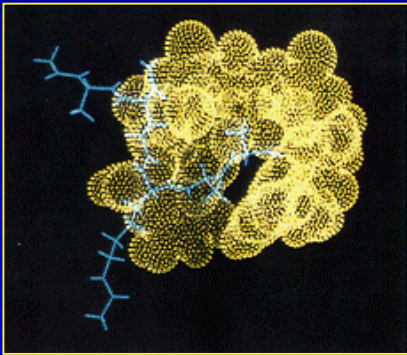


GLYCOPEPTIDE ANTIBIOTICS

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:

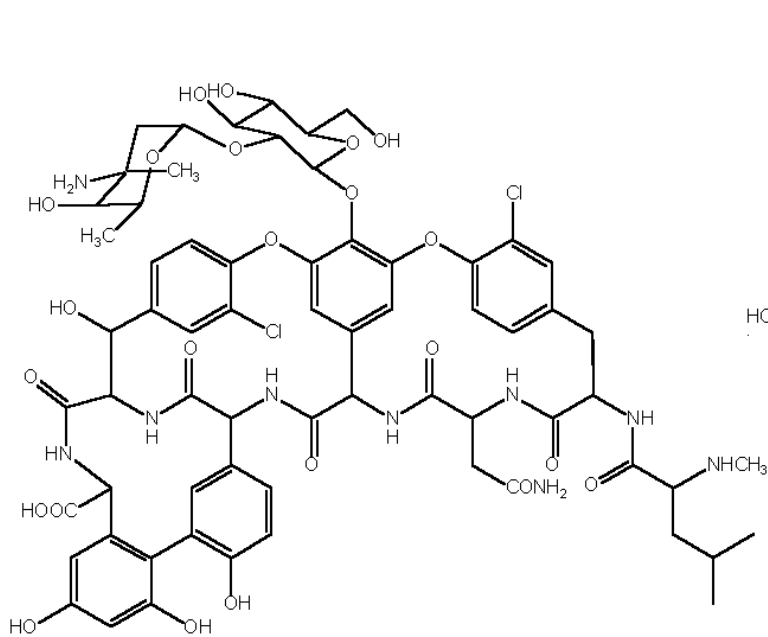
- toxicity of vancomycin due to impurities
→ better purification procedures

~ 1980 :

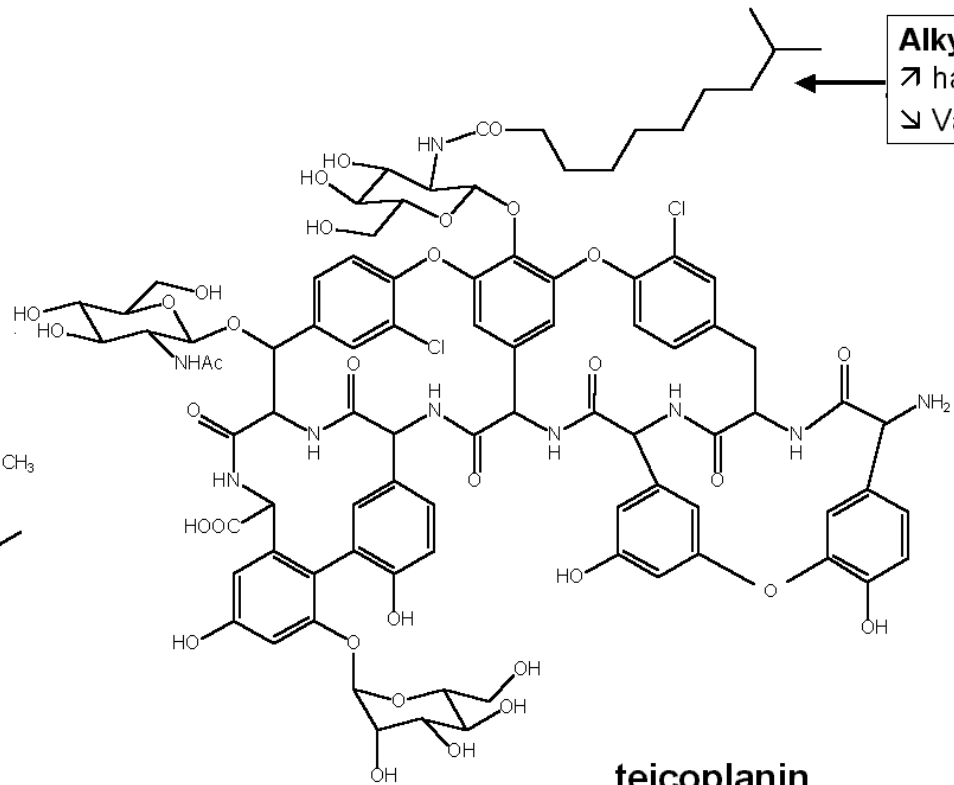
discovery of teicoplanin, as a natural GP with improved PK

