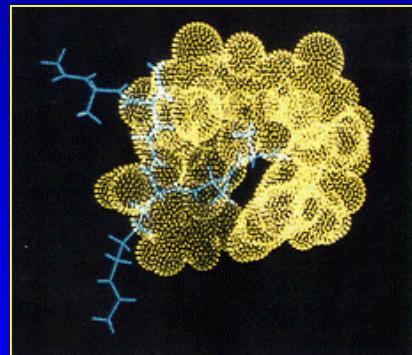


# **GLYCOPEPTIDES :**

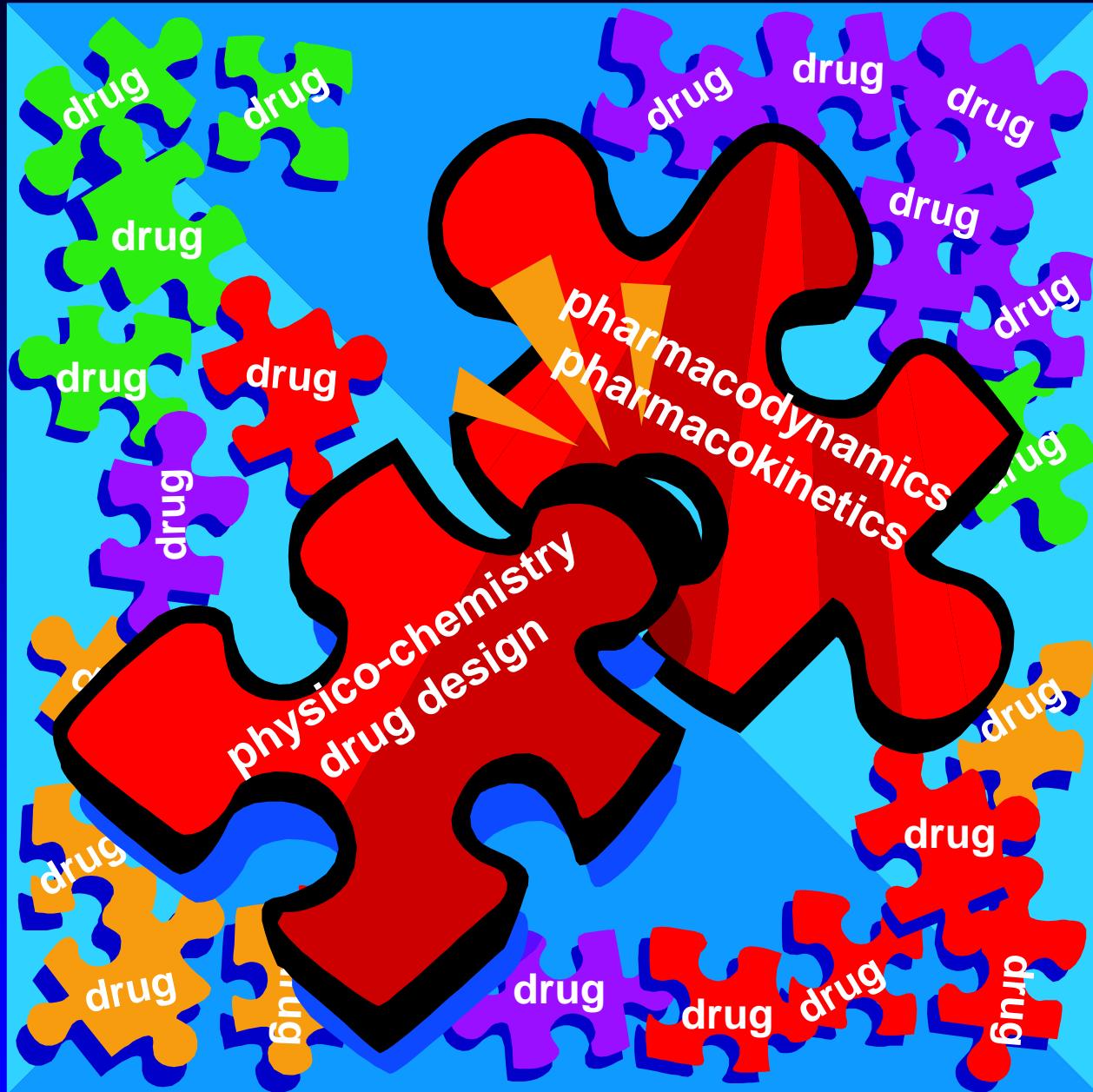
**how can a structural modification bring to  
a new life an old family of antibiotics ?**



**F. Van Bambeke**

Pharmacologie cellulaire et moléculaire

Université catholique de Louvain – Brussels - Belgium



# Glycopeptide story: from natural to semi-synthetic derivatives

~ 1950 :

discovery of vancomycin in Mississippi mud



~ 1985 :

large clinical use in USA

Gram(+) infections and digestive tract decontamination

## Problems:

- toxicity of vancomycin due to impurities
  - better purification procedures (after 1970...)
- emergence of resistance ....

By the way ....~ 1980 :

discovery of teicoplanin, as a natural GP with improved PK

- largely used in Europe

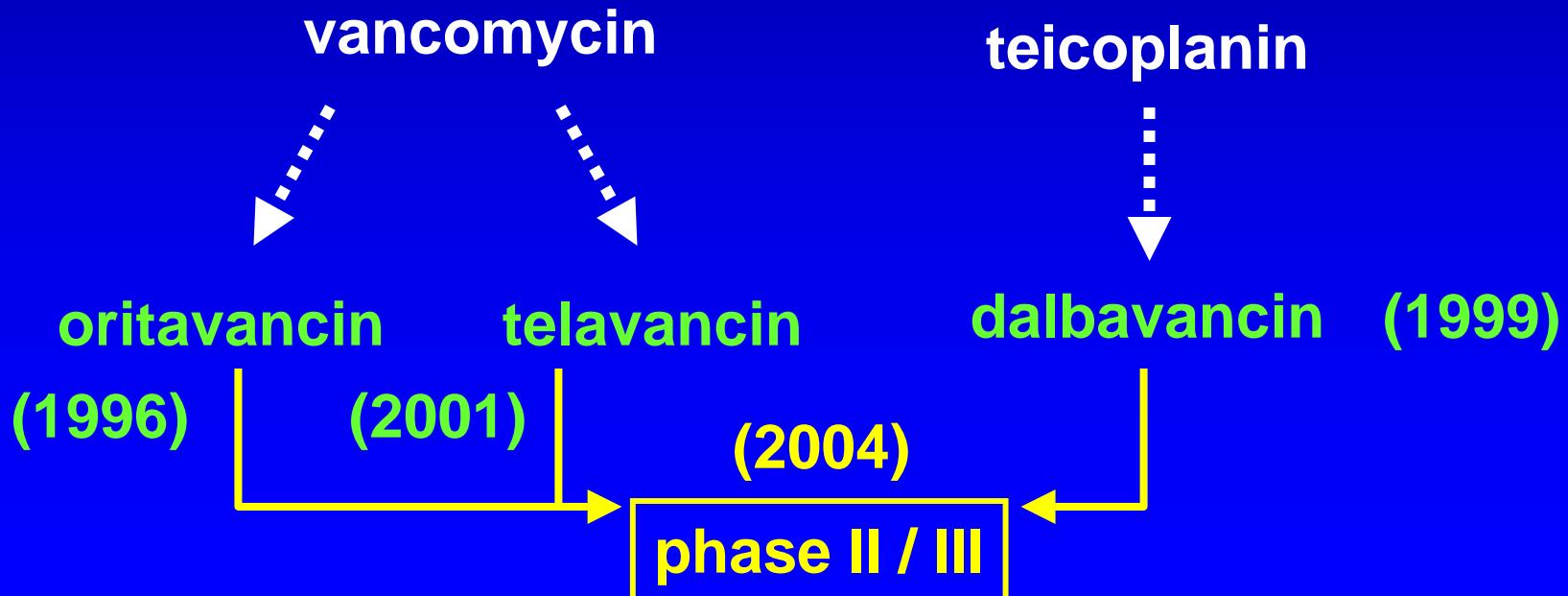
# Glycopeptide story: from natural to semi-synthetic derivatives

~ 1990 :

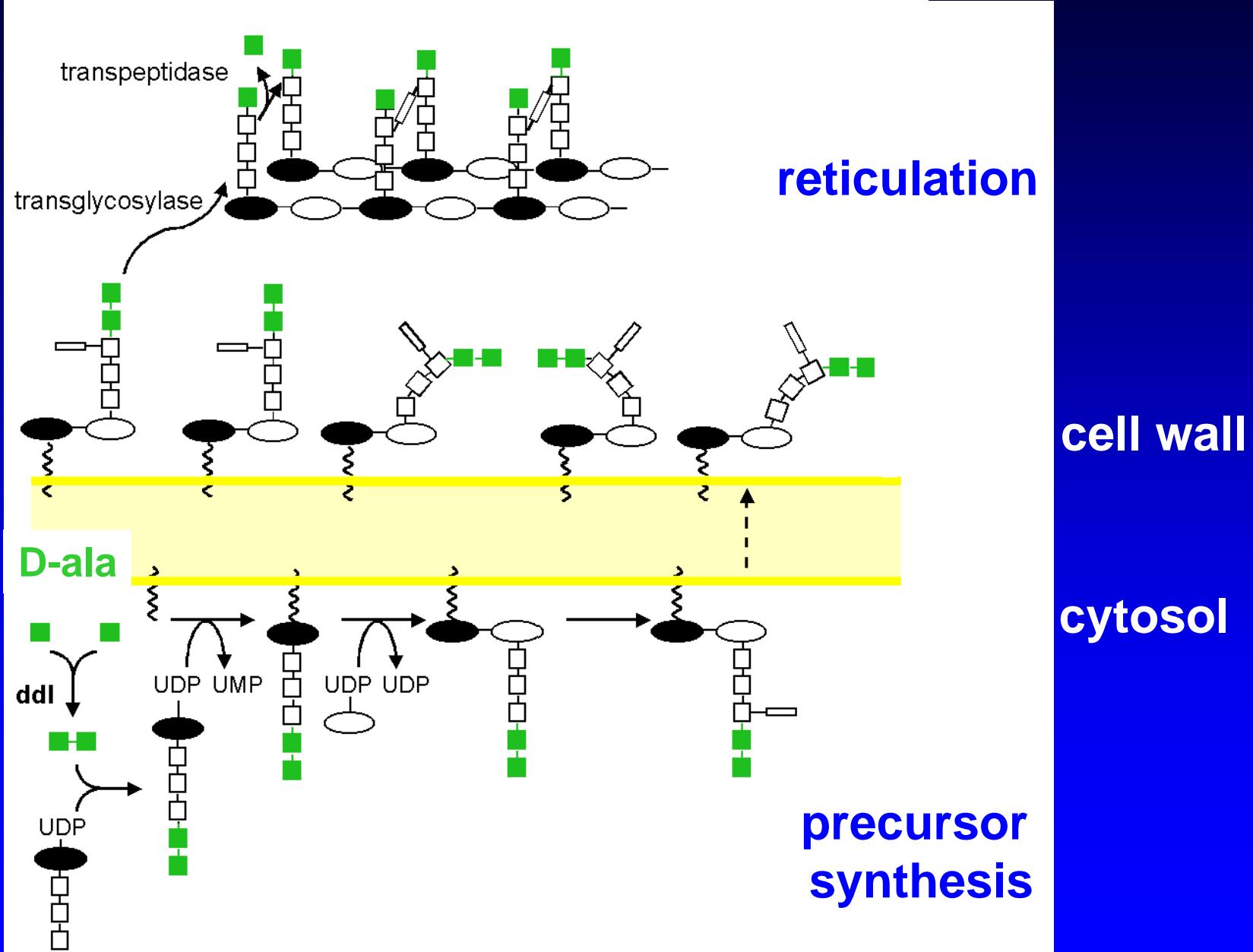
Launching of large scale research program for finding  
GP with optimized properties → hemi-synthetic compounds

Malabarba and Nicas

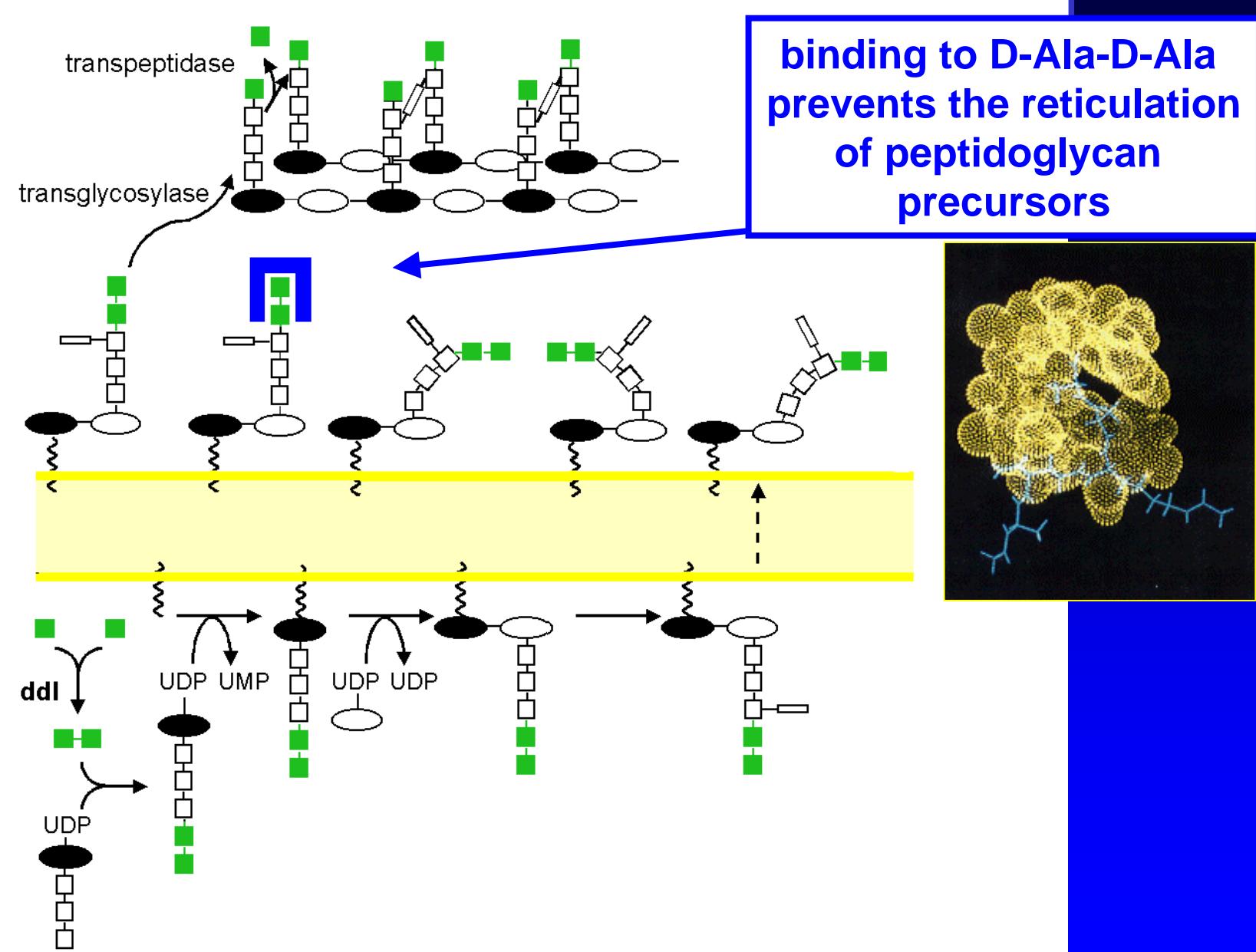
Med Res Rev. (1997) 17:69-137; Curr Med Chem. (2001) 8:1759-7



# Peptidoglycan synthesis



# Glycopeptide mechanism of action



# **But resistance came in ...**

Lancet. 1988 Jan 2-9;1(8575-6):57-8.

## **Vancomycin-resistant enterococci.**

Uttley AH, Collins CH, Naidoo J, George RC.

N Engl J Med. 1988 Jul 21;319(3):157-61.

## **Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*.**

Leclercq R, Derlot E, Duval J, Courvalin P.

Service de Bacteriologie, Virologie Hygiene, Hopital Henri Mondor, Universite Paris XII, France.

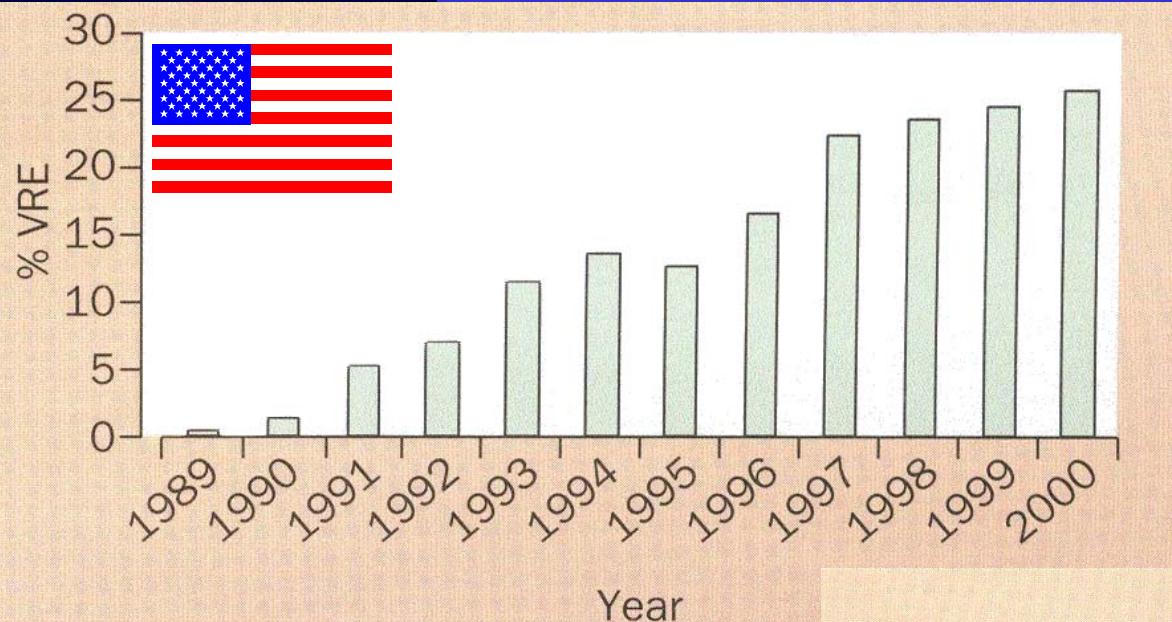
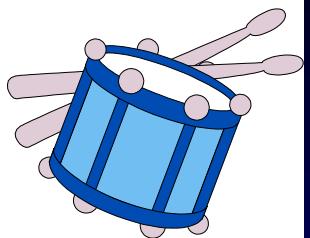
Antimicrob Agents Chemother. 1989 Jul;33(7):1121-4.

## **Characterization of vancomycin resistance in *Enterococcus faecium* and *Enterococcus faecalis*.**

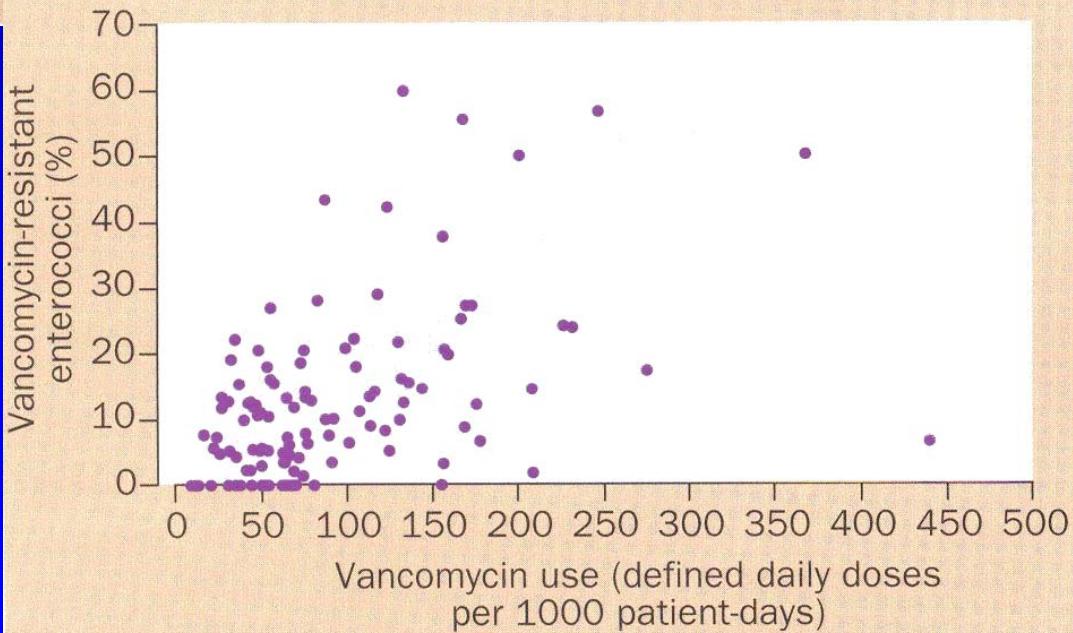
Nicas TI, Wu CY, Hobbs JN Jr, Preston DA, Allen NE.

Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Indiana 46285-0438.

