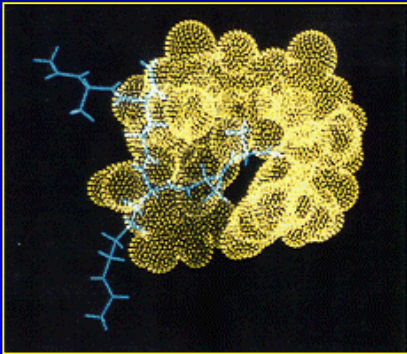


GLYCOPEPTIDE ANTIBIOTICS

from Old Mississippi mud ...



... to molecular mechanisms:

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



Problem:

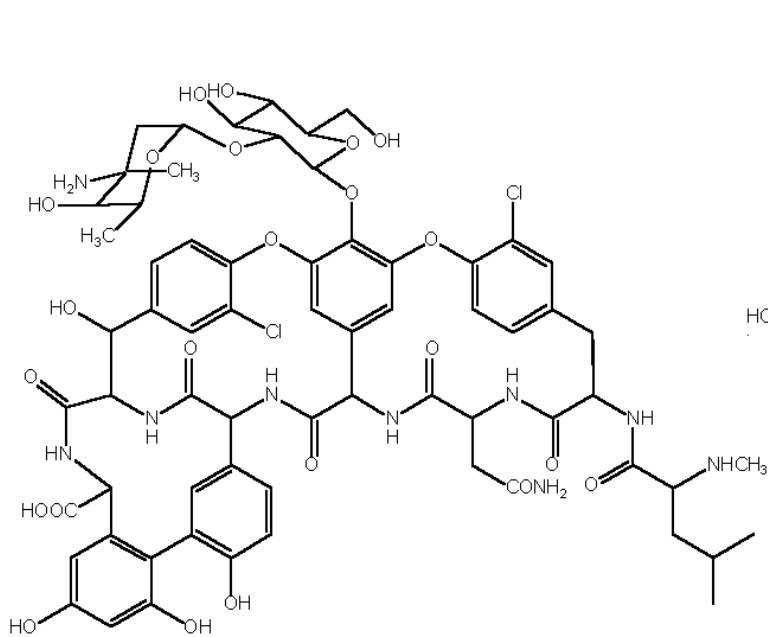
- **toxicity of vancomycin due to impurities**
➔ **better purification procedures**

~ 1980 :

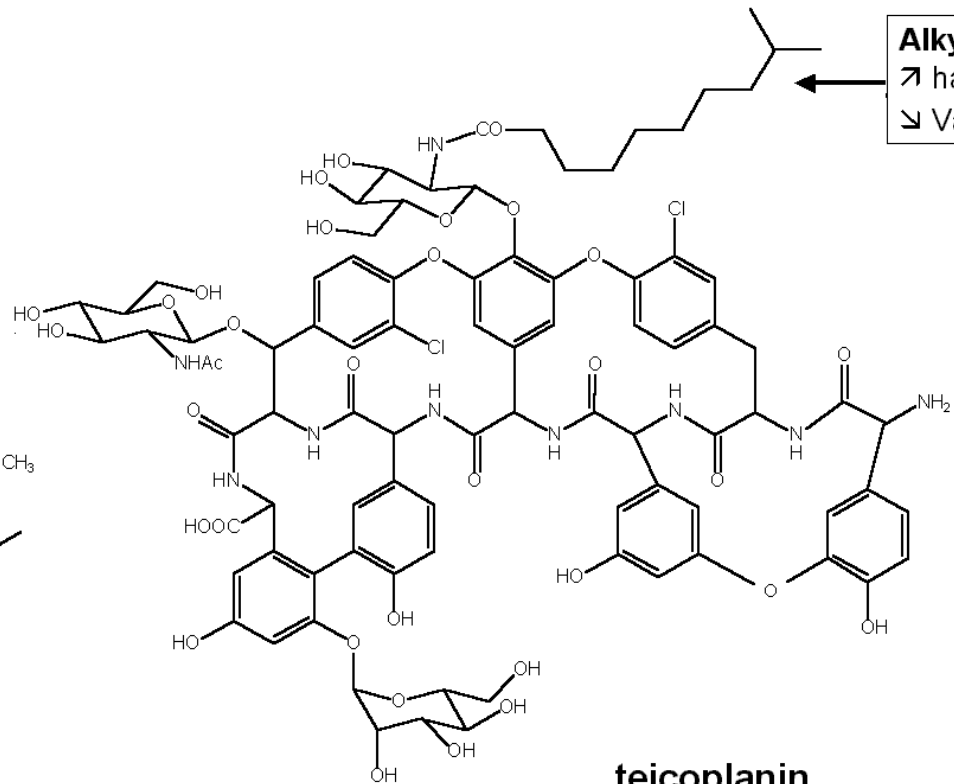
discovery of teicoplanin, as a natural GP with improved PK

