2nd World Conference on Magic Bullets (Ehrlich II)
Nurnberg, Germany

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

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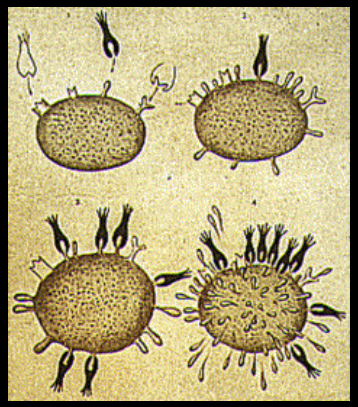
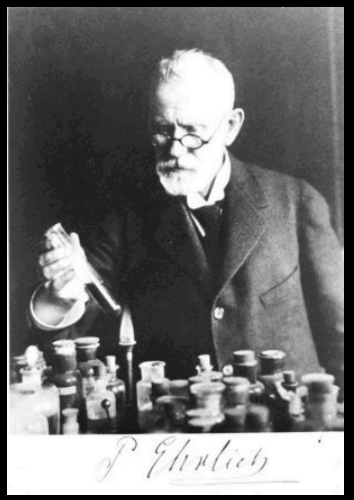
Paul Ehrlich and magic bullets …

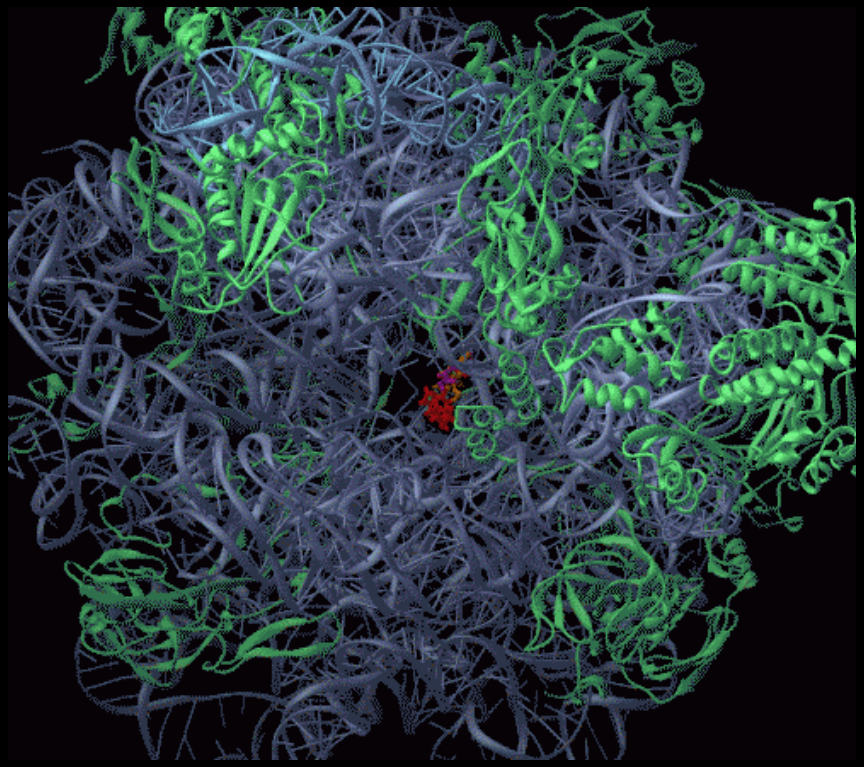


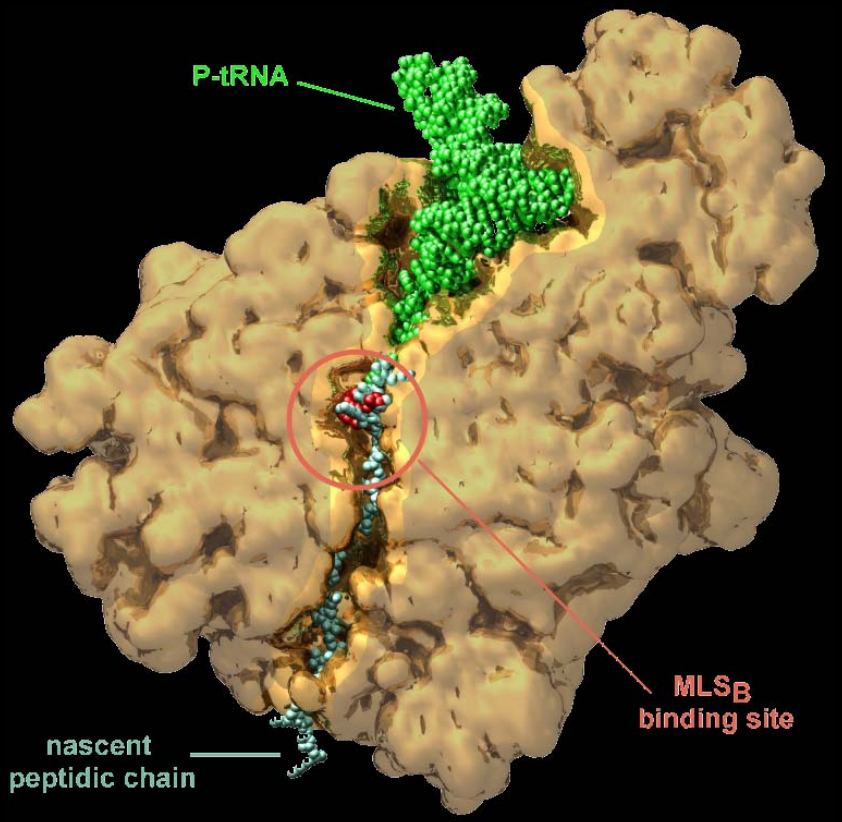
"corpora non agunt nisi fixata"

