From erythromycin to telithromycin:
two bullets for one target:
what makes the difference?

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Paul Ehrlich and magic bullets …

"The goal is … to find chemical substances that have special affinities for pathogenic organisms and that, like magic bullets, go straight to their targets"

"corpora non agunt nisi fixata"
Macrolides block the entrance to the ribosomal exit tunnel, without blocking the peptidyl transferase center of the 50S subunit. The ribosome can still produce a short peptide chain… before the traffic jam!

J. Harms; http://www.riboworld.com/
The bullets: erythromycin & telithromycin

carbamate and heteroarylalkyl group

NO hydroxyl

NO cladinose
What makes the difference ~ mode of action?

H bond with domain II

H bond with A2058 in domain V

Figure prepared by J. Harms; in Van Bambeke et al., Exp Op Pharmacother (2008) 9:267-283
What makes the difference ~ resistance?

Target methylation/mutation of A2058

H bond with domain II; high mobility

Absence of cladinose favors mobility and repositioning

Figure prepared by J. Harms; in Van Bambeke et al., Exp Op Pharmacother (2008) 9:267-283
What makes the difference ~ resistance?

Efflux

lower recognition by efflux pumps

Yes, but ....

S. pyogenes
- S
- MLS
- Efflux
- Efflux + MLS

Canton et al, JAC (2005) 55:489-95

Slight increase in MIC!
**What makes the difference ~ resistance?**

**S or R? This is a question of Breakpoint!**

<table>
<thead>
<tr>
<th>species</th>
<th>phenotype</th>
<th>AB</th>
<th>MIC 50</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pyogenes</em> (n=486)</td>
<td>EryS</td>
<td>ERY</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td></td>
<td>MLSB</td>
<td>ERY</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Efflux</td>
<td>ERY</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> (n=375)</td>
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<td>ERY</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>≤ 0.06</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>MLSB</td>
<td>ERY</td>
<td>&gt; 256</td>
<td>&gt; 256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>≤ 0.06</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Efflux</td>
<td>ERY</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TEL</td>
<td>0.25</td>
<td>0.5</td>
</tr>
</tbody>
</table>

ERY & TEL

S: ≤ 0.25
I: 0.5
R: > 0.5

What makes the difference ~ pharmacokinetics?

- Oral biodisponibility

Protects from hemi-ketal and ketal formation

Adapted from Kirst and Sides, AAC (1989) 33: 1413-1418
What makes the difference ~ pharmacokinetics?

**Distribution**

Lipophilicity ➔ ➔

Calculated logD pH7: TEL 3.36 >> ERY 1.65

Cellular accumulation (diffusion segregation in acidic subcellular compartments)

Lysosomotropic accumulation of cationic amphiphilic drugs

Theory of our local Nobel Price,
C. De Duve

What makes the difference ~ pharmacokinetics?

<table>
<thead>
<tr>
<th>parameter</th>
<th>ERY</th>
<th>TEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>3</td>
<td>1.9-2.5</td>
</tr>
<tr>
<td>ELF/serum</td>
<td></td>
<td>2-20</td>
</tr>
<tr>
<td>MΦ/serum</td>
<td>4-10</td>
<td>4-25</td>
</tr>
<tr>
<td>AUC (mg.h/L)</td>
<td>4-14</td>
<td>10-13</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>2</td>
<td>10-13</td>
</tr>
<tr>
<td>Prot binding (%)</td>
<td>65-90</td>
<td>70</td>
</tr>
<tr>
<td>PD Bkpt (mg/L) (fAUC/MIC &gt; 25)</td>
<td>~ 0.25</td>
<td>~ 0.25</td>
</tr>
</tbody>
</table>

What makes the difference ~ pharmacokinetics?

But only bacteriostatic against intracellular *S. aureus*!

What makes the difference ~ toxicity?

CYP450

?? Steric hindrance ??

ML-CYP complex

Drug interactions with telithromycin (SSPC)

**Contra-indicated drugs**
cisapride
ergotamine
pimozide

**Risk of increased toxicity of the coadministered drug**
simvastatin (lovastatin or atorvastatin)
digoxin
midazolam
metoprolol
oral anticoagulants
(carbamazepine, cyclosporine, tacrolimus, sirolimus, hexobarbital, and phenytoin)

**Risk of reduced efficacy of the antibiotic**
rifampin
phenytoin, carbamazepine, or phenobarbital
Can we do better to get « the » magic ketolide ?

- Activity on resistant strains only partially improved
  - can we increase affinity for methylated ribosome ?
  - can we decipher the molecular determinants for recognition by efflux pumps ?

- Pharmacodynamic properties not modified
  - can we make ketolides bactericidal ?
  - can we make ketolides active at acidic pH ?

- Still some drug interactions and rare but severe side effects
  - can we make non-metabolisable ketolides ?
  - can we improve safety profile ?
Can we do better to get « the » magic ketolide ?

BUT THE IDEAL BULLET IS PROBABLY THERE …

Let’s wait and see you at Ehrlich III !…
Magic bullets at UCL, Brussels ...

de Duve Institute

Louvain Drug Research Institute

cellular and molecular Pharmacology

Ehrlich Building