- **largely used in Europe**

vancomycin - téicoplanine



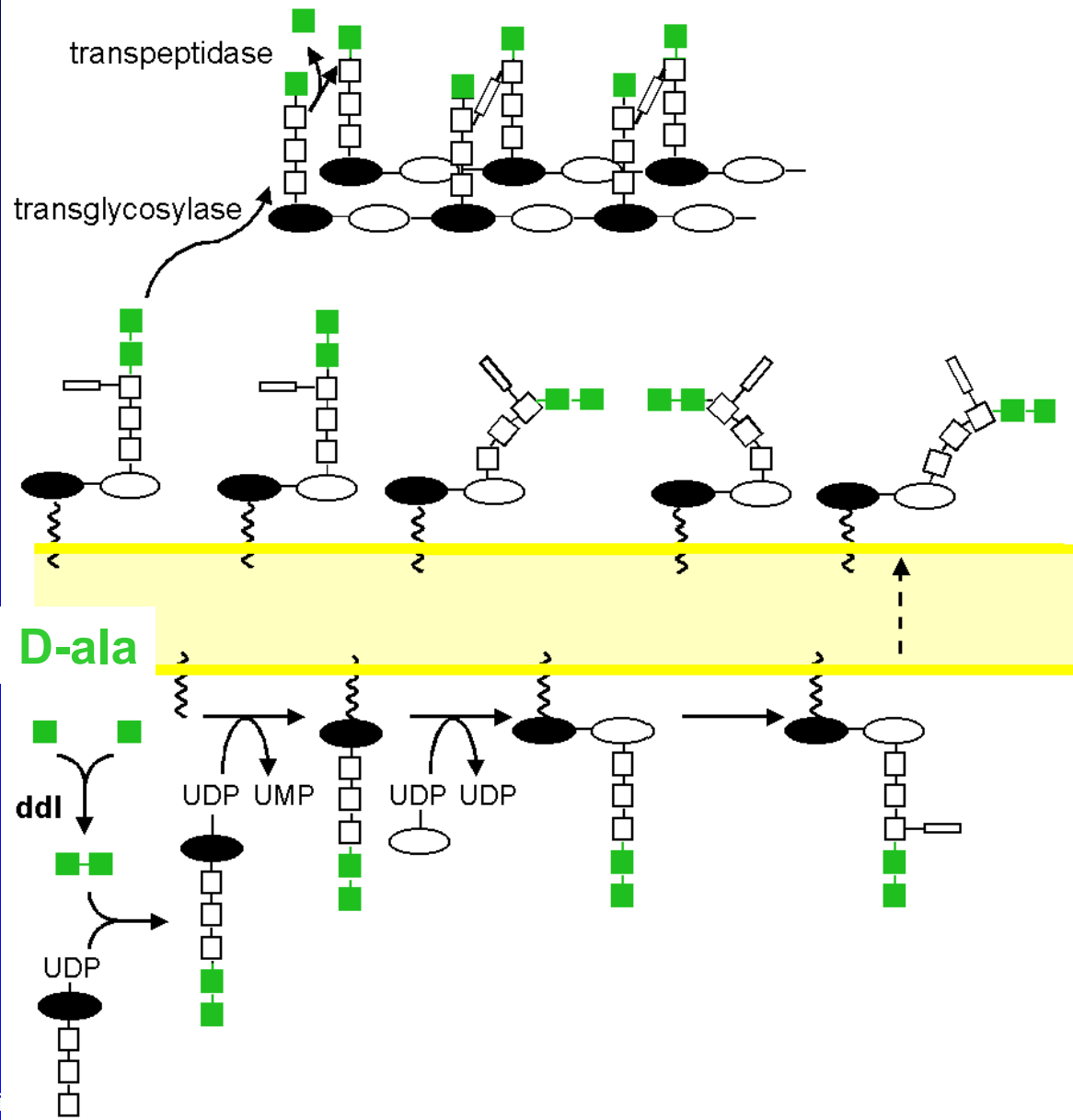
vancomycin



teicoplanin

Alkyl:
↗ half-life
↘ VanB induction

Peptidoglycan synthesis



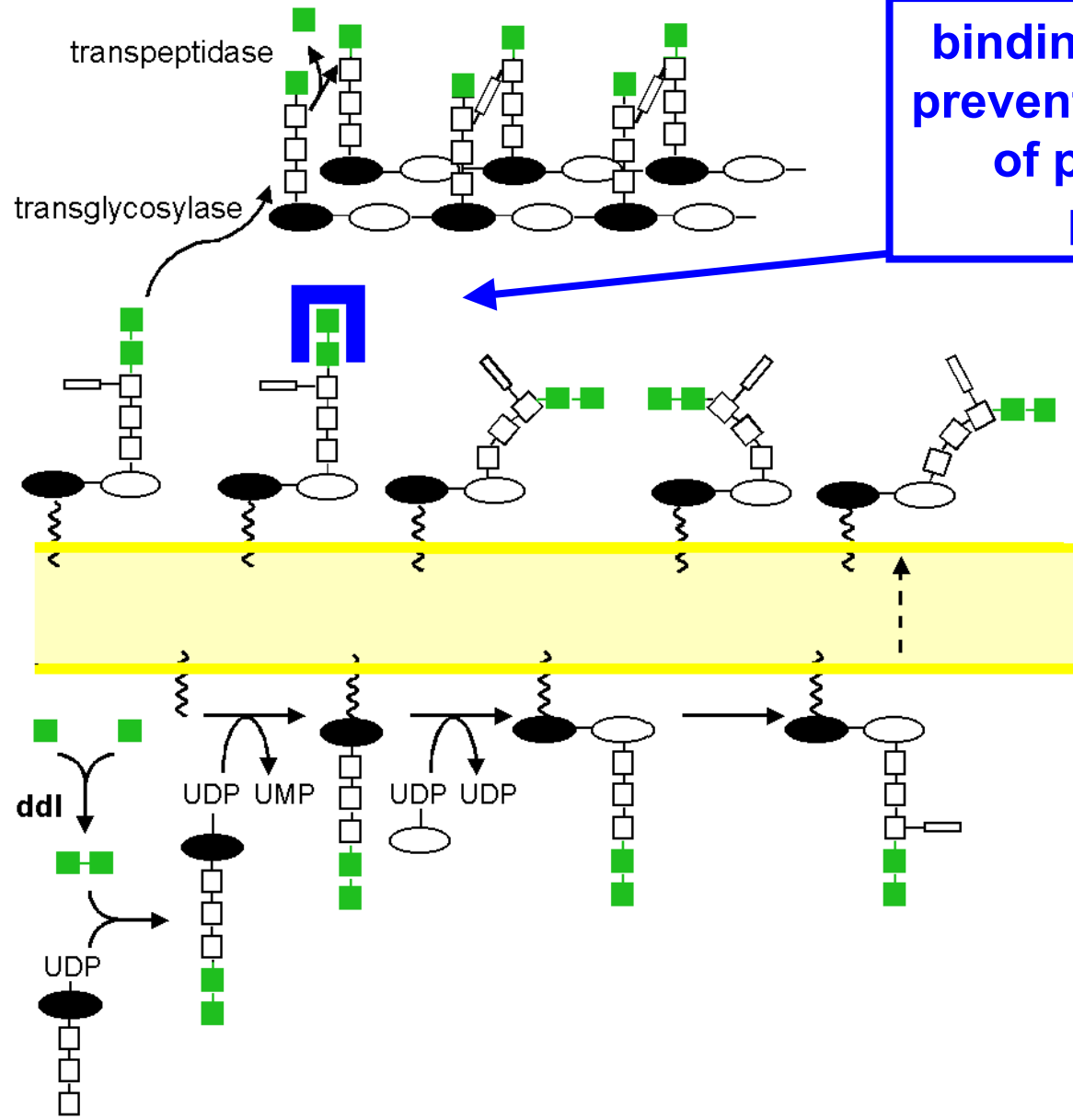
ation

cell wall

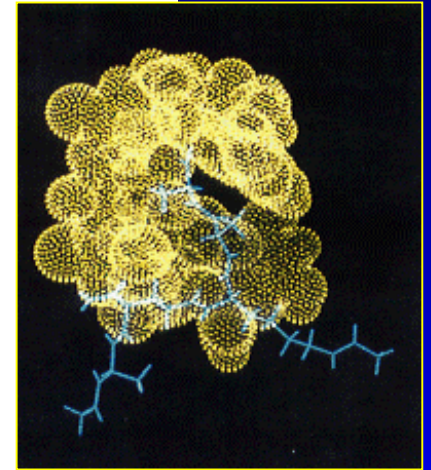