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



The target : 50S subunit of ribosome

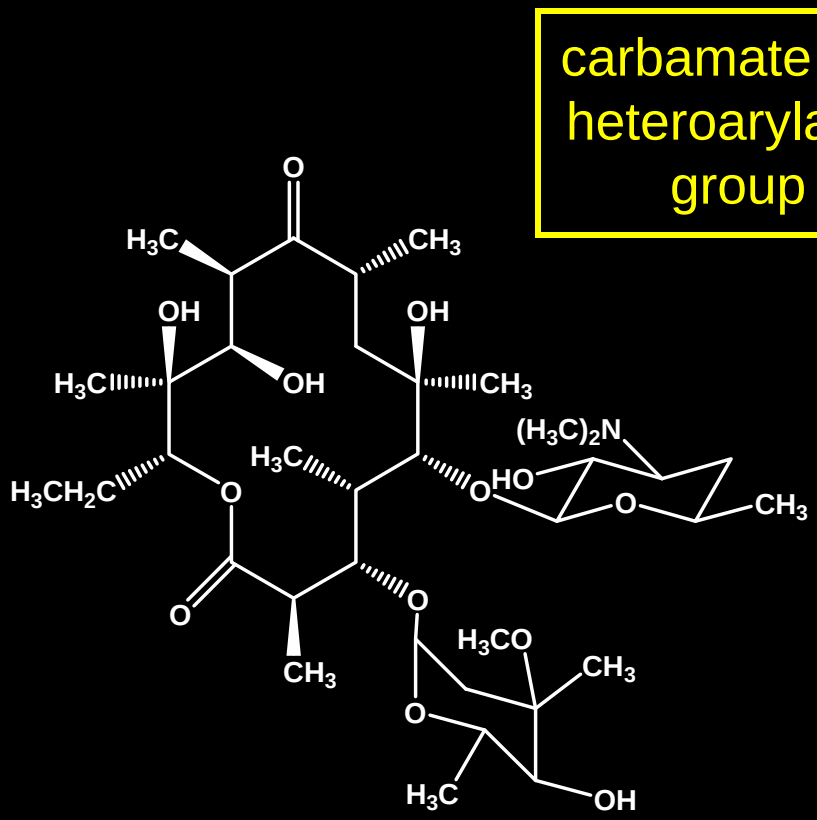




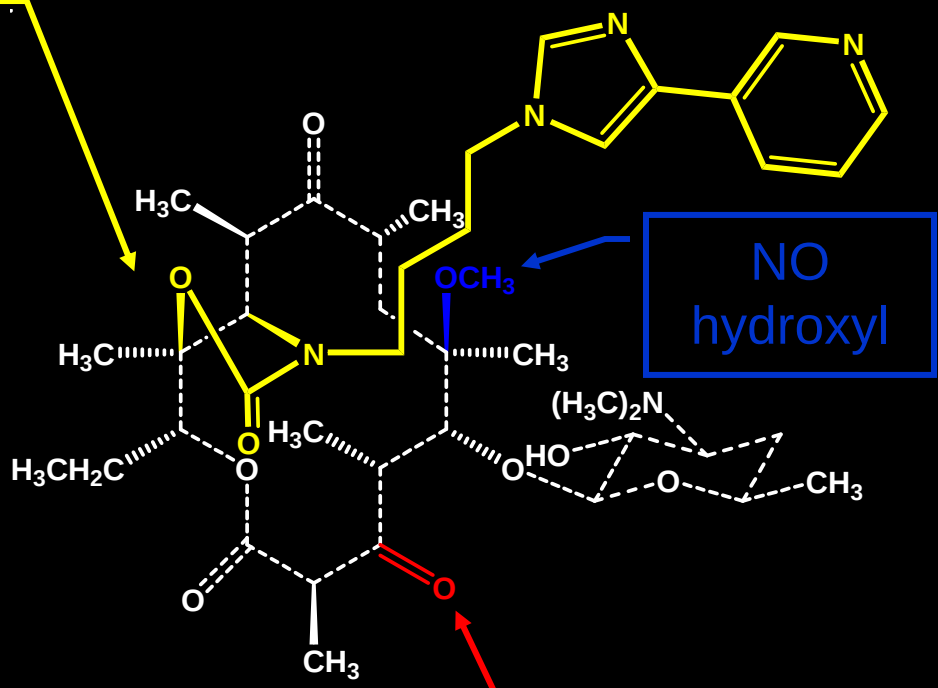
Macrolides block the entrance to the ribosomal exit tunnel,
without blocking the peptidyl transferase center of the 50S subunit.
The ribosome can still produce a short peptide chain…
before the traffic jam !