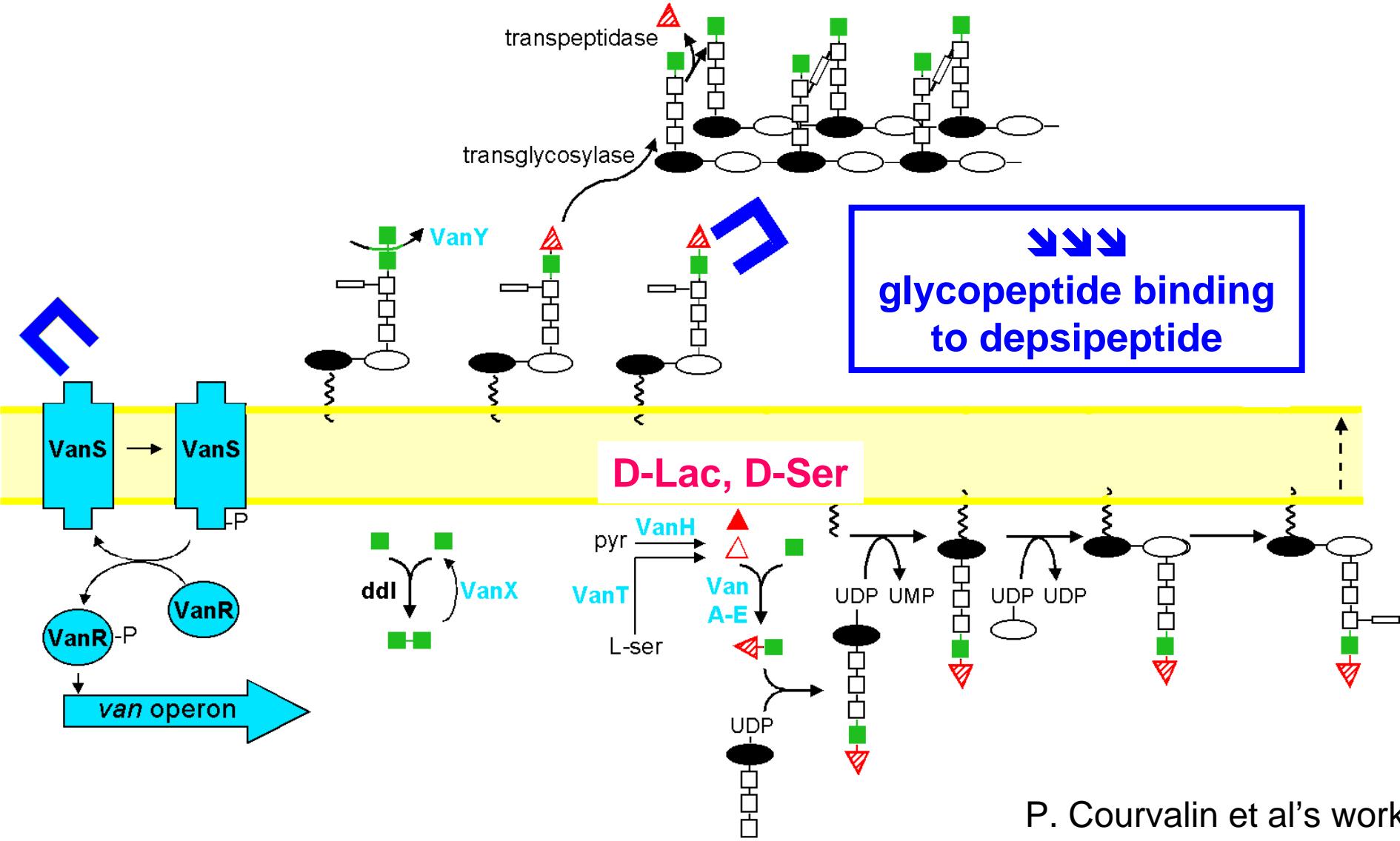
# Resistance in enterococci



large clinical use  
in USA  
started in ~ 1985

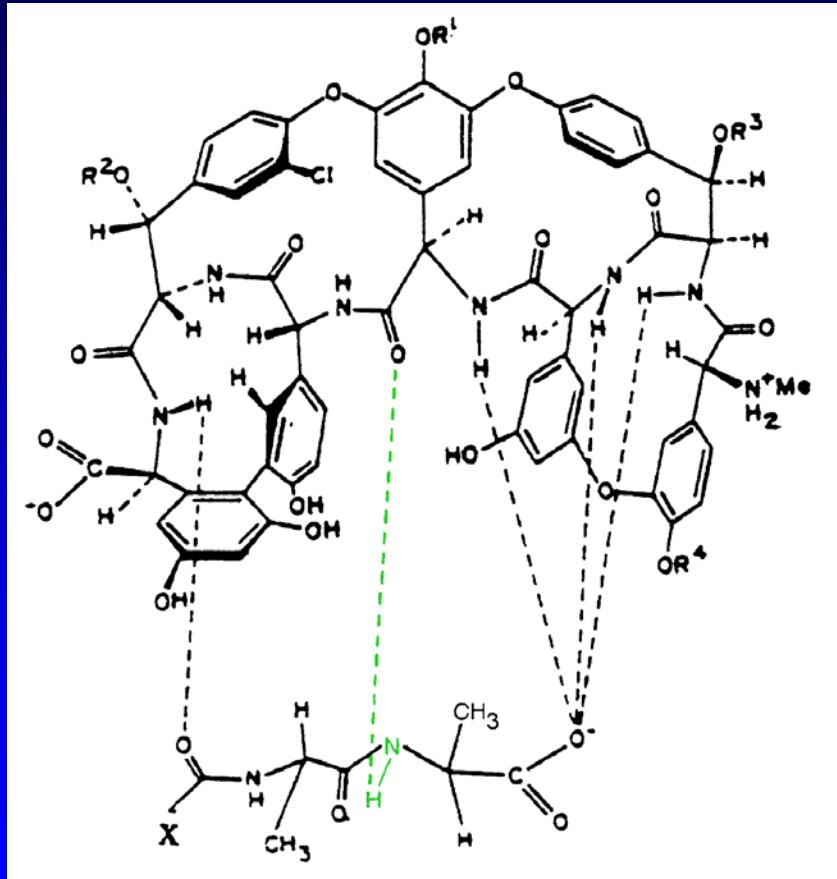


# Resistance in enterococci

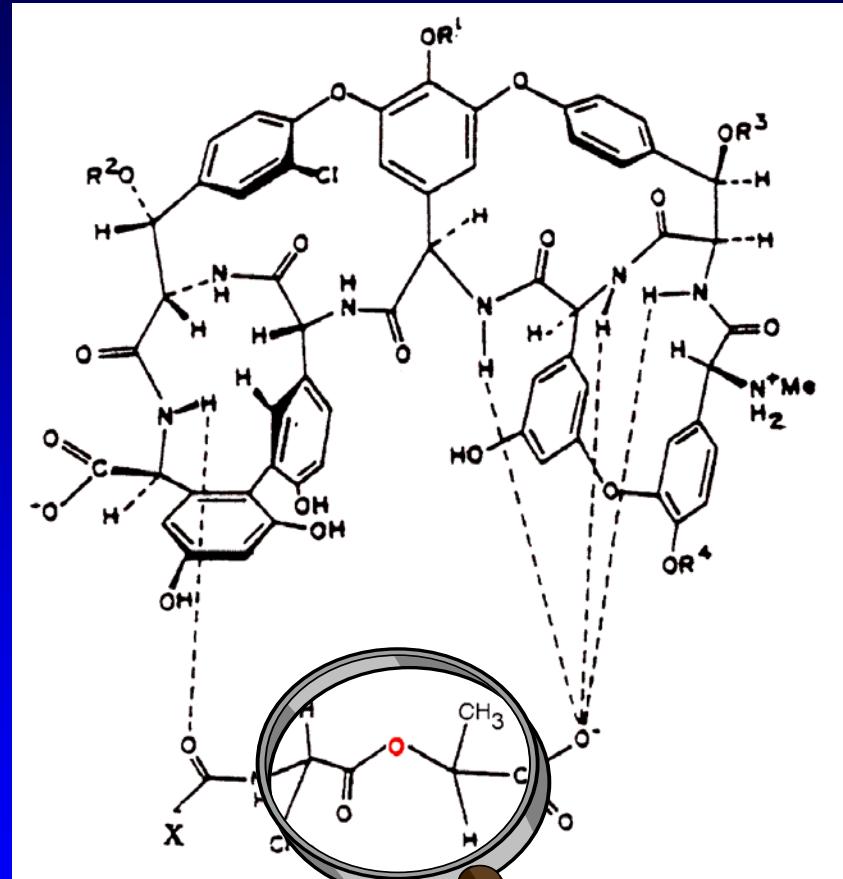


# Resistance in enterococci

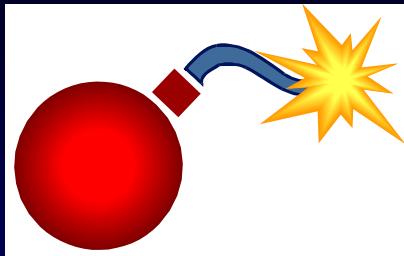
from susceptible ...



... to resistant



1 hydrogen bound is missing !



# Resistance in staphylococci (GISA)

**Methicillin-resistant *Staphylococcus aureus*  
clinical strain with reduced vancomycin  
susceptibility**

*J Antimicrob Chemother* 1997; **40**: 135–136

K. Hiramatsu<sup>a\*</sup>, H. Hanaki<sup>a</sup>, T. Ino<sup>b</sup>, K. Yabuta<sup>b</sup>,  
T. Oguri<sup>c</sup> and F. C. Tenover<sup>d</sup>

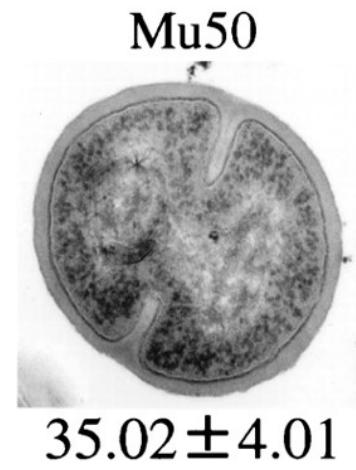
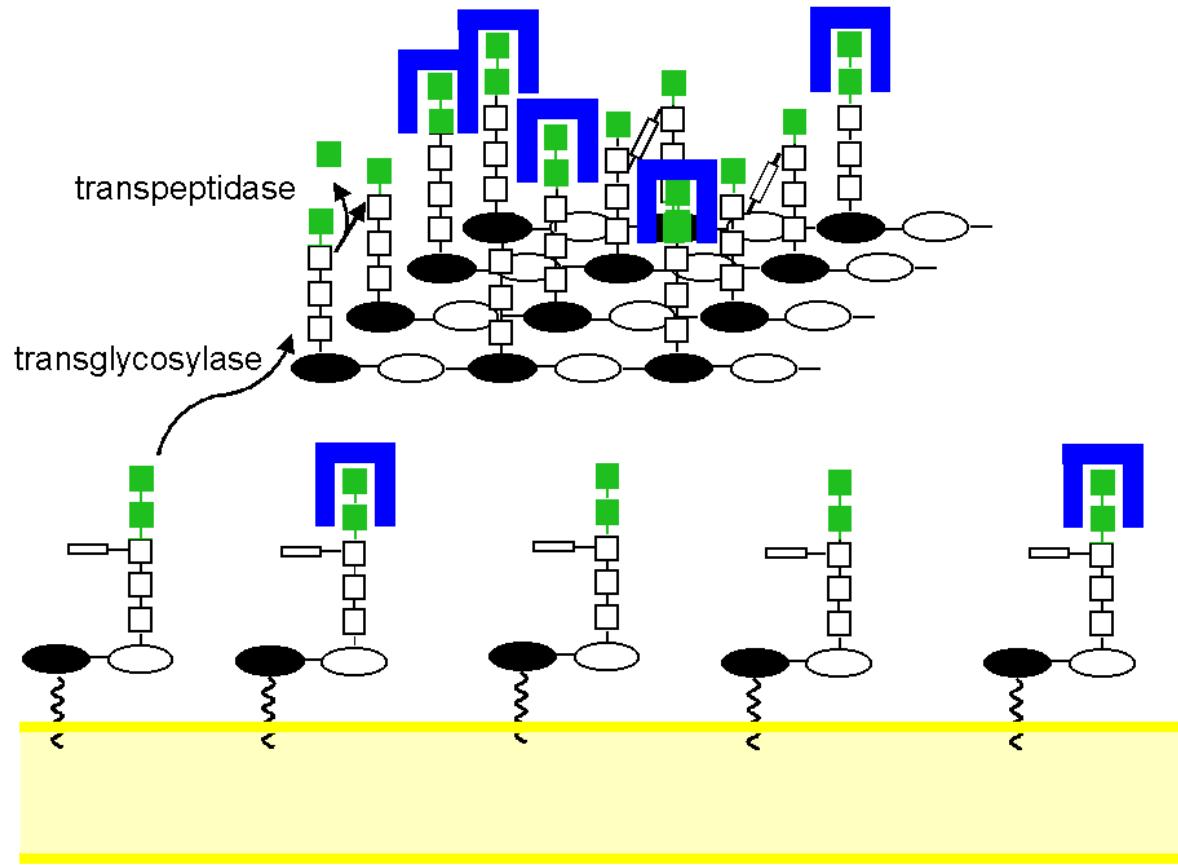
<sup>a</sup>Department of Bacteriology; <sup>b</sup>Department of Pediatrics, Juntendo University, Tokyo; <sup>c</sup>Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; <sup>d</sup>Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

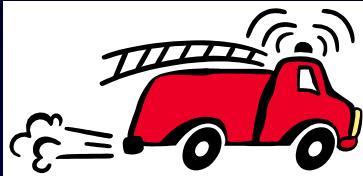
AB	MIC
AMP	64
VAN	8
GEN	128
RIF	2048
LVX	8
TET	128
SMX	0.125
Q-D	0.5
LZD	2

# Resistance in staphylococci (GISA)

multiplication  
of the target !

tickened  
Cell wall





# Resistance in staphylococci (GRSA)



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**ORIGINAL ARTICLE**

**BRIEF REPORT**

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Volume 348:1342-1347

April 3, 2003

Number 14

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## Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the vanA Resistance Gene

*Sooju Chang, M.D., M.P.H., Dawn M. Sievert, M.S., Jeffrey C. Hageman, M.H.S., Matthew L. Boulton, M.D., Fred C. Tenover, Ph.D., M.P.H., Frances Pouch Downes, Dr.P.H., Sandip Shah, M.S., James T. Riedrik, Ph.D., Guy R. Pupp, D.P.M., William J. Brown, Ph.D., Denise Cardo, M.D., Scott K. Fridkin, M.D., for the Vancomycin-Resistant Staphylococcus aureus Investigative Team*



## MICs and kill kinetics of antibacterials against vancomycin resistant *Staphylococcus aureus* (VRSA) with vanA gene isolated at Penn State Hershey Medical Center

B. Bozdogan<sup>1</sup>, J. Chaitram<sup>2</sup>, P. C. Appelbaum<sup>1</sup>, C. Whitener<sup>1</sup>, F. A. Browne<sup>1</sup>, F. C. Tenover<sup>2</sup>

<sup>1</sup>Penn State Hershey Medical Center, Hershey, PA, <sup>2</sup>Centers for Disease Control and Prevention, Atlanta,

**AB MIC**

VAN	32
TEC	4

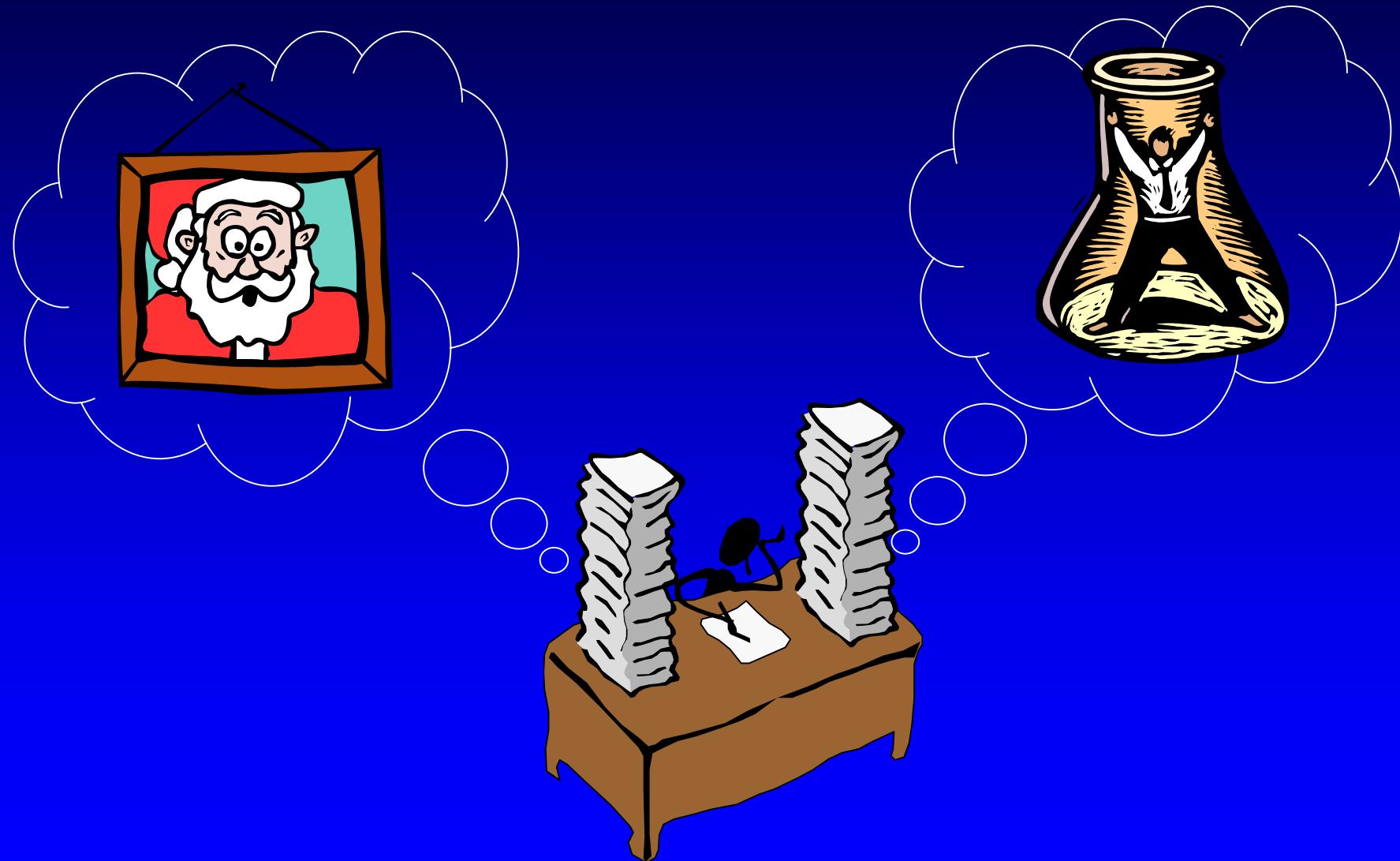
# Current glycopeptides: what do they offer to us ?

parameter	vanco - teico
spectrum	Gram (+) & MRSA <b>but</b> VRE – GI/RSA
PD	<b>static or slowly bactericidal</b>
PK	<b>t ½ short for vanco</b>
safety	(red-man syndrome) oto-& nephrotoxicity

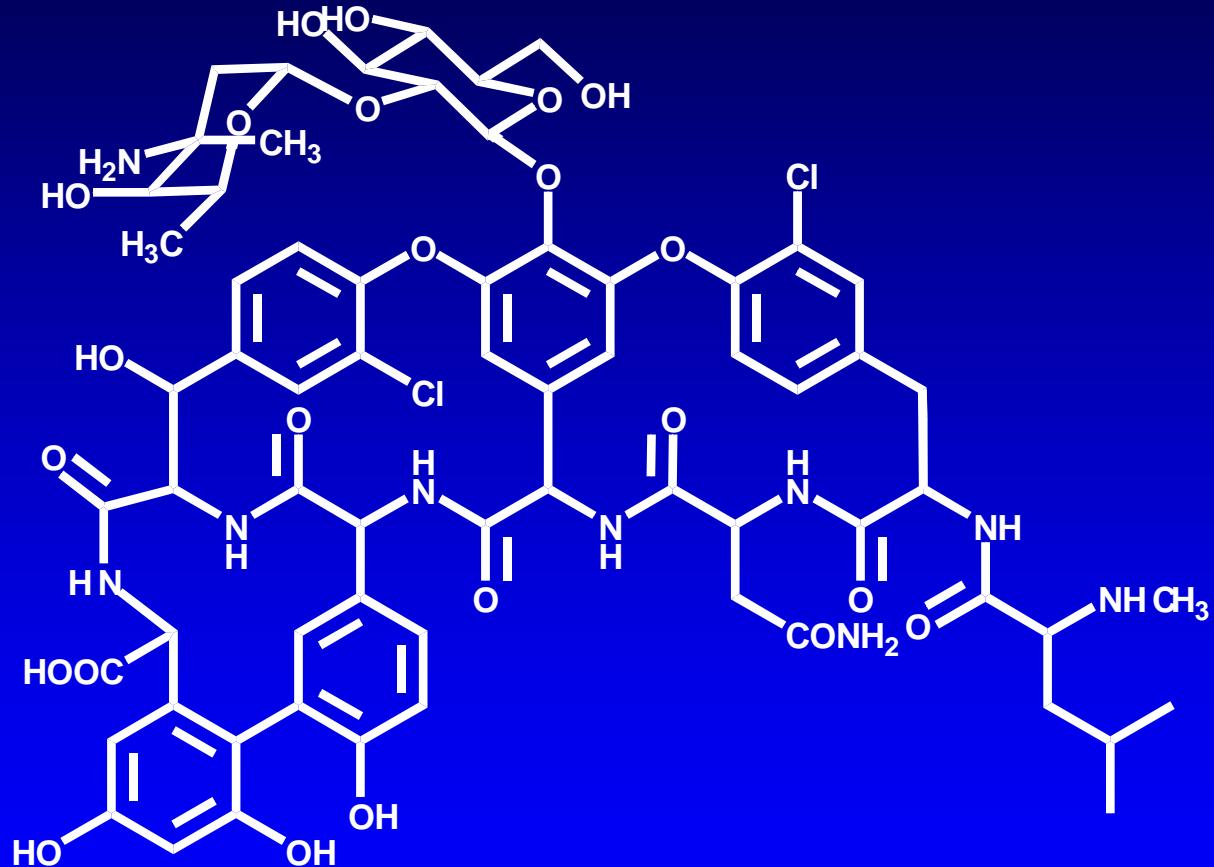
# Glycopeptides: how can we improve ?