cytosol

rsor
iesis

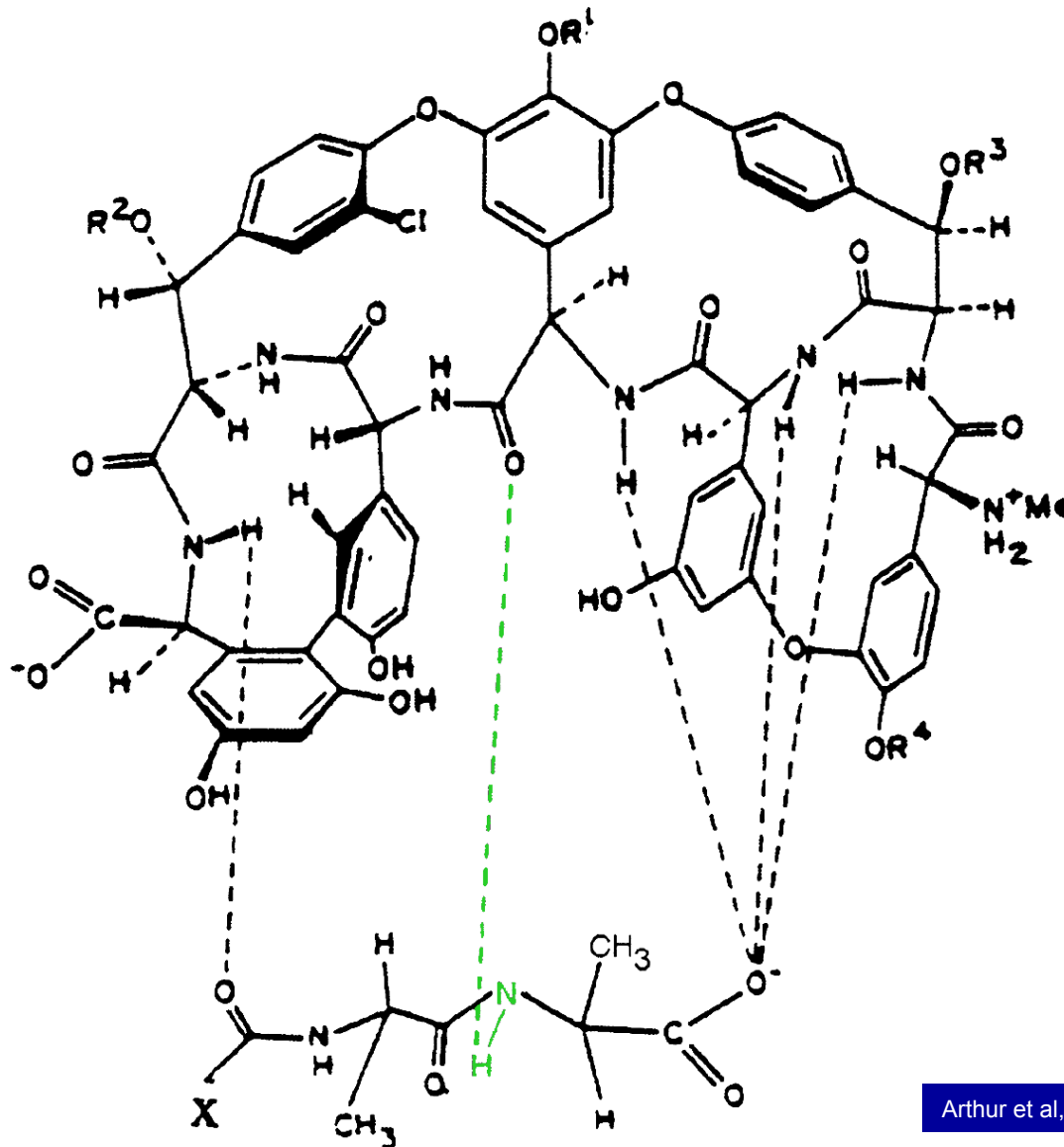
Glycopeptide mechanism of action



