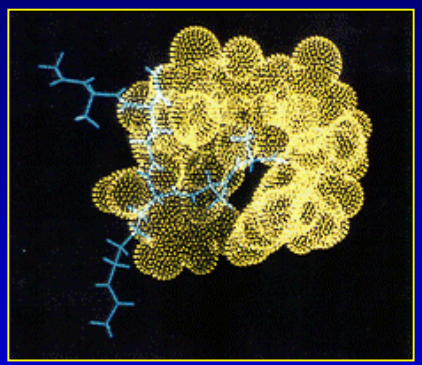
GLYCOPEPTIDE ANTIBIOTICS

from Old Mississipi mud …



… to new derivatives:

a critical appraisal

F. Van Bambeke & P.M. Tulkens
Pharmacologie cellulaire et moléculaire
Université catholique de Louvain – Brussels - Belgium

Presented at the 5th European Congress of Chemotherapy,
Rhodes, Greece, 17-20 October 2003

Glycopeptide story: from natural to semi-synthetic derivatives

~ 1950 :
discovery of vancomycin in Mississipi mud

~ 1985 :
large clinical use in USA
Gram(+) infections and digestive tract decontamination

Problem:

- **toxicity of vancomycin due to impurities**
  - **➔ better purification procedures**

~ 1980 :
discovery of teicoplanin, as a natural GP with improved PK

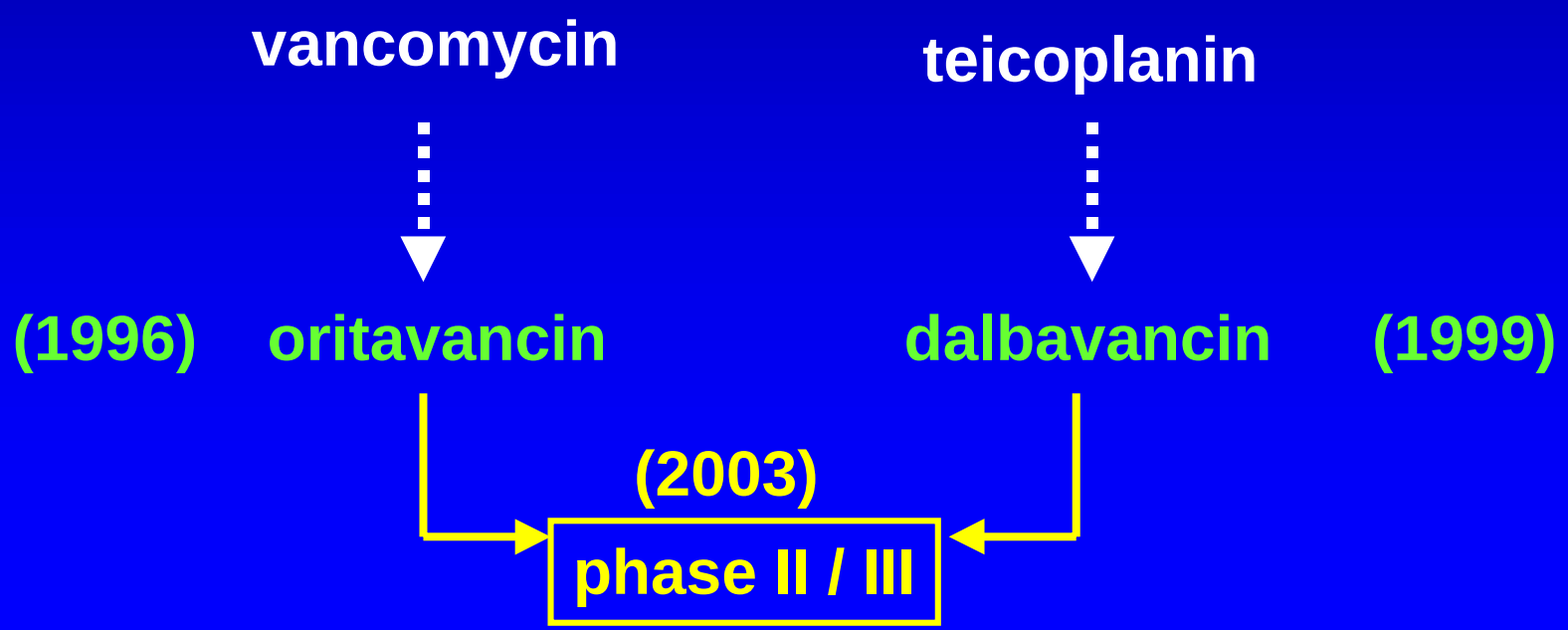
- **largely used in Europe**

Glycopeptide story: from natural to semi-synthetic derivatives

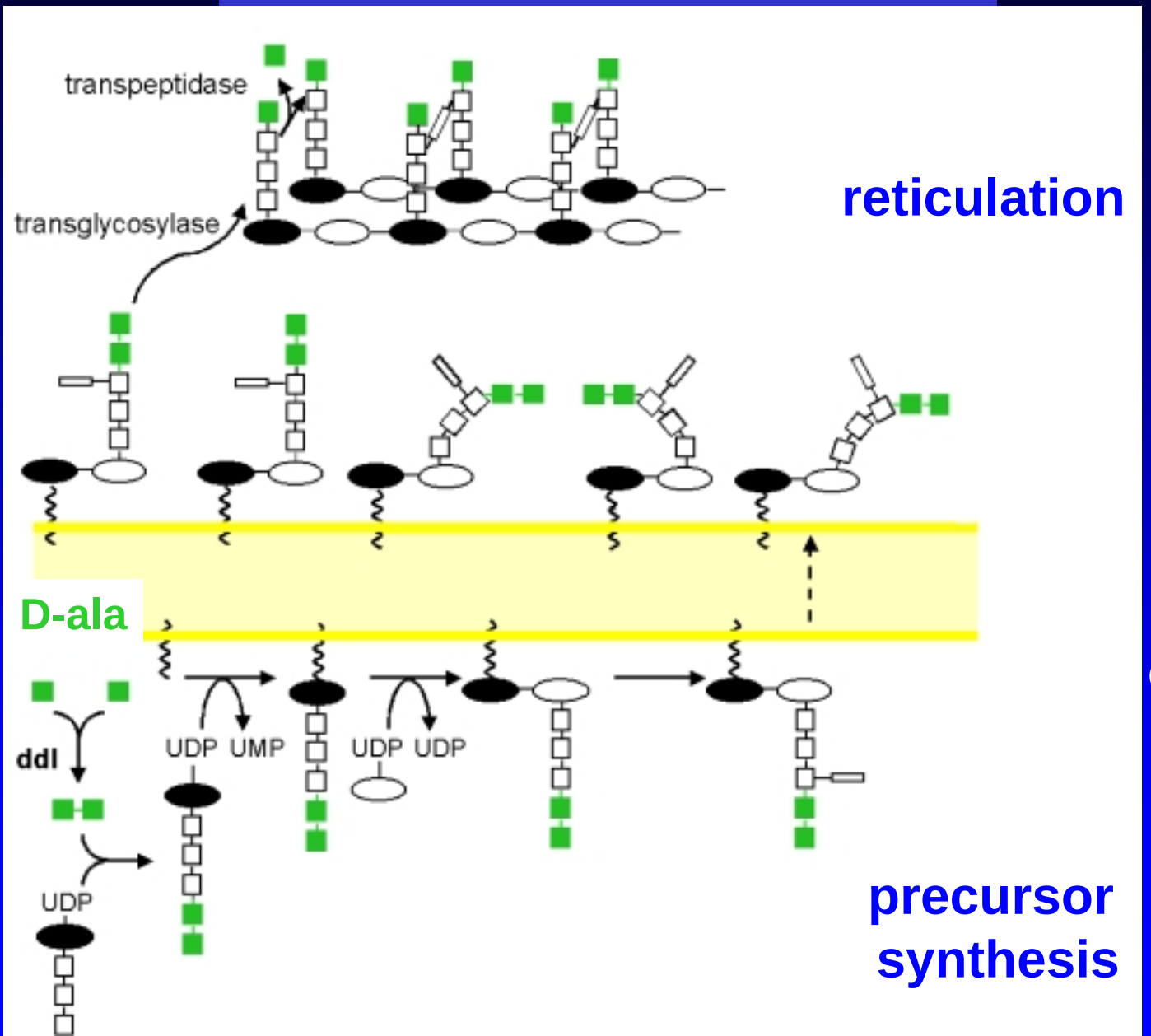
~ 1990 :

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

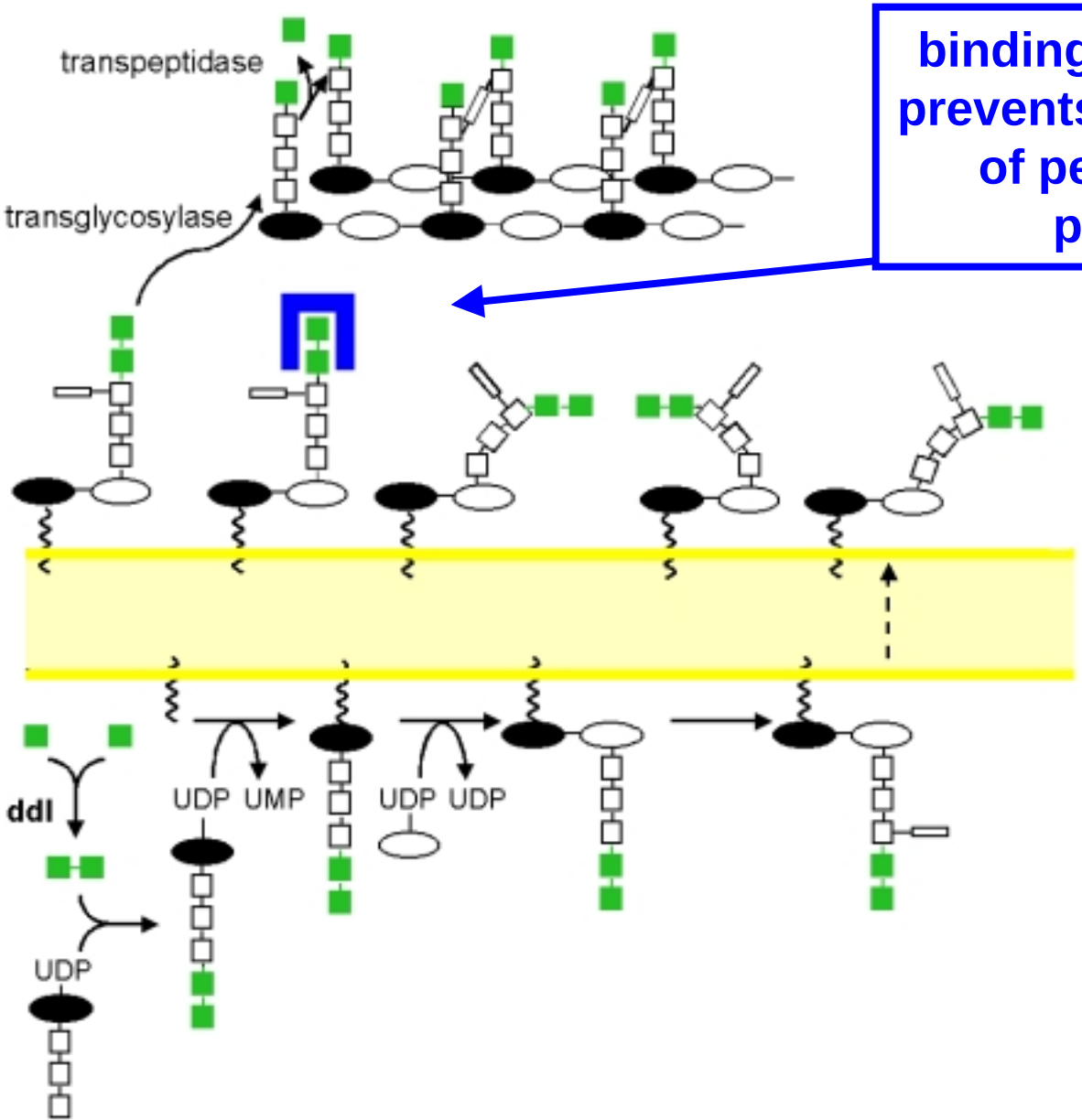
Malabarba and Nicas
Med Res Rev. (1997) 17:69-137; Curr Med Chem. (2001) 8:1759-7



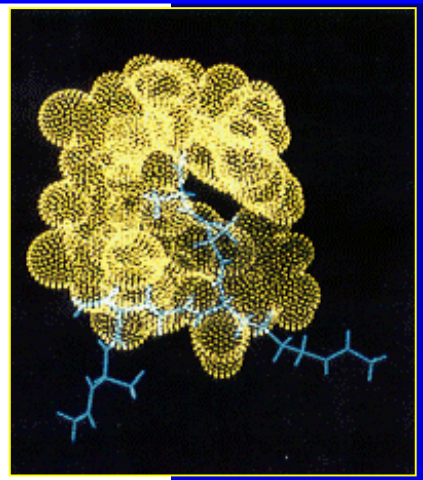
Peptidoglycan synthesis



Glycopeptide mechanism of action



binding to D-Ala-D-ala prevents the reticulation of peptidoglycan precursors



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.

