinetics

	tissue	AUC_{24h} (mg.h/L)	serum/tissue AUC ratio
Single dose: 100 mg	bile	2815	537
	bladder	120	23
	colon	17.3	2.6
	lung	9.19	2
	bone	2.05	0.4
	synovial fluid	1.68	0.31
	CSF	0.46	0.11
100 mg + 6x50 mg q12h	ELF	4.54	1.31
	alveolar MΦ	268	77.5

Rodvold, JAntimicrob Chemother (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

PK/PD of tigecycline – animal models

Mouse thigh - *S. pneumoniae*



Efficacy for AUC_{24h}/MIC of
- 1-5 (free fraction)
- ~ 10-50 (total conc.)

van Ogtrop *et al.,* AAC (2000) 44:943-9

Tigecycline EUCAST breakpoints

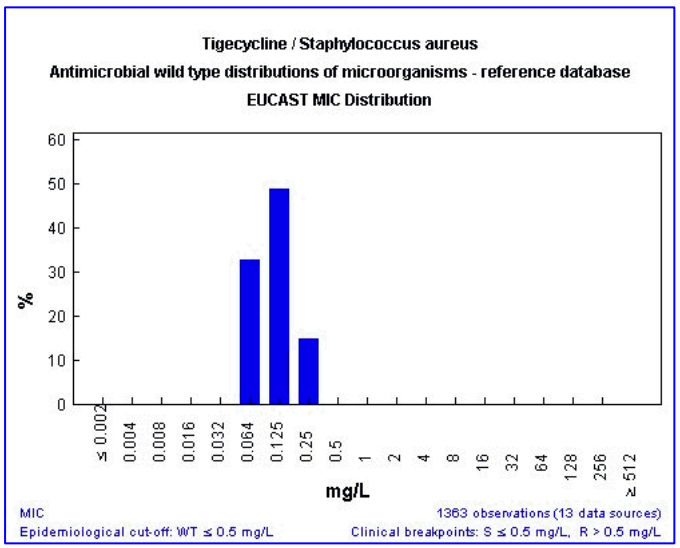
Tetracyclines - EUCAST clinical MIC breakpoints 2008-06-19 (v 2.2)

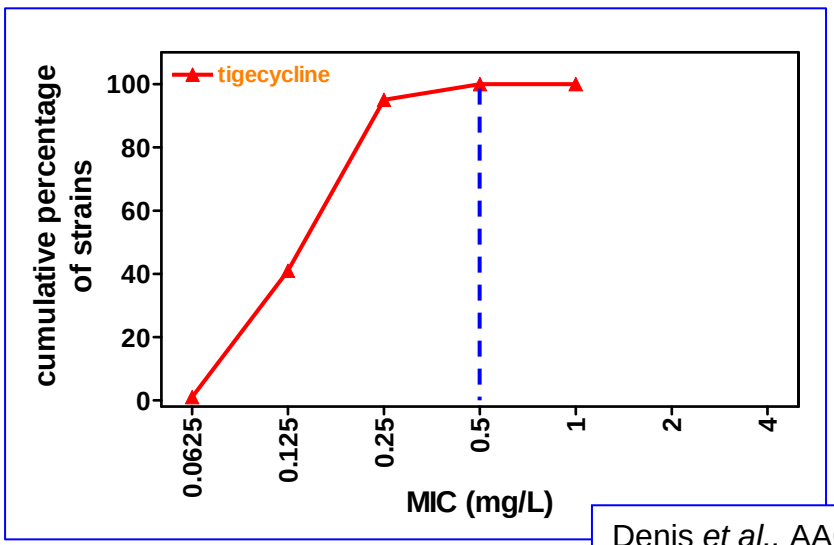
Tetracyclines Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.		Species-related breakpoints (S≤/R>)				
		Enterobac-teriaceae	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*
Tigecycline	RD	1/2[E]	IE	0.5/0.5[F,G]	0.25/0.5[G]	0.25/0.5[G]

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.





But will this last ?
(T.E.S.T. will tell but TK reports MIC_{90} at 0.75 In 2008)

Denis *et al.*, AAC (2006) 50:2680-5

Launching tigecycline in EU

1993 **2005-6**

European Medicines Agency

4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Paediatric patients
Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

* pediatric studies are ongoing and/or proposed to Regulatory Authorities

Other novel antibiotics (pipeline…[with leaks…])

- **Ceftobiprole** (Basilea / Johnson & Johnson)
  - first cephalosporin with anti-MRSA action (is also active against *P. aeruginosa*)
  - 2 X 750 mg ou 3 x 500 mg … (limited because of toxicity ?)
  - "*target attainment rate*" : MIC of 4 mg/L (EUCAST breakpoint)
  - submitted for "complicated skin and soft tissue infections" in EU and in the USA but no decision expected before end of 2009 or even later …
  - failure in nosocomial pneumonia (reason still unclear ?)