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

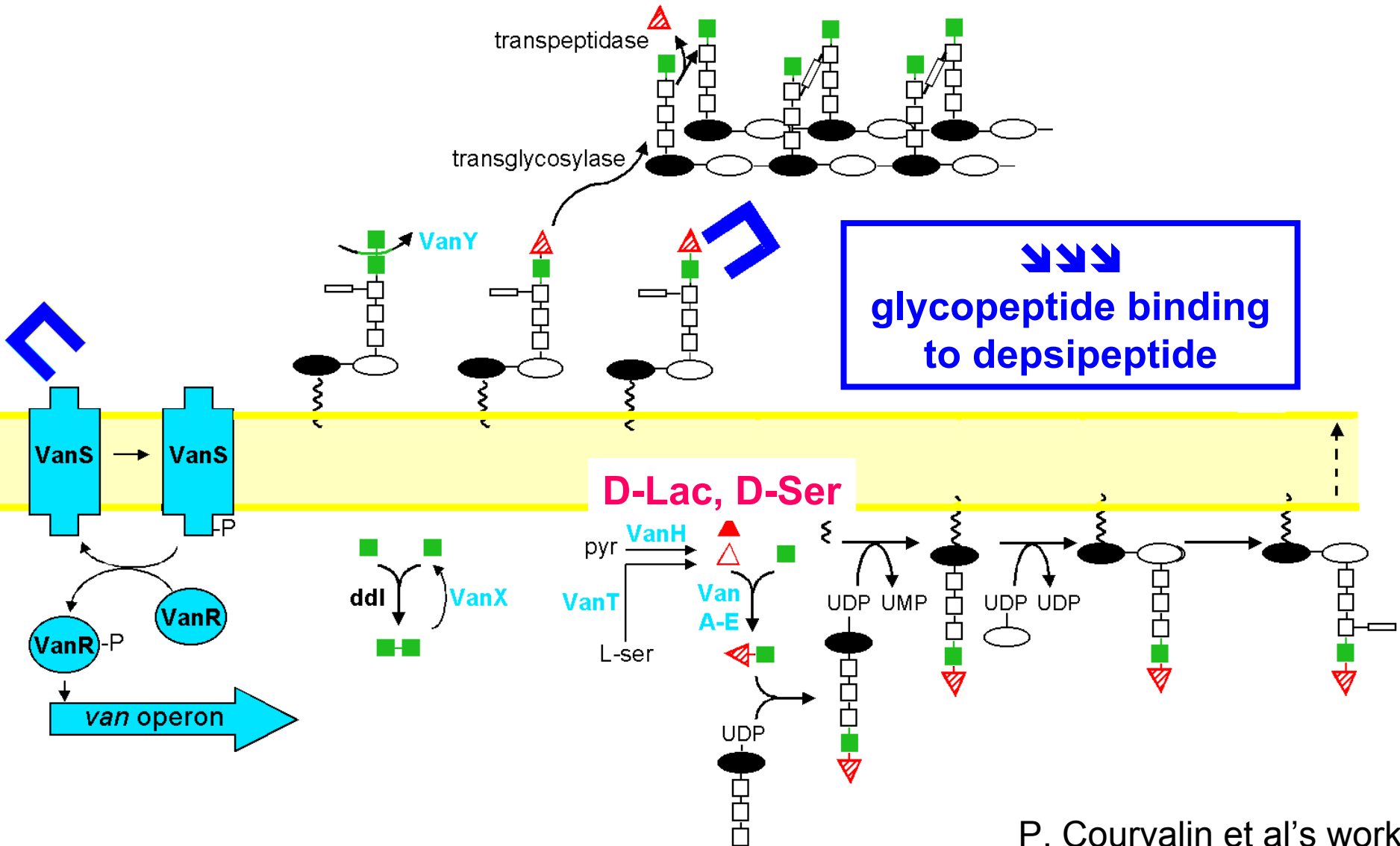


Binding of vancomycin to D-Ala-D-Ala