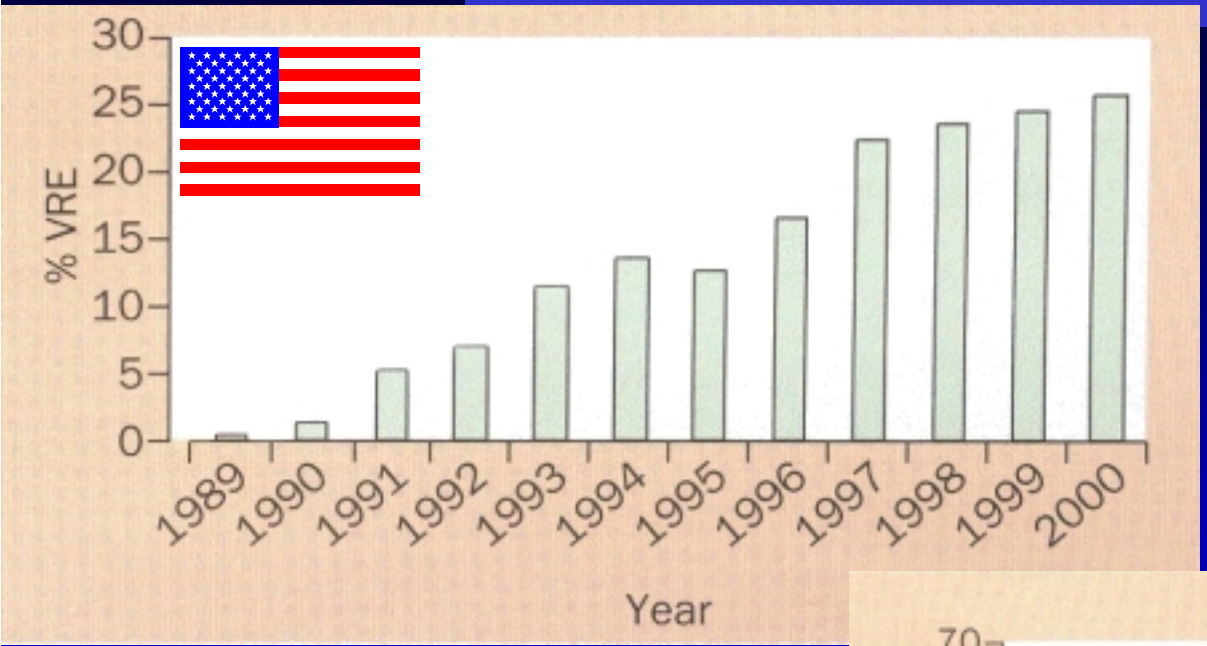
Antimicrob Agents Chemother. 1989 Jul;33(7):1121-4.

Characterization of vancomycin resistance in Enterococcus faecium and Enterococcus faecalis.

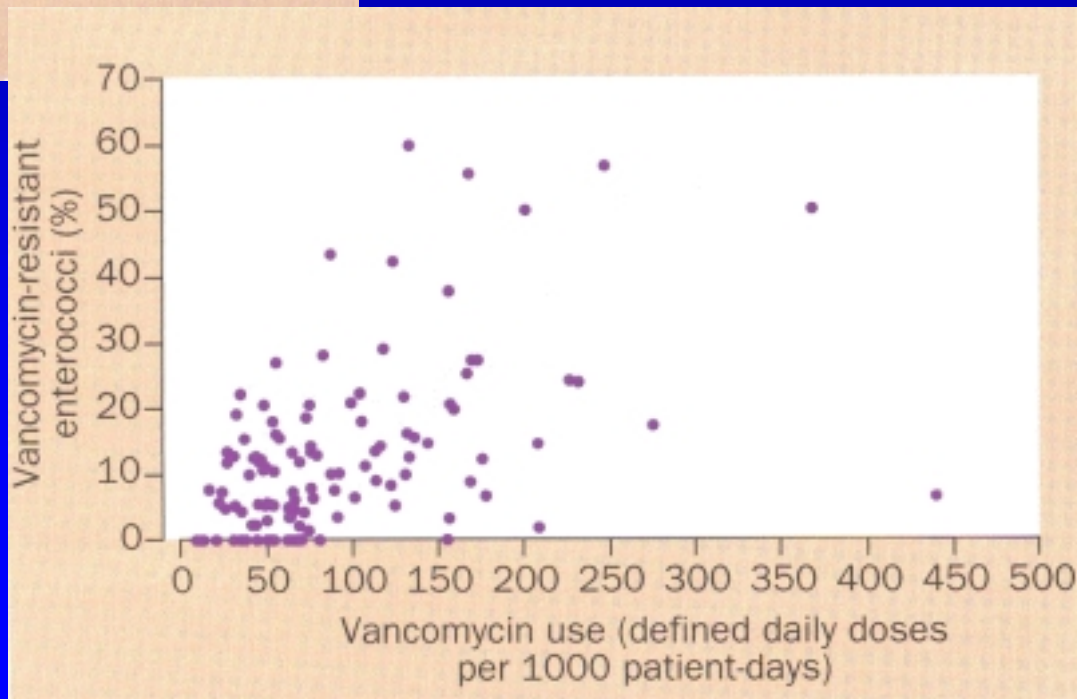
Nicas TI, Wu CY, Hobbs JN Jr, Preston DA, Allen NE.