J. Harms; http://www.riboworld.com/

The bullets : erythromycin & telithromycin



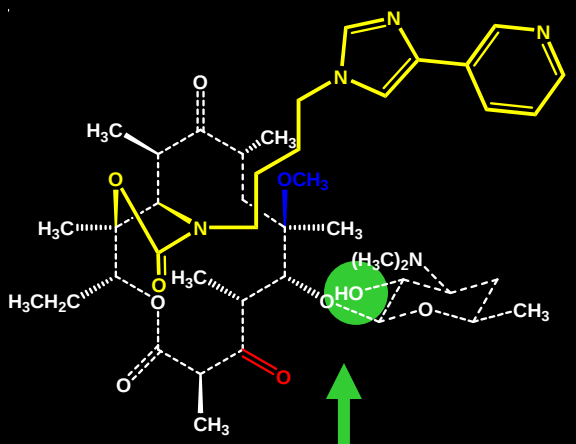
carbamate and heteroarylalkyl group



NO hydroxyl

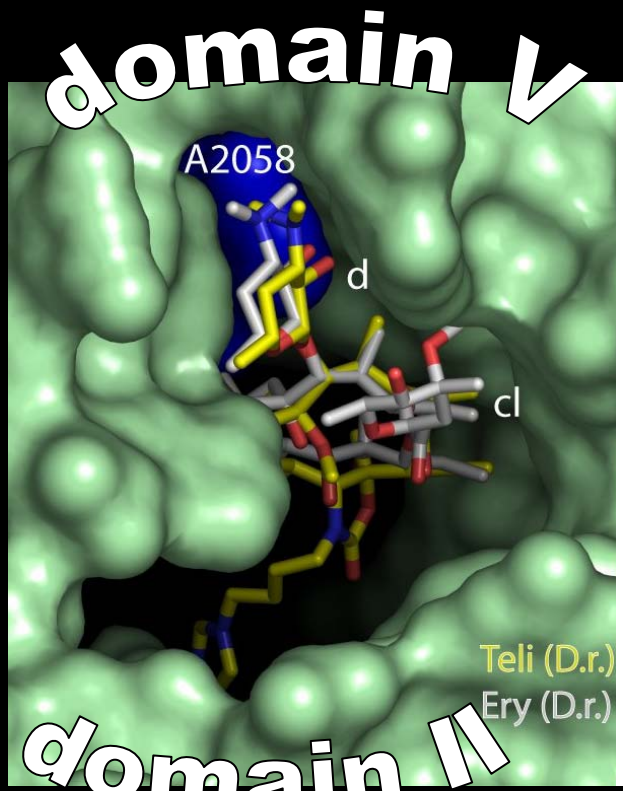
NO cladinose

What makes the difference ~ mode of action ?



H bond
with domain II

H bond
with A2058
in domain V



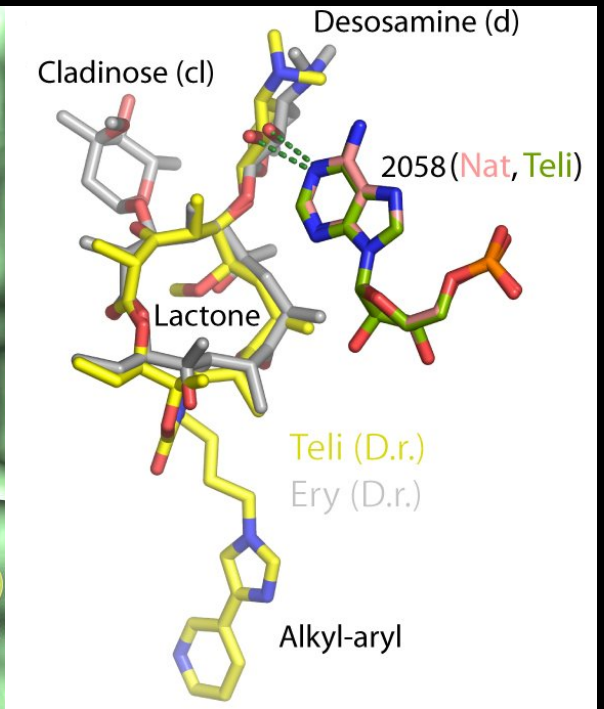
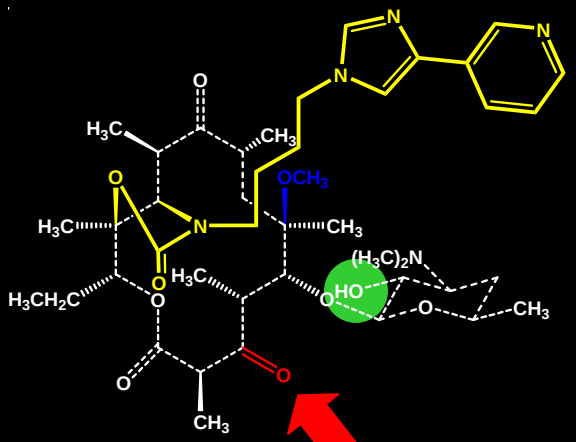


Figure prepared by J. Harms; in
Van Bambeke *et al.*, Exp Op Pharmacother (2008) 9:267-283

D.r. Deinococcus radiodurans

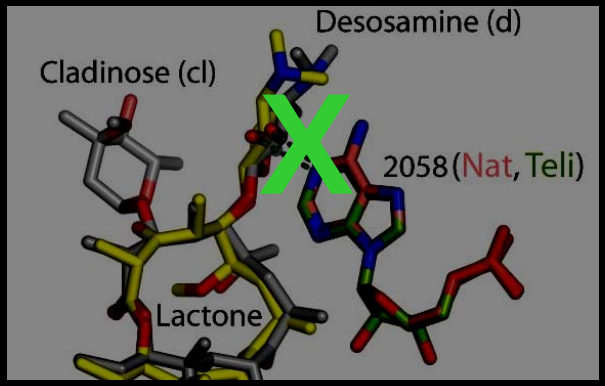
What makes the difference ~ resistance ?