- **Telavancin** (Theravance / Astellas)
  - first lipoglycopeptide with FDA "near approval"; status uncertain in EU (safety issues)
  - very bactericidal (but Gram + ONLY); once-daily dosing
  - trend towards superiority in "complicated skin and soft tissue"
  - success in nosocomial pneumonia (*S. aureus*)

- **Oritavancin** (The Medicines Company)
  - lipopeptide very active against Gram +, with activity against SCV [incl. cystic fibrosis] and biofilm
  - very long half-life and large cellular accumulation
  - uncertain future (new phase 3 study requested by the FDA plus additional safety studies; withdrawn from EMEA)

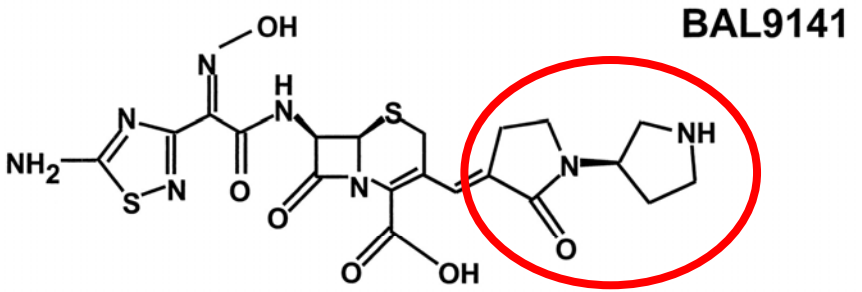
MIC of novel anti-Gram (+) antibiotics and EUCAST breakpoints

organism	**ceftobiprole (4/4)**	**telavancin (1/1)****	**oritavancin (0.125/0.25)****	**vancomycin (2/2)****
MSSA	0.12-1	0.25/0.5	0.25/0.5	1/1
MRSA	0.25-4	0.25/0.25	0.25/0.5	1/1
VISA	0.5-2	0.5-1	**1/1**	**4/4**
VRSA	1-2	**2-4**	0.5	**16**
S. pneumo Pen non-S	0.25-1 *	≤ 0.06/≤ 0.06	≤0.002/0.004	≤ 0.25/≤ 0.5
Enteroc. Van S	0.064-16 *	0.12/0.5	0.12/0.5	1/2
Enteroc. Van R	*	**4-16**	0.03	**16**

* no EUCAST breakpoint set (insufficient evidence)
** draft (submitted for consultation)

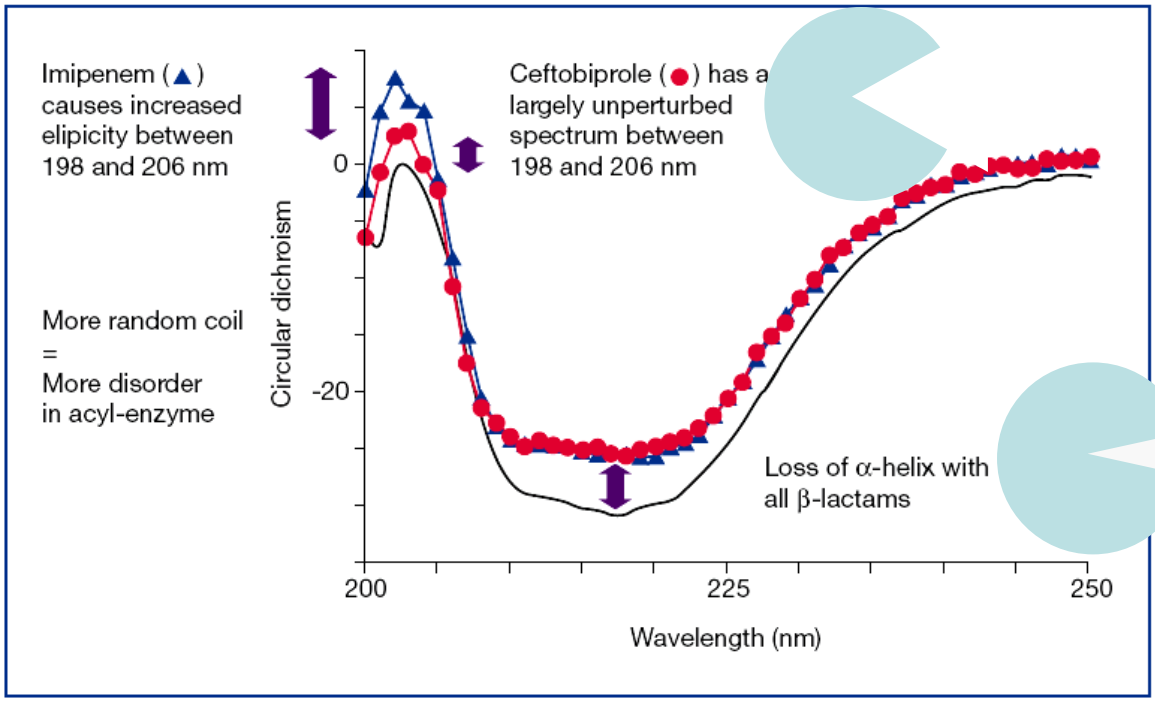
Pillar et al., JAC (2008)61:595-602; Ge et al., AAC (2008) 52:3398-404; Draghi et al.,AAC (2008) 52:2383-2388; ICAAC (2008) C1-146,150,151; Lemaire et al. AAC (2009) Mar 16. [Epub]

