

ATP synthase, an exciting new target for TB treatment

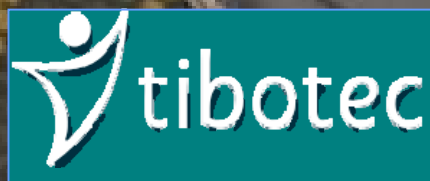


Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT

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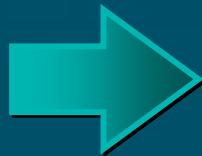
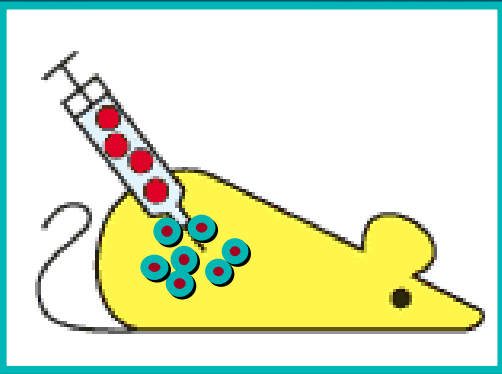
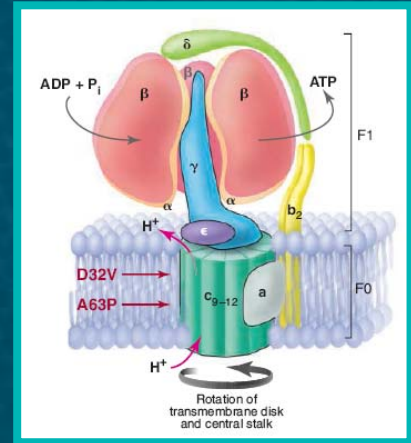
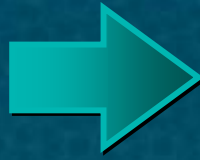
**Nacer Lounis
Nicolas Veziris
Vincent Jarlier**

We Need a Faster Cure...

- Shorten treatment duration
- Address MDR-TB
- Simplify treatment
- Address latency

- Better bactericidal and sterilizing activity
- New mechanism of action
- Lower dosing frequency
- Activity on dormant bacilli



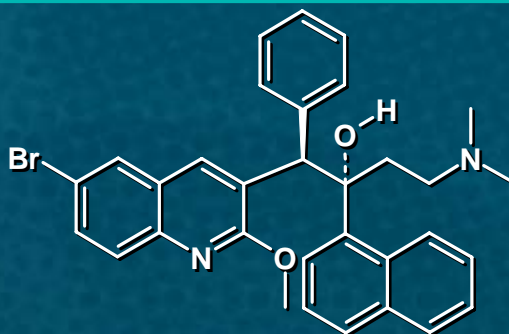




A Unique Antibacterial Spectrum

Non-mycobacteria:
MIC ≥ 4 $\mu\text{g/ml}$

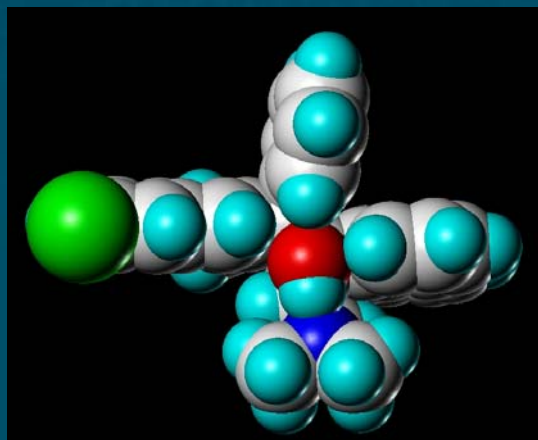
- *H. pylori*
- *Str. pyogenes*
- *St. aureus*
- *S. typhimurium*
- *M. pneumoniae*
- *E. coli*
- *E. faecalis*
- *E. faecium*
- *P. aeruginosa*
- *H. influenzae*