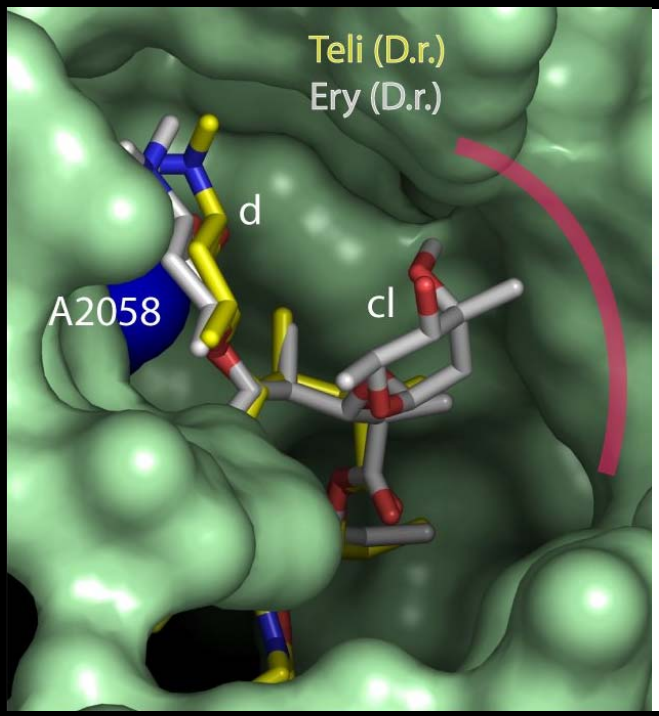
➔ **Target methylation/mutation of A2058**



H bond
with domain II;
high mobility

absence
of cladinose
favors mobility
and repositioning





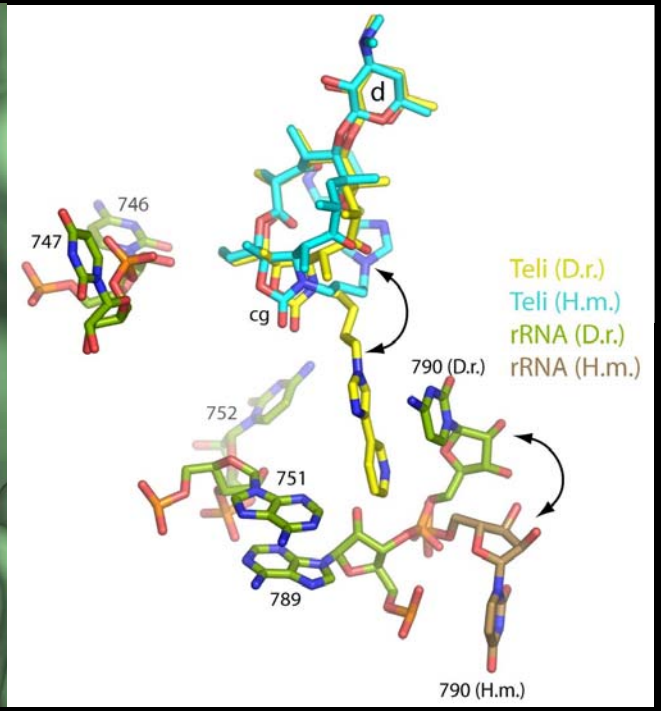
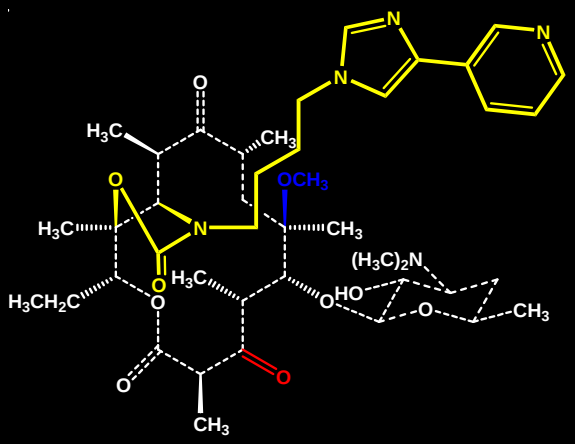


Figure prepared by J. Harms; in
Van Bambeke *et al.*, Exp Op Pharmacother (2008) 9:267-283

D.r. Deinococcus radiodurans
H.m. Haemophilus influenzae

What makes the difference ~ resistance ?