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

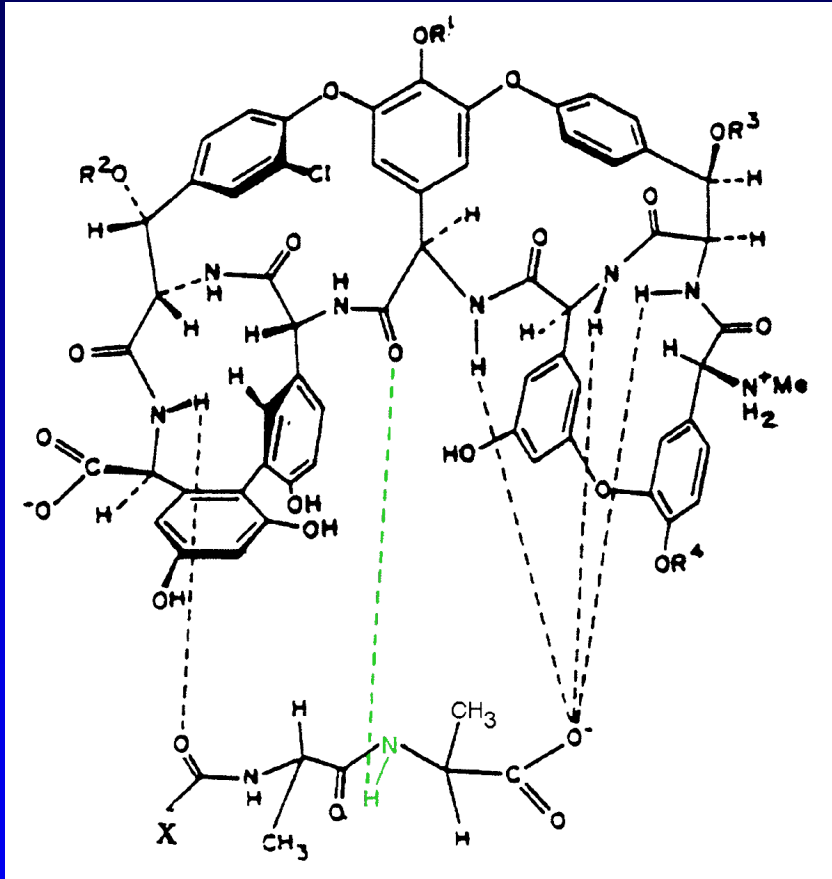
Resistance in enterococci



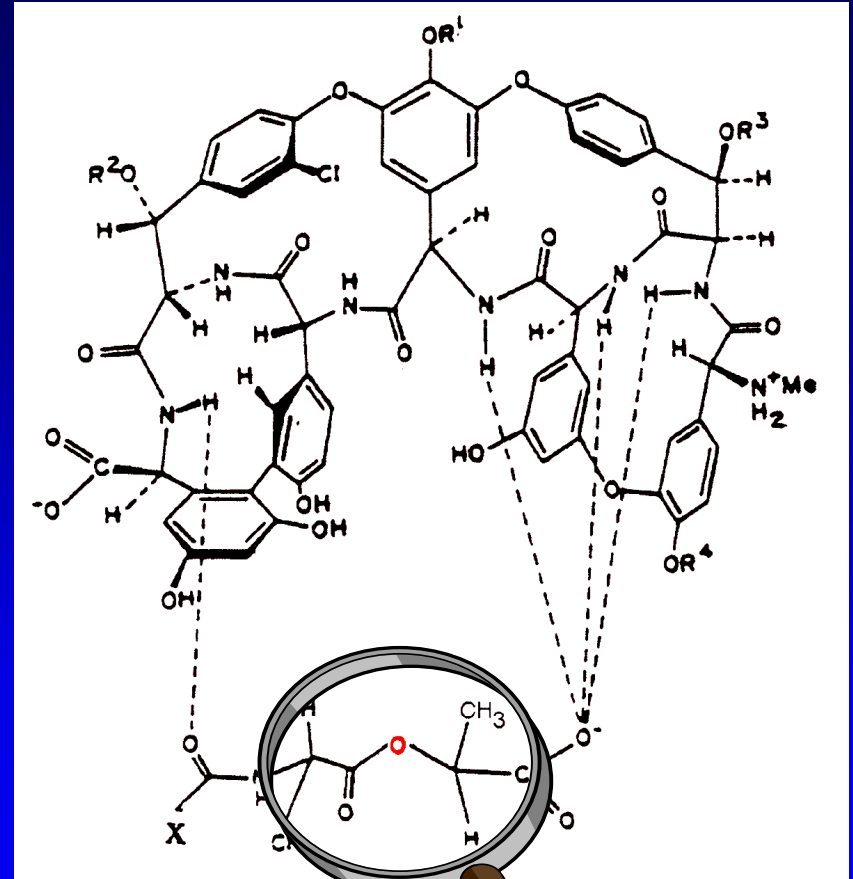
P. Courvalin et al's work

Resistance in enterococci

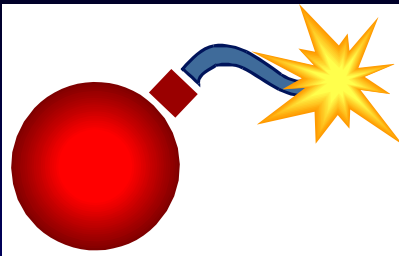
from susceptible ...