Ceftobiprole: mode of action



ceftobiprole and PBP2a

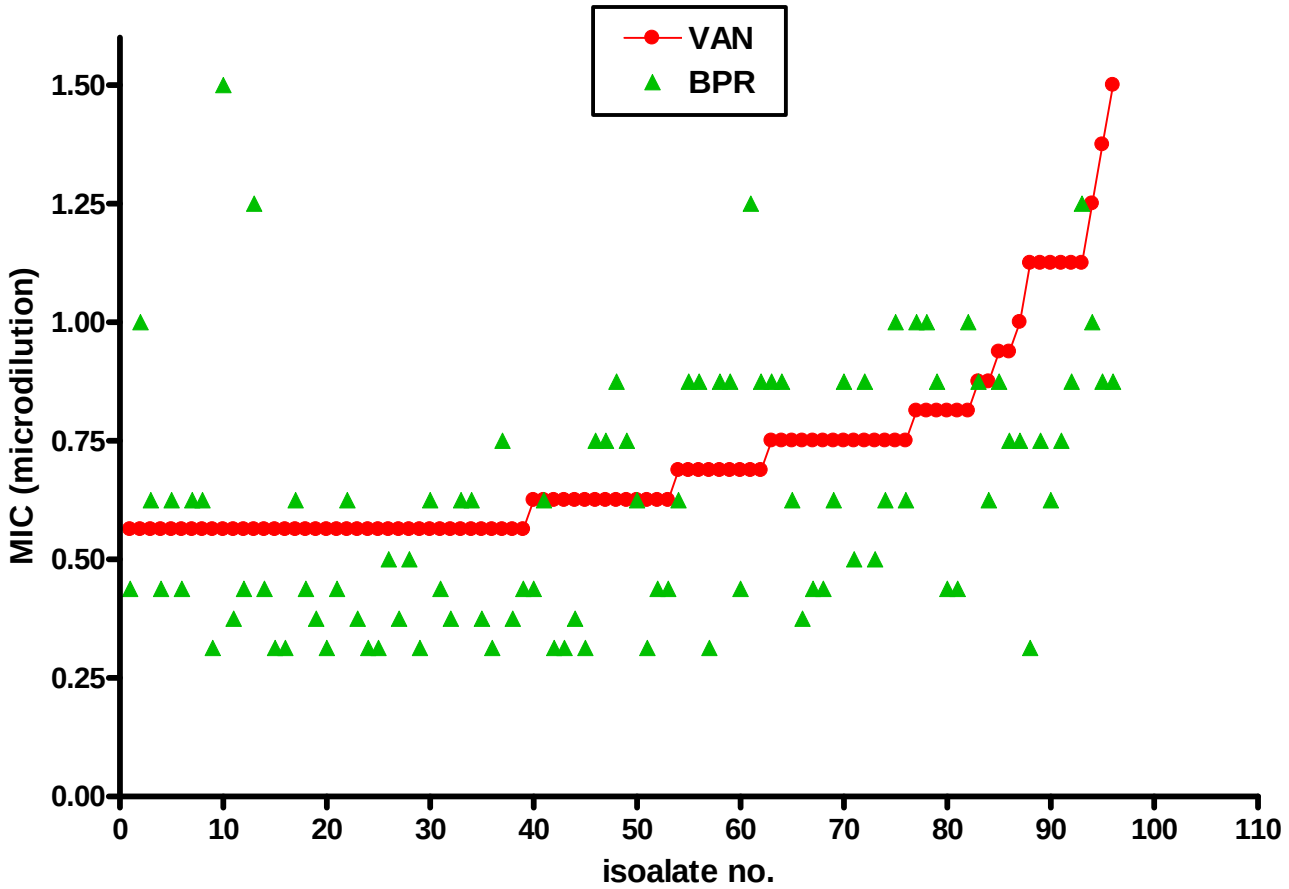
Figure 5. Loss of secondary structure accompanies acylation.