- largely used in Europe

vancomycin - téicoplanine



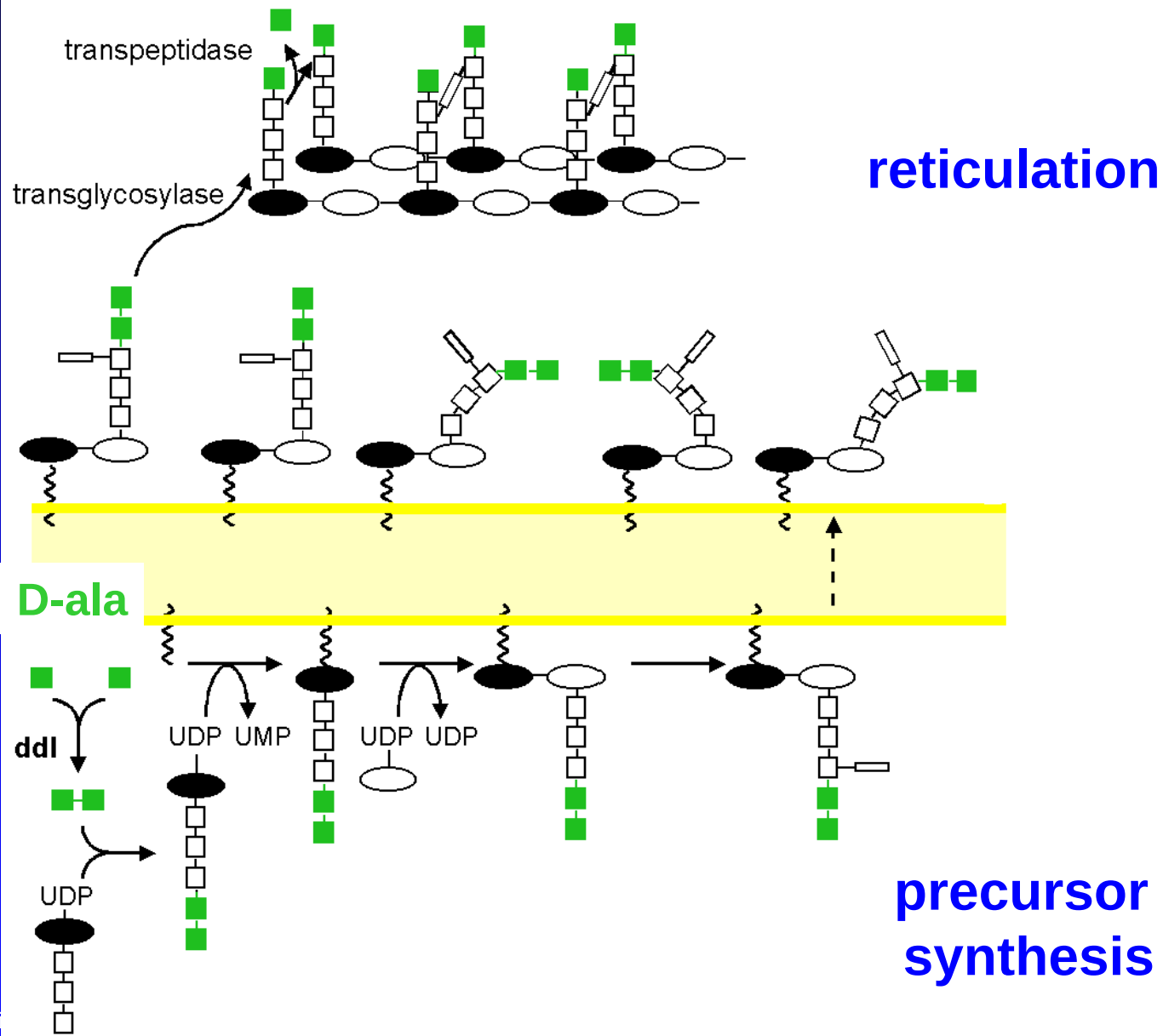
vancomycin



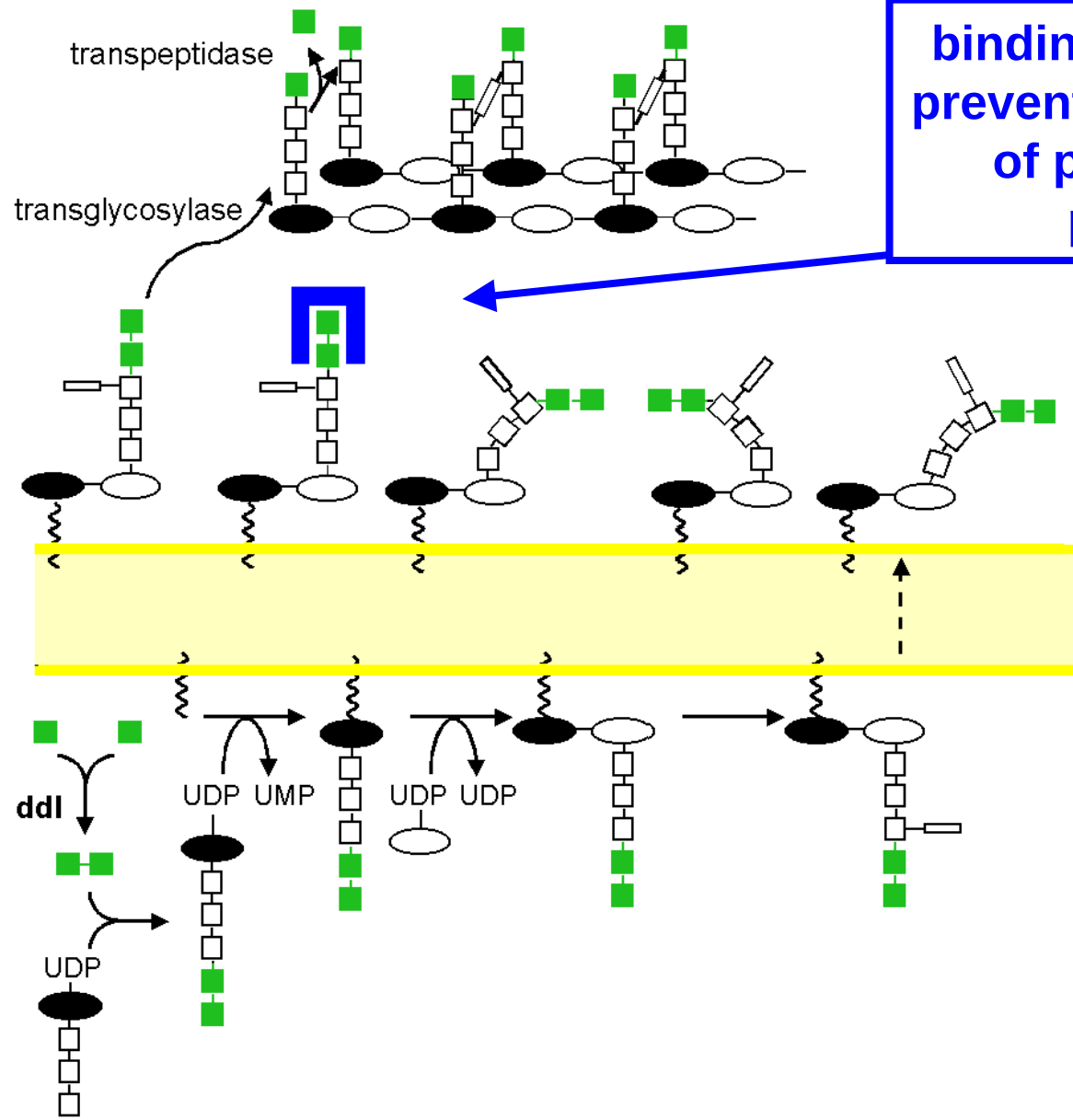