... 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^{a*}, H. Hanaki^a, T. Ino^b, K. Yabuta^b,
T. Oguri^c and F. C. Tenover^d

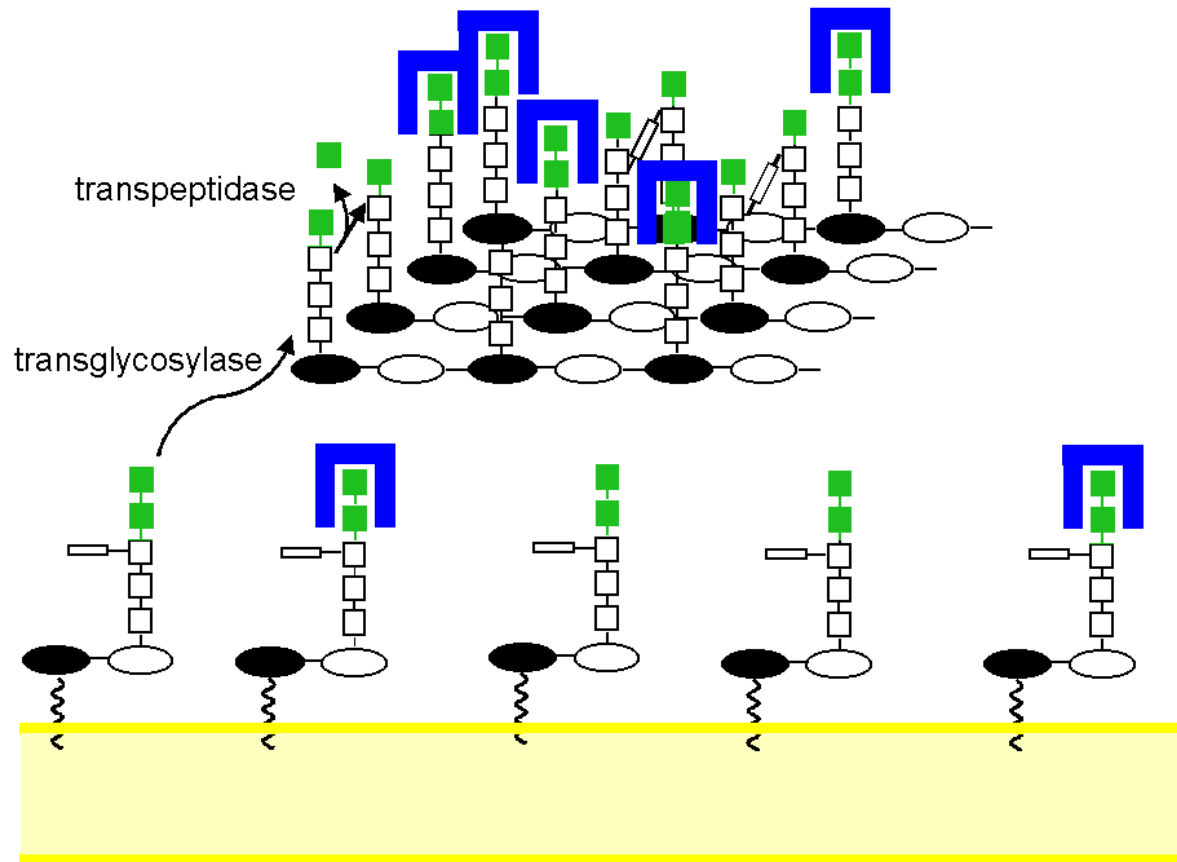
^aDepartment of Bacteriology; ^bDepartment of Pediatrics, Juntendo University, Tokyo; ^cClinical Laboratory, Juntendo Hospital, Tokyo, Japan; ^dNosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

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



Mu50



35.02 ± 4.01



Resistance in staphylococci (GRSA)



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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

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

B. Bozdogan¹, J. Chaitram², P. C. Appelbaum¹, C. Whitener¹, F. A. Browne¹, F. C. Tenover²

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

AB	MIC
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VAN	32
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TEC	4
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