parameter	vanco - teico	ideal glycopeptide
spectrum	Gram (+) & MRSA <b>but</b> VRE – GI/RSA	Gram (+) & MRSA, GI/RSA, VRE
PD	<b>static</b> or slowly bactericidal	quickly, conc. dependent bactericidal
PK	<b>t ½ short for vanco</b>	$t \frac{1}{2} \nearrow$ diffusibility (CNS)
safety	(red-man syndrome) oto-& nephrotoxicity	side effects ↘

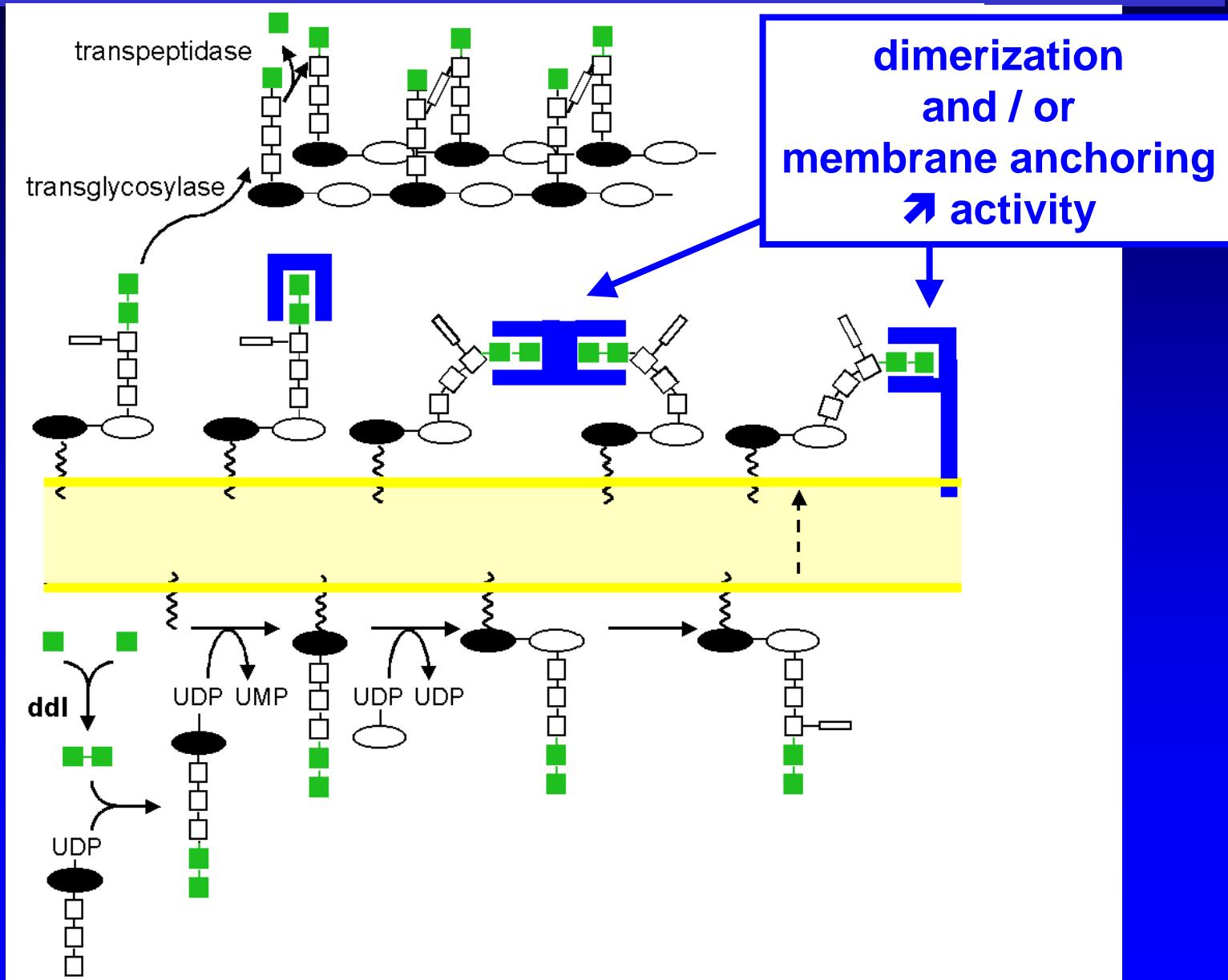
# Glycopeptides: how can we improve ?



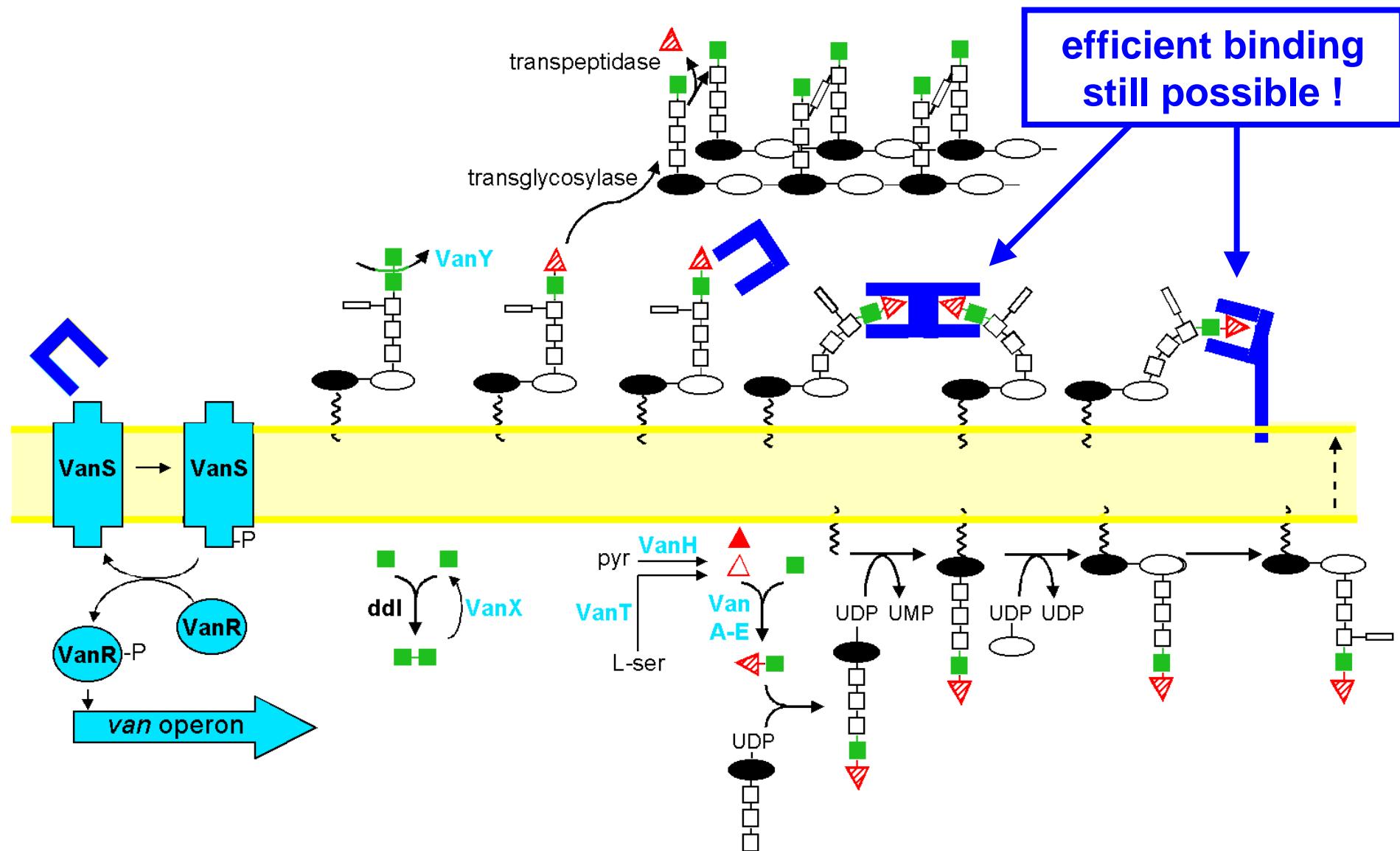
# Glycopeptides: how can we improve ?



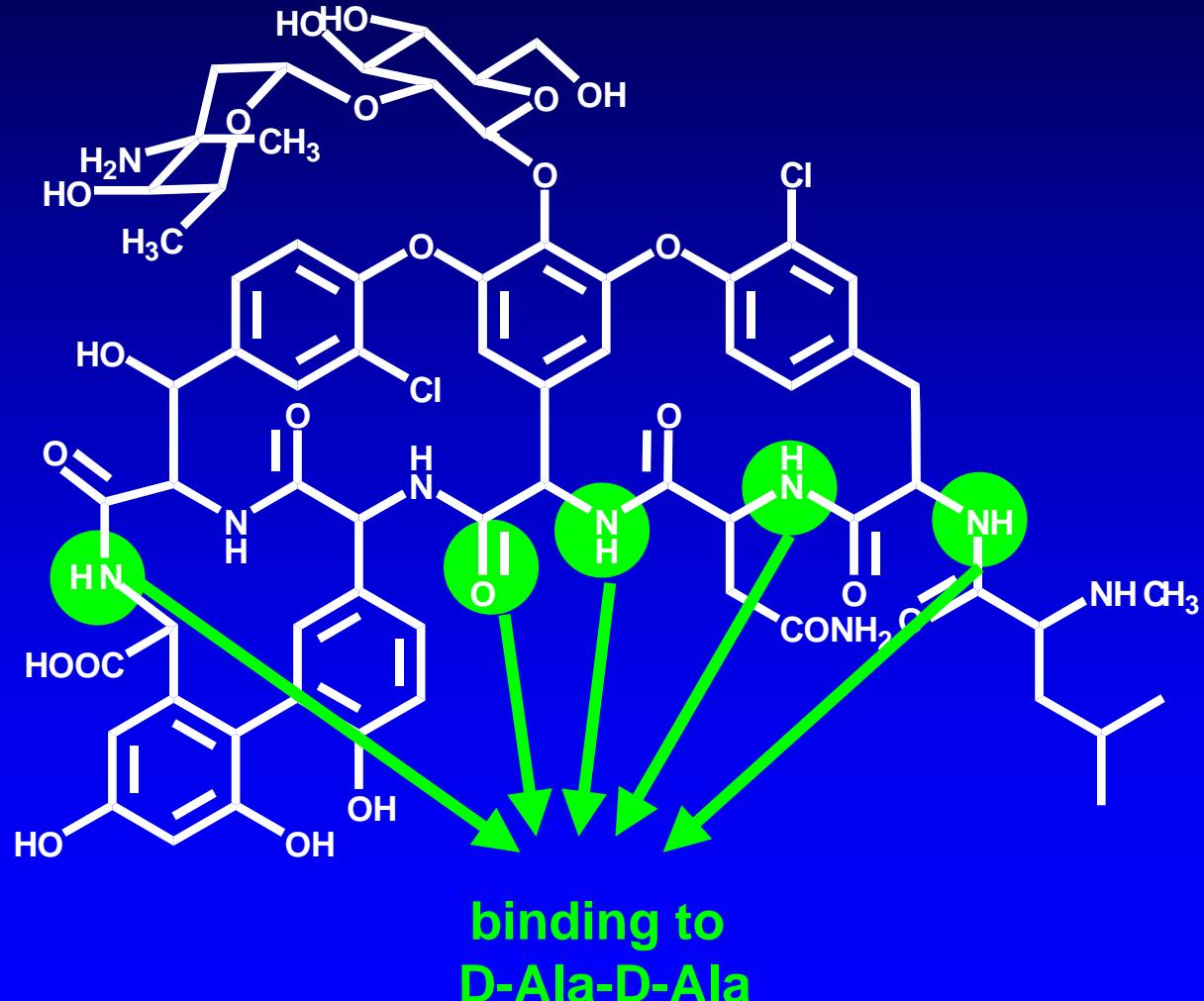
# Glycopeptide updated mechanism of action



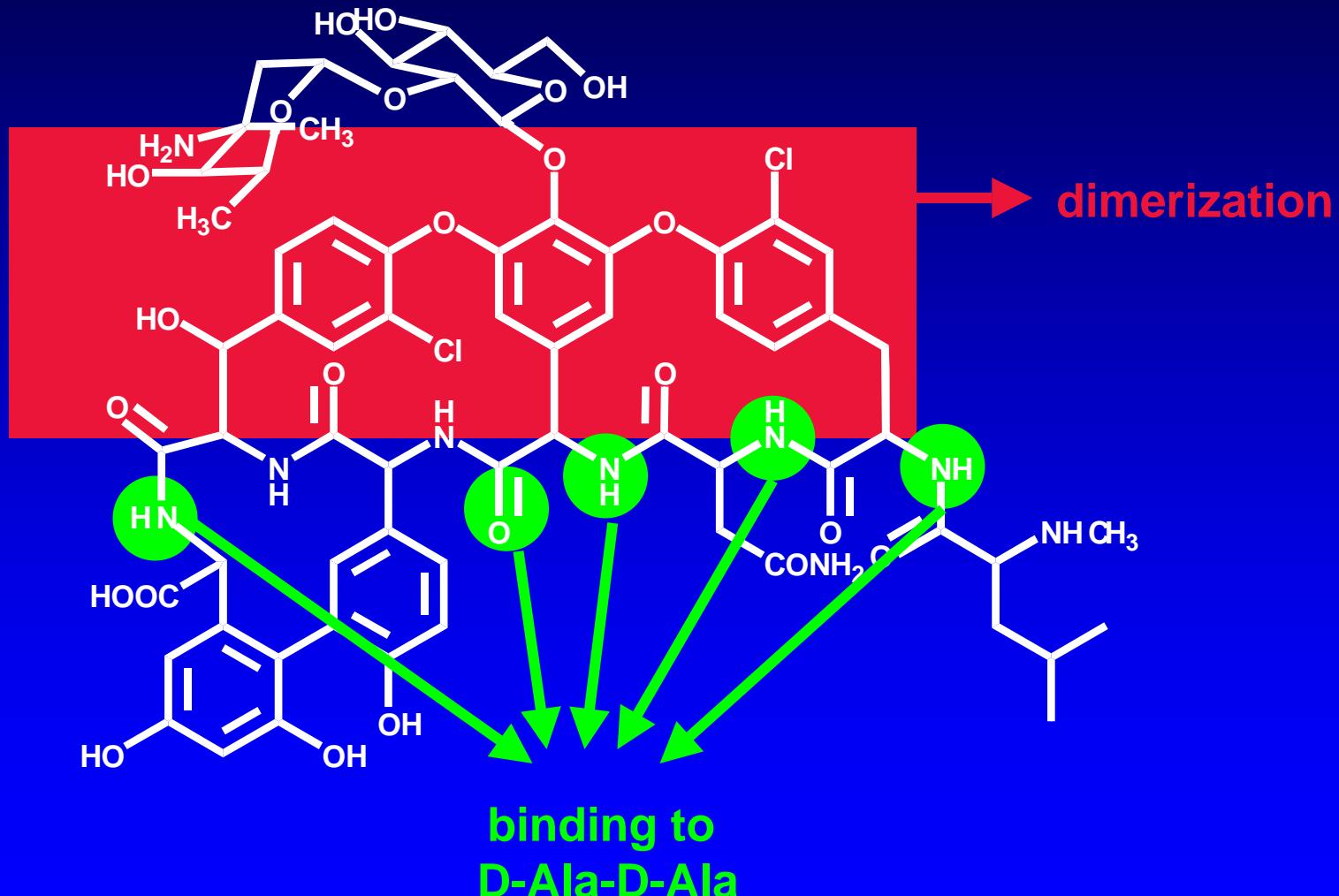
# Glycopeptide updated mechanism of action in VRE



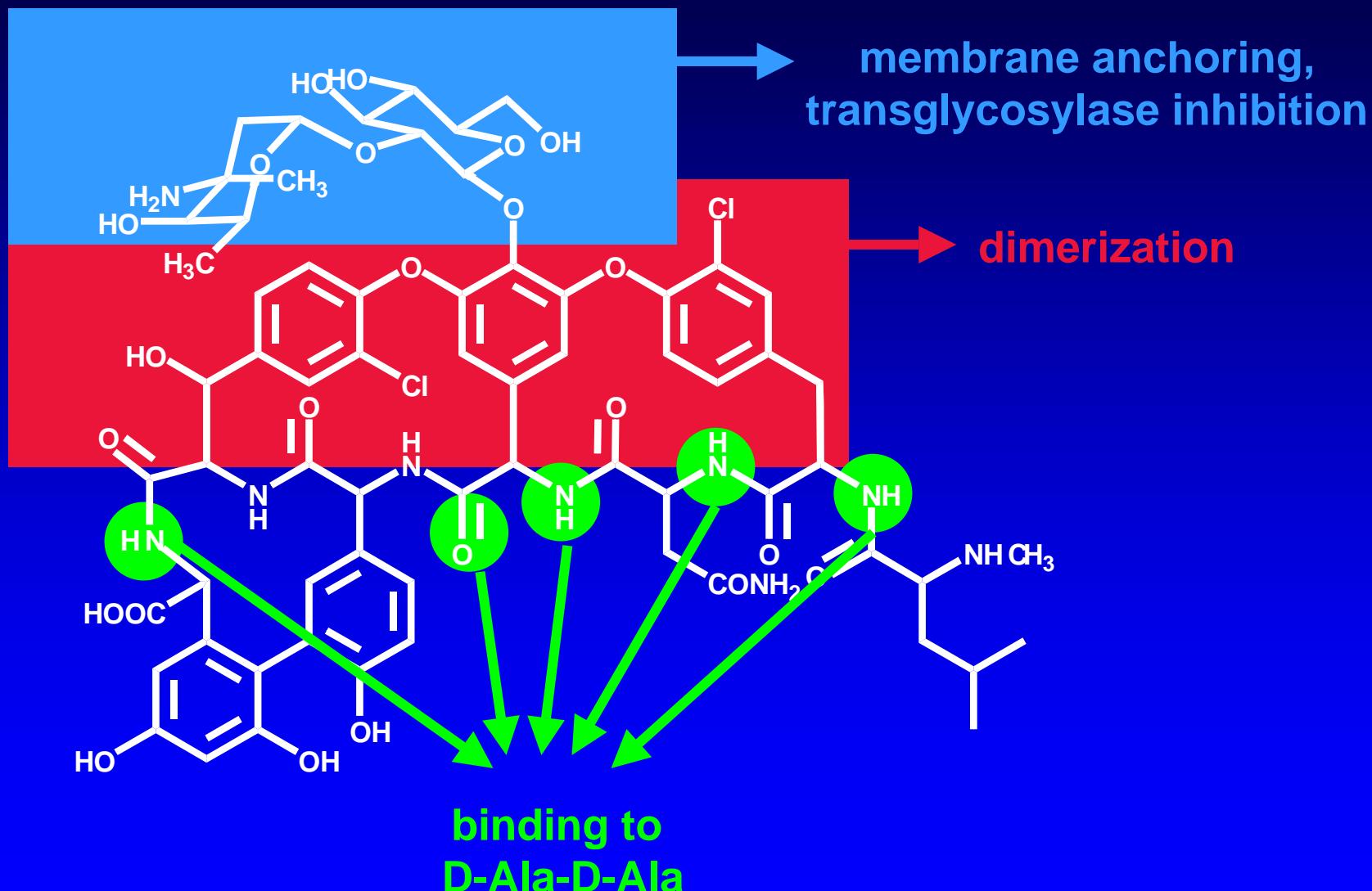
# Glycopeptides: how can we improve ?