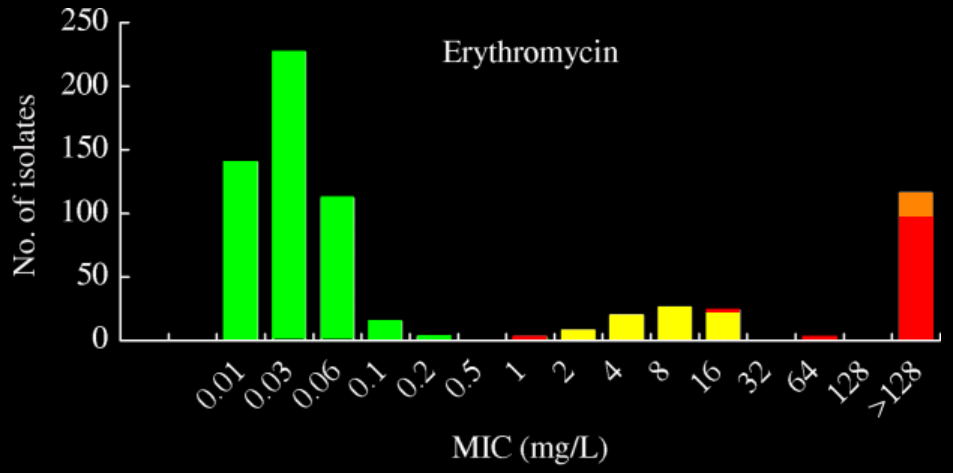
➔ **Efflux**

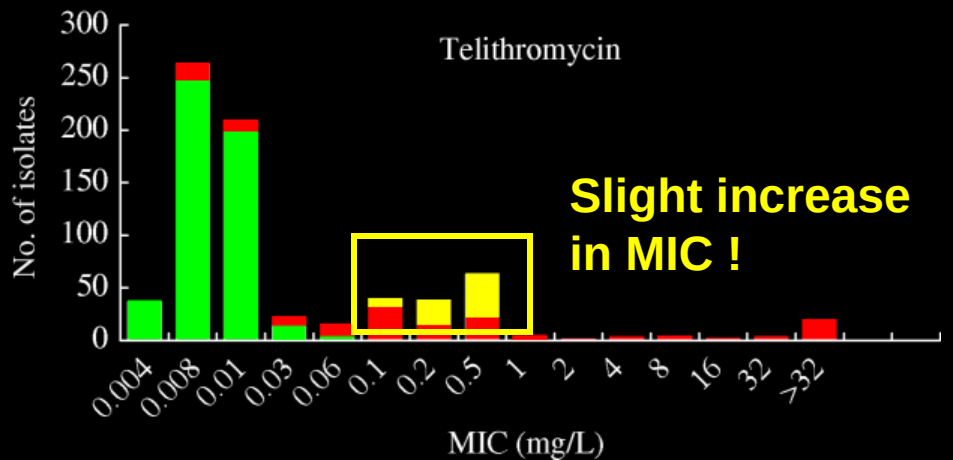


lower recognition by efflux pumps

Yes, but ….

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





Slight increase in MIC !

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

What makes the difference ~ resistance ?

S or R ? This is a question of Breakpoint !

ERY & TEL
S: ≤ 0.25
I : 0.5
R: > 0.5

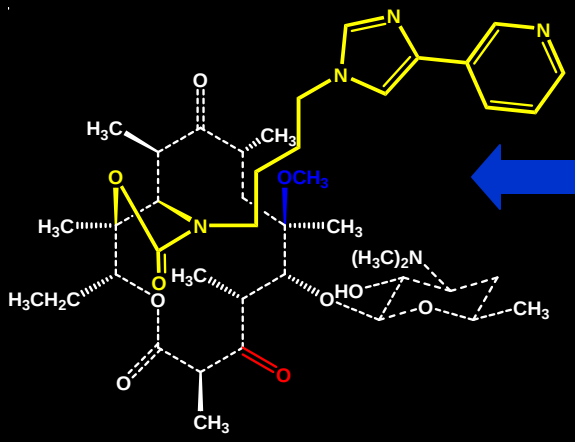
eucast

species	phenotype	AB	MIC 50	MIC 90
S. pyogenes (n=486)	EryS	ERY	≤ 0.06	≤ 0.06
		TEL	≤ 0.06	≤ 0.06
	MLS_B	ERY	> 256	> 256
		TEL	**4**	**32**
	Efflux	ERY	4	8
		TEL	**0.5**	**0.5**
S. pneumoniae (n= 375)	EryS	ERY	≤ 0.06	≤ 0.06
		TEL	≤ 0.06	0.06
	MLS_B	ERY	> 256	> 256
		TEL	≤ 0.06	0.12
	Efflux	ERY	4	32
		TEL	0.25	**0.5**

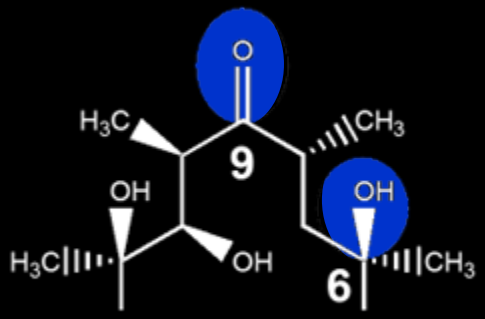
Mazzariol *et al*, JAC (2007) 59:1171-76

What makes the difference ~ pharmacokinetics ?

