GLYCOPEPTIDE ANTIBIOTICS
from Old Mississippi mud …
… to new derivatives:
a critical appraisal

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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


oritavancin ➔ phase II / III ➔ dalbavancin

teicoplanin ➔ (1999)

Peptidoglycan synthesis

cytosol

transpeptidase

transglycosylase

reticulation

cell wall

D-ala

ddl

precursor synthesis

UDP, UMP, UDP, UDP
Glycopeptide mechanism of action

binding to D-Ala-D-ala prevents the reticulation of peptidoglycan precursors
But resistance came in ...


**Vancomycin-resistant enterococci.**

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


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

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

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


**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

glycopeptide binding to depsipeptide

D-Lac, D-Ser

VanS → VanS

VanR

van operon

P. Courvalin et al’s work
Resistance in enterococci

from susceptible …

… to resistant

1 hydrogen bound is missing!

Resistance in enterococci

glycopeptide binding to depsipeptide

VanS → VanS
VanR-P
VanR

D-Lac, D-Ser

Van operon

transpeptidase
transglycosylase

VanY
VanX
VanT
VanH
Van A-E

VanR

 ddl

pyr

L-ser

UDP

UDP

UDP

UDP

UMP
**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 Pediatrics, Juntendo University, Tokyo; \(^c\)Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; \(^d\)Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

<table>
<thead>
<tr>
<th>AB</th>
<th>MIC</th>
</tr>
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<tbody>
<tr>
<td>AMP</td>
<td>64</td>
</tr>
<tr>
<td>VAN</td>
<td>8</td>
</tr>
<tr>
<td>GEN</td>
<td>128</td>
</tr>
<tr>
<td>RIF</td>
<td>2048</td>
</tr>
<tr>
<td>LVX</td>
<td>8</td>
</tr>
<tr>
<td>TET</td>
<td>128</td>
</tr>
<tr>
<td>SMX</td>
<td>0.125</td>
</tr>
<tr>
<td>Q-D</td>
<td>0.5</td>
</tr>
<tr>
<td>LZD</td>
<td>2</td>
</tr>
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</table>
Resistance in staphylococci (GISA)

Multiplication of the target!

Tickened Cell wall

Cui et al J Clin Microbiol (2003) 41:5-14
Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the *vanA* Resistance Gene

Saju 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.F.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

<table>
<thead>
<tr>
<th>AB</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAN</td>
<td>32</td>
</tr>
<tr>
<td>TEC</td>
<td>4</td>
</tr>
</tbody>
</table>
**Glycopeptides: what can we improve?**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vanco - Teico</th>
<th>Ideal Glycopeptide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectrum</strong></td>
<td>Gram (+) &amp; MRSA but VRE - GISA</td>
<td>Gram (+) &amp; MRSA, GISA, VRE</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>Static or slowly bactericidal</td>
<td>Quickly, conc. dependent bactericidal</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td>t½ short for vanco</td>
<td>t½ ↑ diffusibility (CNS)</td>
</tr>
<tr>
<td><strong>PK/PD</strong></td>
<td>High doses to reach appropriate AUC/MIC &amp; Cmax/MIC</td>
<td>AUC/MIC &amp; Cmax/MIC ↑</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>(red-man syndrome) oto- &amp; nephrotoxicity</td>
<td>Side effects ↓</td>
</tr>
</tbody>
</table>
Glycopeptide updated mechanism of action

dimerization and / or membrane anchoring => activity
Glycopeptide updated mechanism of action in VRE

Efficient binding still possible!
Glycopeptides: how can we improve?
Glycopeptides: how can we improve?
Glycopeptides: how can we improve?

binding to D-Ala-D-Ala

dimerization
Glycopeptides: how can we improve?

membrane anchoring, transglycosylase inhibition

dimerization

binding to D-Ala-D-Ala
Molecules in clinical development:

DESIGN
From vancomycin to oritavancin

epi-vancosamine
From vancomycin to oritavancin

4- *epi*-vancosamine

颢 self-association capacity

LY264626
From vancomycin to oritavancin

lipophilic side chain

→ activity

including against resistant enterococci
From teicoplanin to dalbavancin
From teicoplanin to dalbavancin
removal of N-acetylglucosamine activity (against resistant enterococci)

From teicoplanin to dalbavancin
From teicoplanin to dalbavancin

ți activity
Molecules in clinical development:

IN VITRO DATA
microbiology
pharmacodynamics
<table>
<thead>
<tr>
<th>Strain</th>
<th>Resist.</th>
<th>Vanco</th>
<th>Orita</th>
<th>Teico</th>
<th>Dalba</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococci</td>
<td>Susc. VanA VanB</td>
<td>0.25-4</td>
<td>0.06-0.25</td>
<td>0.13-0.5</td>
<td>0.06-0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;128</td>
<td>0.06-1</td>
<td>64-&gt;128</td>
<td>0.5-&gt;128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-128</td>
<td>≤0.03-0.13</td>
<td>0.13-8</td>
<td>0.02-2</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Methi-S Methi-R</td>
<td>0.13-1</td>
<td>0.13-1</td>
<td>1-8</td>
<td>&lt; 0.03-0.5</td>
</tr>
<tr>
<td></td>
<td>VISA VRSA</td>
<td>0.5-4</td>
<td>0.13-4</td>
<td>0.13-8</td>
<td>0.06-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>1-8</td>
<td>8-32</td>
<td>0.06-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>0.25</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>Methi-S Methi-R</td>
<td>0.13-1</td>
<td>0.25-1</td>
<td>0.25-16</td>
<td>≤0.03-0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>0.25-4</td>
<td>1-16</td>
<td>≤0.03-1</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>Peni-S Peni-R</td>
<td>0.5-0.5</td>
<td>≤0.002-0.06</td>
<td>0.008-0.06</td>
<td>≤0.002-0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.13-0.5</td>
<td>≤0.002-0.06</td>
<td>0.008-0.06</td>
<td>0.016-0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25-2</td>
<td>≤0.002-0.06</td>
<td>0.016-0.13</td>
<td>0.008-0.13</td>
</tr>
</tbody>
</table>

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

- Static effect
- Concentration-dependent, bactericidal effect

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

<table>
<thead>
<tr>
<th>parameter</th>
<th>Vanco (15 mg/kg)</th>
<th>Orita (3 mg/kg)</th>
<th>Teico (6 mg/kg)</th>
<th>Dalba (15 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>peak (mg/L)</td>
<td>20-50</td>
<td>31</td>
<td>43</td>
<td>300</td>
</tr>
<tr>
<td>through (mg/L)</td>
<td>5-12 (24 h)</td>
<td>1.7 (24 h)</td>
<td>&lt; 5 (24 h)</td>
<td>40 (168 h)</td>
</tr>
<tr>
<td>protein binding</td>
<td>10-55 %</td>
<td>90 %</td>
<td>90 %</td>
<td>98 %</td>
</tr>
<tr>
<td>terminal t½ (h)</td>
<td>4-8</td>
<td>≤ 360</td>
<td>83-168</td>
<td>257 h</td>
</tr>
</tbody>
</table>

Intermune, Inc, data on file

**once-a-day administration**

**once-a-week administration**
### PK/PD Breakpoints:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vanco (15 mg/kg) bid</th>
<th>Orita (3 mg/kg) qd</th>
<th>Teico (6 mg/kg) qd</th>
<th>Dalba (15 mg/kg) qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC / MIC = 125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total free</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>185</td>
</tr>
<tr>
<td>total free</td>
<td>2</td>
<td>0.1</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>Cmax / MIC = 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total free</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>total free</td>
<td>5</td>
<td>0.3</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

### MIC of Target Bugs:

<table>
<thead>
<tr>
<th>Bug</th>
<th>Vanco</th>
<th>Orita</th>
<th>Teico</th>
<th>Dalba</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>0.5-4</td>
<td>0.13-4</td>
<td>0.13-8</td>
<td>0.06-1</td>
</tr>
<tr>
<td>VISA</td>
<td>8</td>
<td>1-8</td>
<td>8-32</td>
<td>2</td>
</tr>
<tr>
<td>VRE</td>
<td>&gt;128</td>
<td>0.06-1</td>
<td>64-&gt;128</td>
<td>0.5-&gt;128</td>
</tr>
</tbody>
</table>
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 3-7 days
followed by oral cephalexin 10-14 days

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

SUCCESS:
bacteriological
clinical with MRSA

76 % 74 %
80 % 76 %
80 % 74 %

Wasilewski et al 41st ICAAC (2001)
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:
bacteriiological 64 % 73 %
clinical 76 % 94 %

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

- 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?