# Glycopeptides: how can we improve ?

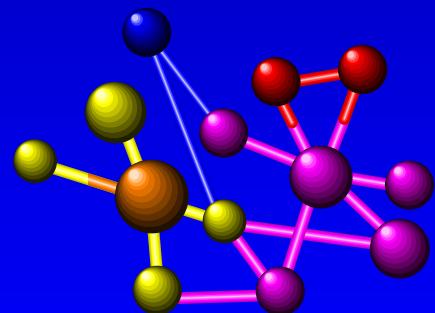


# Glycopeptides: how can we improve ?

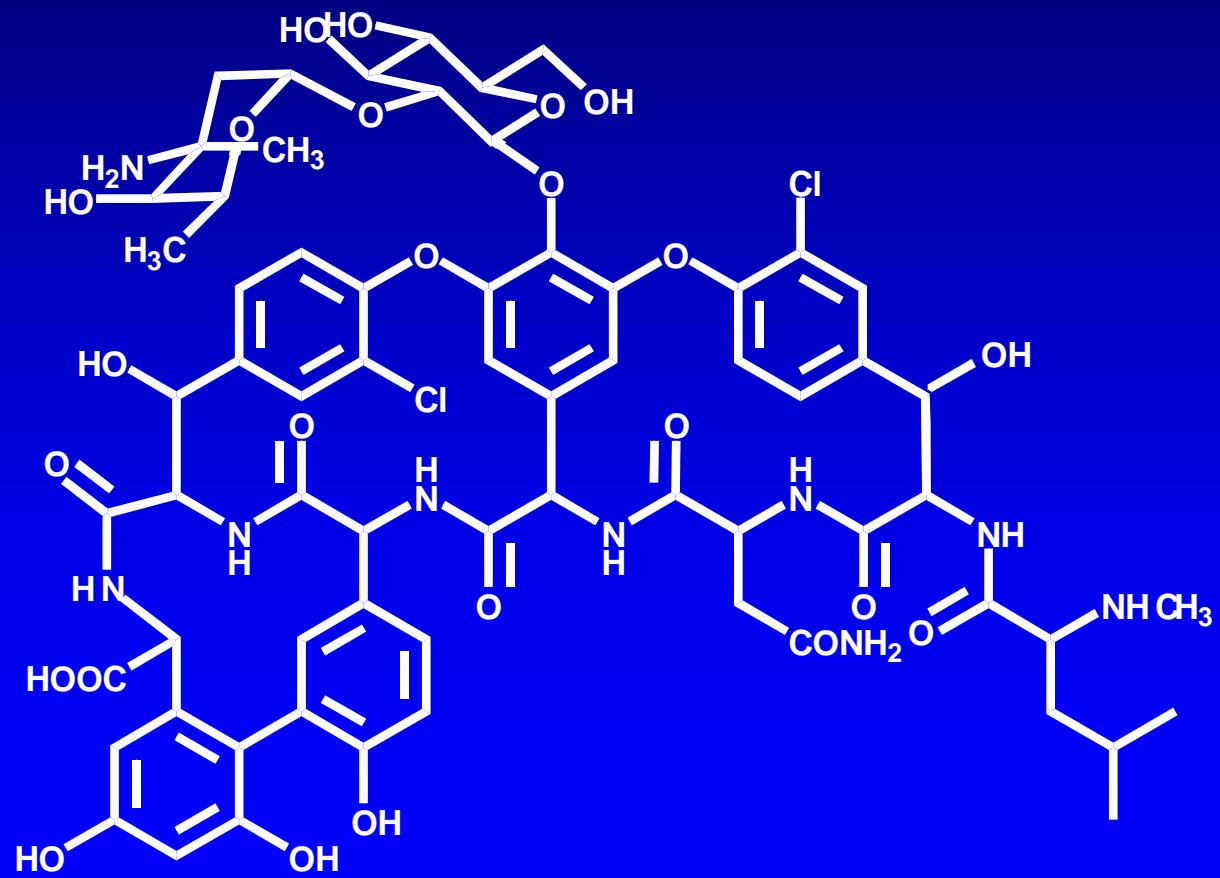


# **Molecules in clinical development:**

## **DESIGN**

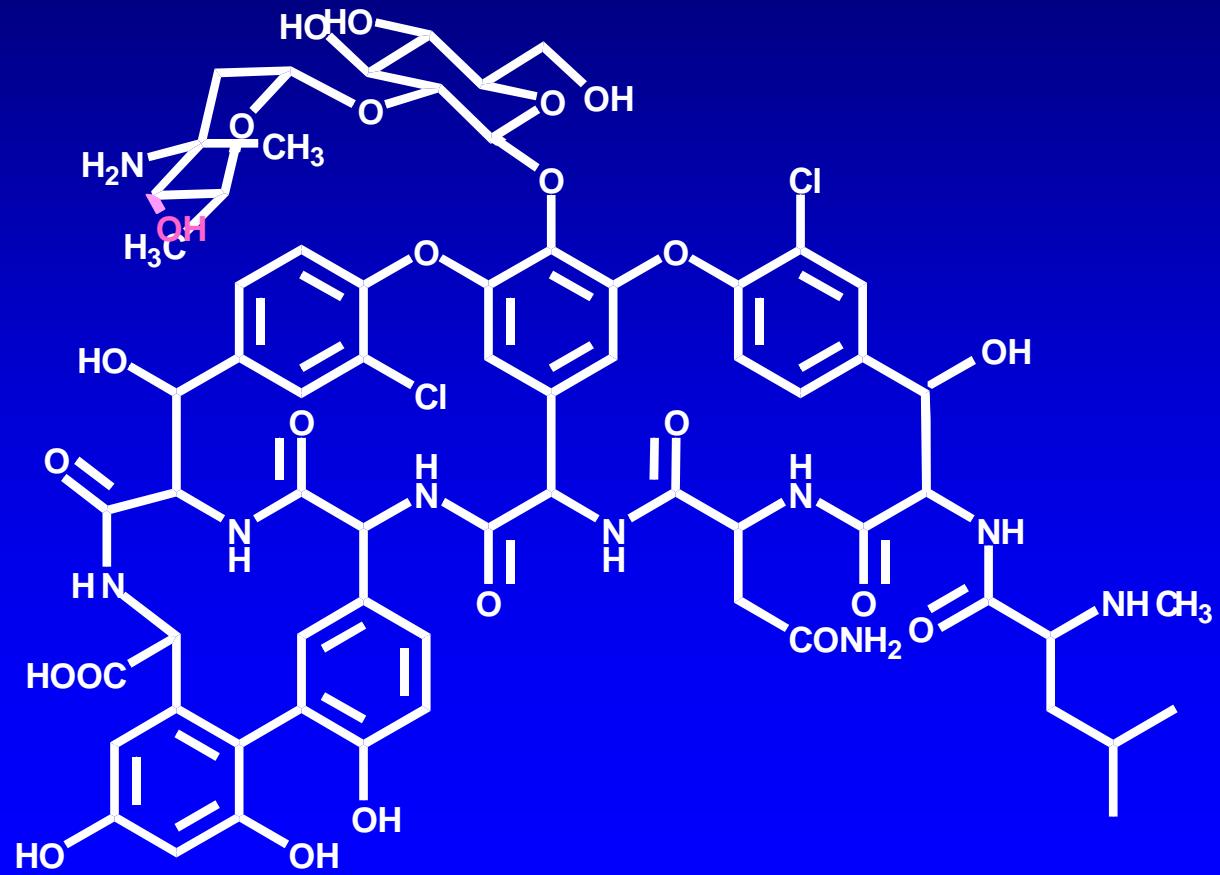


# From vancomycin to oritavancin



# From vancomycin to oritavancin

epi-vancosamine



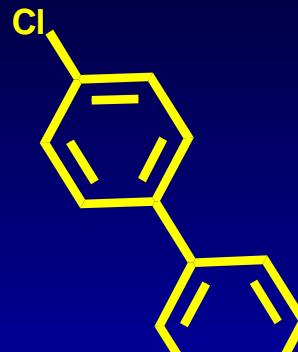
# From vancomycin to oritavancin

4-*epi*-vancosamine  
→ self-association capacity



LY264626

# From vancomycin to oritavancin



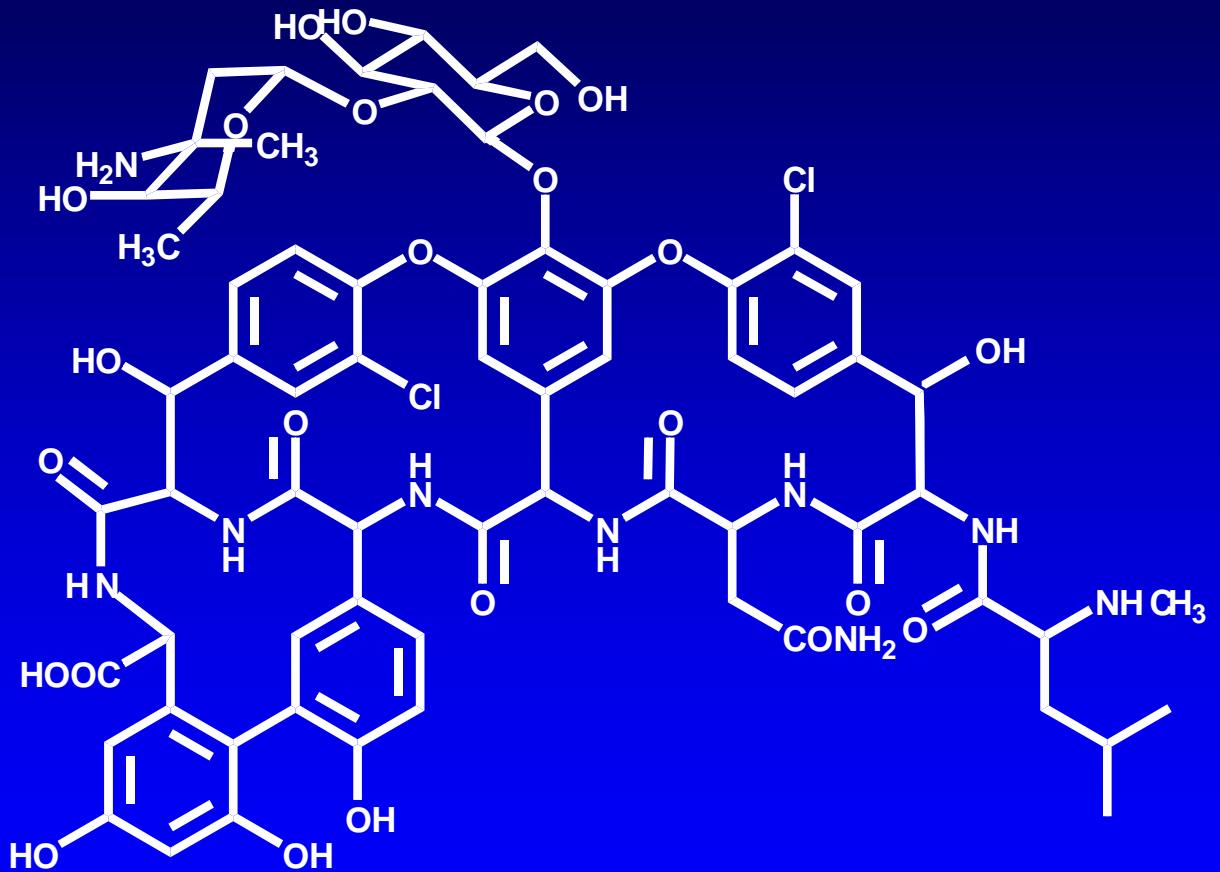
lipophilic side chain

↗ activity

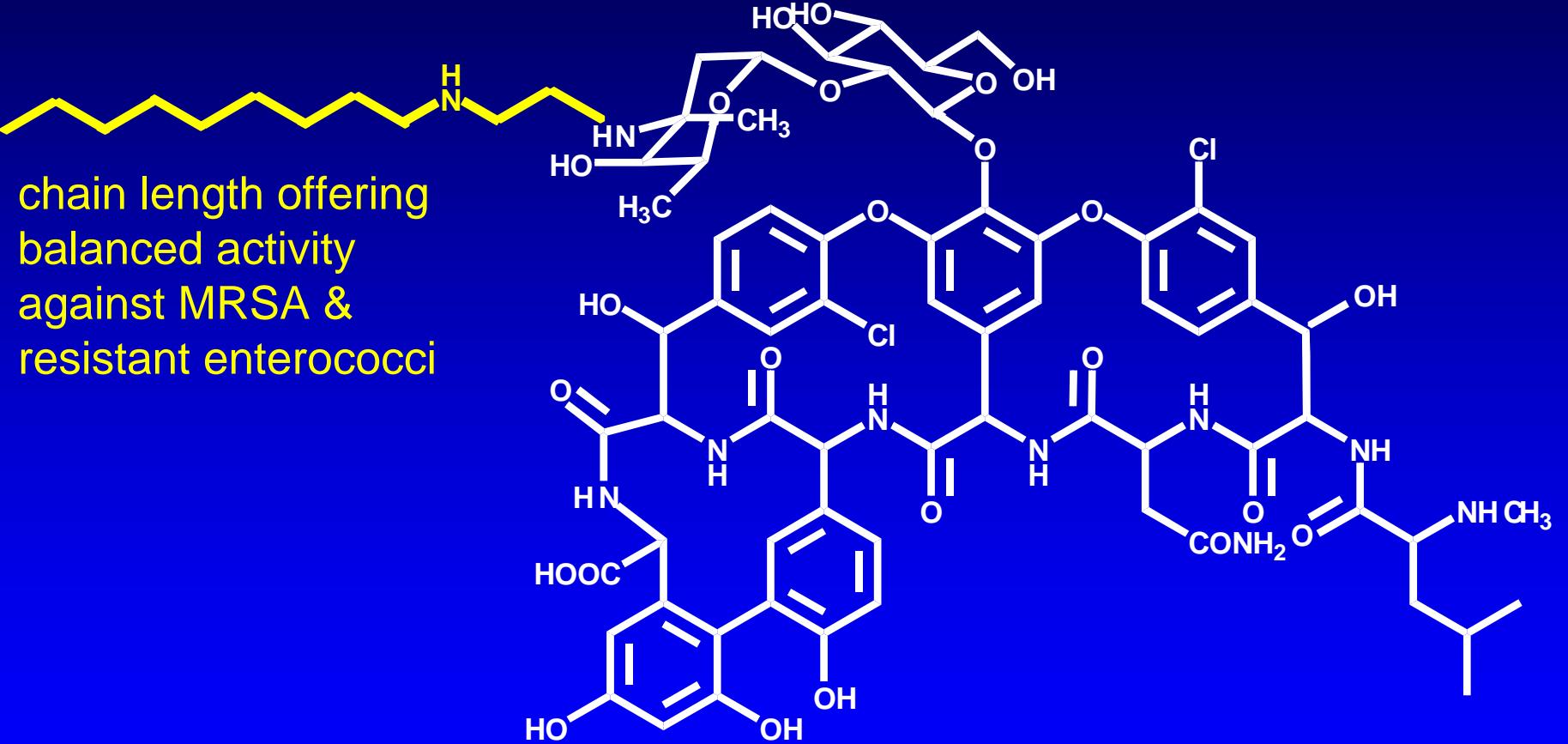
including against resistant enterococci



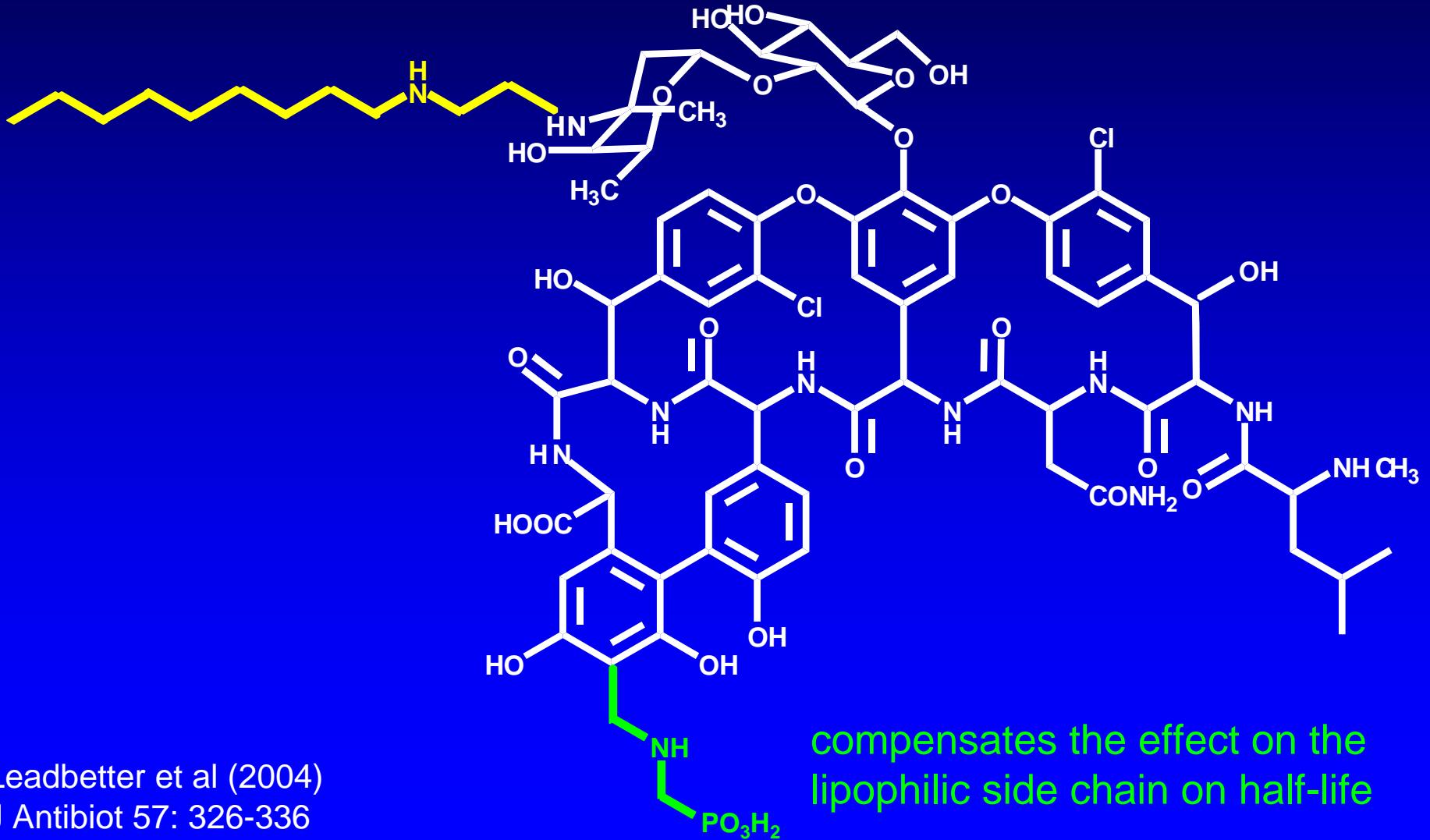
# From vancomycin to telavancin



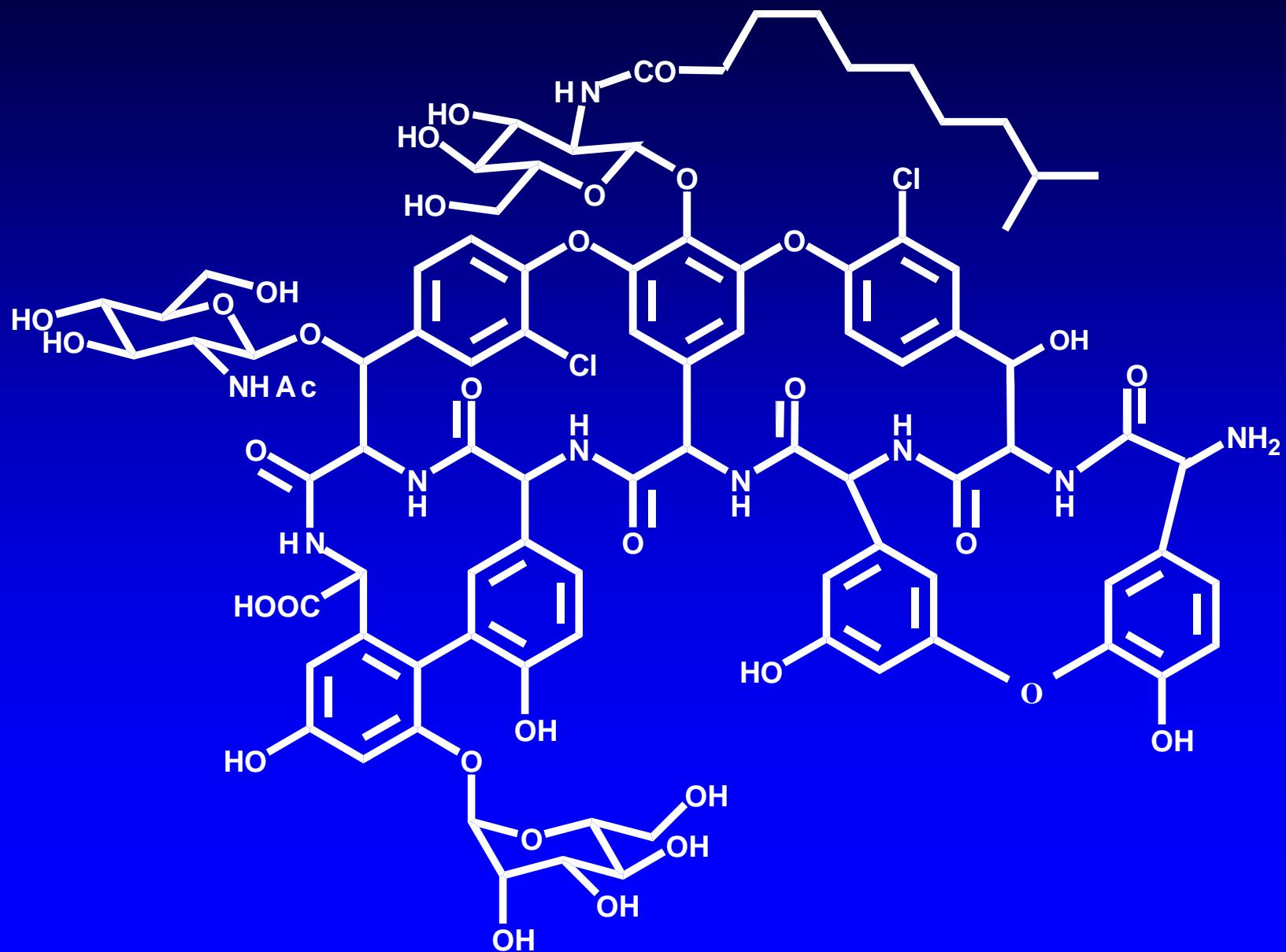
# From vancomycin to telavancin



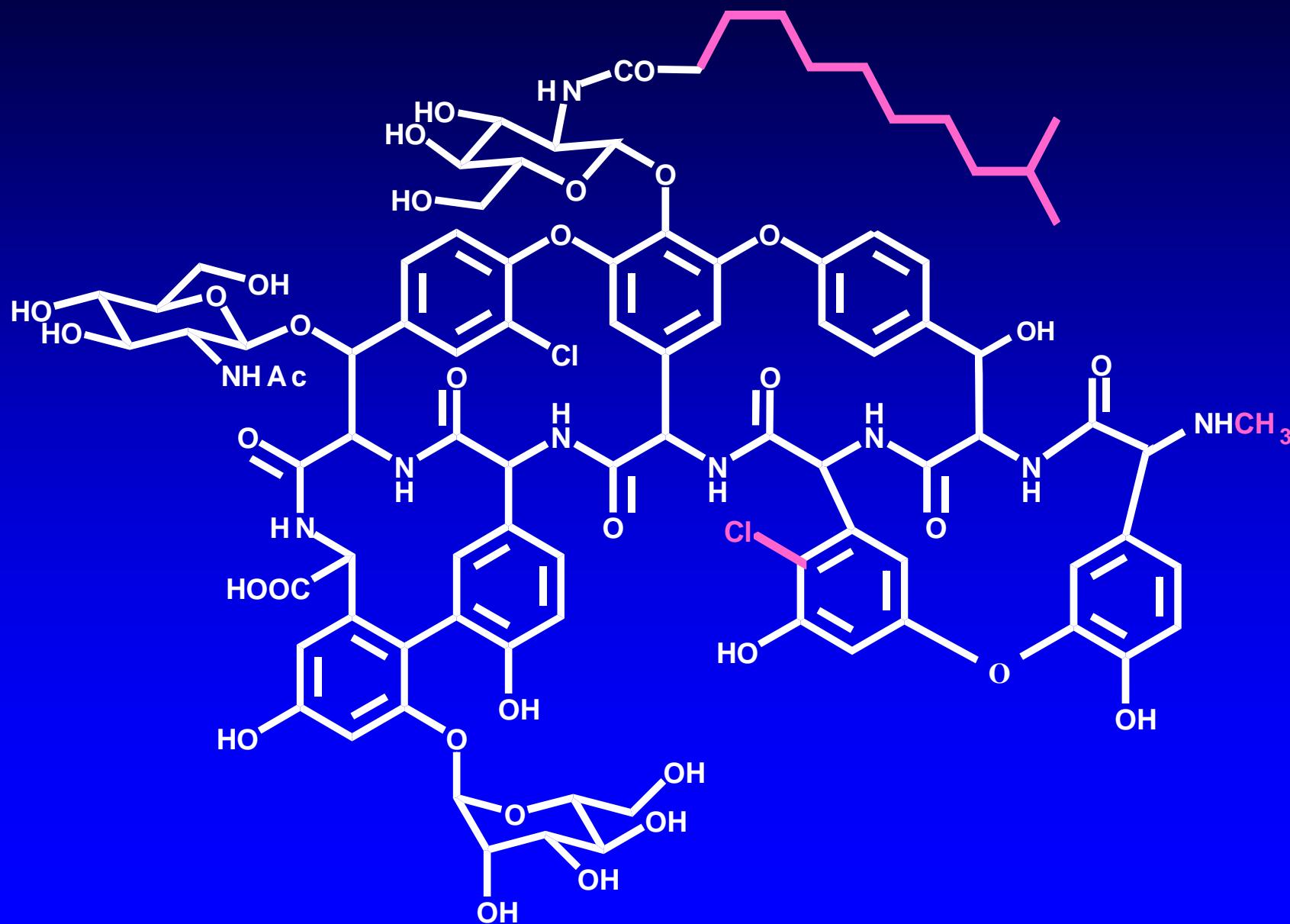
# From vancomycin to telavancin



# From teicoplanin to dalbavancin



# From teicoplanin to dalbavancin

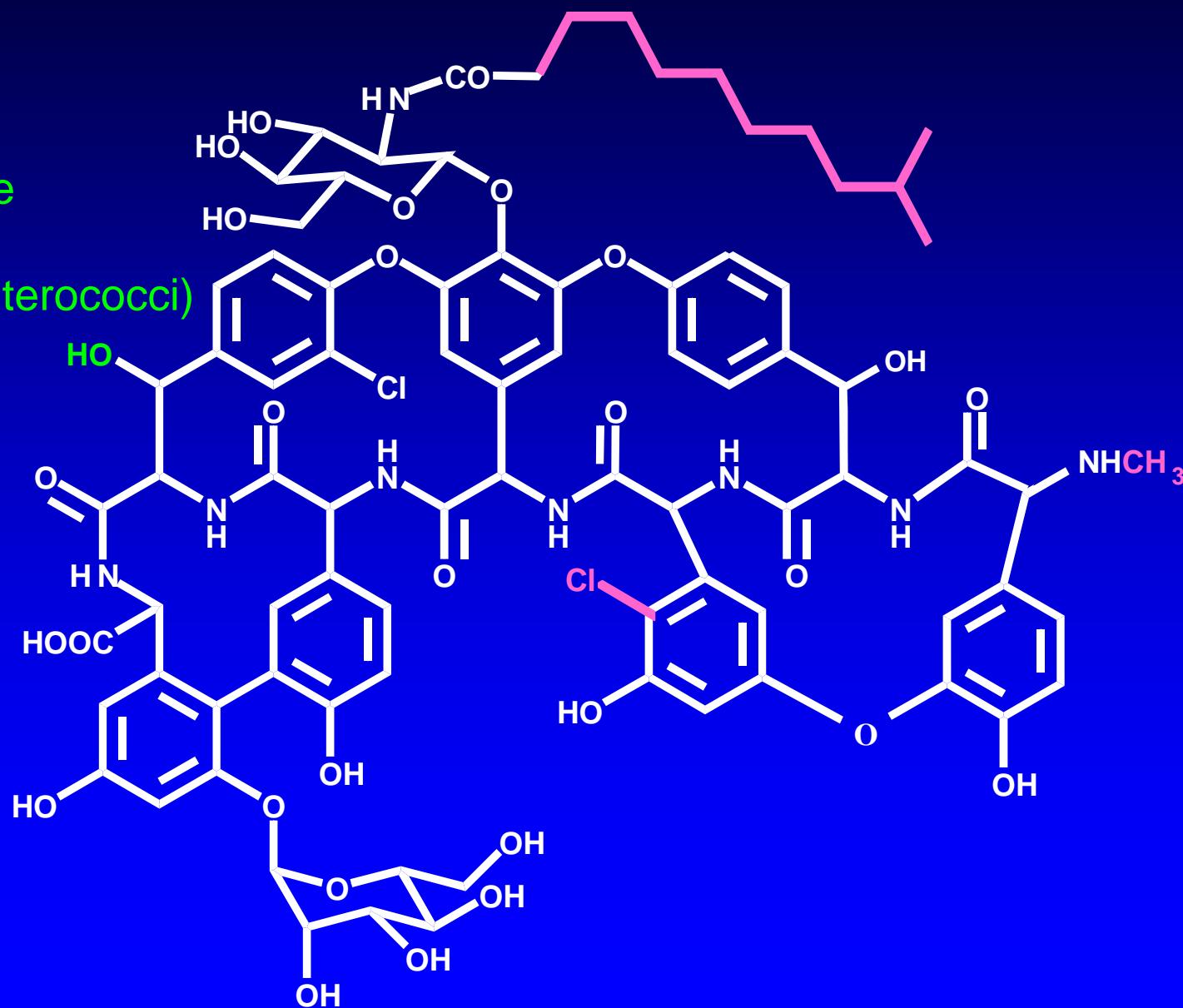


# From teicoplanin to dalbavancin

removal of  
N-acetylglucosamine

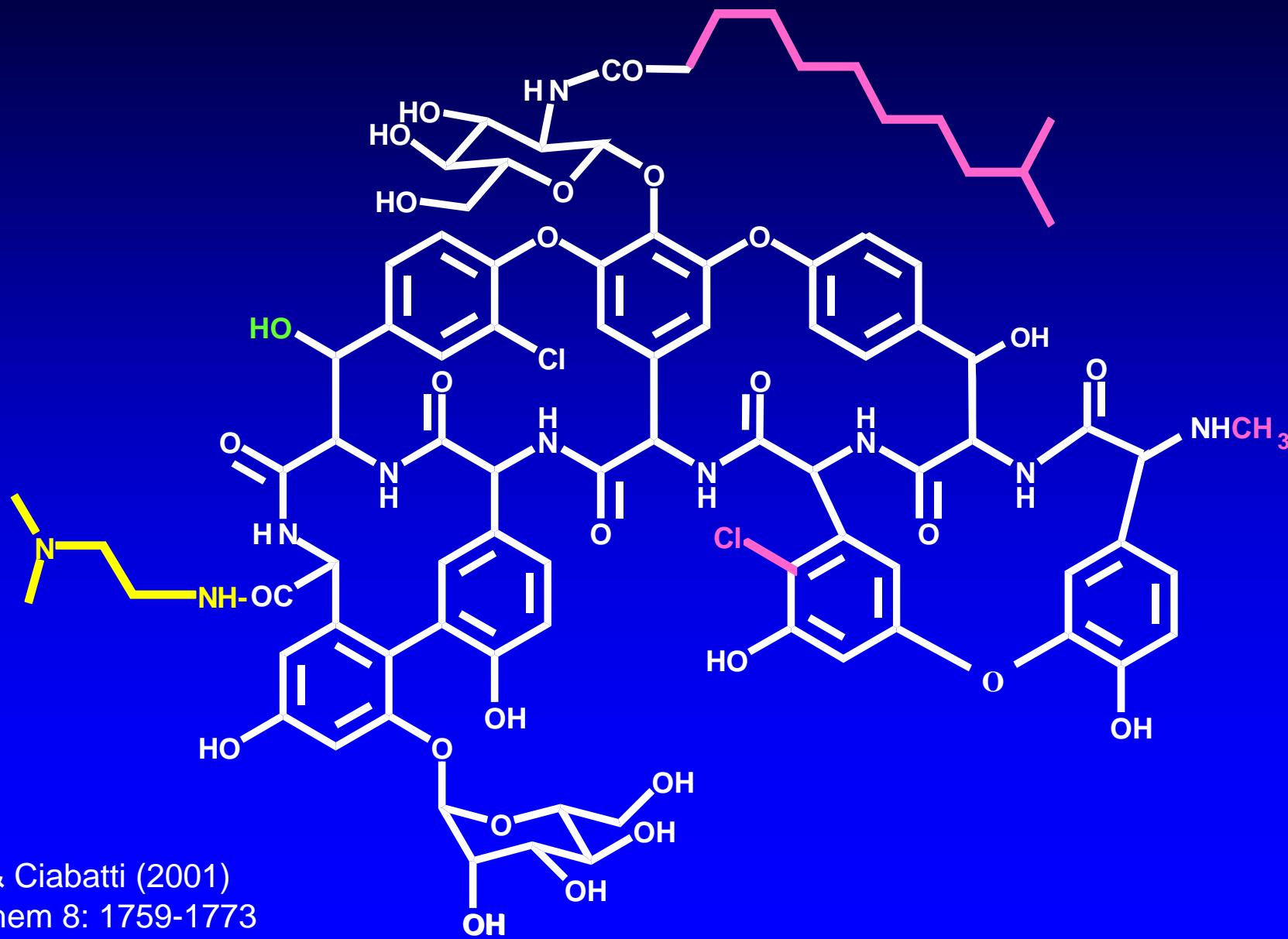
↗ activity

(against resistant enterococci)

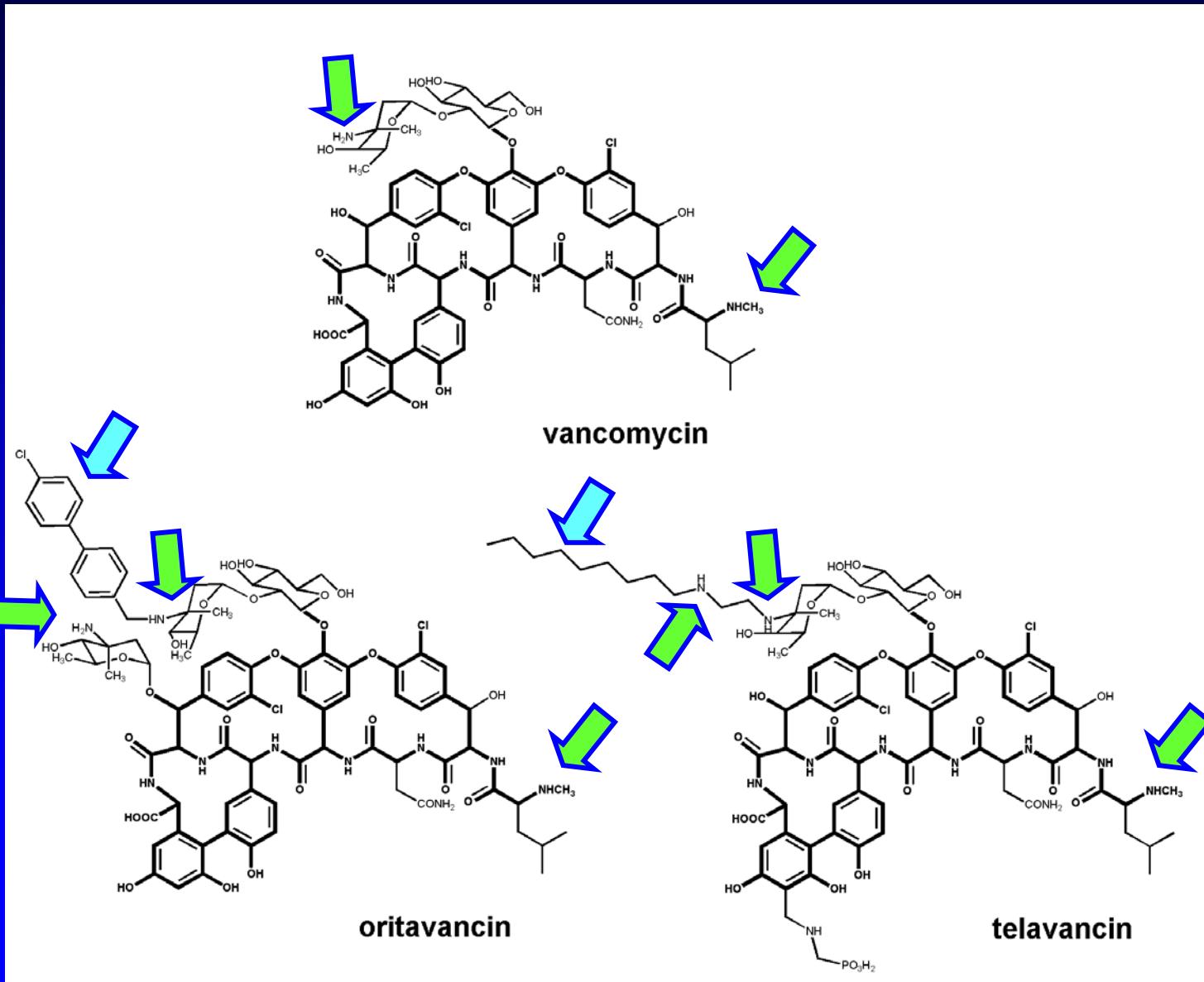


A40926