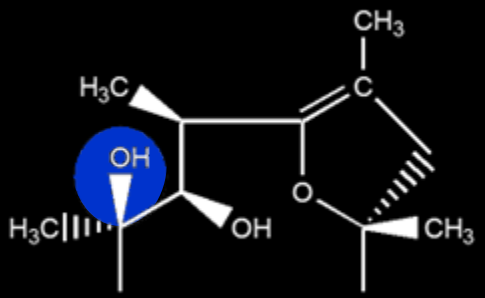
➔ **Oral biodisponibility**



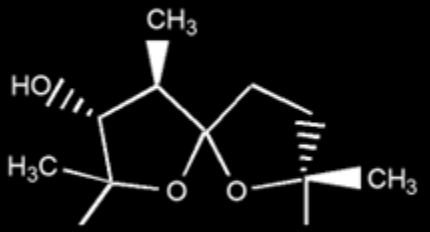
Protects from hemi-ketal and ketal formation



acidic medium



acidic medium

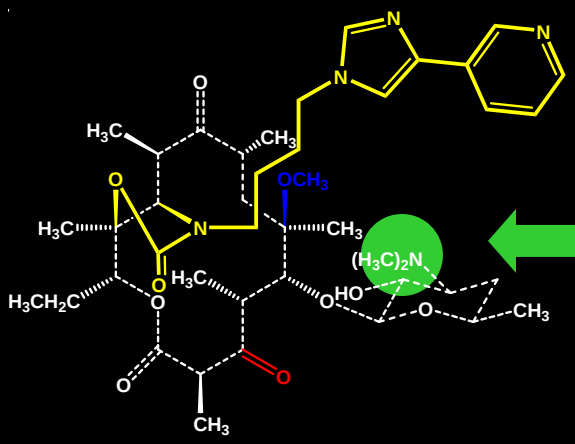


inactive

Adapted from Kirst and Sides, AAC (1989) 33: 1413-1418

What makes the difference ~ pharmacokinetics ?

➔ Distribution

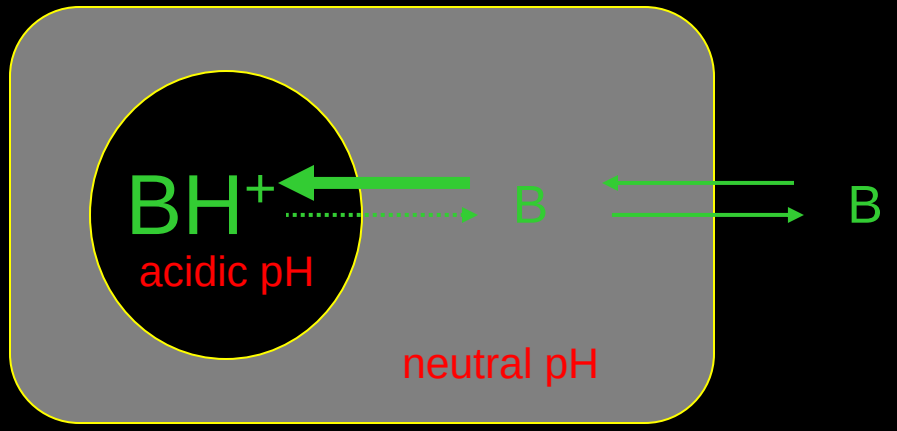


Lipophilicity ↗ ↗
calculated logD pH7 : TEL 3.36 >> ERY 1.65

cellular accumulation
(diffusion segregation
in acidic subcellular compartments)

Theory of our local Nobel Price,
C. De Duve

Lysosomotropic accumulation
of cationic amphiphilic drugs



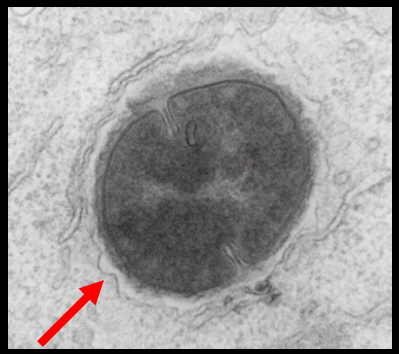
De Duve *et al.* Biochem Pharmacol. (1974) 23:2495-531

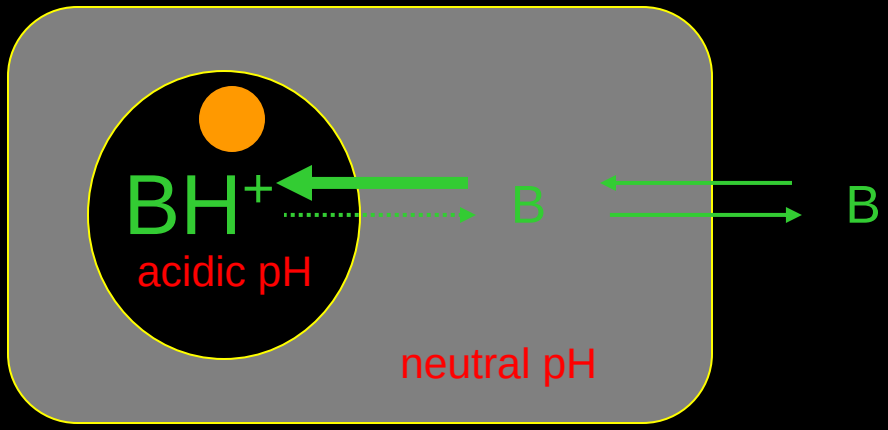
What makes the difference ~ pharmacokinetics ?