Lovering et al. ECCMID 2006, Abstract P1586.

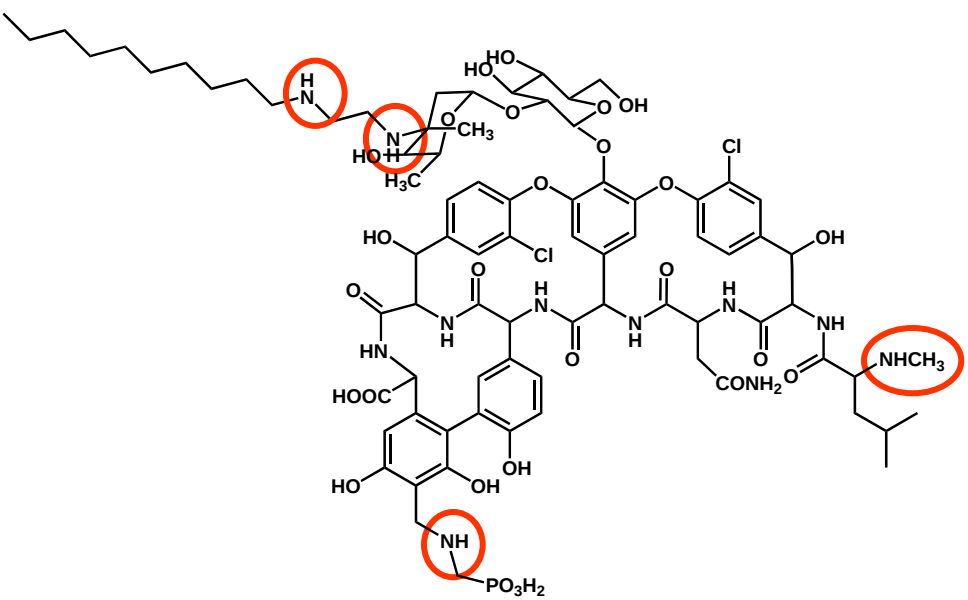
Ceftobiprole: susceptibility in Belgium

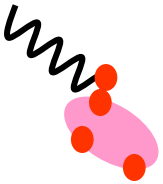
Comparison of 96 MRSA isolates from wound and skin-structure infections