# From teicoplanin to dalbavancin



# New glycopeptides are more cationic and amphiphilic than vancomycin



**New glycopeptides are  
more cationic and amphiphilic than vancomycin**

## **New chemical entities**

- ➔ New mode of action and new pharmacodynamic properties
- ➔ New pharmacokinetic profile
- ➔ But also .... new potential side effects

# **New glycopeptides: new mode of action and pharmacodynamic properties**



# Spectrum of activity

strain	resist.	vanco	orita	tela	teico	dalba
enterococci	susc.	1-2	0.06-0.25	0.5	0.13-0.5	0.125
	VanA	>128	1-4	4-8	64->128	0.5->128
	VanB	8-128	0.125		0.125-8	1
<i>S. aureus</i>	Methi-S	1-2	1	0.5	1-8	< 0.5
	Methi-R	1-4	1-2	0.5-1	1-8	0.06-1
	GISA	8	1-8	2	8-32	2
	GRSA	> 128	0.5	2	4	

Candiani et al., J.Antimicrob.Chemother. (1999) 44:179-192

Judice & Pace, Bioorg.Med Chem.Lett. (2003) 13:4165-4168

King et al., J Antimicrob.Chemother. (2004) 53:797-803.

Streit et al., Diagn.Microbiol.Infect.Dis. (2004) 48:137-143

# Spectrum of activity

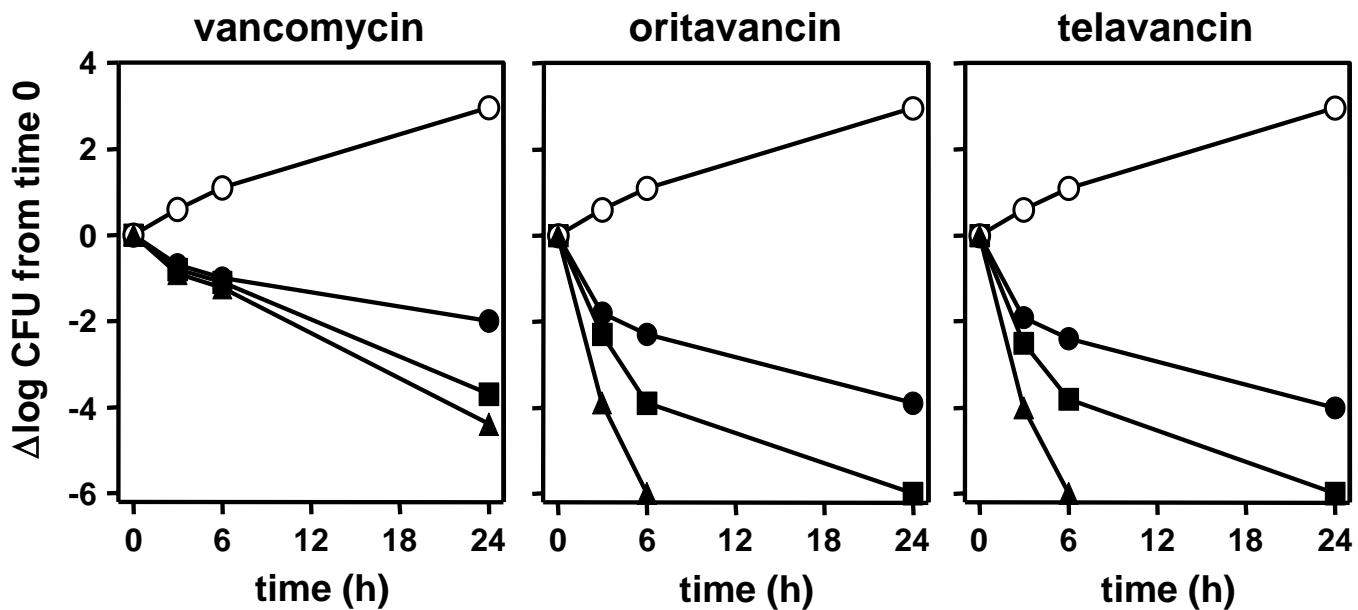
strain	resist.	vanco	orita	tela	teico	dalba
enterococci	susc.	1-2	0.06-0.25	0.5	0.13-0.5	0.125
	VanA	>128	1-4	4-8	64->128	0.5->128
	VanB	8-128	0.125		0.125-8	1
<i>S. aureus</i>	Methi-S	1-2	1	0.5	1-8	< 0.5
	Methi-R	1-4	1-2	0.5-1	1-8	0.06-1
	GISA	8	1-8	2	8-32	2
	GRSA	> 128	0.5	2	4	