teicoplanin

Alkyl:
↗ half-life
↘ VanB induction

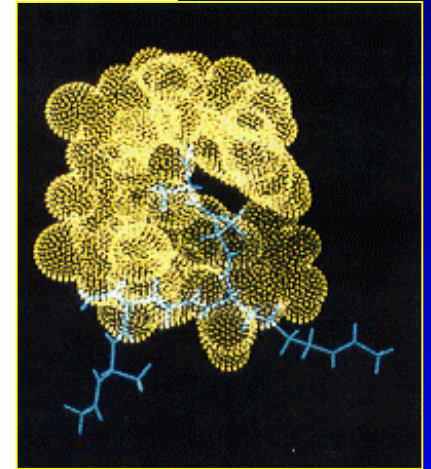
Peptidoglycan synthesis



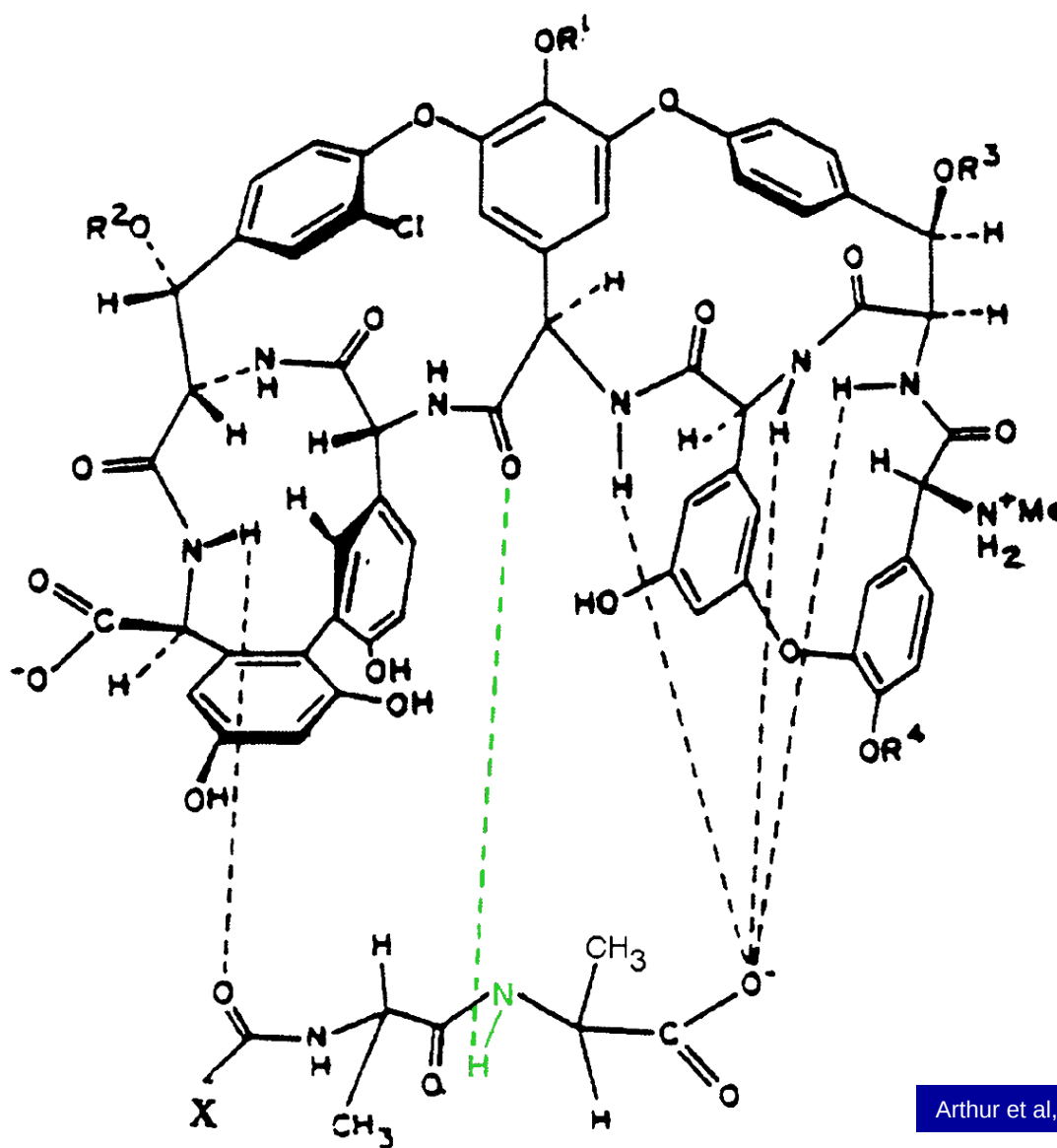
Glycopeptide mechanism of action



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

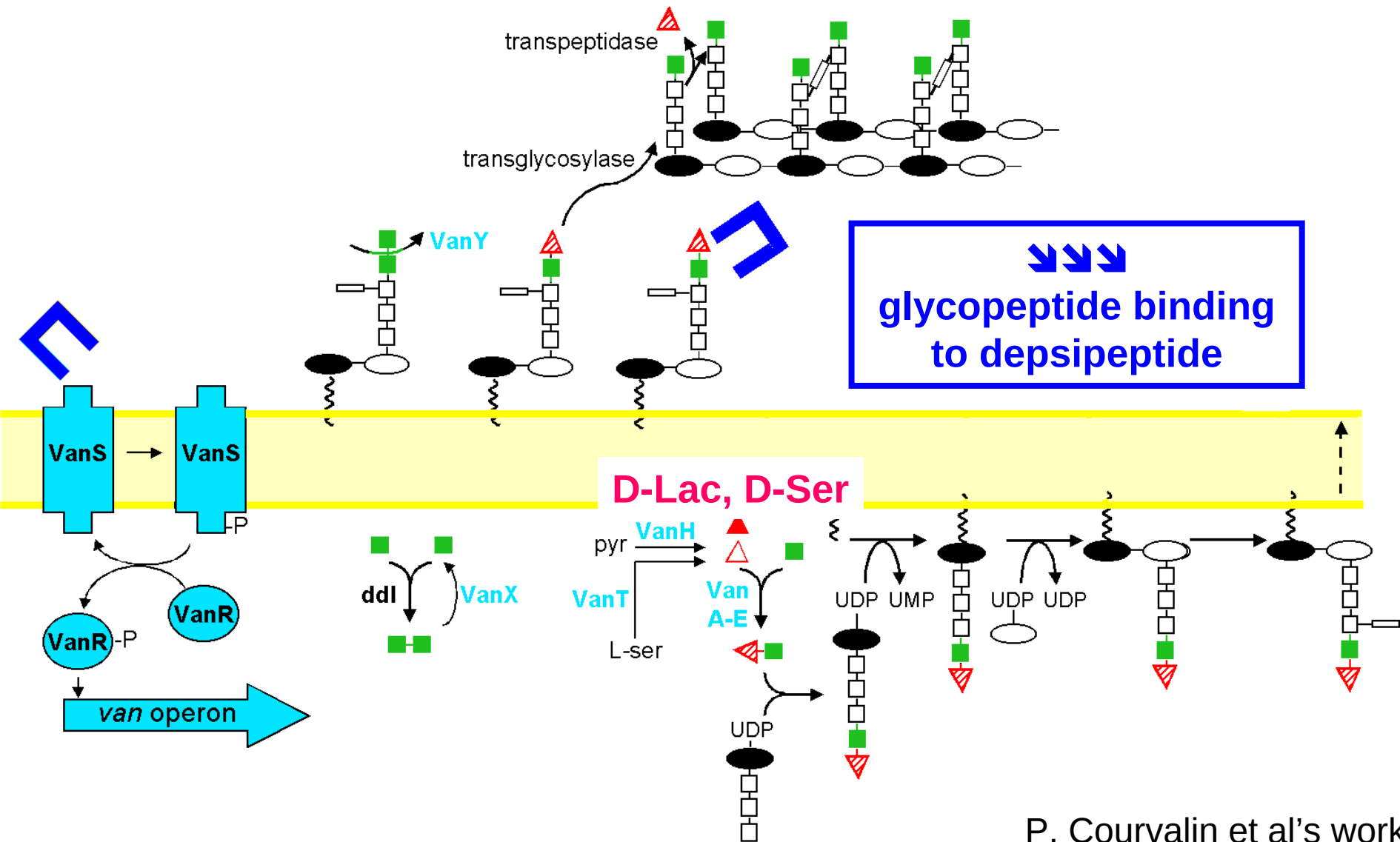