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

Resistance in enterococci

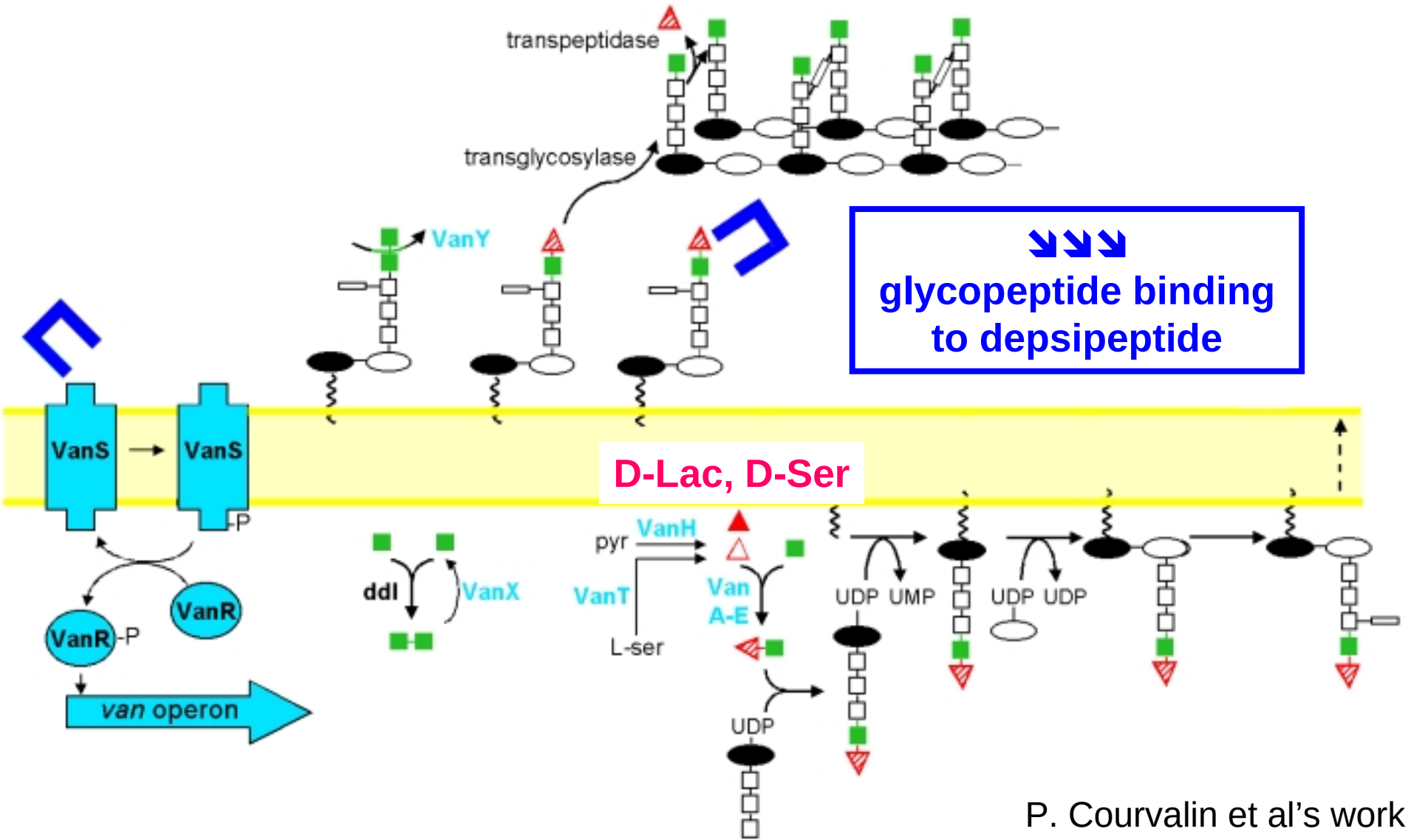


large clinical use in USA started in ~ 1985



Bonten et al,
Lancet ID (2001) 1:314-325

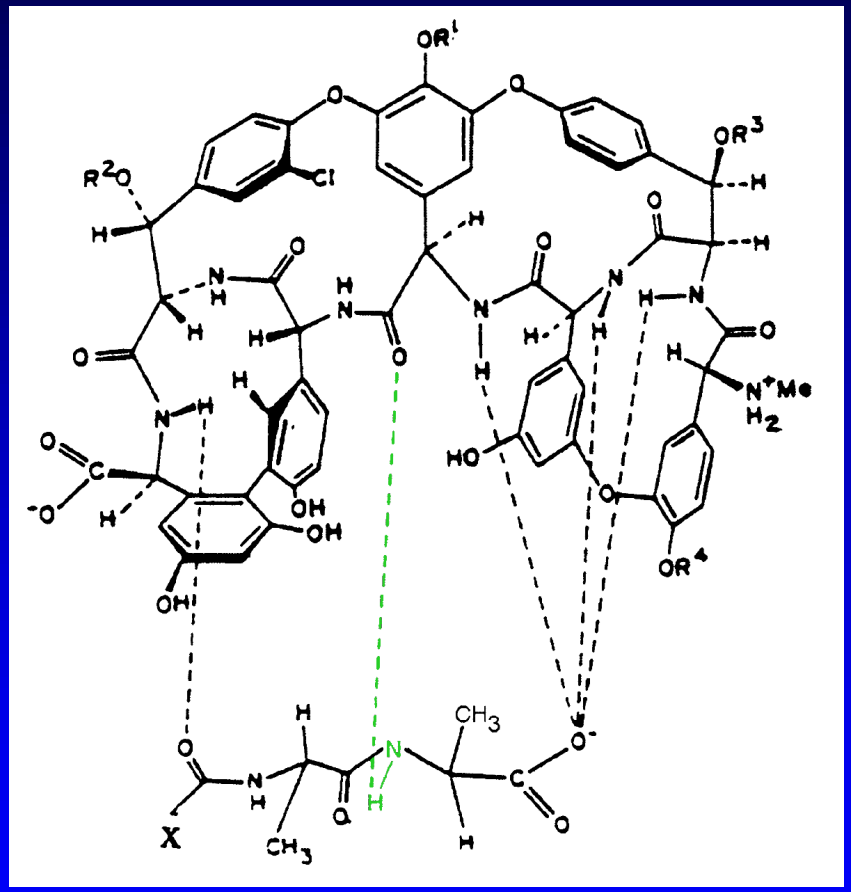
Resistance in enterococci



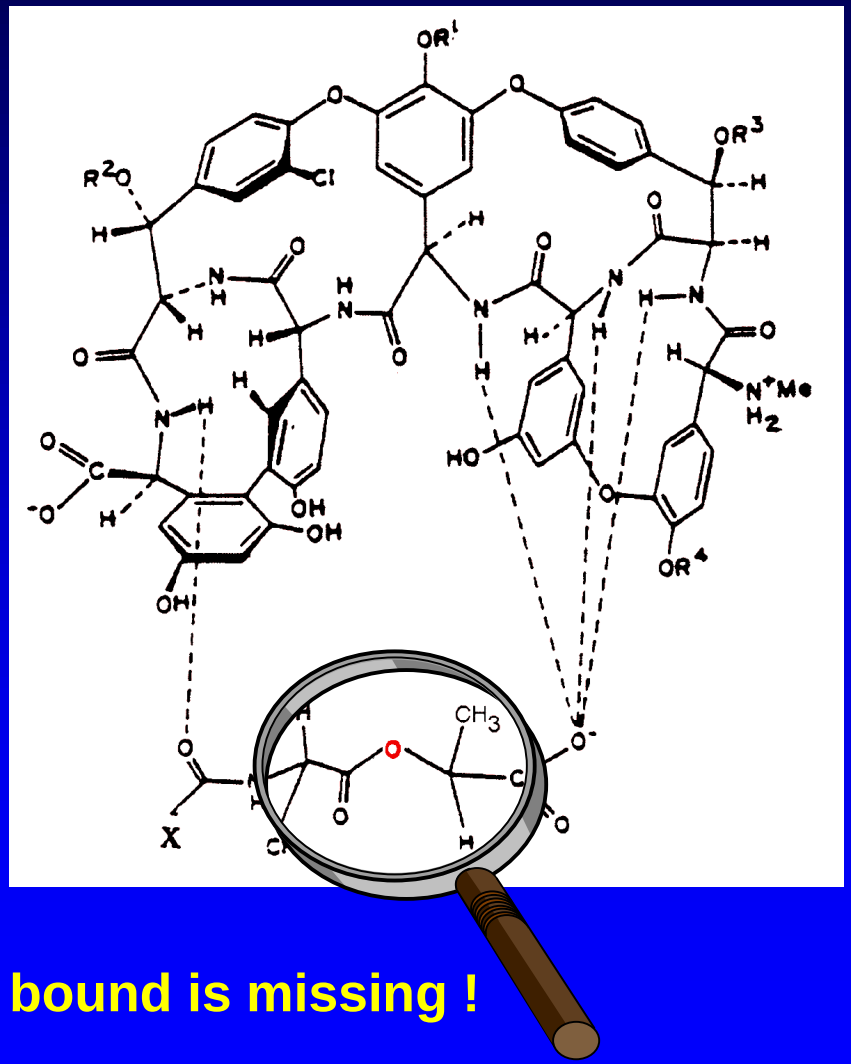
P. Courvalin et al's work

Resistance in enterococci

from susceptible …



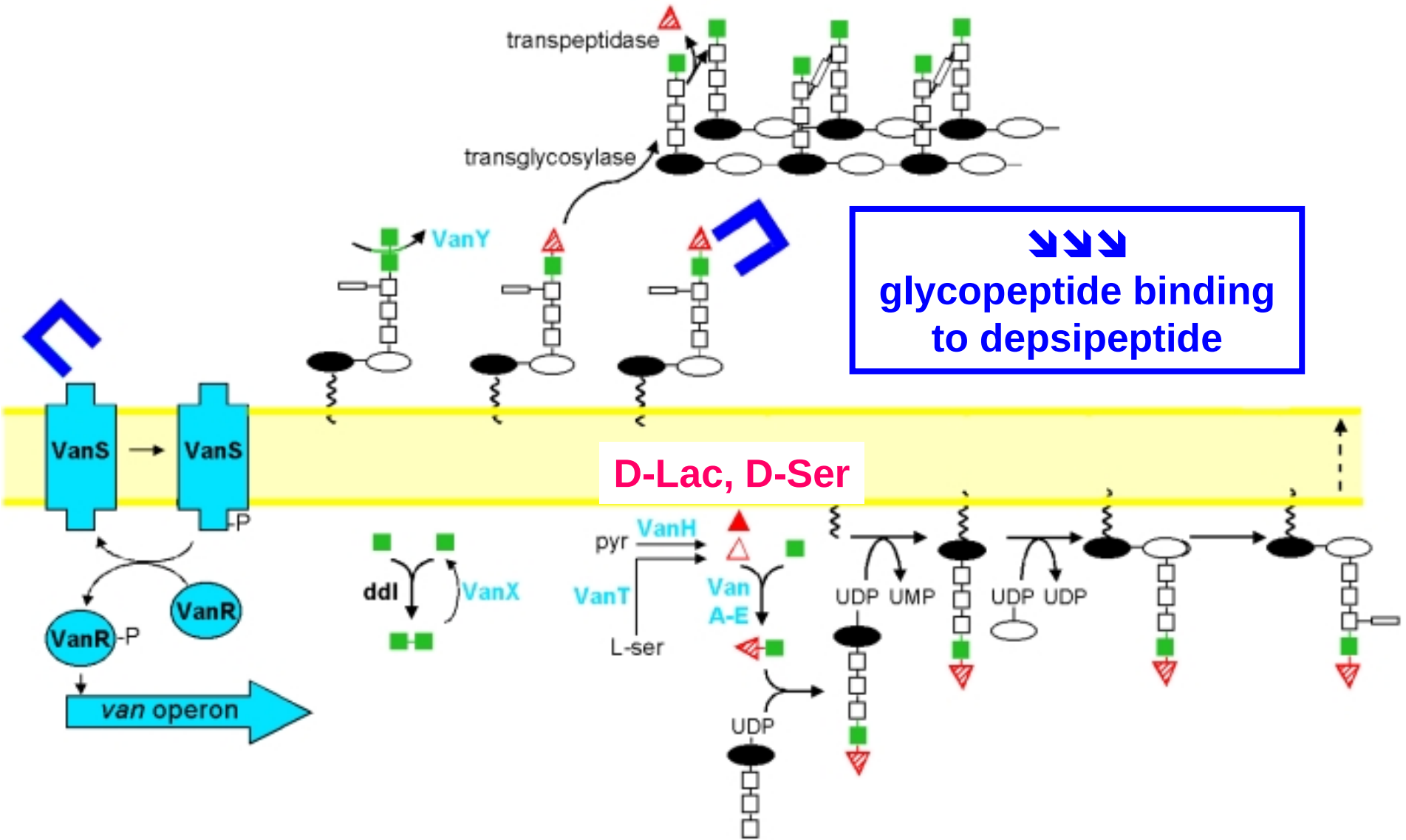
… to resistant

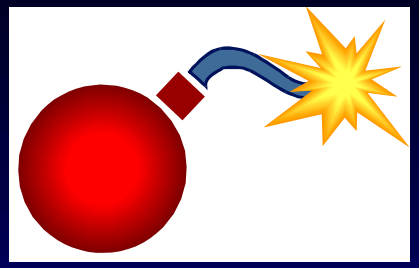


1 hydrogen bound is missing !

Arthur et al, Trends Microbiol (1996) 4:401-407

Resistance in enterococci





Resistance in staphylococci (GISA)

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

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

K. Hiramatsu[a]*, H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

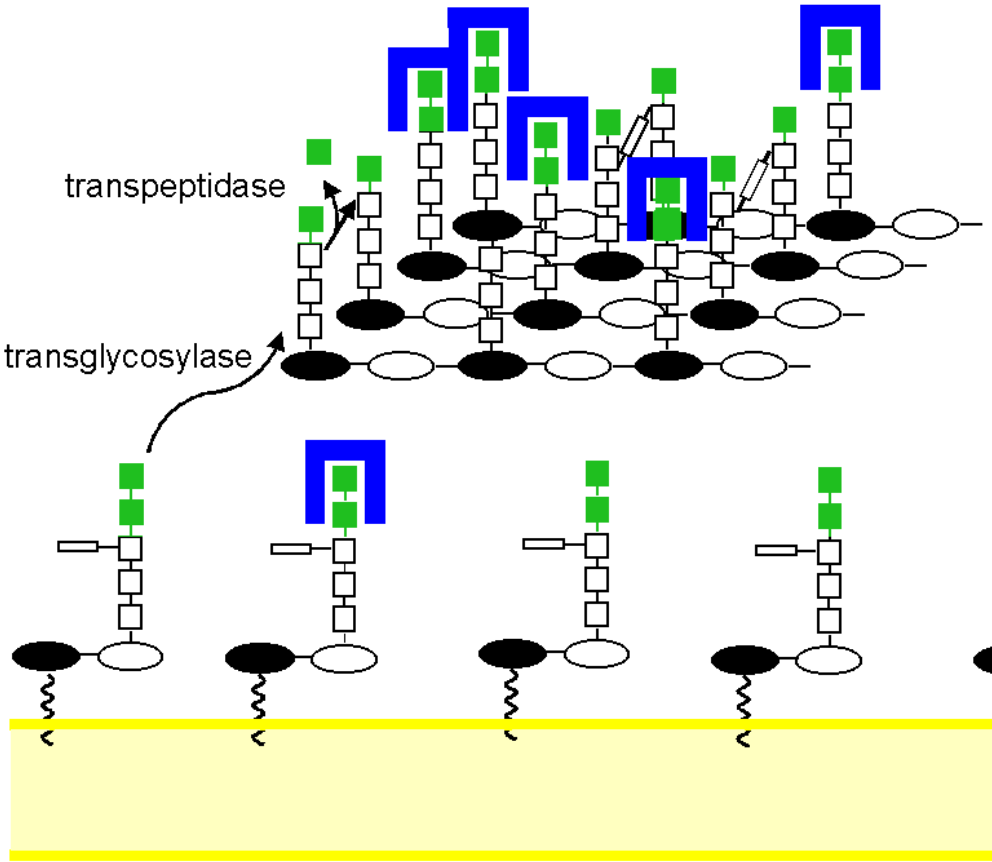
[a]*Department of Bacteriology;* [b]*Department of Pedi - atrics, Juntendo University, Tokyo;* [c]*Clinical Labora - tory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

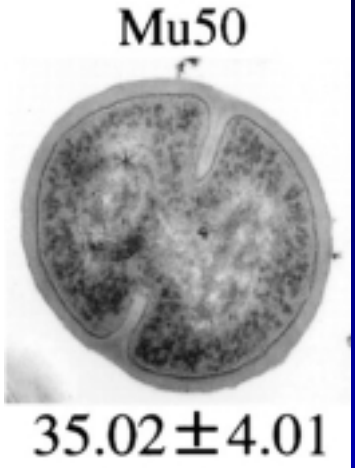
AB	MIC
AMP	64
VAN	8
GEN	128
RIF	2048
LVX	8
TET	128
SMX	0.125
Q-D	0.5
LZD	2

Resistance in staphylococci (GISA)

multiplication of the target !

tickened Cell wall





Hiramatsu Lancet ID (2001) 1:147-155

Cui et al J Clin Microbiol (2003) 41:5-14

Resistance in staphylococci (GRSA)

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ORIGINAL ARTICLE

BRIEF REPORT

◄ Previous Volume 348:1342-1347 April 3, 2003 Number 14 Next ►

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

Soju 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. Rudrik, 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

42nd Annual ICAAC San Diego

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

B. Bozdogan[1], J. Chaitram[2], P. C. Appelbaum[1], C. Whitener[1], F. A. Browne[1], F. C. Tenover[2]

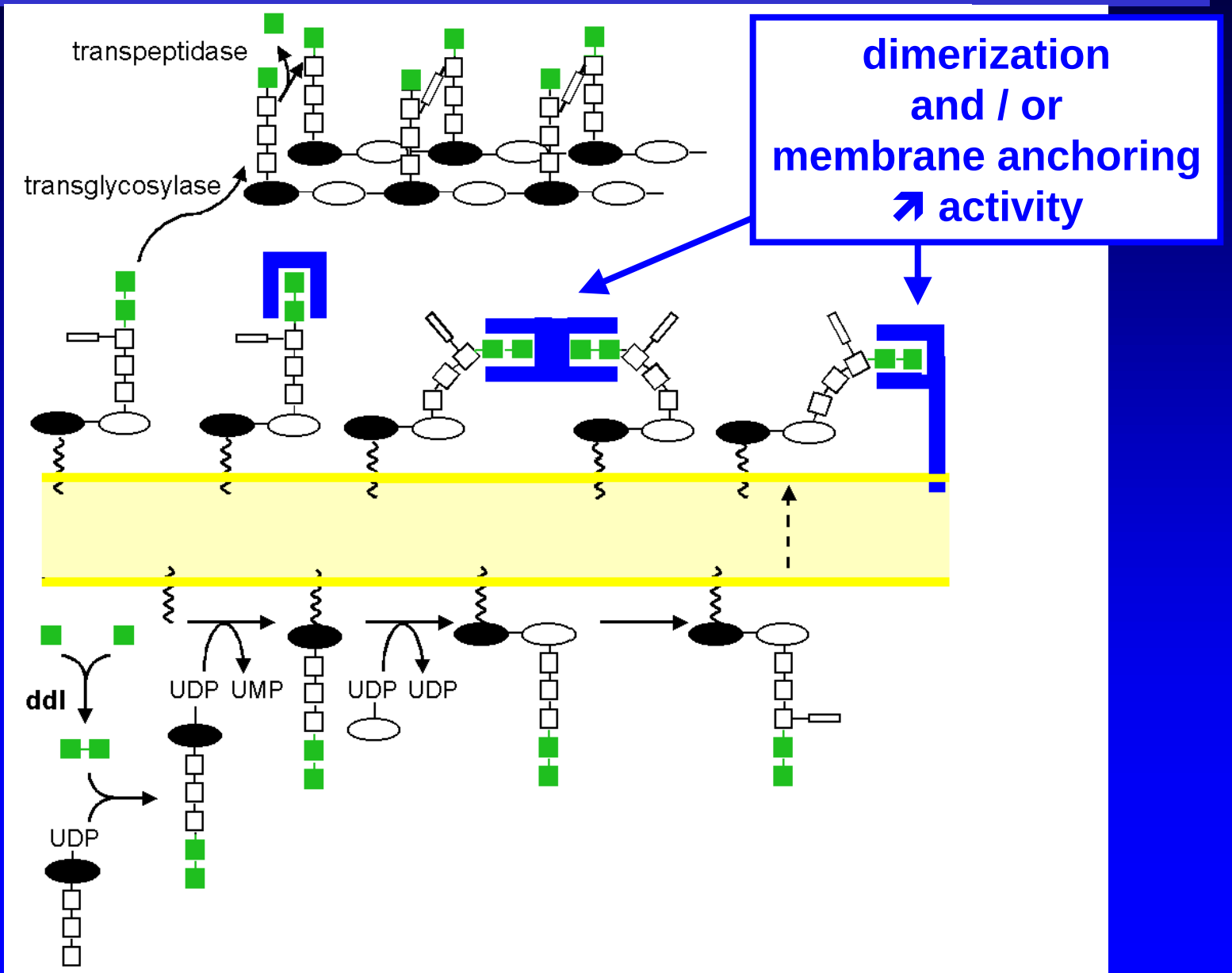
[1]Penn State Hershey Medical Center, Hershey, PA, [2]Centers for Disease Control and Prevention, Atlanta,