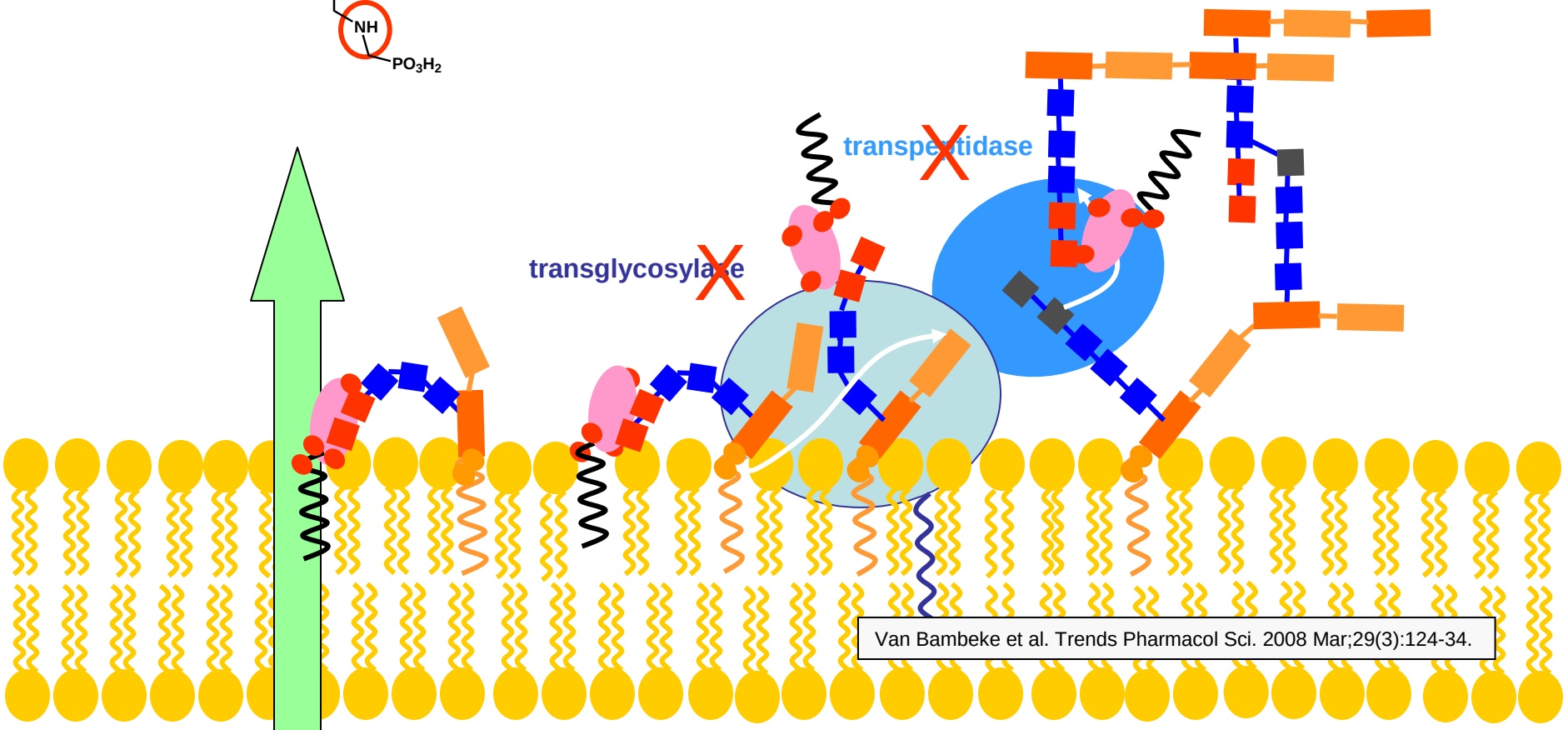


Lemaire et al., submitted

Telavancin: mode of action



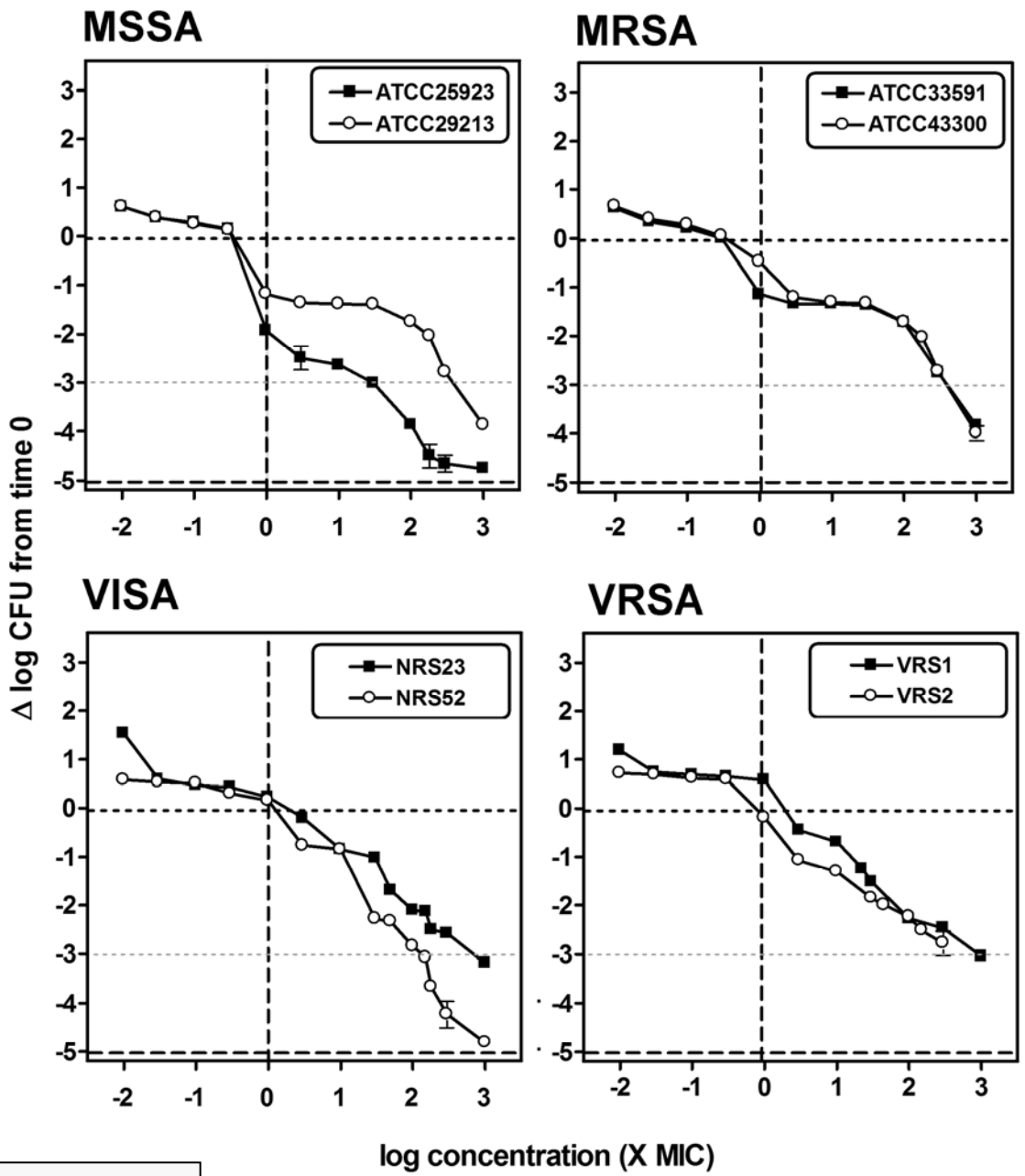




Van Bambeke et al. Trends Pharmacol Sci. 2008 Mar;29(3):124-34.