activity  
against strains  
resistant to vancomycin

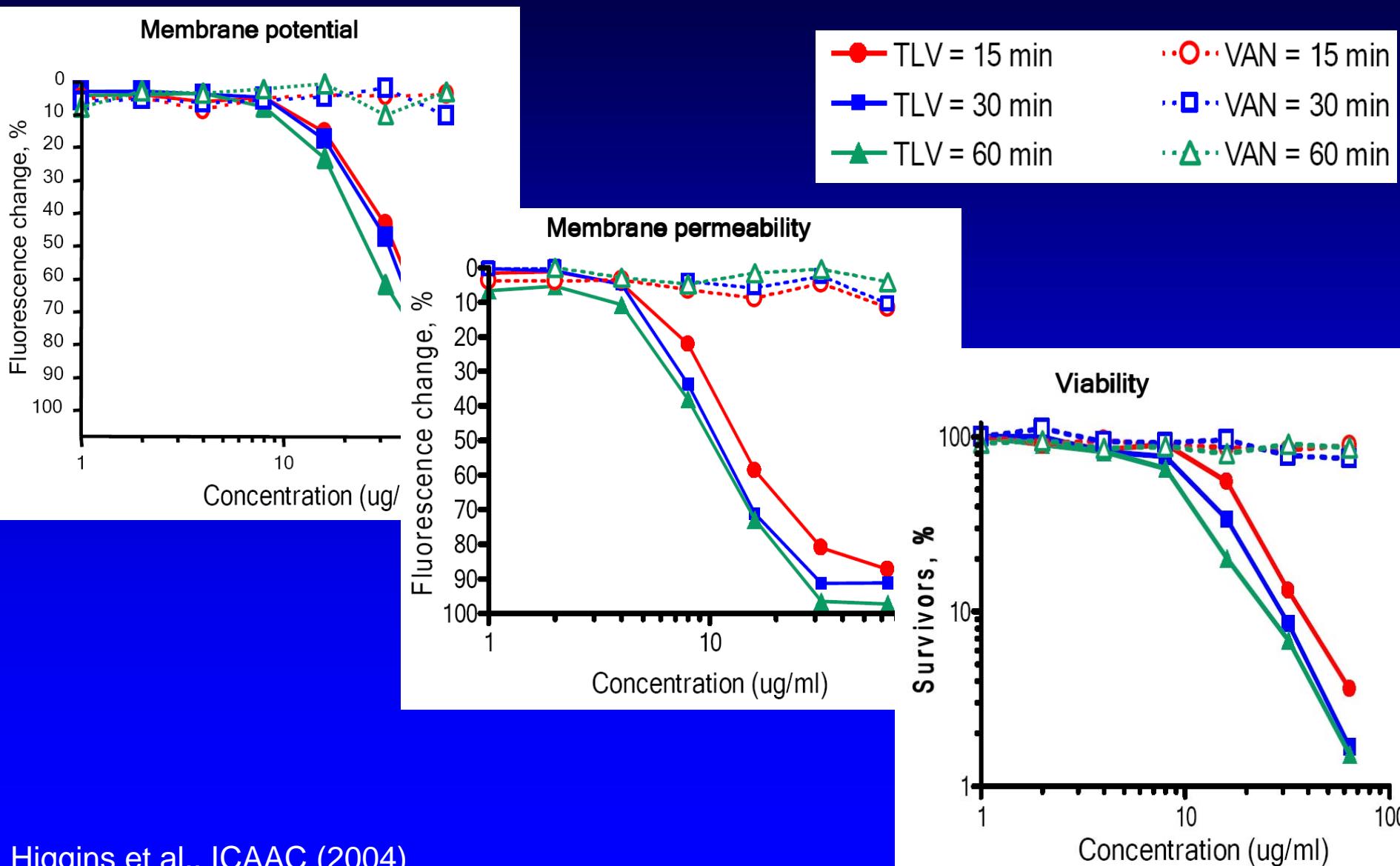
# Pharmacodynamic properties

slowly  
cidal effect

conc. dependent,  
bactericidal effect



# Alteration of membrane integrity

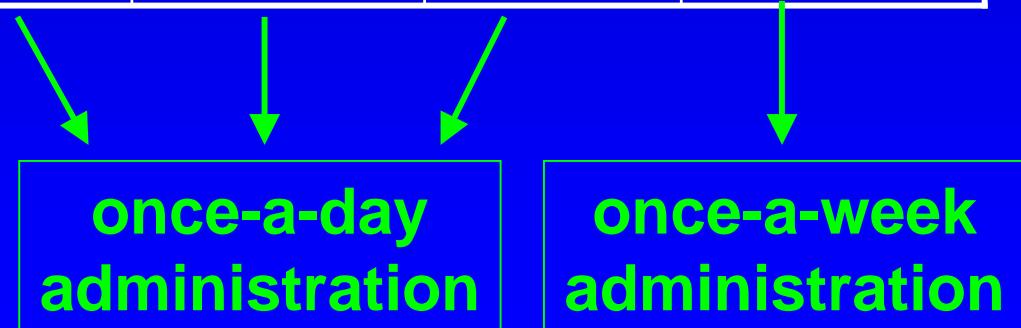


# New glycopeptides: new pharmacokinetic profile



# Pharmacokinetic properties in humans

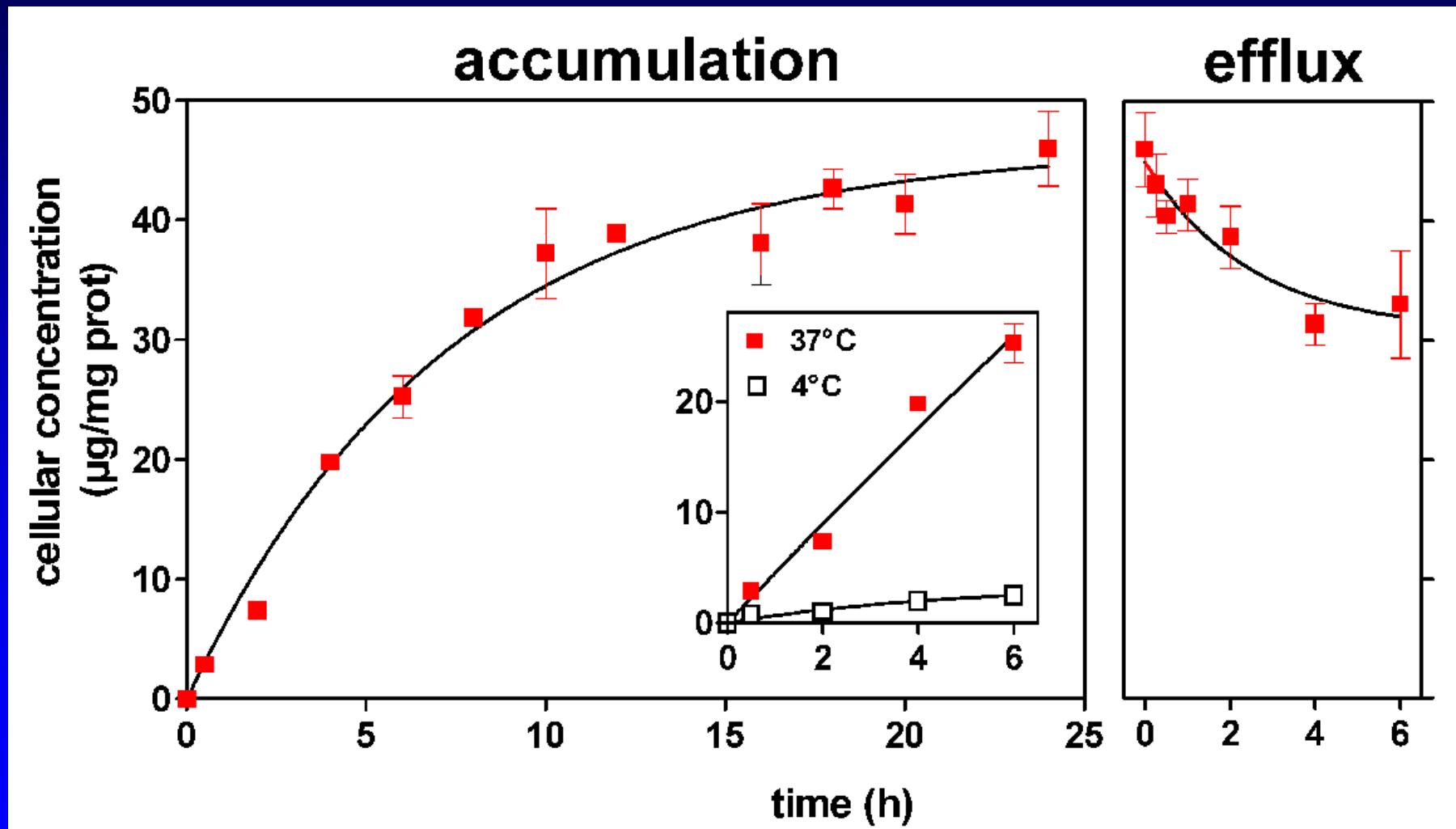
parameter	Vanco (15 mg/kg)	Orita (3 mg/kg)	Tela (7.5 mg/kg)	Teico (6 mg/kg)	Dalba (15 mg/kg)
peak (mg/L)	20-50	31	89	43	300
through (mg/L)	5-12 (24 h)	1.7 (24 h)		< 5 (24 h)	40 (168 h)
protein binding	10-55 %	90 %	90-93%	90 %	98 %
terminal t <sup>1/2</sup> (h)	4-8	≤ 360	7	83-168	257 h



Intermune, Inc, data on file  
Barriere et al, ICAAC 2003  
Steiert & Schmitz,  
Curr.Opin.Investig.Drugs (2002) 3:229-233

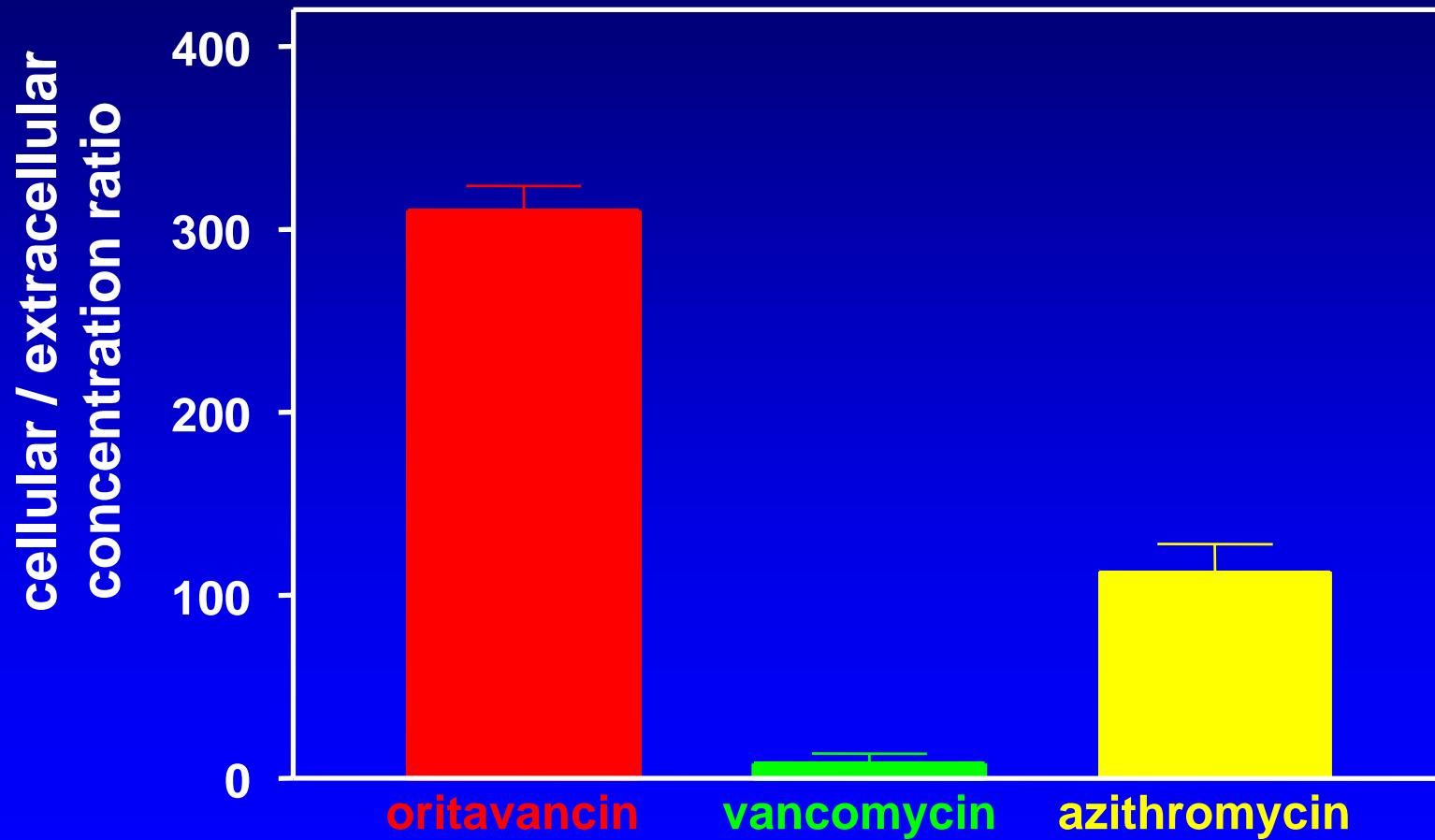
# Cellular pharmacokinetics

J774 macrophages; extracellular concentration: 25 mg/L; 24 h

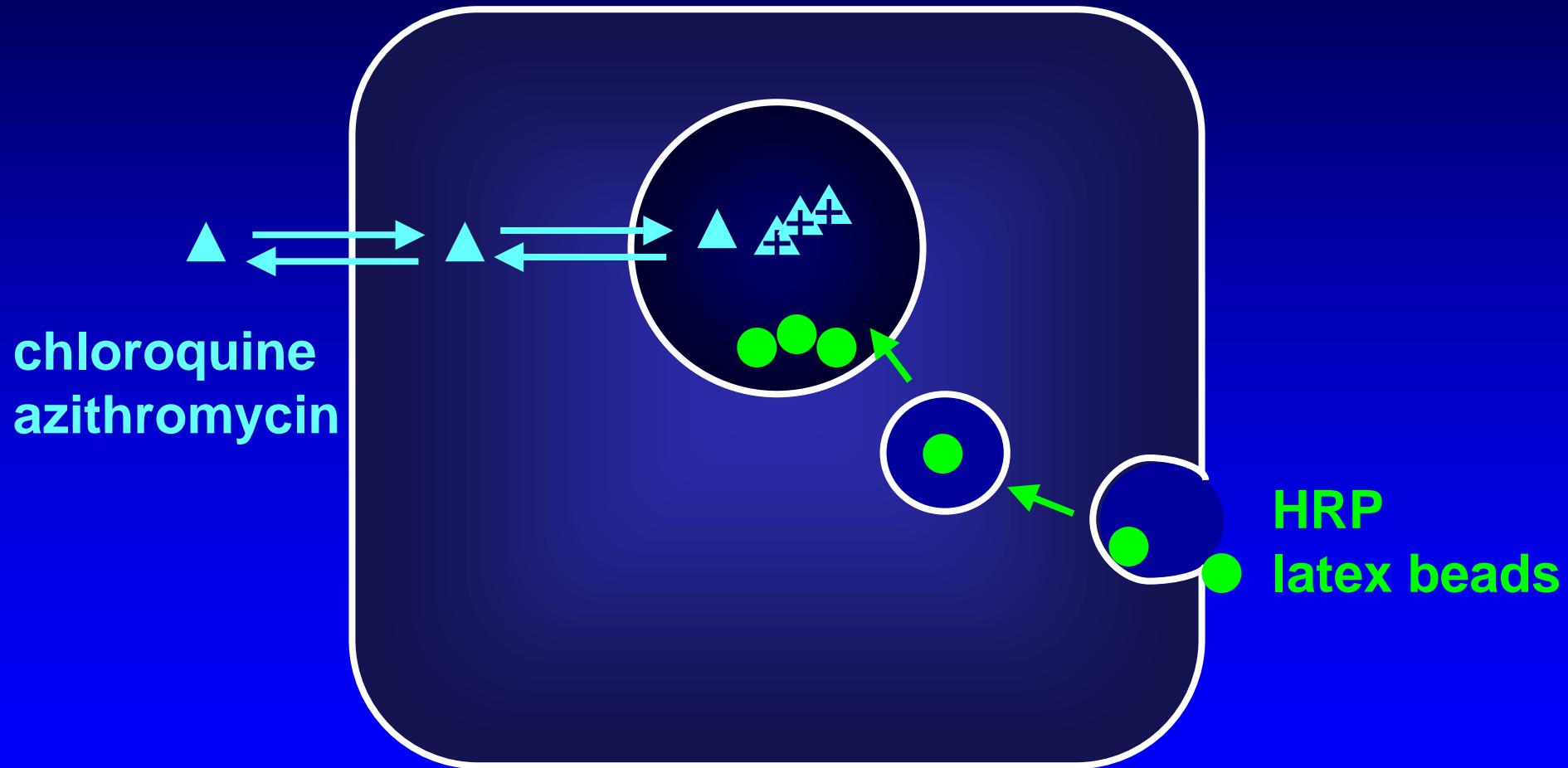


# Comparison with other antibiotics

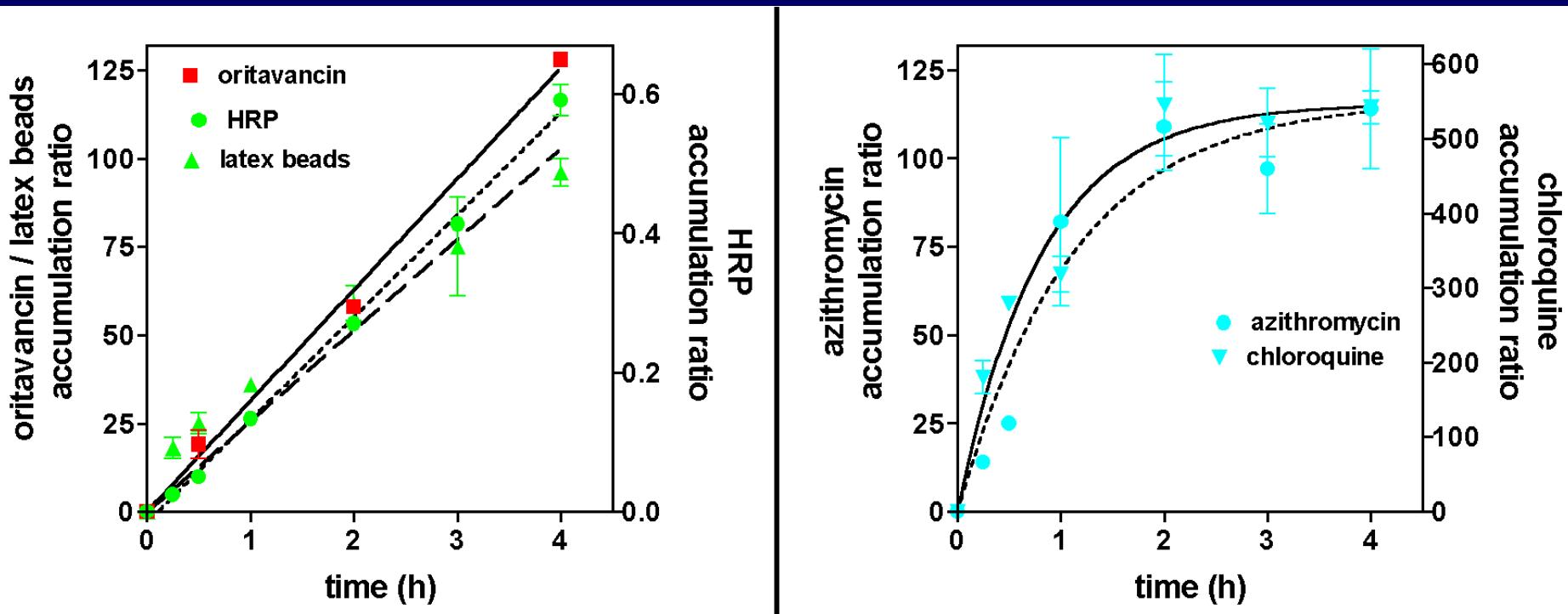
J774 macrophages; extracellular concentration: 25 mg/L; 24 h



# Mechanism of cellular accumulation



# Mechanism of cellular accumulation



- Uptake linear over 4 h as for markers of endocytosis
- Rate of uptake similar to that of a marker of adsorptive endocytosis

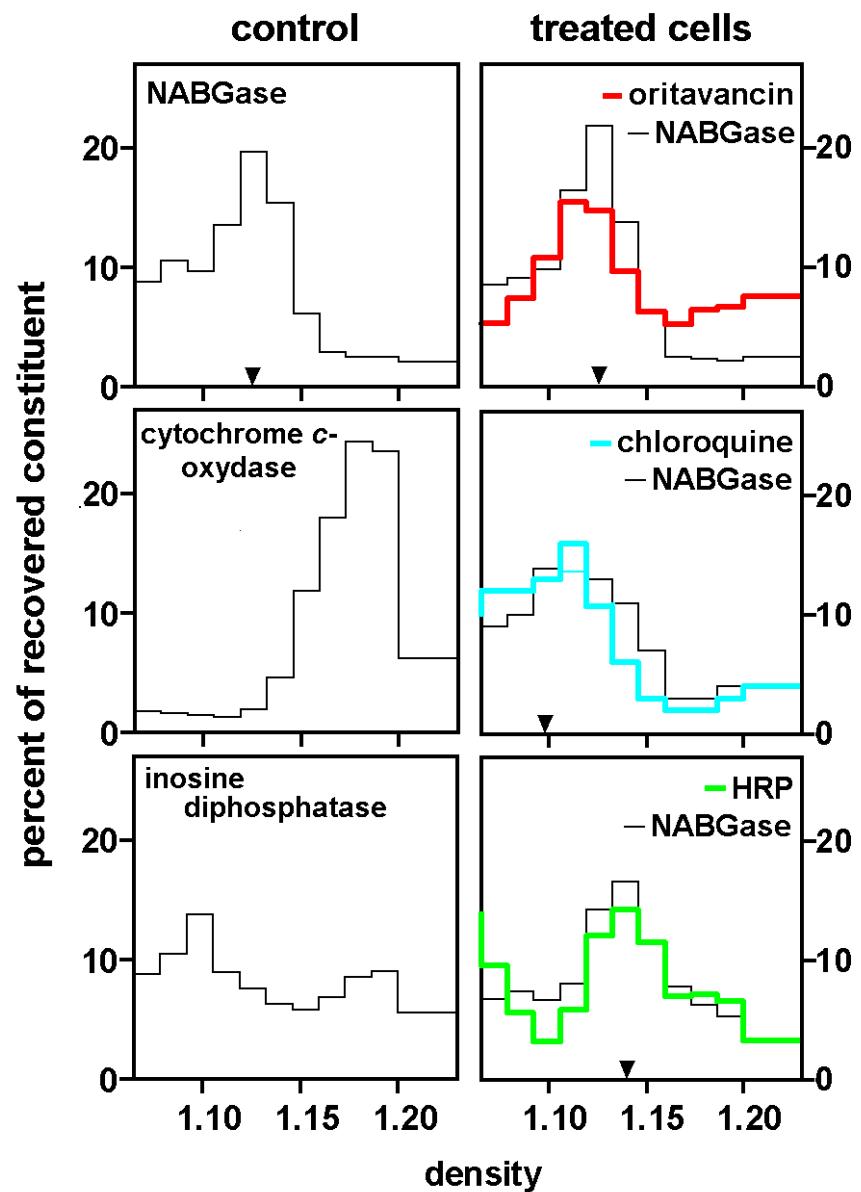
# Subcellular localization

MARKERS OF :