AB	MIC
VAN	32
TEC	4

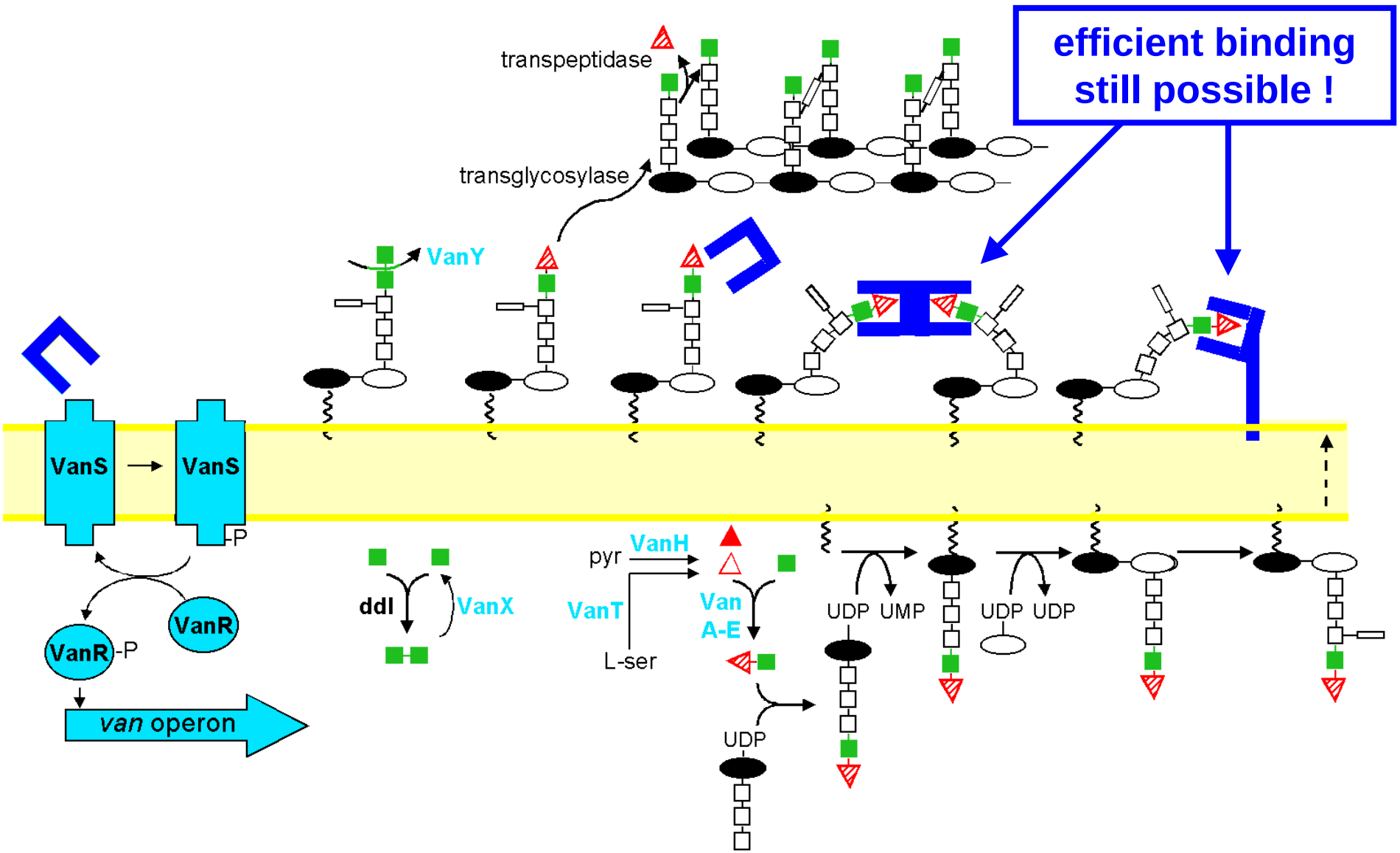
Glycopeptides: what can we improve ?

parameter	vanco - teico	ideal glycopeptide
spectrum	Gram (+) & MRSA but VRE - GISA	Gram (+) & MRSA, GISA, VRE
PD	static or slowly bactericidal	quickly, conc. dependent bactericidal
PK	t ½ short for vanco	t ½ ↗ diffusibility (CNS)
PK/PD	high doses to reach appropriate AUC/MIC & Cmax/MIC	AUC/MIC & Cmax/MIC ↗
safety	(red-man syndrome) oto-& nephrotoxicity	side effects ↘

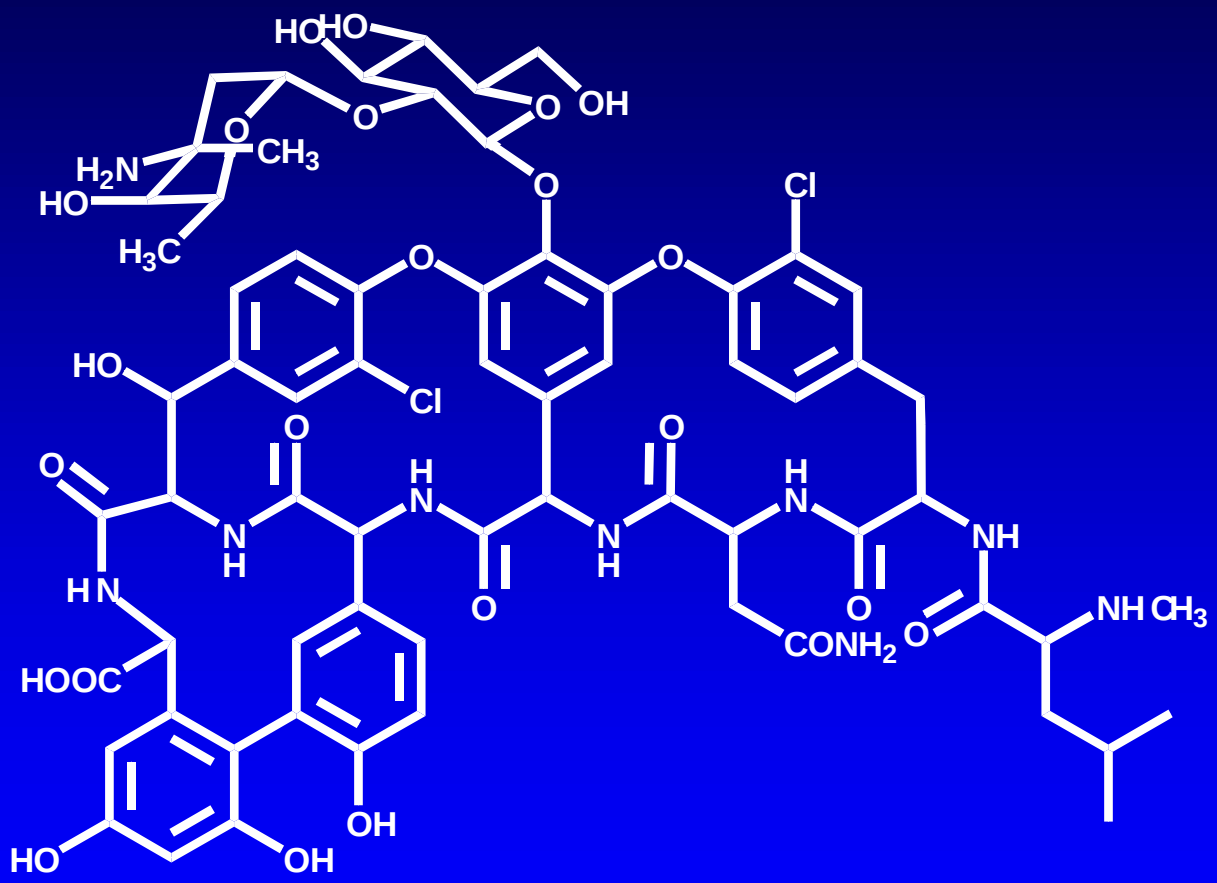
Glycopeptide updated mechanism of action



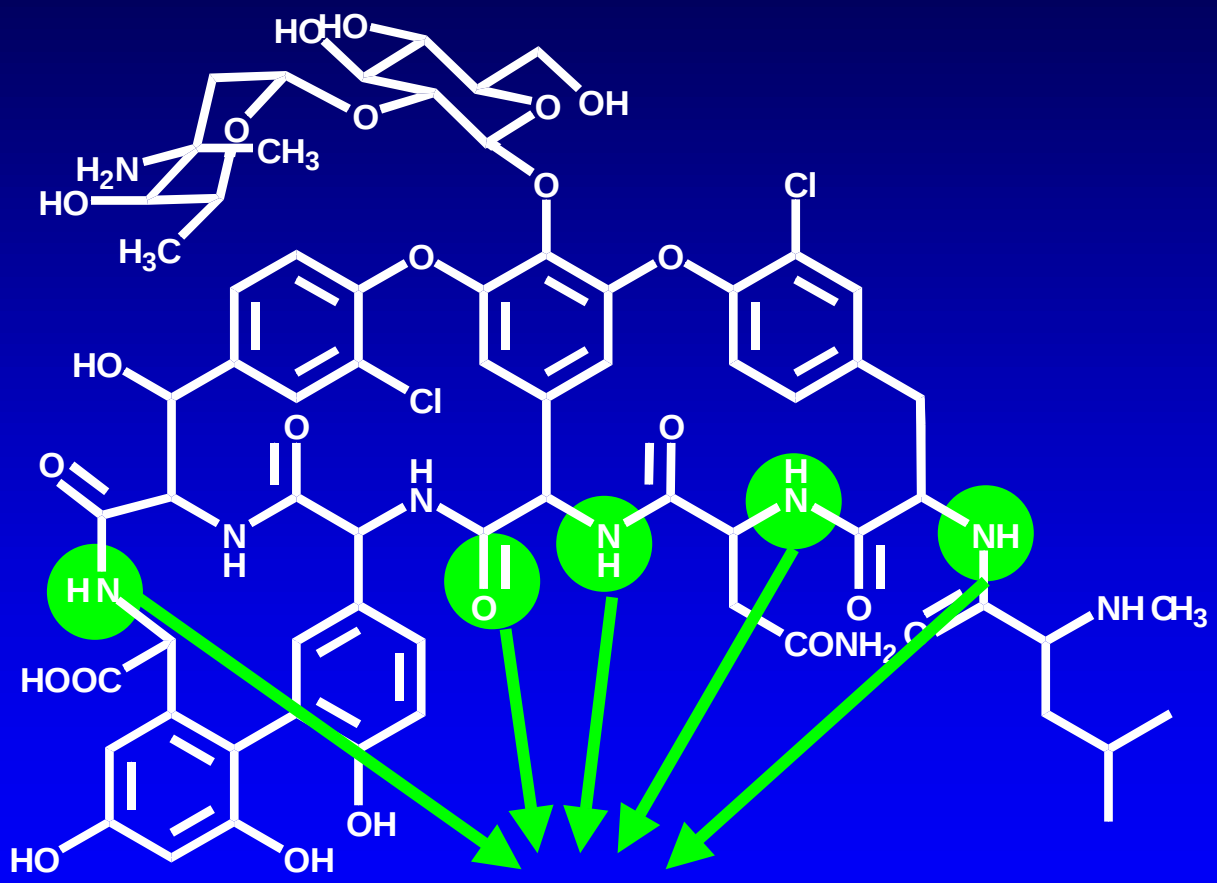
Glycopeptide updated mechanism of action in VRE



Glycopeptides: how can we improve ?

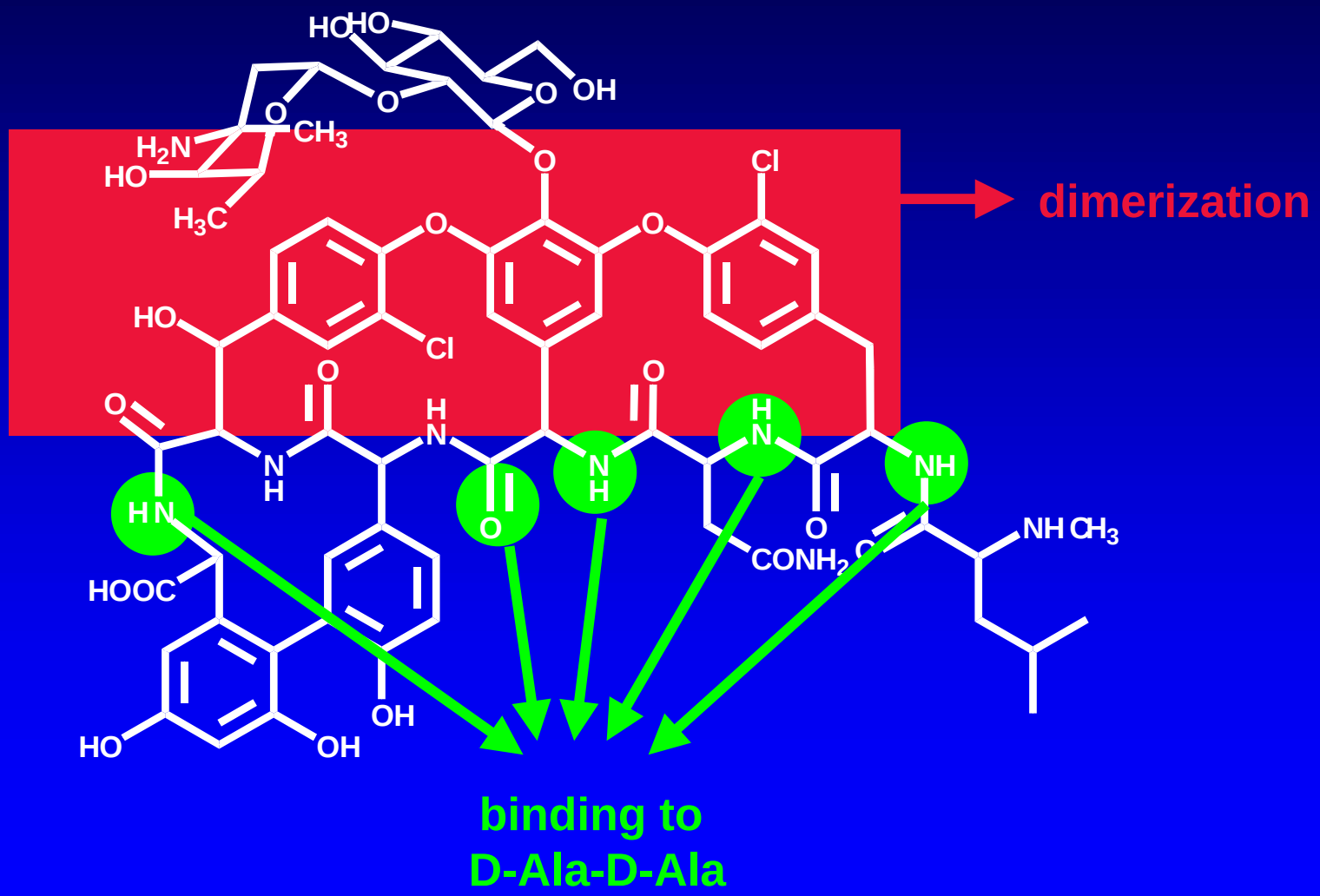


Glycopeptides: how can we improve ?