Telavancin
and
MSSA
MRSA
VISA
VRSA

3 h kill curves

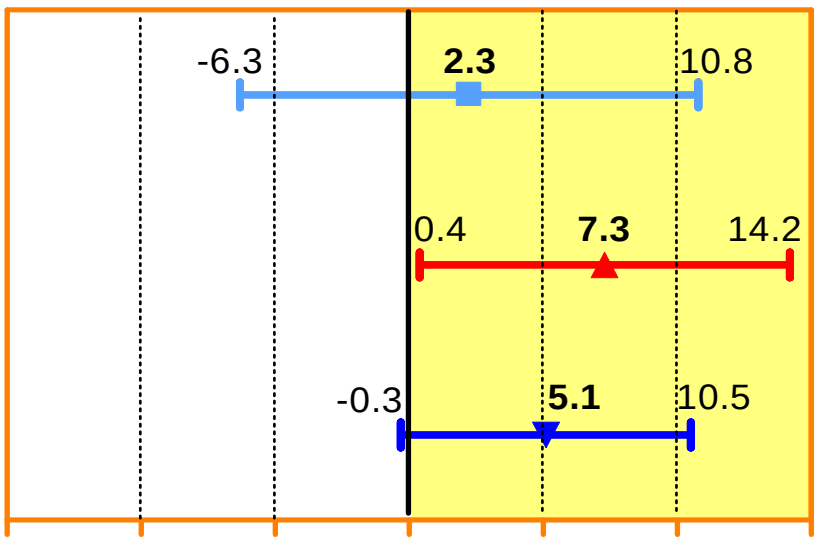


Barcia-Macay *et al.,* J Antimicrob Chemother. 2006; 58(6):1177-84.