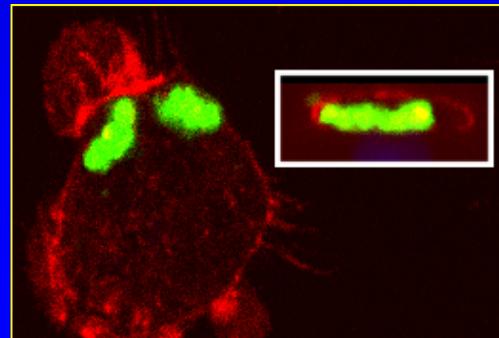
lysosomes

mitochondria

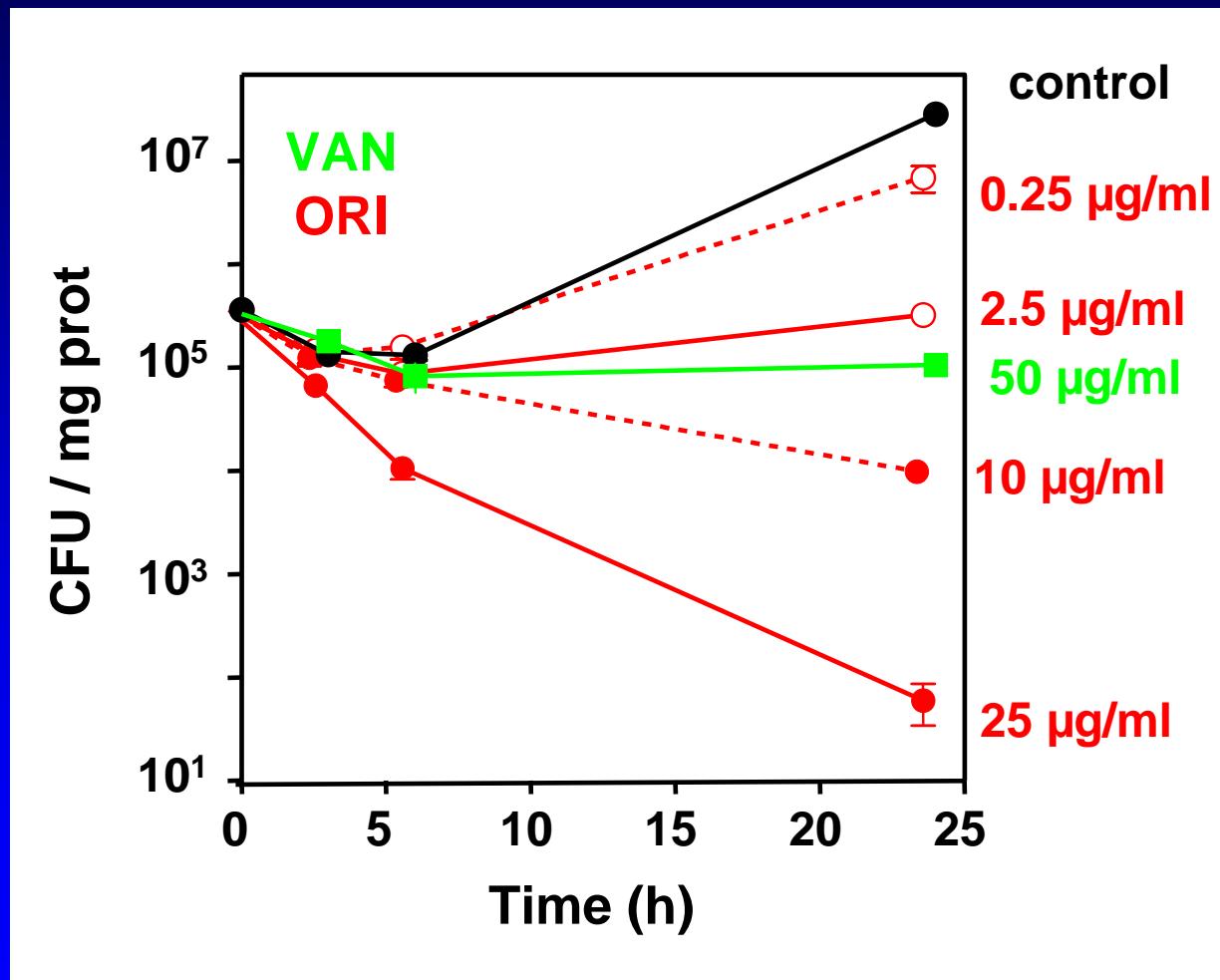
membranes



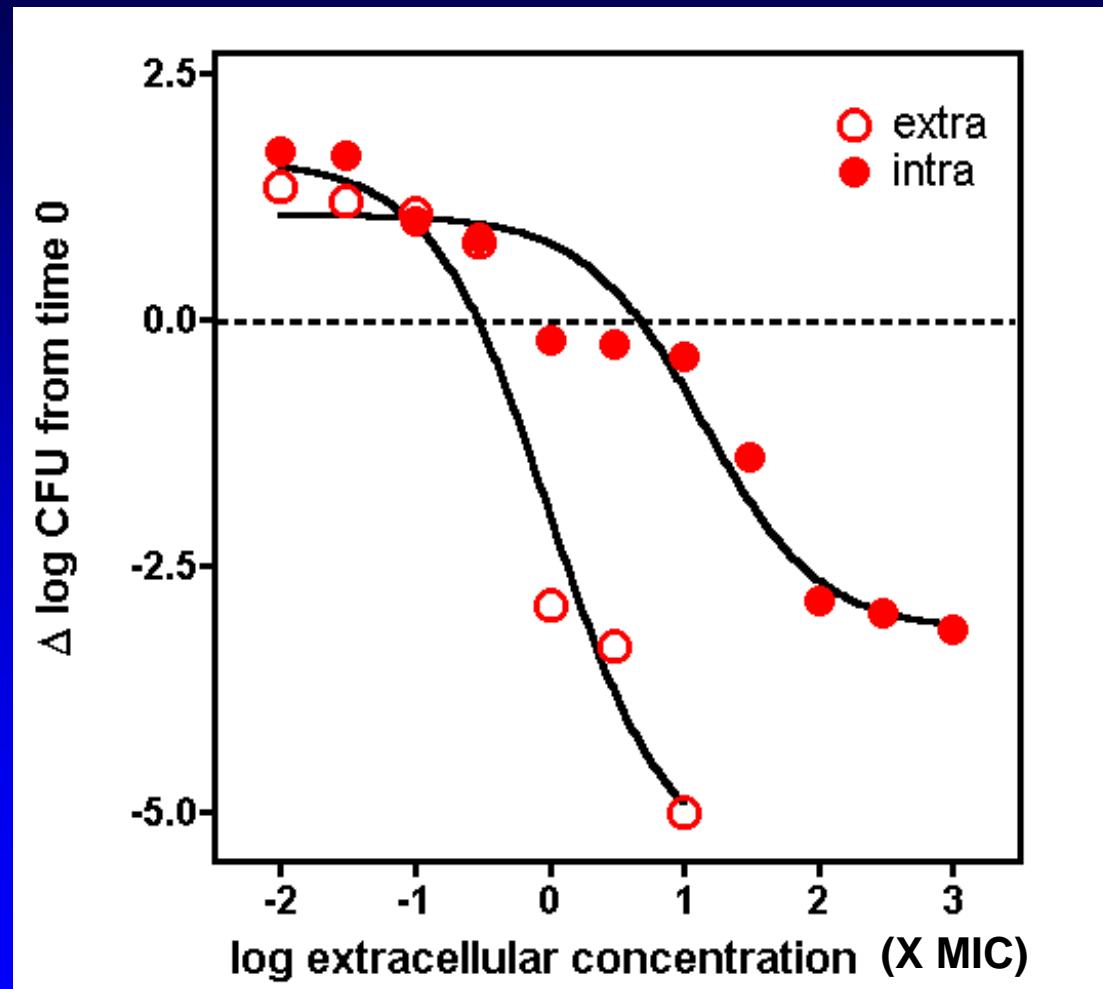
New glycopeptides:  
cellular pharmacokinetics  
↓  
cellular pharmacodynamics



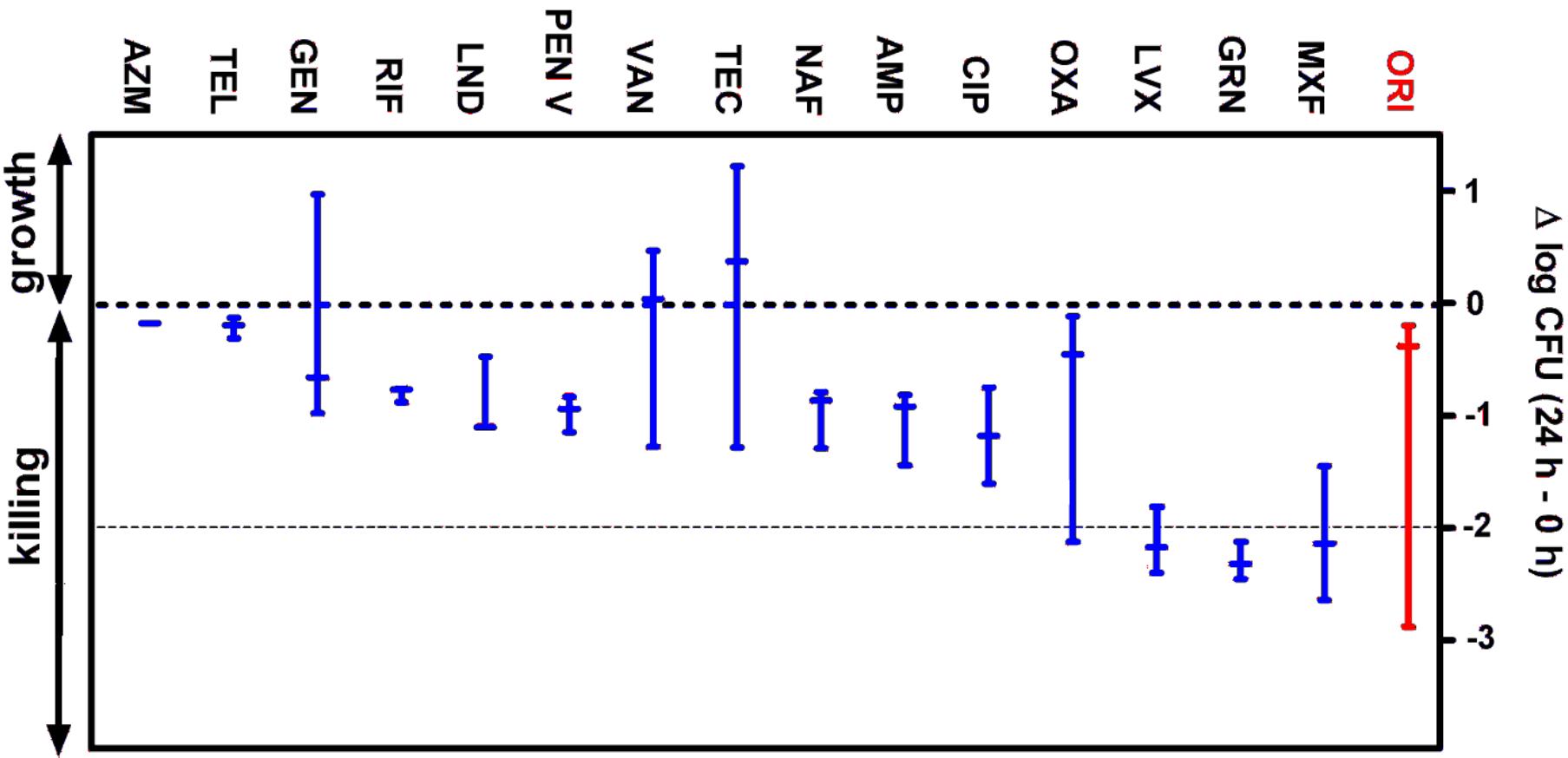
# PK/PD properties of oritavancin in a model of *S.aureus* infected macrophages



# PK/PD properties of oritavancin in a model of *S.aureus* infected macrophages

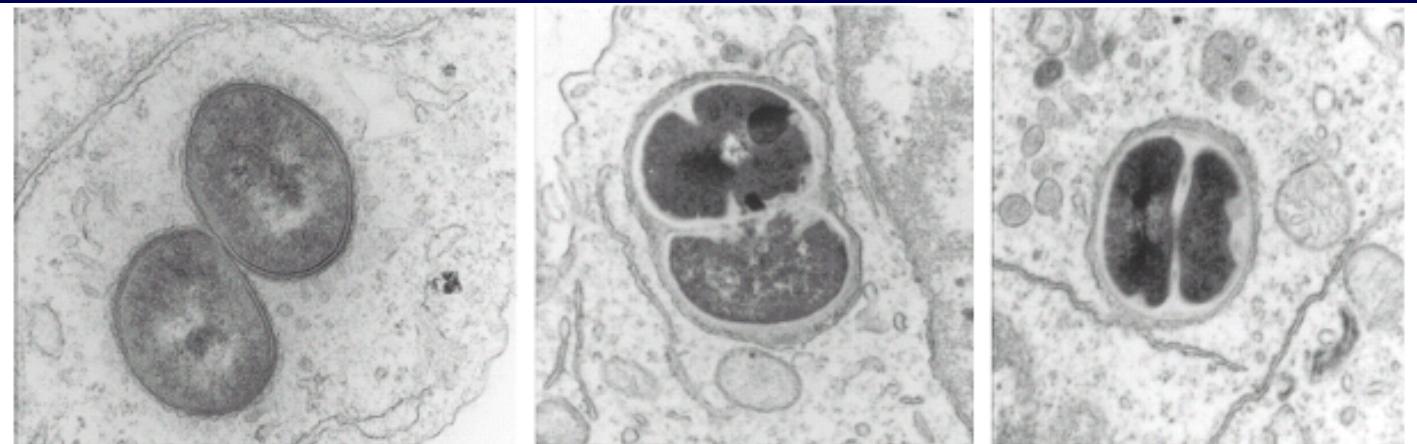


# Oritavancin is the most active antibiotic against intracellular *S. aureus* among those tested so far !

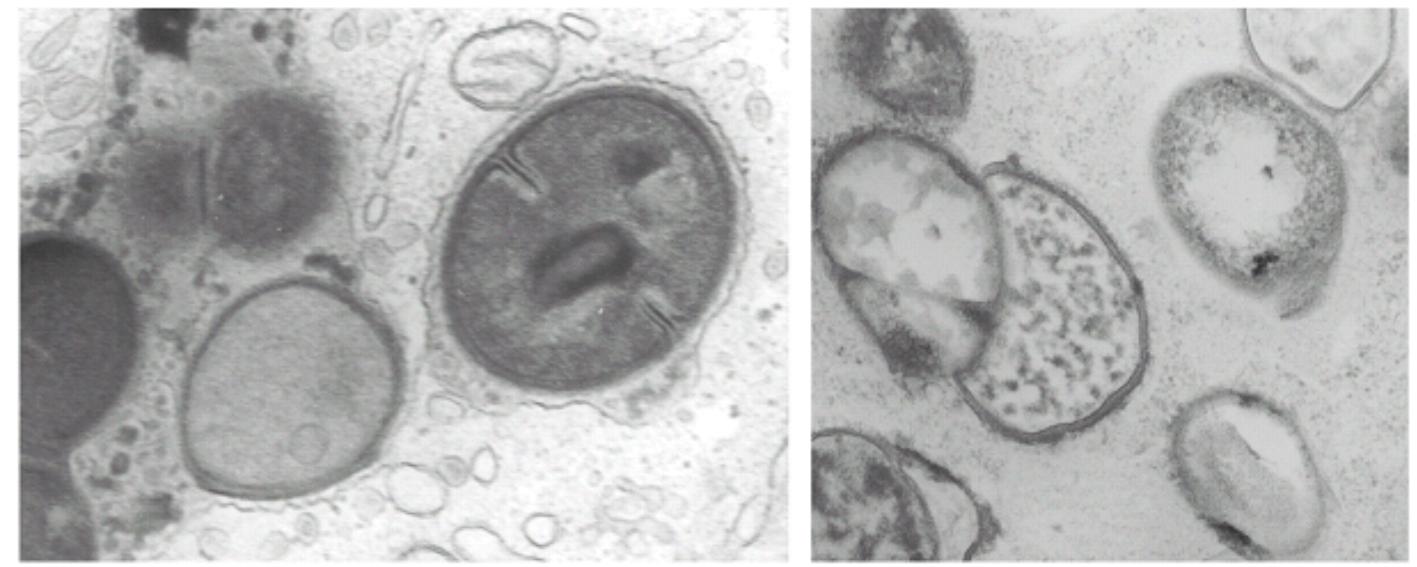


# Intracellular bactericidal activity is visible !

control



oritavancin



# New glycopeptides:

## IN VIVO DATA animal models



Combined extra-and intracellular activity



recurrent infections, including by resistant organisms

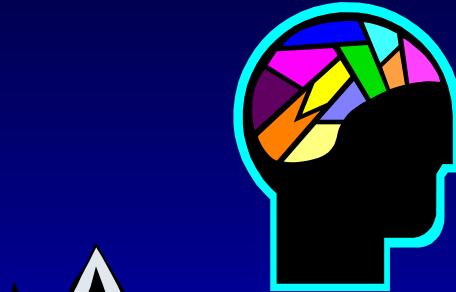
# efficacy shown in ....



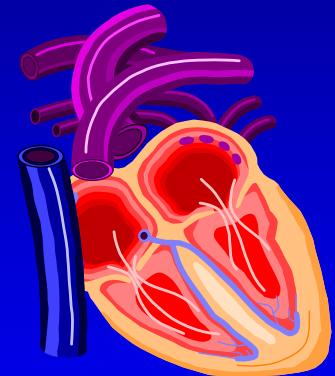
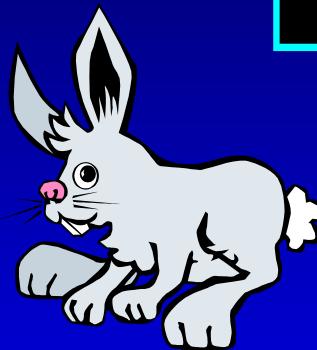
pouch



catheter



meningitis



endocarditis

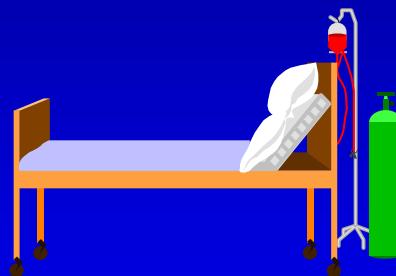
Combined extra-and intracellular activity



recurrent infections, including by resistant organisms

# New glycopeptides:

## IN VIVO DATA clinical studies



Combined extra-and intracellular activity



recurrent infections, including by resistant organisms

# Clinical experience

complicated skin and skin structure infection  
caused by Gram (+) including MRSA

(phase II/III; double blind, randomized)

517 pts

**Vancomycin 15 mg/kg bid  
3-7 days**

**Oritavancin 1.5-3 mg/kg qd  
3-7 days**

**followed by oral cephalexin  
10-14 days**

**SUCCESS :**

bacteriological

76 %

74 %

clinical

80 %

=

76 %

with MRSA

80 %

74 %

# Clinical experience

complicated skin and skin structure infection  
caused by Gram (+) including MRSA

(phase II; double blind, randomized)

167 pts

vancomycin / penicillin

telavancin

**SUCCESS :**  
**bacteriological**

74 %

**clinical**  
**with MRSA**

77 %

69 %

=  
<

84 %

80 %

82 %

# Clinical experience

complicated skin and skin structure infection  
caused by Gram (+) including MRSA

(phase II; controlled, randomized)

62 pts

**Vancomycin, ceftriaxone,  
cefazolin or clindamycin  
for 7-21 days**

**Dalbavancin  
15 mg/kg day 1  
+ 7.5 mg/kg day 8**

**SUCCESS :**  
**bacteriological**  
  
**clinical**

**64 %**

**76 %**

**73 %**

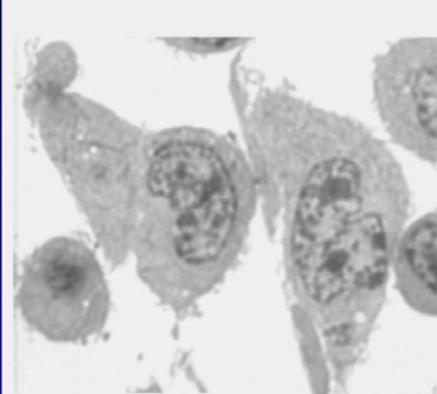
**94 %**

New glycopeptides:  
cellular pharmacokinetics  
↓  
cellular toxicity ?