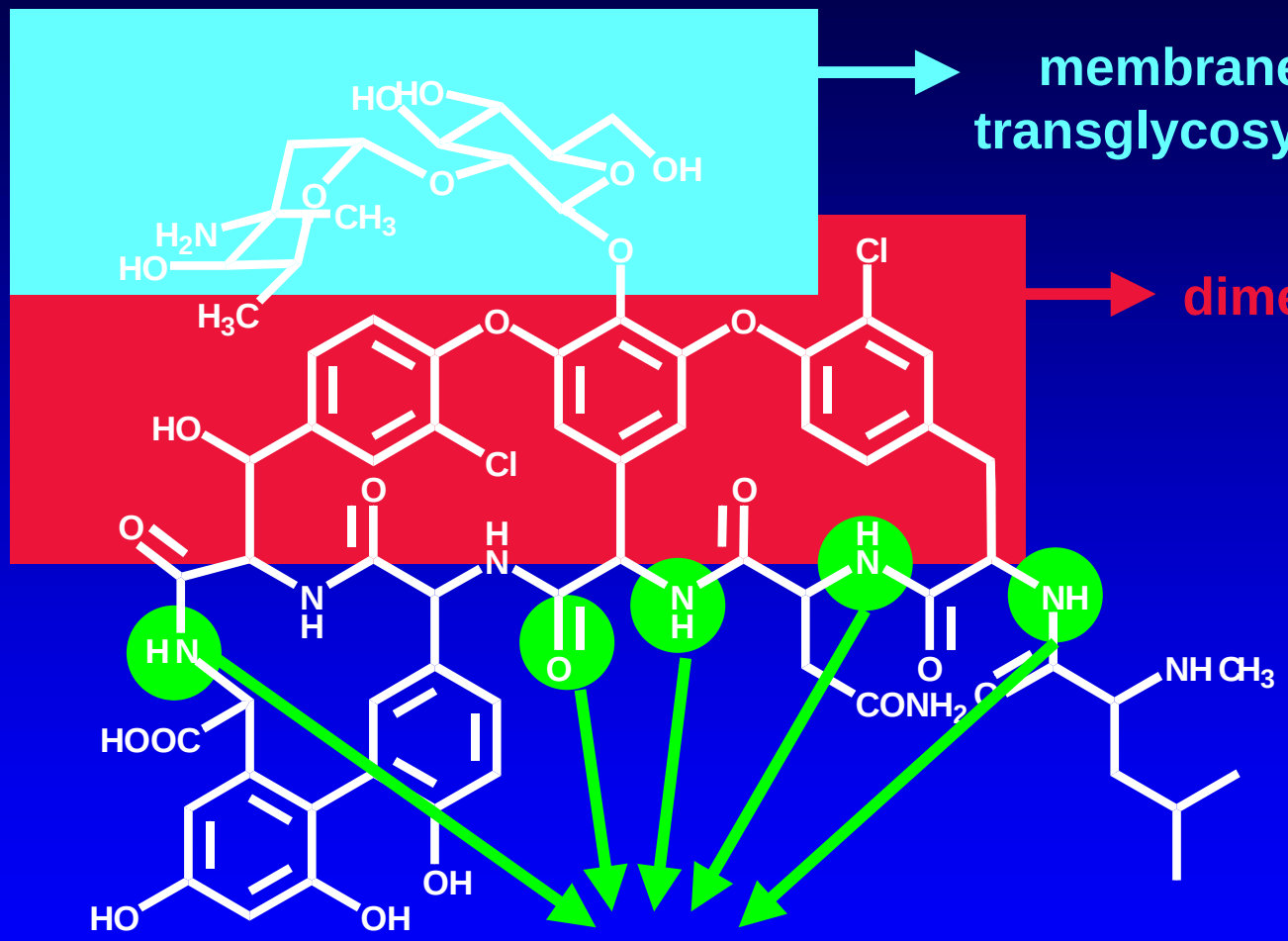


binding to
D-Ala-D-Ala

Glycopeptides: how can we improve ?

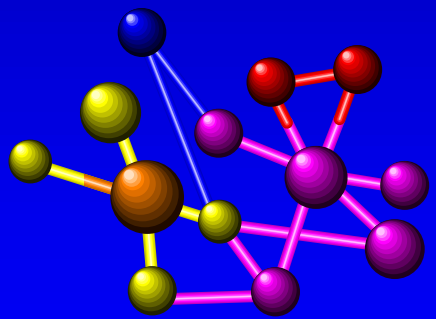


Glycopeptides: how can we improve ?

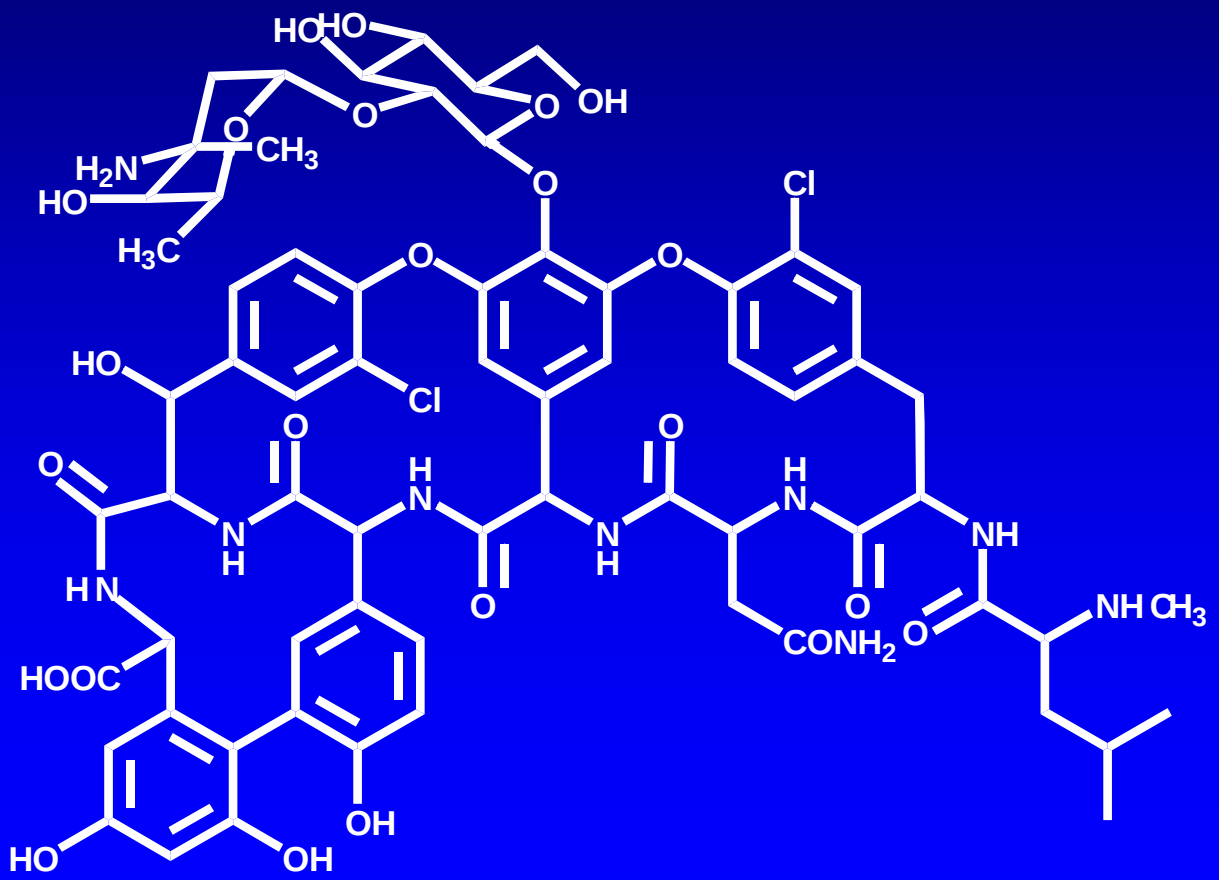


Molecules in clinical development:

DESIGN

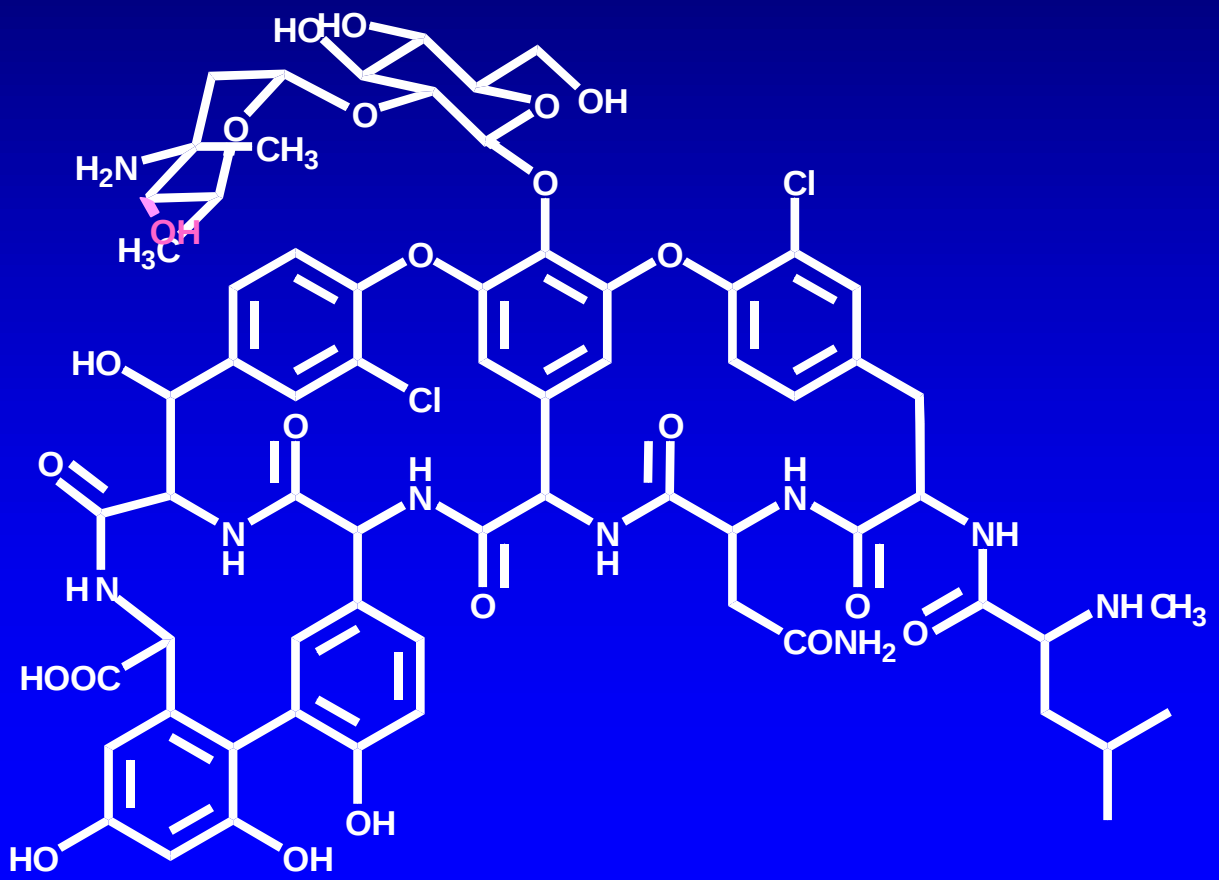


From vancomycin to oritavancin



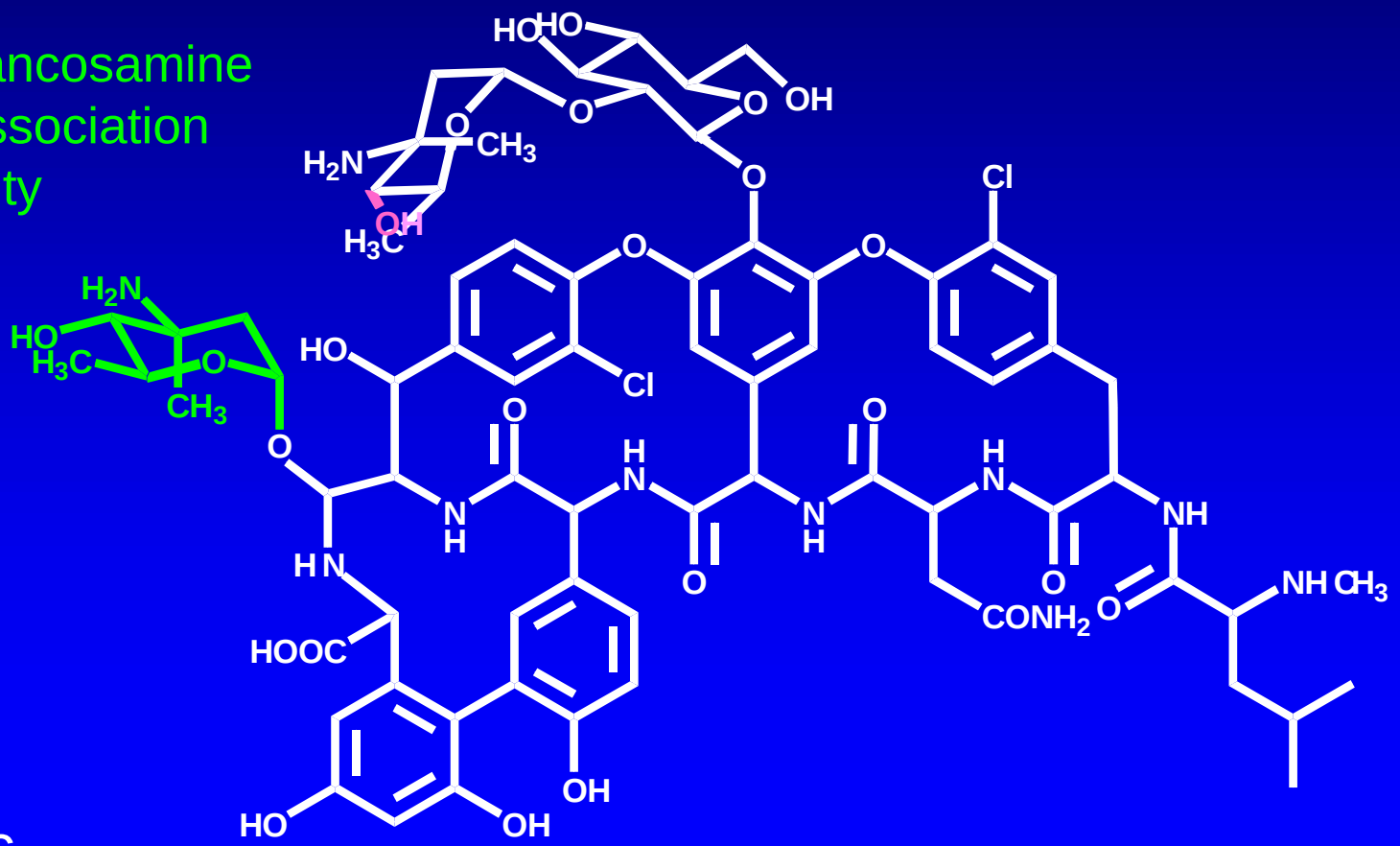
From vancomycin to oritavancin

epi-vancosamine



From vancomycin to oritavancin

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



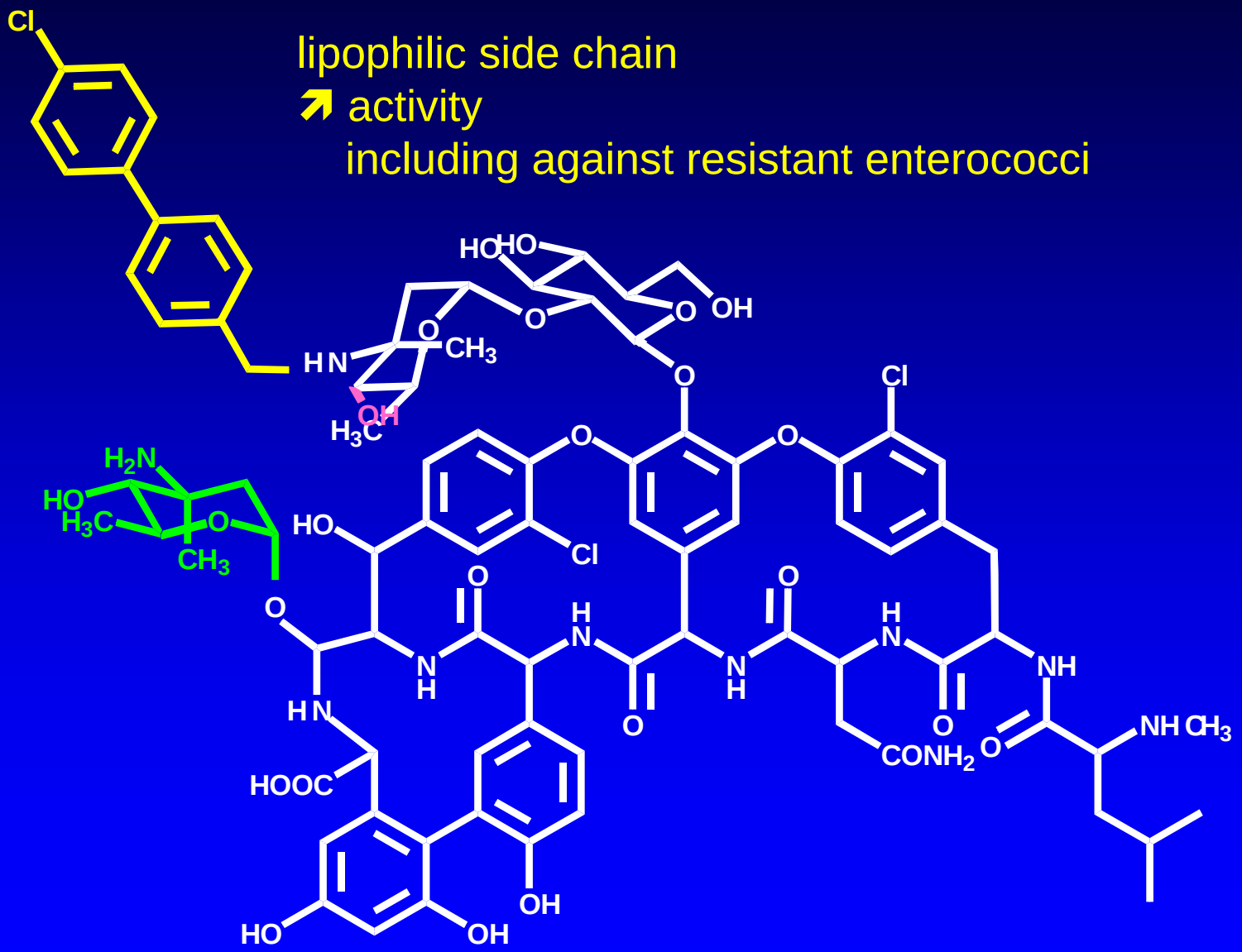
LY264626

From vancomycin to oritavancin

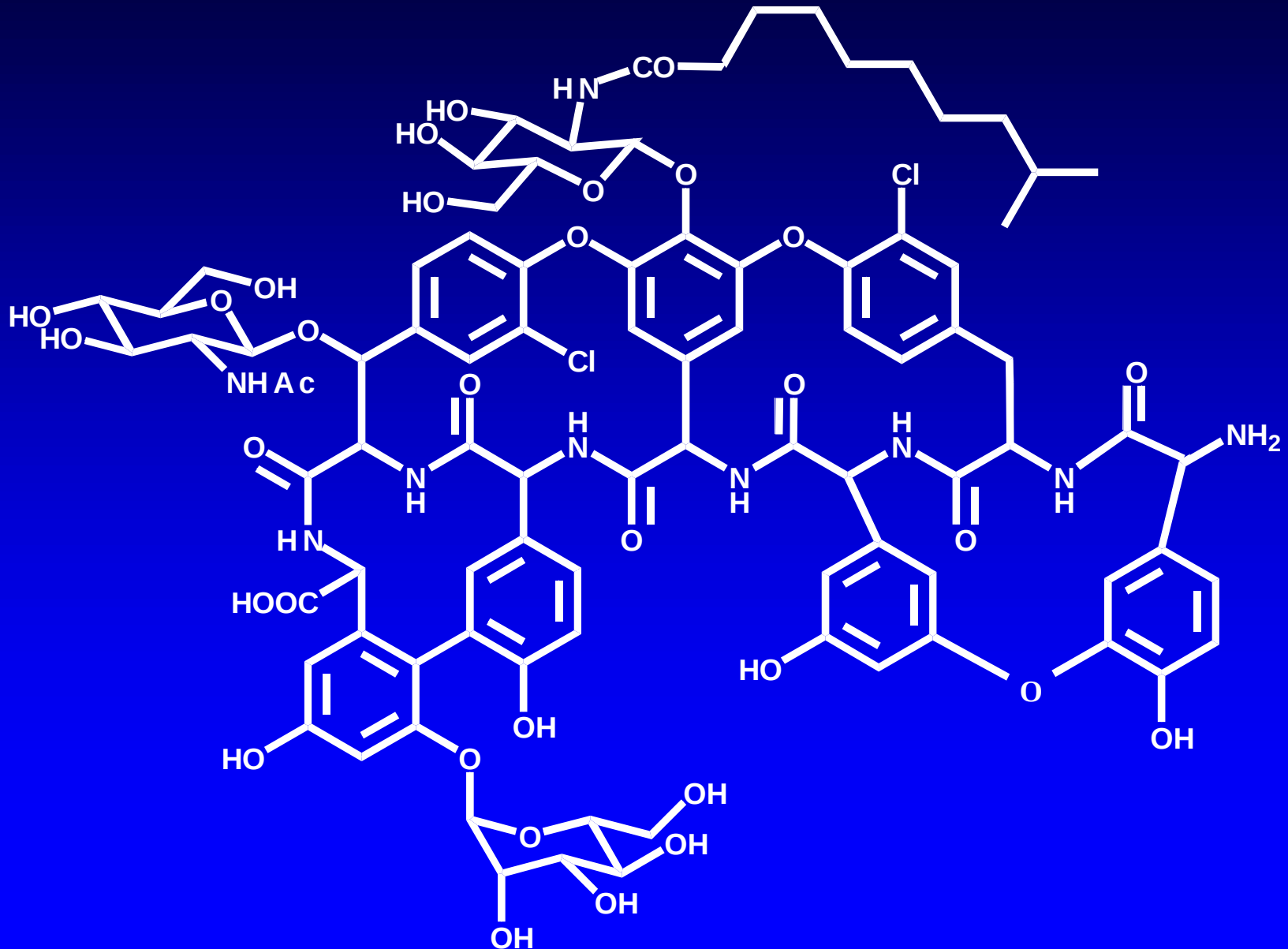
lipophilic side chain

↗ activity

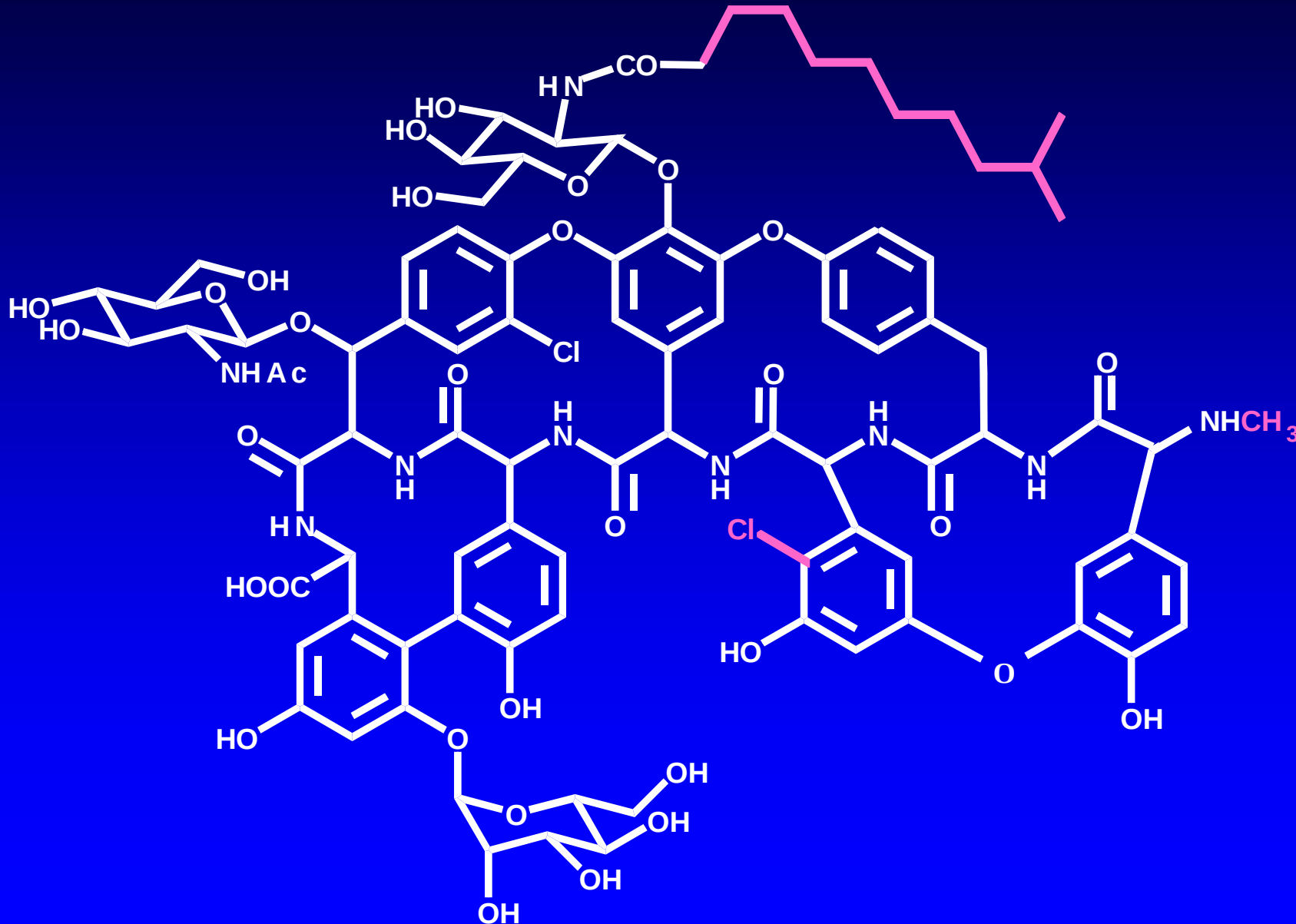
including against resistant enterococci



From teicoplanin to dalbavancin

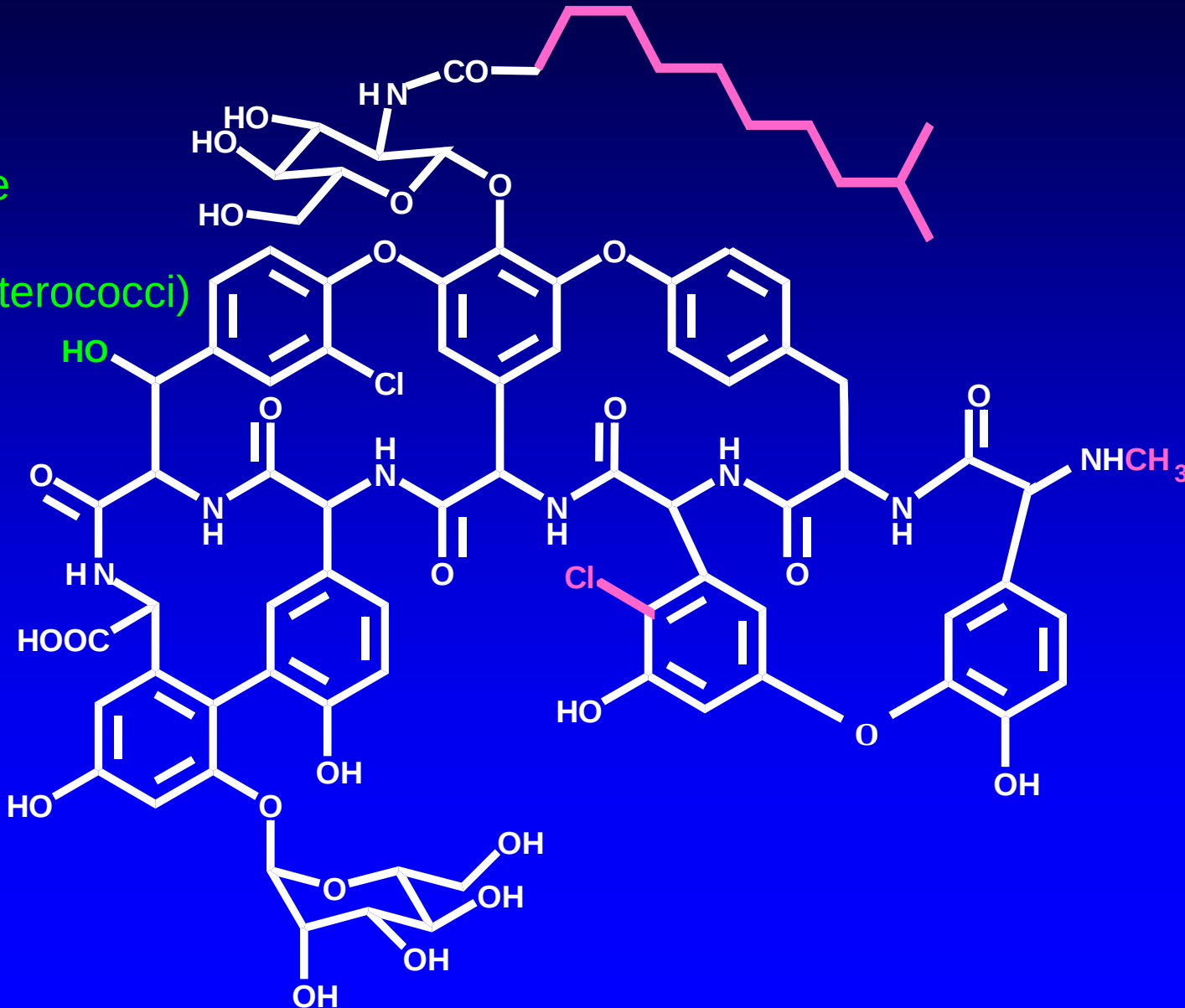


From teicoplanin to dalbavancin



From teicoplanin to dalbavancin

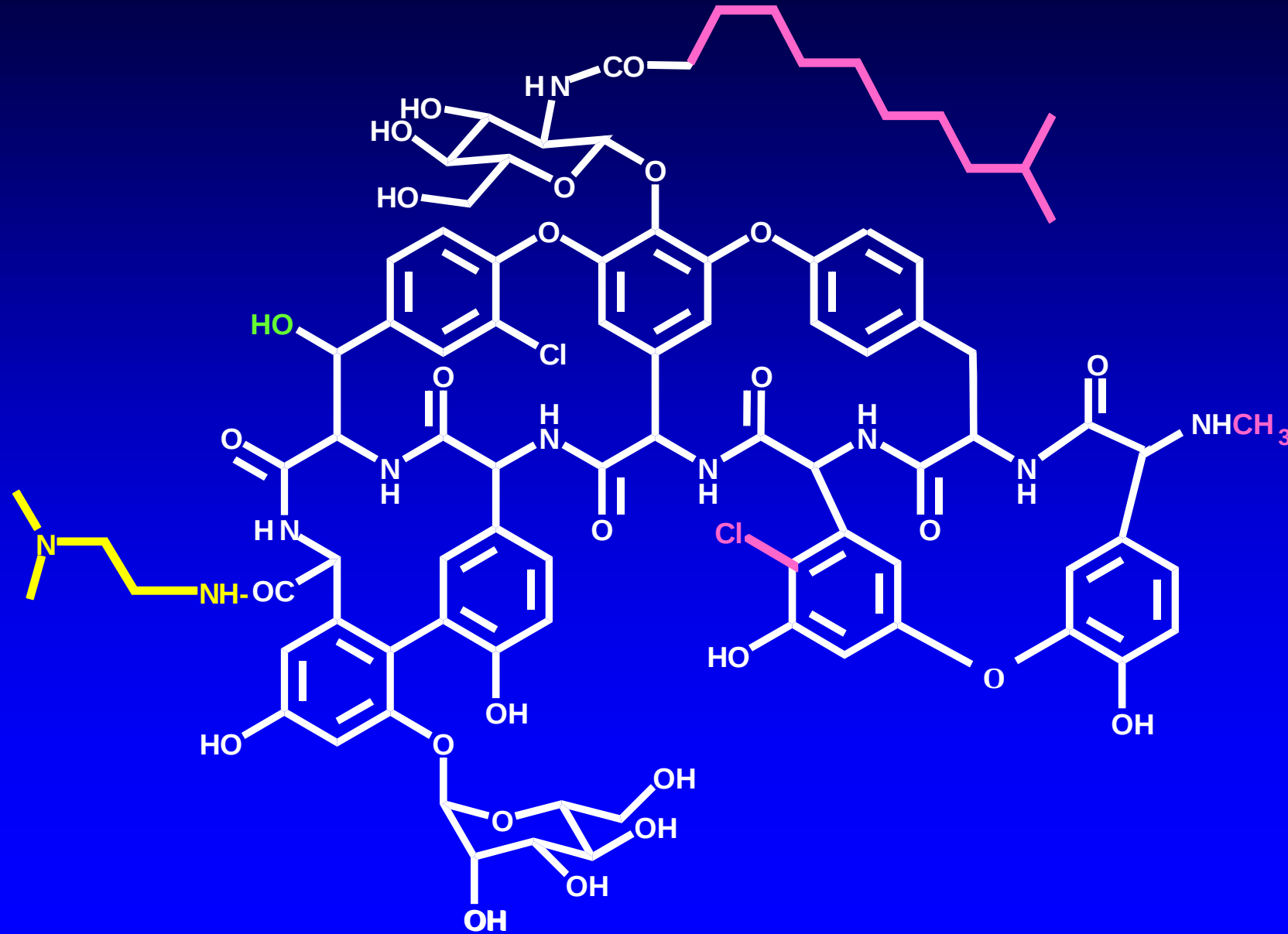
removal of
N-acetylglucosamine
↗ activity
(against resistant enterococci)



A40926

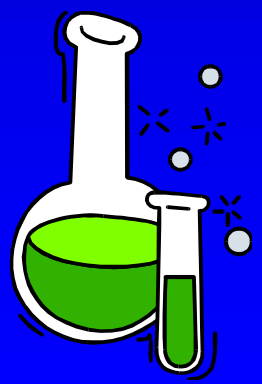