R207910

TMC207

Compound J



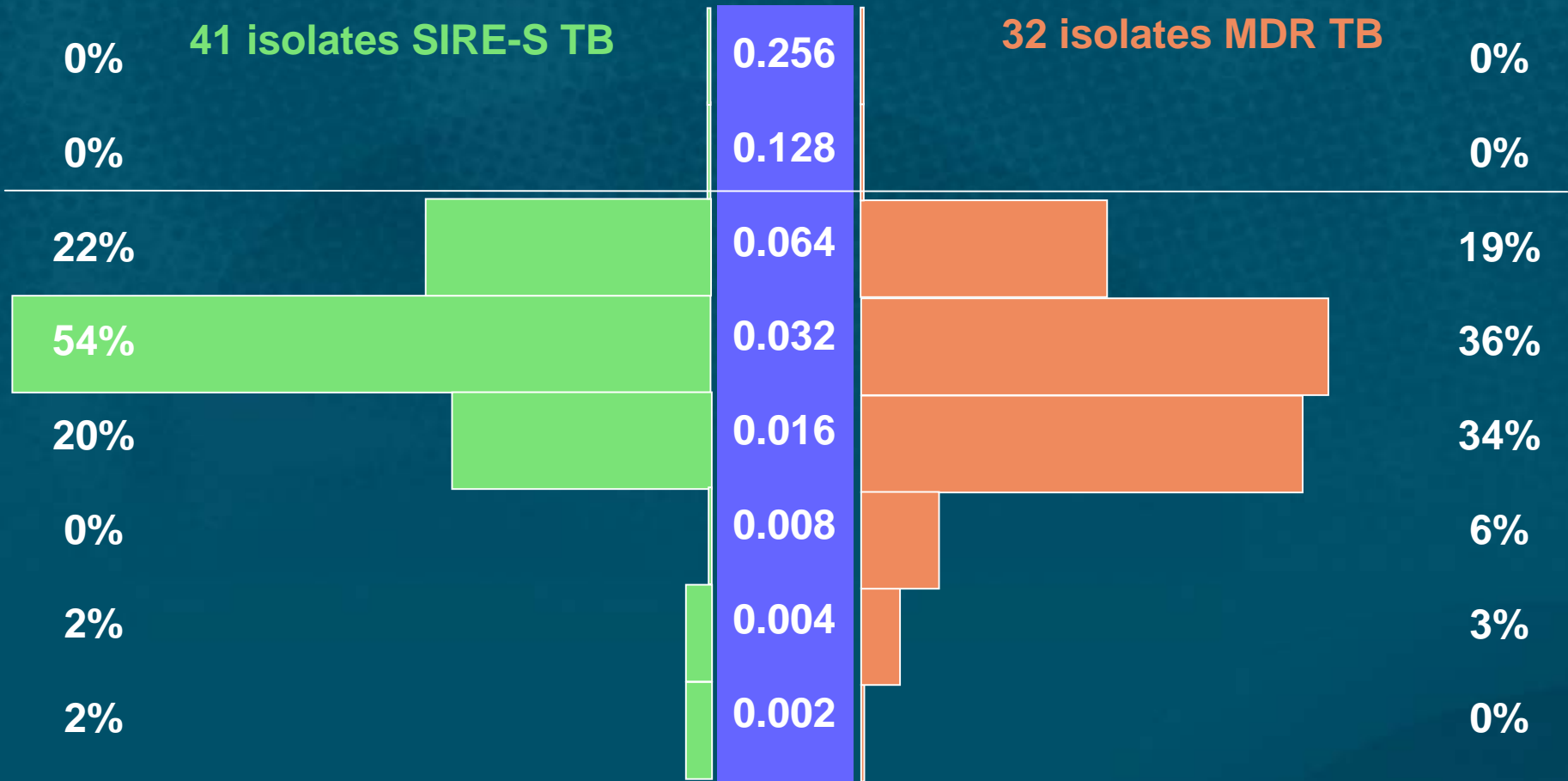
Mycobacteria:
MIC ≤ 0.060 $\mu\text{g/ml}$

- *M. tuberculosis*
- *MDR M. tuberculosis*

- *M. avium*
- *M. bovis*
- *M. fortuitum*
- *M. marinum*
- *M. kansasii*
- *M. smegmatis*



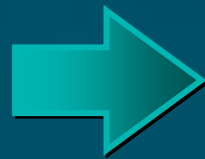
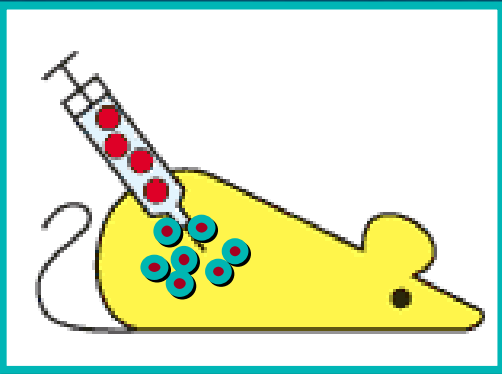
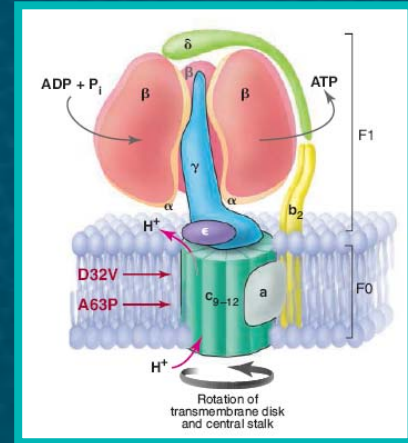
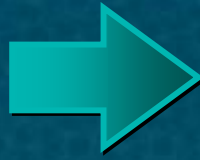
MIC distribution in DS and MDR TB Isolates