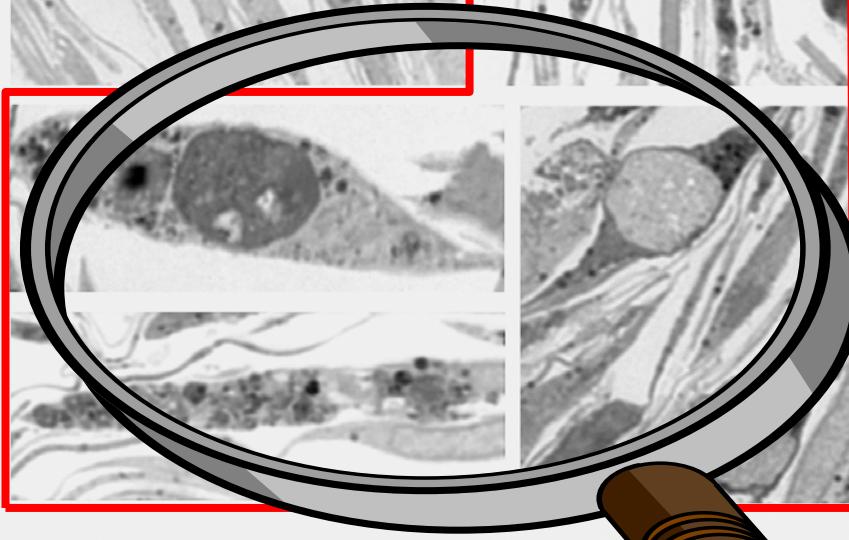
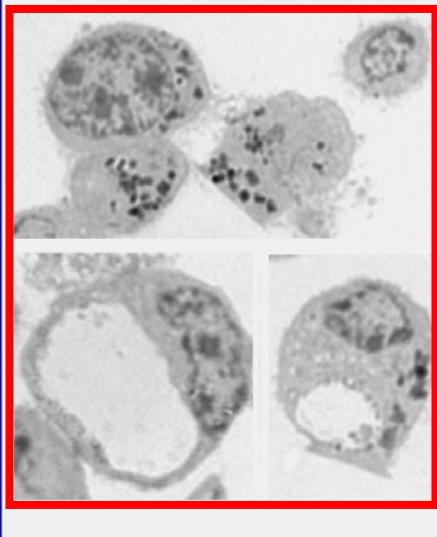
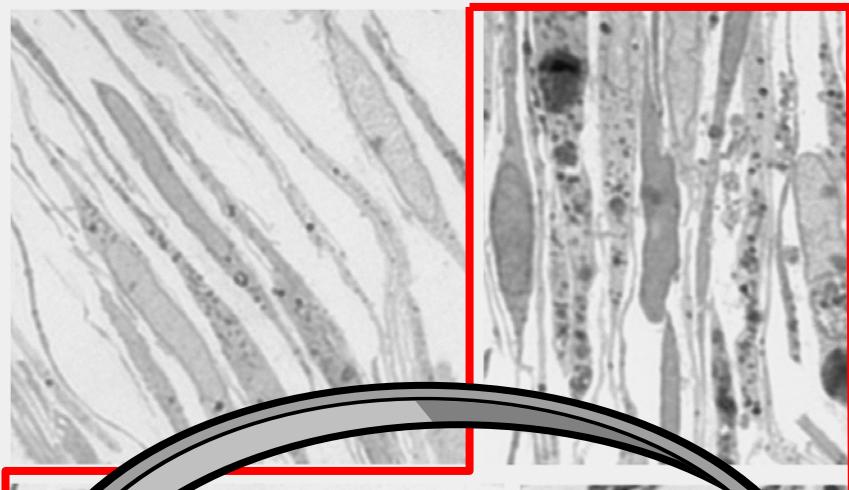


# Microscopic examination of oritavancin treated cells

macrophages

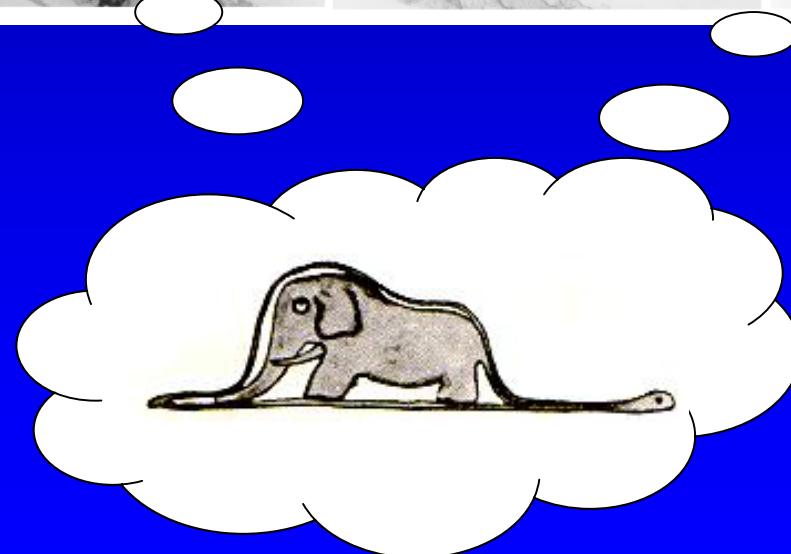
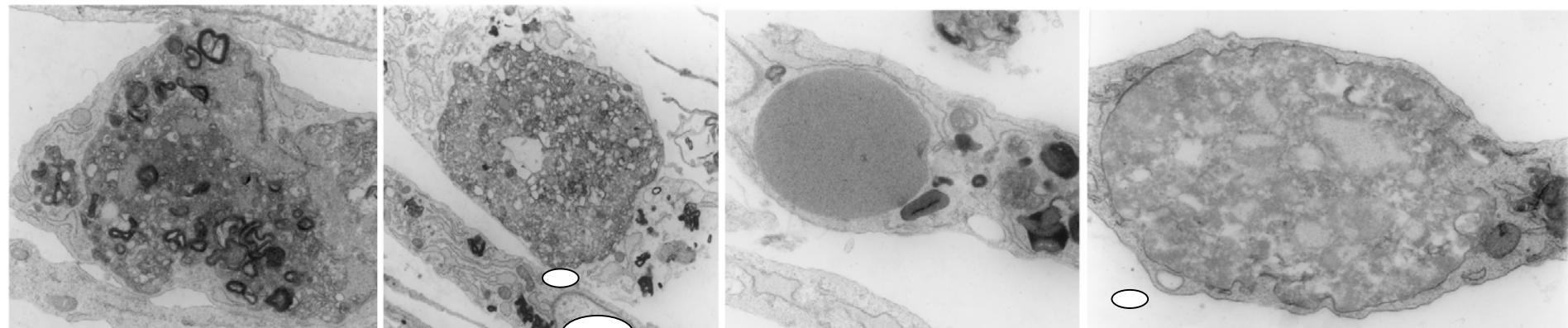


fibroblasts

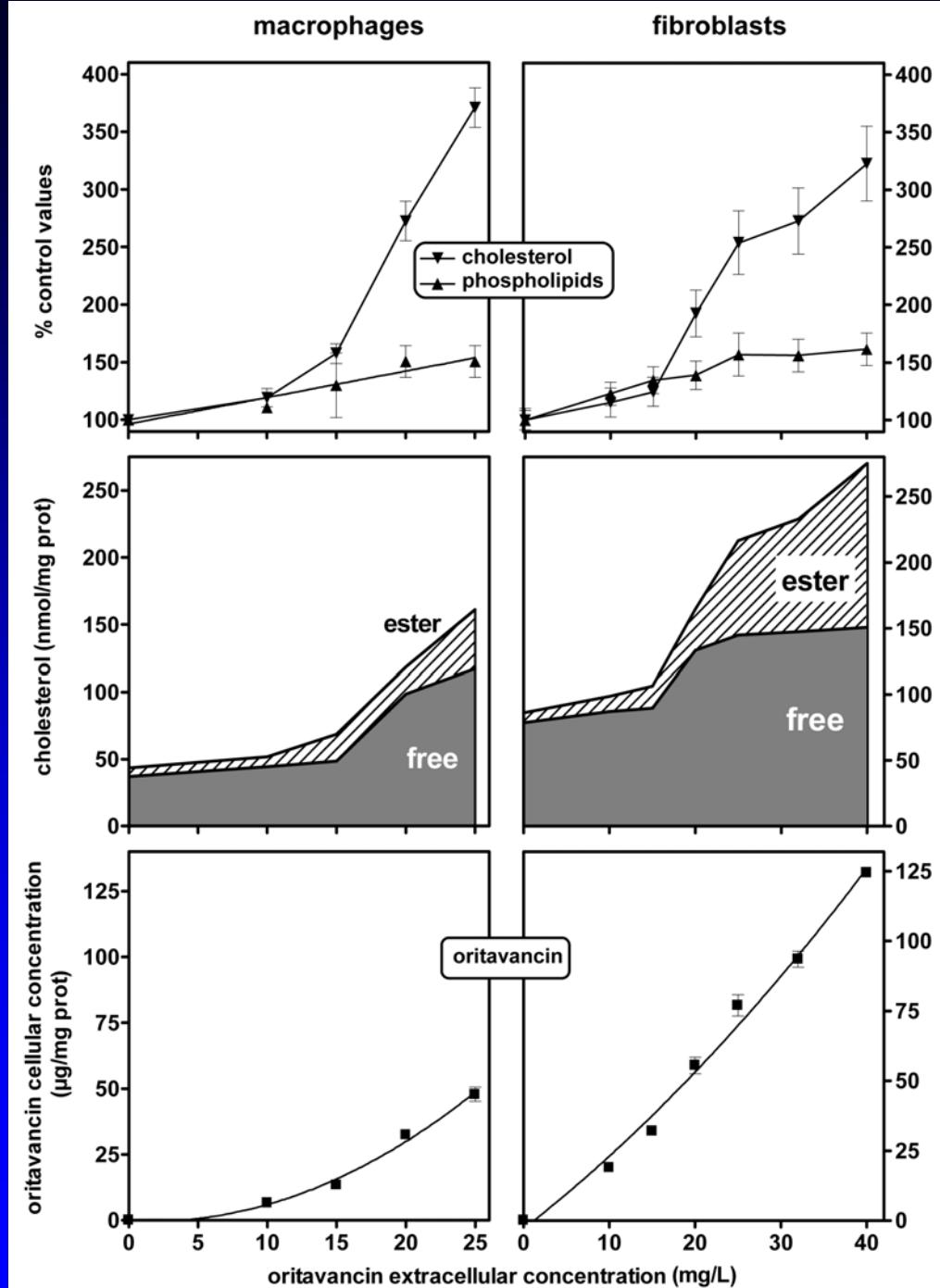


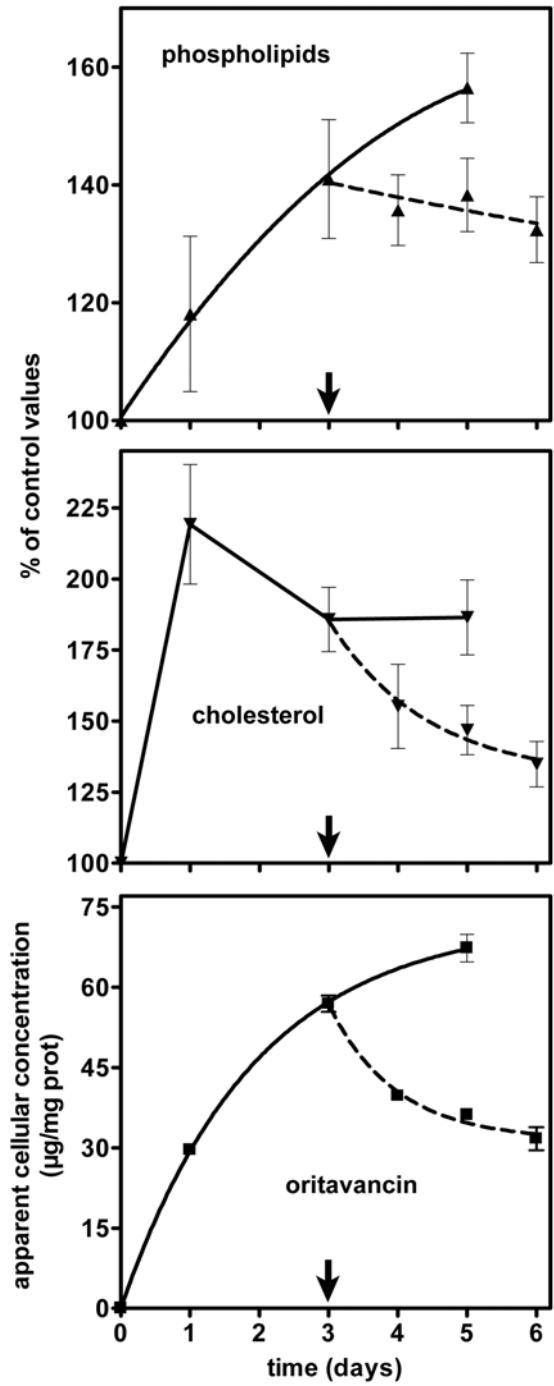
# Microscopic examination of oritavancin treated cells

fibroblasts



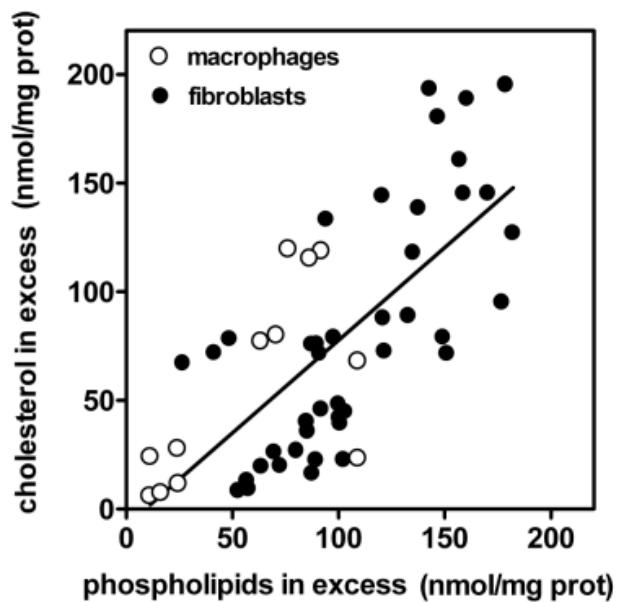
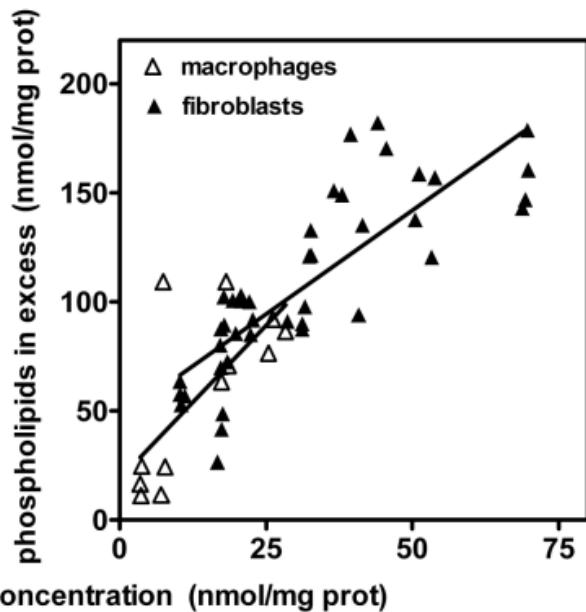
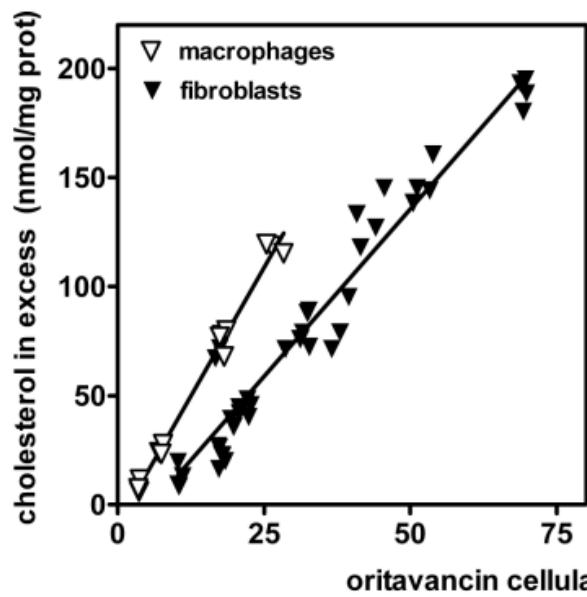
# Lipid accumulation: concentration-effect relationships





## Lipid accumulation: time effect and reversibility

# Lipid accumulation: correlations



## Safety profile in humans

No major side effect in clinical trials,

BUT

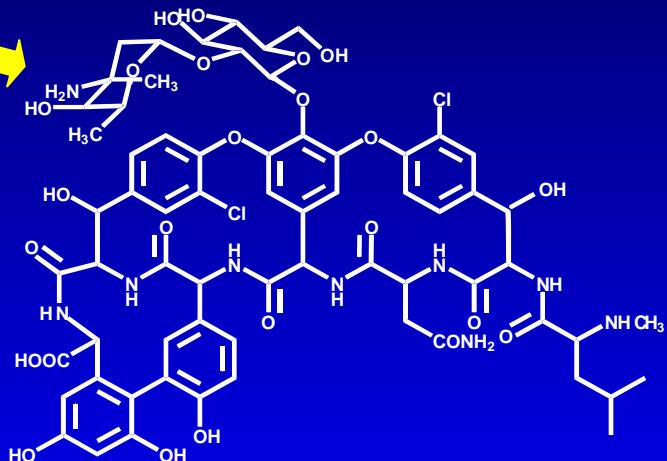
- small number of patients
- appropriate techniques should be used to detect cellular alterations ....

# how can a structural modification bring to a new life an old family of antibiotics ?

- **new mode of action**

- activity against resistant strains
- bactericidal, conc.-dependent effect
  - ideal PD profile

*lipophilic side chain*



- **new pharmacokinetic profile**

- prolonged half-life/high prot. binding
- high cell accumulation/intracell. activity
  - infrequent administrations
  - recurrent infections

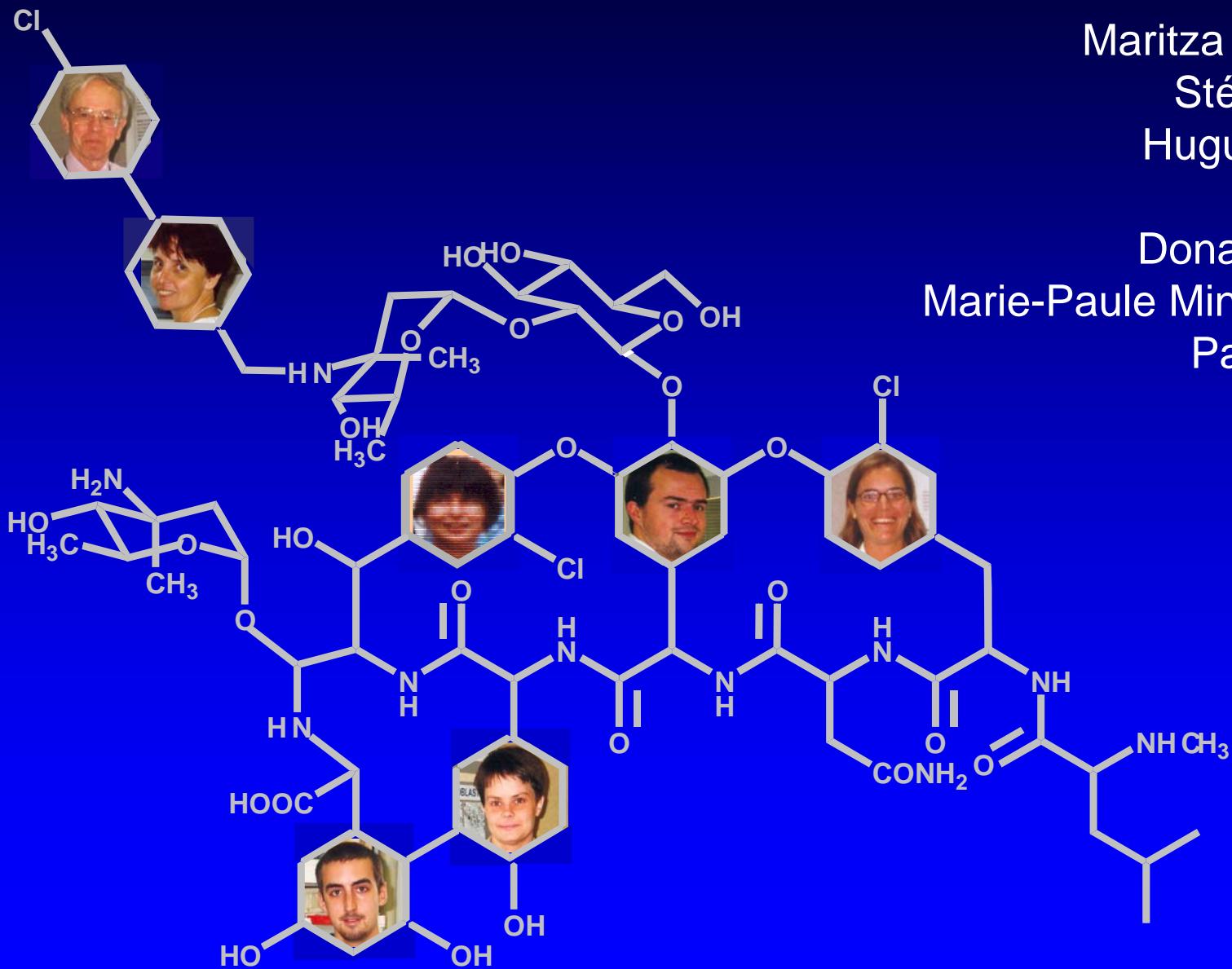
- **new toxic effects in vitro**

- thesaurismosis
  - safety issues ?????

# Glycopeptides: have we improved ?

parameter	vanco - teico	new glycopeptides
spectrum	Gram (+) & MRSA <b>but VRE - GISA</b>	Gram (+) & <b>MRSA, GISA, VRE</b> 
PD	<b>static</b> or slowly bactericidal	quickly, conc. dependent bactericidal 
PK	<b>t ½ short for vanco</b>	$t \frac{1}{2} \nearrow$ diffusibility (CNS) 
safety	(red-man syndrome) oto-& nephrotoxicity	side effects 

# Thanks to ...



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