From teicoplanin to dalbavancin

↗ activity



Molecules in clinical development:

IN VITRO DATA
microbiology
pharmacodynamics



Spectrum of activity

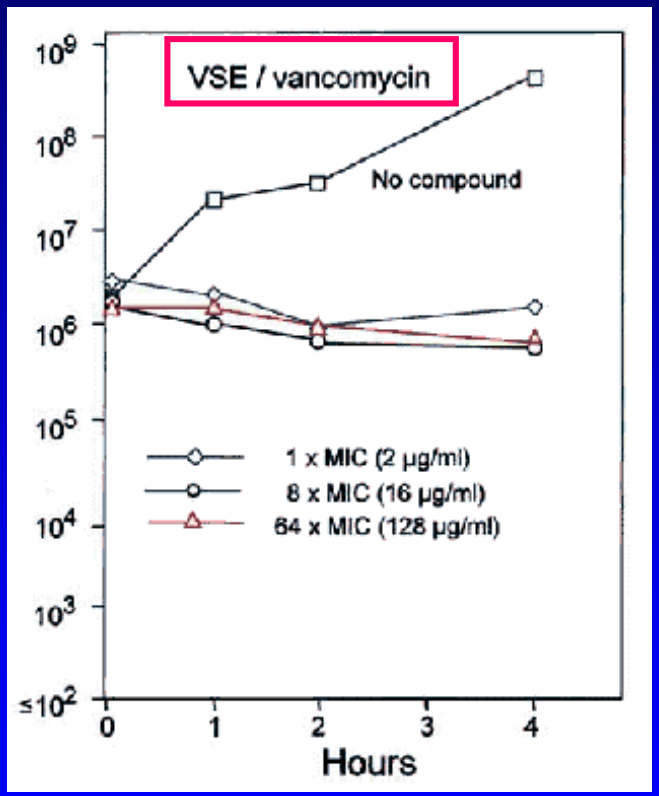
strain	resist.	vanco	orita	teico	dalba
enterococci	susc.	0.25-4	0.06-0.25	0.13-0.5	0.06-0.13
	VanA	>128	0.06-1	64->128	0.5->128
	VanB	8-128	≤ 0.03-0.13	0.13-8	0.02-2
S. aureus	Methi-S	0.13-1	0.13-1	1-8	< 0.03- 0.5
	Methi-R	0.5-4	0.13-4	0.13-8	0.06-1
	VISA	8	1-8	8-32	2
	VRSA	32	0.25	4	
S. epiderm.	Methi-S	0.13-1	0.25-1	0.25-16	≤ 0.03-0.25
	Methi-R	1-4	0.25-4	1-16	≤ 0.03-1
S. pyogenes		0.5-0.5	0.016-0.13	0.008-0.06	≤ 0.002-0.06
S. pneumo	Peni-S	0.13-0.5	≤0.002-0.06	0.008-0.06	0.016-0.13
	Peni-R	0.25-2	≤0.002-0.06	0.016-0.13	0.008-0.13

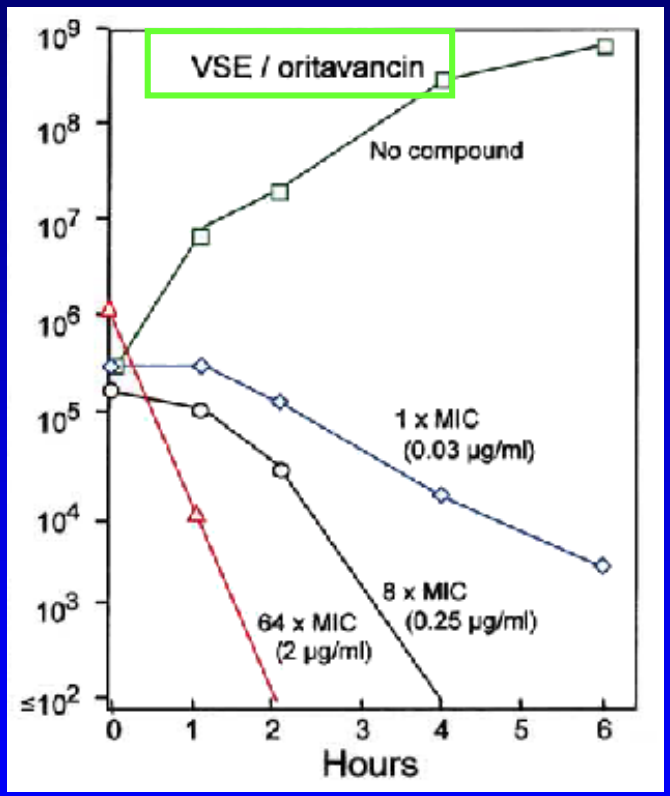
Most of data from Candiani, *et al.* (1999) JAC 44: 179-92