Telavancin: clinical trials in cSSI caused by MRSA

Therapeutic regimens

- **Telavancin - 10 mg/kg IV q 24hr; or**
- **Vancomycin - 1 gm IV q 12 hr (adjusted per site SOP)**



Atlas

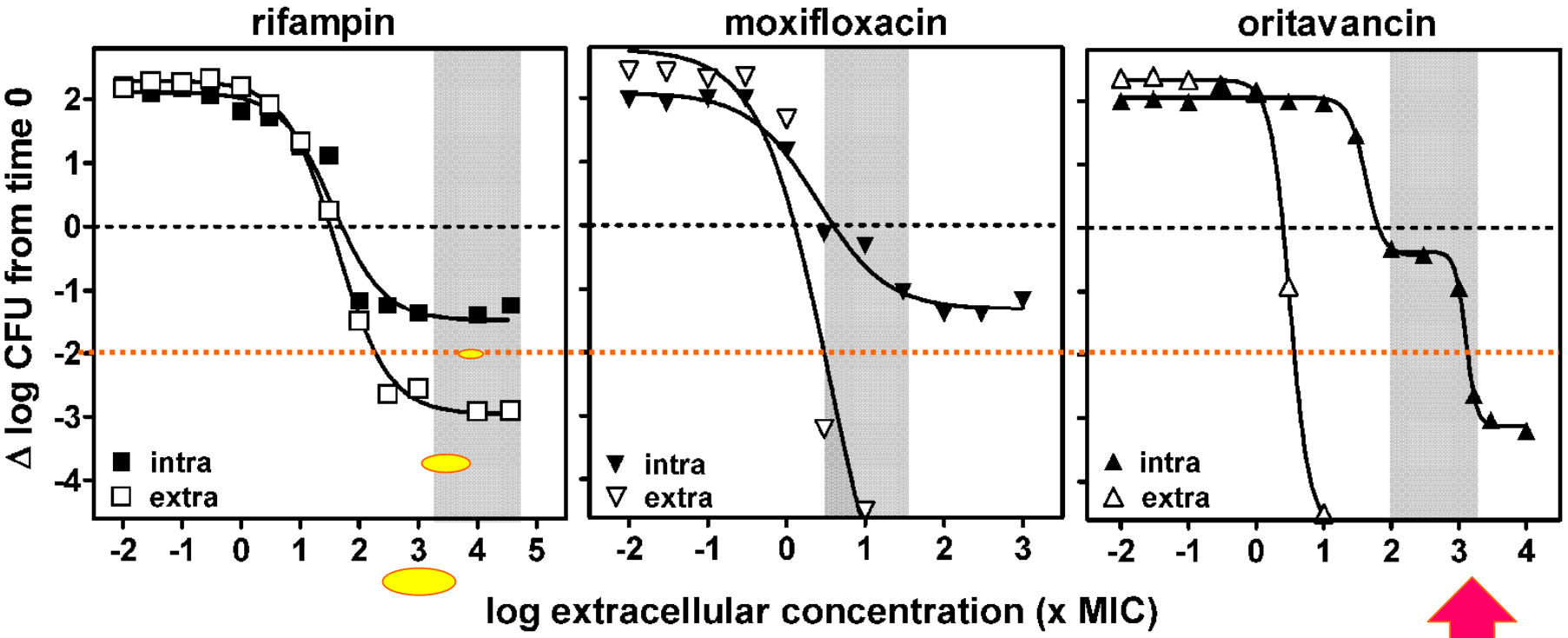
	TLV % success n	VAN % success n
ATLAS 1	87.1 % (116)	84.8 % (138)
ATLAS 2	92.0 % (162)	84.7 % (163)
ATLAS 1+2	89.9 % (278)	84.7 % (301)

See full data in Stryjewski *et al.* Clin Infect Dis. 2008;46:1683-93

Telavancin data presented at the FDA (public hearing – November 2008)

- comparable to standard therapy for the cSSI
- Trials finalized for S. aureus pneumonia and bacteremia
- adverse effects: taste disturbance, foamy urine, headache, procedural site pain, nausea, renal toxicity (3 %), QTc prolongation without clinical effect, potentially teratogenic

Oritavancin and SCV



it's hard to exceed 2 log drop intracellularly

Perhaps due to membrane-detabilization effect …

- Domenech et al. Biochim Biophys Acta. 2009 May 18. [Epub]
- Baudoux et al. ICAAC 2009 [C1-1354]

Drugs with a (still) more incertain future ?

- **anti MRSA β-lactams**
  - **ceftaroline**: low MICs but still from 0.25 to 2 mg/L
  - less favorable pharmacokinetics than ceftobiprole ($t_{1/2}$ = 2.6h *vs.* 3-4h)
  - what will be the dose (presently 600mg q12h) and the breakpoint ?