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

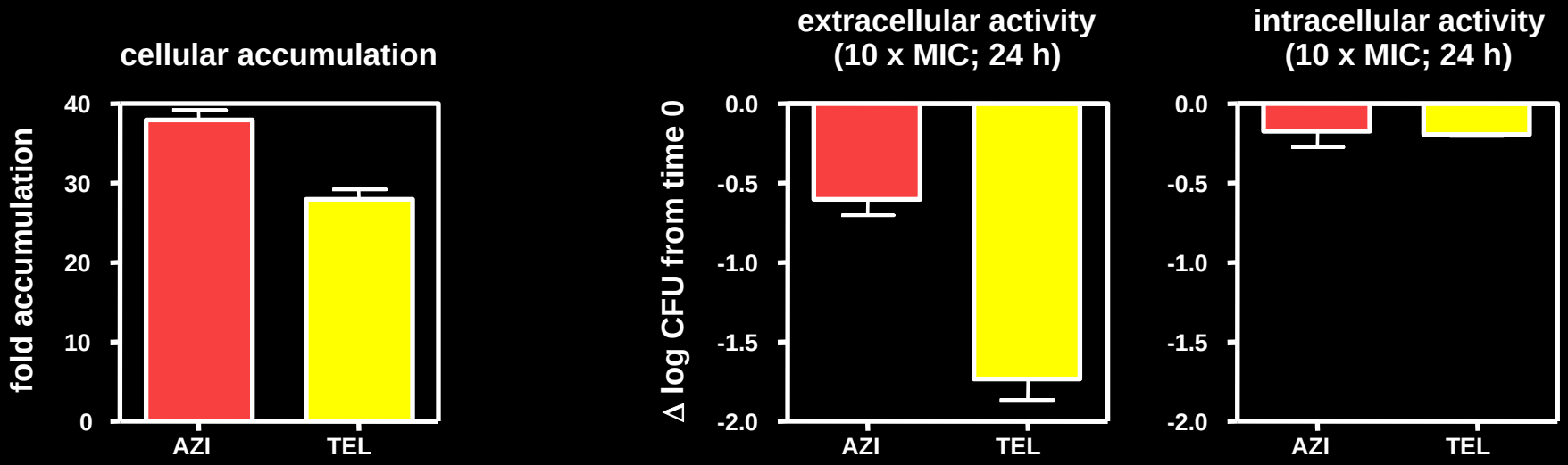
Adapted from
Mulazimoglu *et al*., Macrolides In: Antimicrobial Therapy and Vaccines (2005);
Van Bambeke *et al.,* Exp Op Pharmacother (2008) 9:267-283

What makes the difference ~ pharmacokinetics ?





But only bacteriostatic against intracellular *S. aureus* !