TMC207 mutants not cross-resistant

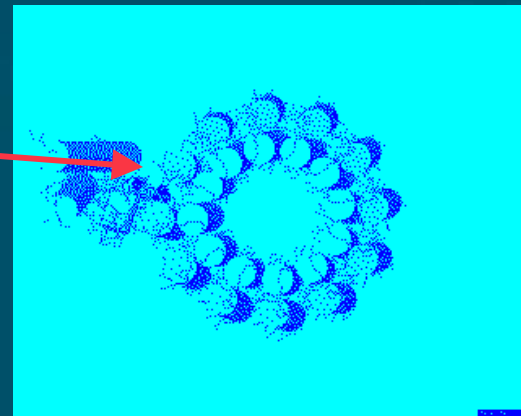
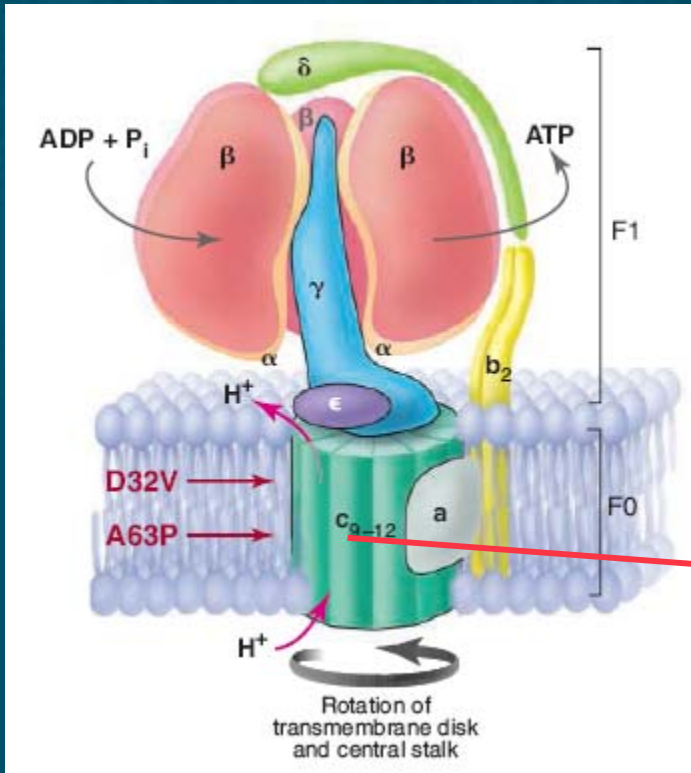
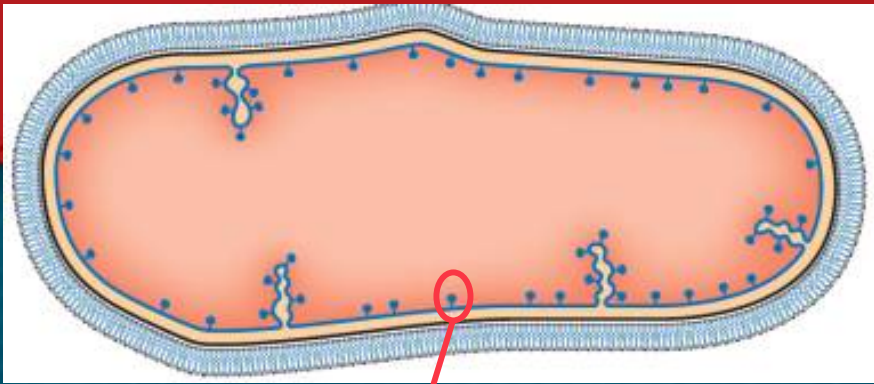
	MIC ($\mu\text{g/ml}$) for	
	<i>M. tuberculosis</i>	<i>M. tuberculosis</i> BK12
TMC207	0.030	4.000
Isoniazid	0.120	0.120
Rifampin	0.500	0.120
Ethambutol	2.000	4.000
Streptomycin	1.000	1.000
Amikacin	1.000	2.000
Moxifloxacin	0.250	0.250
PA-824	0.250	0.250