Pharmacodynamic properties of oritavancin

static effect

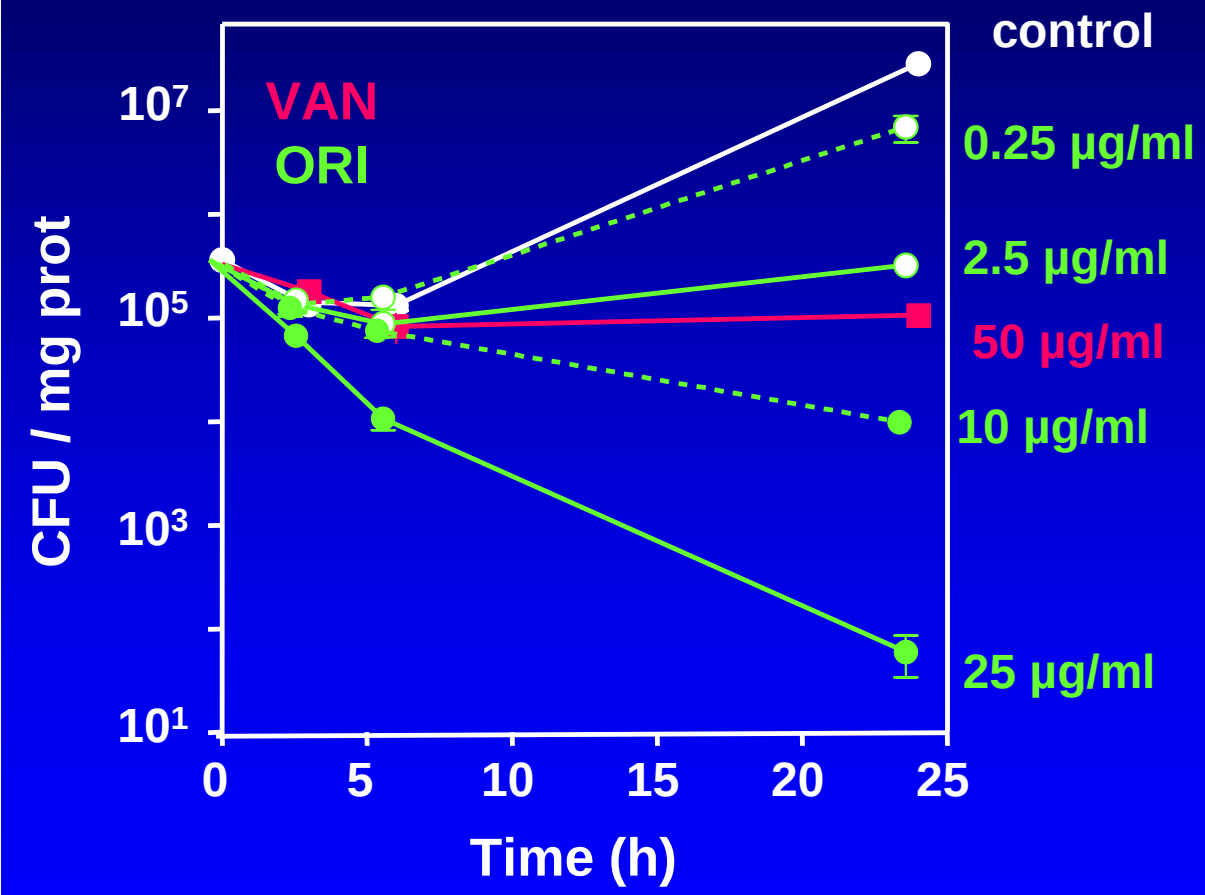
conc. dependent, bactericidal effect

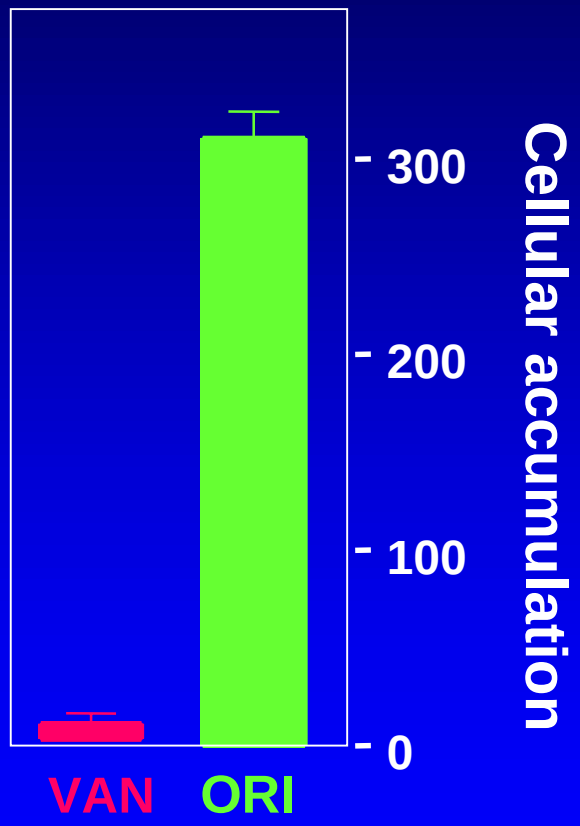




Allen & Nicas, FEMS Microbiology Rev (2003) 26:511-532

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

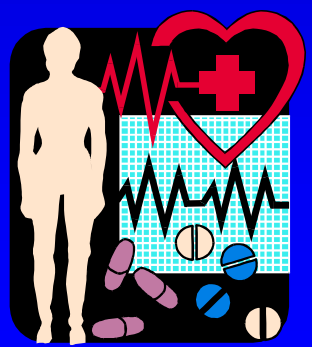




Seral et al AAC (2003) 47 : 2283-2292

Molecules in clinical development:

IN VIVO DATA
pharmacokinetics
pharmacodynamics



Pharmacokinetic properties

parameter	Vanco (15 mg/kg)	Orita (3 mg/kg)	Teico (6 mg/kg)	Dalba (15 mg/kg)
peak (mg/L)	20-50	31	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 %	98 %
terminal t½ (h)	4-8	≤ 360	83-168	257 h

once-a-day administration

once-a-week administration

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

PK/PD profile

PK/PD breakpoints :

parameter	Vanco (15 mg/kg) bid	Orita (3 mg/kg) qd	Teico (6 mg/kg) qd	Dalba (15 mg/kg) qd
AUC / MIC = 125				
total	4	1	4	185
free	2	0.1	0.4	4
Cmax / MIC = 10				
total	10	3	4	30
free	5	0.3	0.4	0.6

MIC of target bugs :

MRSA	0.5-4	0.13-4	0.13-8	0.06-1
VISA	8	1-8	8-32	2
VRE	>128	0.06-1	64->128	0.5->128

Safety profile

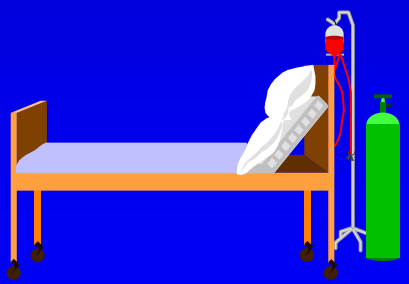
preclinical studies
preliminary data from Phase I and Phase II

oritavancin and dalbavancin
well tolerated

but more patients are needed …

Molecules in clinical development:

IN VIVO DATA clinical studies



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 3-7days **followed by oral cephalexin 10-14 days**		**Oritavancin 1.5-3 mg/kg qd 3-7 days**
SUCCESS :			
bacteriological	**76 %**	=	**74 %**
clinical	**80 %**		**76 %**
with MRSA	**80 %**		**74 %**

Wasilewski et al 41st ICAAC (2001)

Clinical experience

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

(phase II; controlled, randomized)

42 pts

	Vancomycin, ceftriaxone, cefazolin or clindamycin for 7-21 days	Dalbavancin 15 mg/kg day 1 + 7.5 mg/kg day 8
SUCCESS :		
bacteriological	**64 %**	**73 %**
clinical	**76 %**	**94 %**

Selzer et al 13th ECCMID (2003)

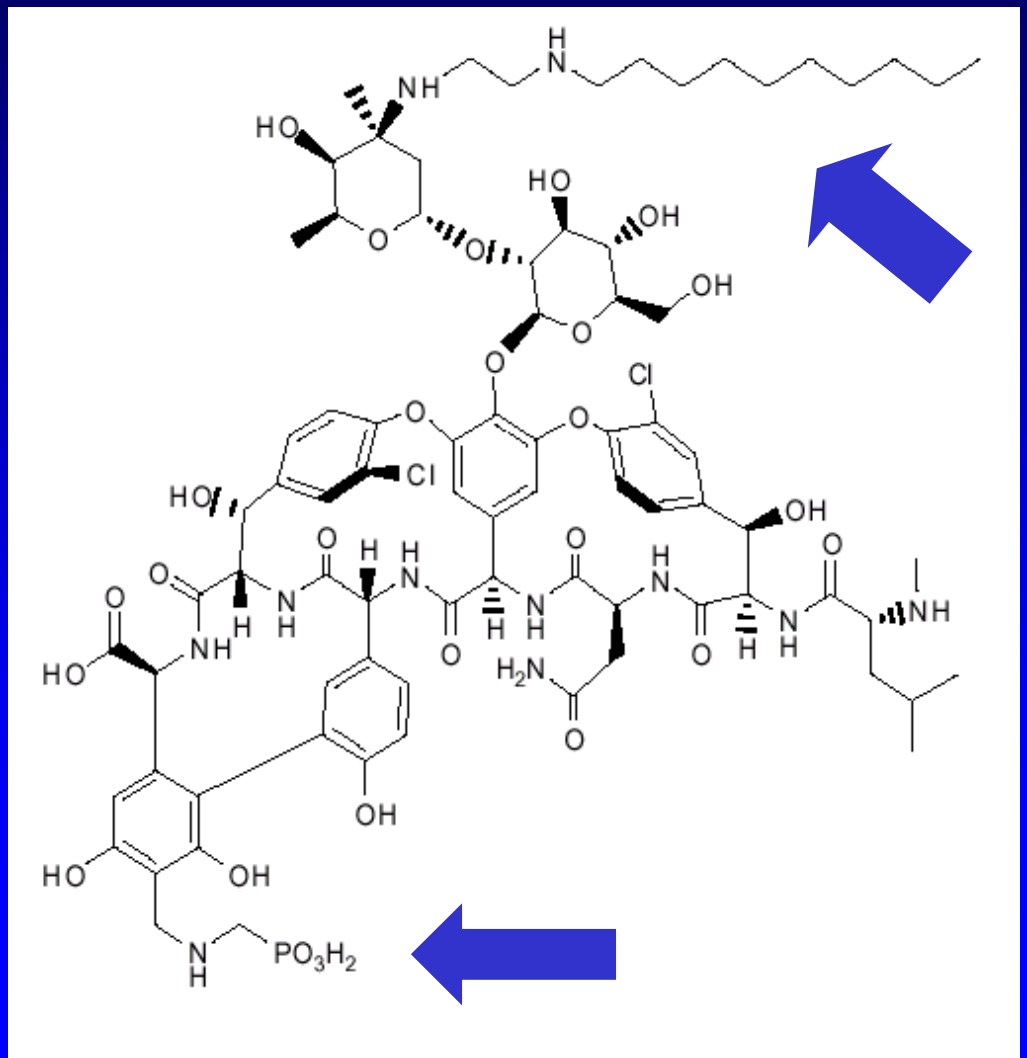
In which indications could they be useful ?

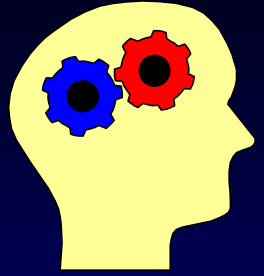
- **which organisms ?**
  - **MRSA** — **certainly YES**
  - **VRE** — **oritavancin only**
  - **VISA** — **limited activity,**
    … but synergy for dalba + β-lactam
  - **S. pneumo** — **other alternatives**

- **which organs ?**
  - **severe skin and soft tissues**
  - **septicemia / deep organs**
  - **endocarditis (combination ?)**
  - **CNS infections (penetration ?)**

Research is still active …

TD-6424





Research is still active …

43rd Annual ICAAC chicago

TD-6424

- **in vitro data:** MIC MRSA 1 µg/ml
MIC VISA 4 µg/ml
- **antibacterial activity:** bactericidal
inhibitor of lipid synthesis
- **activity in animal models** endocarditis
subcutaneous infections
- **Phase I studies** t ½ ~ 8 h → once-a-day

We are looking forward these new antibiotics …

… but how strong will they be ?