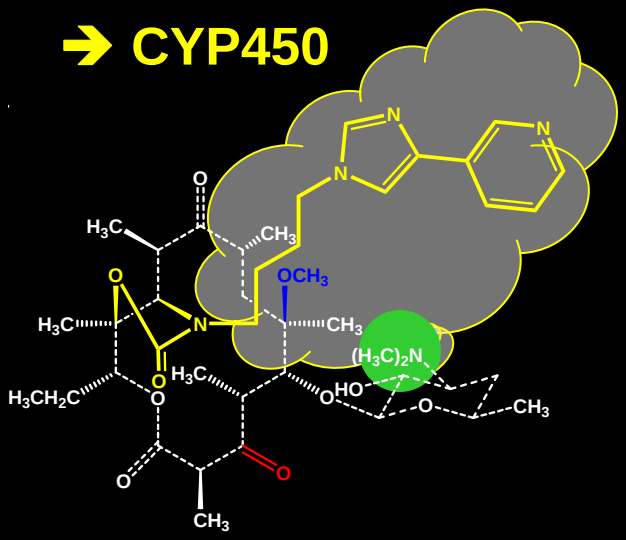


MIC (pH 7.3)	0.5	0.06	(pH 5)	512	4

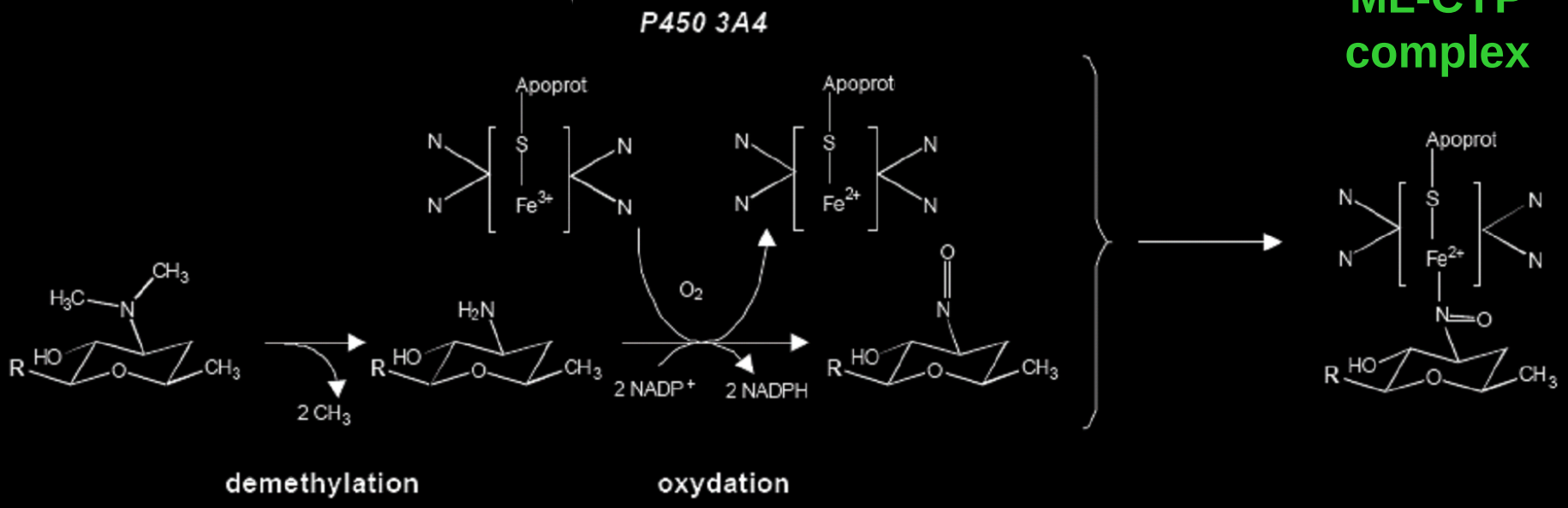
Barcia-Macay *et al.* AAC (2006) 50:841-51

What makes the difference ~ toxicity ?

➔ **CYP450**

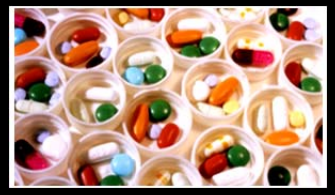


?? Steric hindrance ??



ML-CYP complex

Adapted from Periti et al. Clin. Pharmacokinet. (1992) 23: 106-131



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

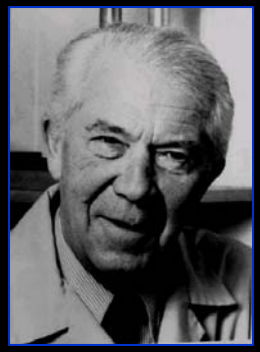
Can we do better to get « the » magic ketolide ?

- 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 ?

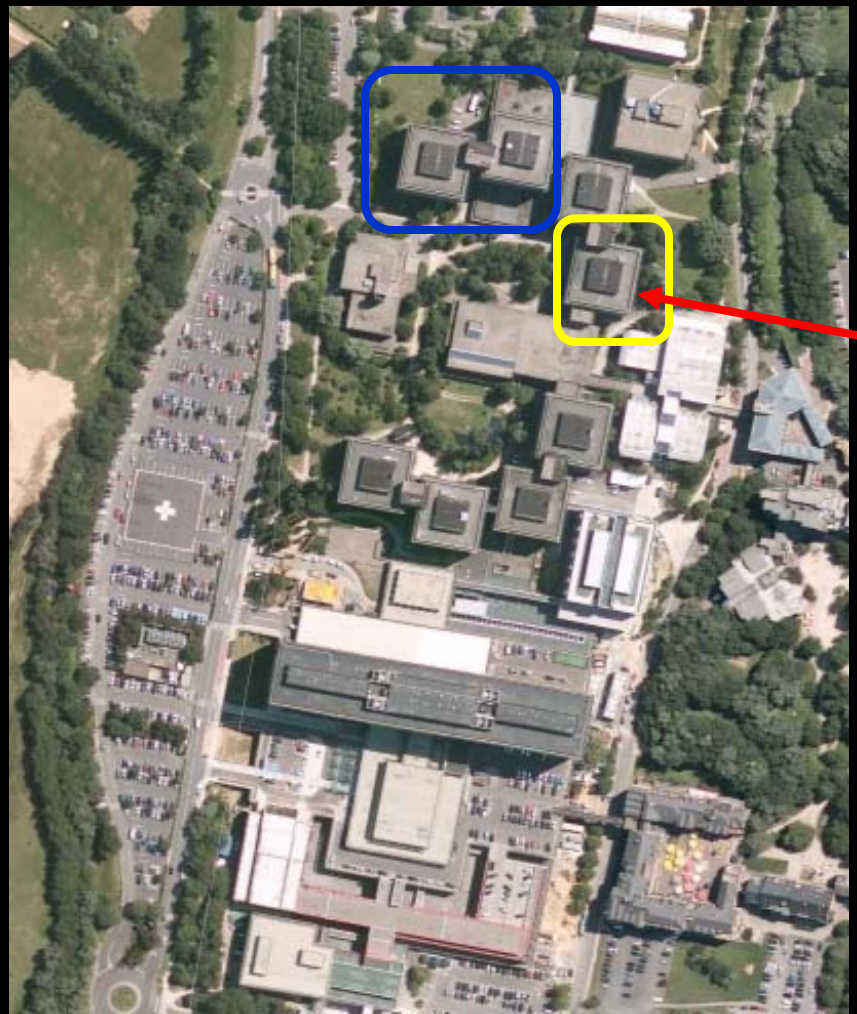
Can we do better to get « the » magic ketolide ?

Magic bullets at UCL, Brussels …

de Duve Institute



Louvain Drug Research Institute



cellular and molecular Pharmacology

Ehrlich Building