Binding of vancomycin to D-Ala-D-Ala



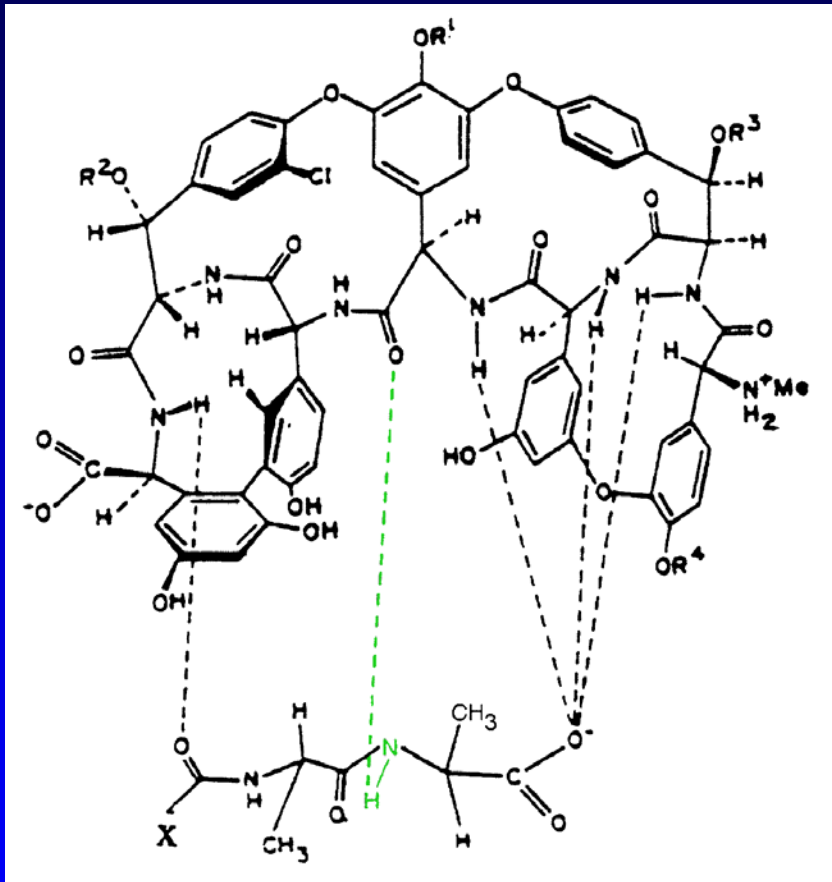
Arthur et al, Trends Microbiol (1996) 4:401-407