- **glycopeptides**
  - **dalbavancin**: very long half life ($t_{1/2}$ ~ 7 days); no useful activity against VRSA and doubtful against VISA
    development on hold…

- **trimethoprim derivatives**
  - **iclaprim**: "impossible" pharmacokinetics; inferior to linezolid in phase 3 trials; further development uncertain…and lively discussions about the future of the compound at the last General Assembly of investors (August 19th, 2009)

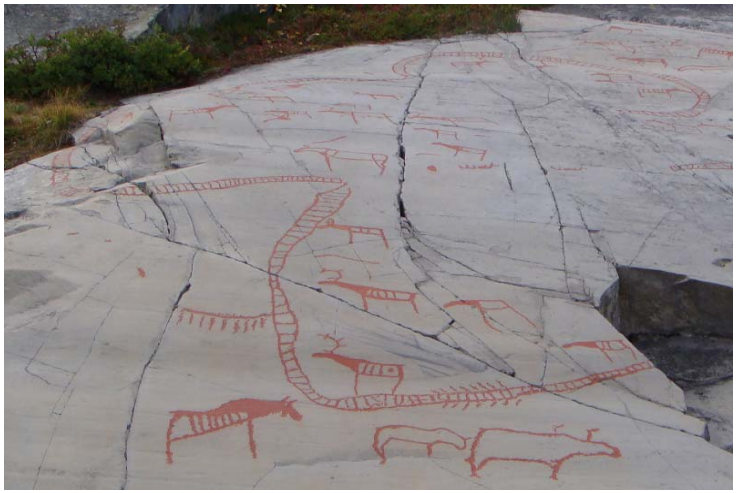
As conclusion…

- Many molecules in development over the last years …
- But …
  - only narrow low margins between acceptable levels of drug exposure (safety) and what is needed to really stay above EUCAST breakpoints (aka = PK/PD plus clinical trials)…
  - difficulties in demonstrating superiority with the clinical trials as they are performed now for registration purposes, and, therefore, in substantiating clinically the superiority properties anticipated from the microbiological and pre-clinical studies
  - toxicity concerns has stopped several products…
  - We see faster than anticipated emergence of resistance…
- So far, only daptomycin and tigecycline are available as new anti-MRSA agents…
- I'm afraid vancomycin has still a lot of work to do … if you have MRSA …

I did not find this by my-self…

It is always difficult to see important things without help

But when someone knowing comes along, you get the picture



It is all a team work…

And here is the team…

A few papers to help …

- Van Bambeke et al. The bacterial envelope as a target for novel anti-MRSA antibiotics. Trends Pharmacol Sci. 2008 Mar;29(3):124-34 *
- Appelbaum PC. Reduced glycopeptide susceptibility in methicillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents. 2007 Nov;30(5):398-408. .
- Lemaire S et al. Activity of ceftobiprole and other cephalosporins against extracellular and intracellular (THP-1 macrophages, keratinocytes) forms of Methicillin-Sensitive (MSSA) and Methicillin-Resistant Staphylococcus aureus (MRSA) * Antimicrobial Agents and Chemotherapy (2009) 53:2289-2297
- Nguyen et al. Intracellular activity of antibiotics in a model of human THP-1 macrophages infected by a Staphylococcus aureus Small Colony Variant isolated from a cystic fibrosis patient : 1. Pharmacodynamic evaluation and comparison with isogenic normal phenotype and revertant strains. Antimicrobial Agents and Chemotherapy (2009) 53:1434–1442 *
- Appelbaum PC. MRSA--the tip of the iceberg. Clin Microbiol Infect. 2006; Suppl 2:3-10.
- Barcia-Macay et al. Evaluation of the Extracellular and Intracellular Activities (human THP-1 macrophages) of Telavancin vs. Vancomycin against Methicillin-susceptible, Methicillin-resistant, Vancomycin-intermediate and Vancomycin-resistant Staphylococcus aureus. Journal of Antimicrobial Chemotherapy (2006) 58:1177–1184 *

* papers available on **www.facm.ucl.ac.be**

"Was auch als
Wahrheit oder Fabel
In tausend Büchern
dir erscheint,
Das alles ist ein Turm
zu Babel,
Wenn es die Liebe
nicht vereint."

J.W. von Goethe

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- the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:

- all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site *
- P.M. Tulkens is member of the Committee organising public campaigns for appropriate use of antibiotics in Belgium since 2000 ** and member of the streering committee of EUCAST***

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* http://www.facm.ucl.ac.be/publicat_facm.htm

** http://www.antibiotiques.org

*** http://wwweucast.org