Resistance in enterococci

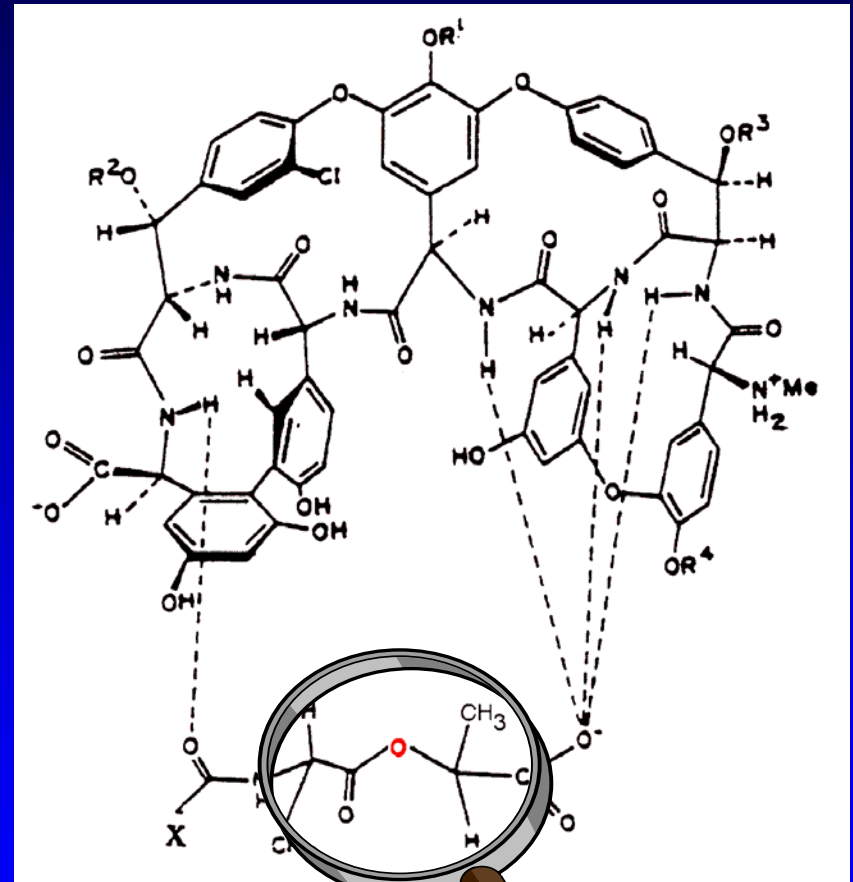


Resistance in enterococci

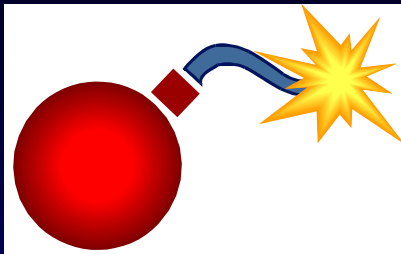
from susceptible ...



... to resistant



1 hydrogen bond 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

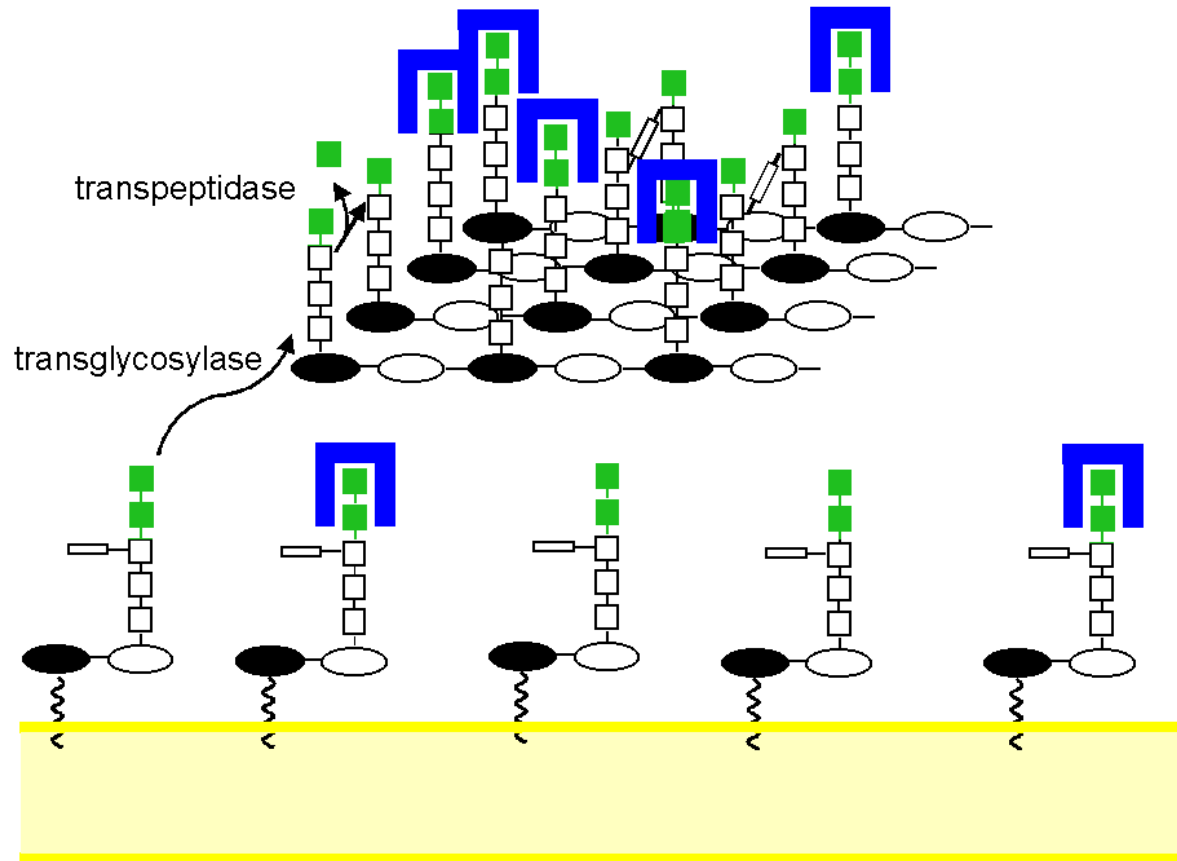
^aDepartment of Bacteriology; ^bDepartment of Pediatrics, Juntendo University, Tokyo; ^cClinical Laboratory, Juntendo Hospital, Tokyo, Japan; ^dNosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

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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April 3, 2003

Number 14

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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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