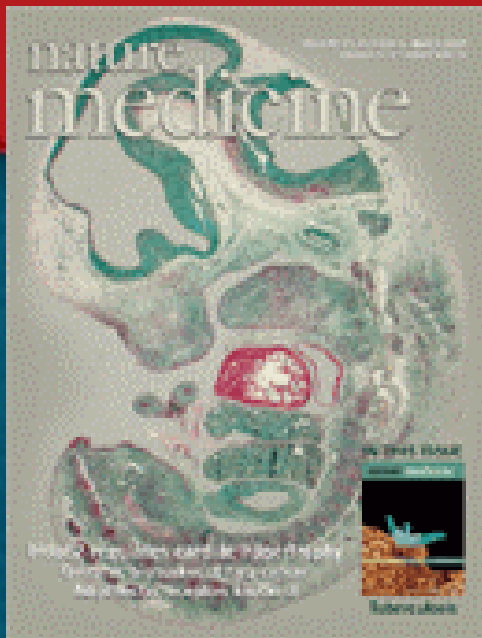


Mechanism of Action

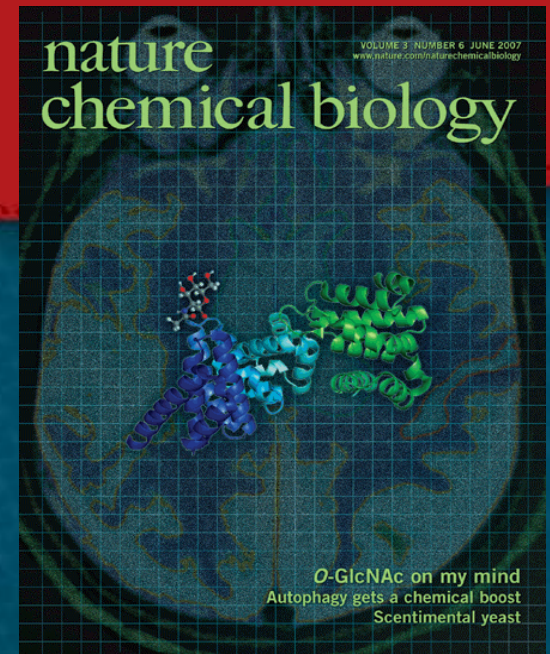
In strains resistant to TMC207, mutations were identified in the gene coding for **ATP synthase**

Provides energy (ATP) from a trans-membrane proton gradient





Target validation



ATP synthase plausible target but...
further work is required to prove this point
Resistant mutations can arise in genes involved in:

1. Prodrug activation
2. Drug inactivation
3. Drug extrusion out of cell
4. Other linked-metabolic pathways

- Genetically
Complementation + SNP
- Biochemically
ATP levels wt and mt strains
- Biophysically
Compound linked affinity chromatography & Biacore)
- Role of ATP synthase during dormancy
- Molecular modeling

Mycobacterial Spectrum

0.016 mg/L

M. vaccae
M. fortuitum
M. phlei
M. mageritense
M. chelonae
M. bovis
M. marinum
M. smegmatis

0.032 mg/L

DS TB
MDR TB
M. avium
M. intracellulare
M. kansasii
M. gordonae
M. simiae
M. szulgai
M. scrofulaceum
M. hibernae
M. interjectum
M. fortuitum
M. ulcerans

0.063 mg/L

M. terrae
M. szulgai

0.125 mg/L

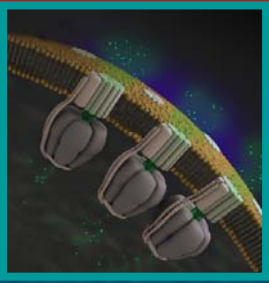
M. malmoense
M. terrae
M. conspicium

0.500 mg/L

M. chelonae
M. abscessus

4-8 mg/L

M. novocastrense
M. shimoidei
M. xenopi



ATP Synthase Target Sequence Alignment

40

63

66

74

ARQPEAQGR LFT PFFITVGL
 ARQPEAQGR LFT PFFITVGL
 ARQPEAQGR LFT PFFITVGL

VEAAY
 VEAPY
 VEAAY

FINLAFM ALF
 FINLAFM ALF
 FMN LAFM ALF

M. tuberculosis
BK12 mutant
LV mutant

ARQPEAQ **S** RLFT PFFITVGL
 ARQPEAQGR LFT PFFITVGL
 ARQPEAQGR LFT PFFITVGL

VEAAY
 VEAAY
 VEAAY

FINLAFM ALF
 FINLAFM ALF
 FINLAFM ALF

M. leprae
M. ulcerans
M. avium

ARQPEAQGR LFT PFFITVGL
 ARQPEAQGR LFT PFFITVGL
 ARQPEAQGR L **V** PFFITVGL

VEAMY
 VEAMY
 VEAMY

FINLAFM ALF
 FINLAFM ALF
 FINLAFM ALF

M. xenopi
M. shimoidei
M. novocastr

ARN **P**SLKQQ **L**FSYA I LGFA

SEAMG

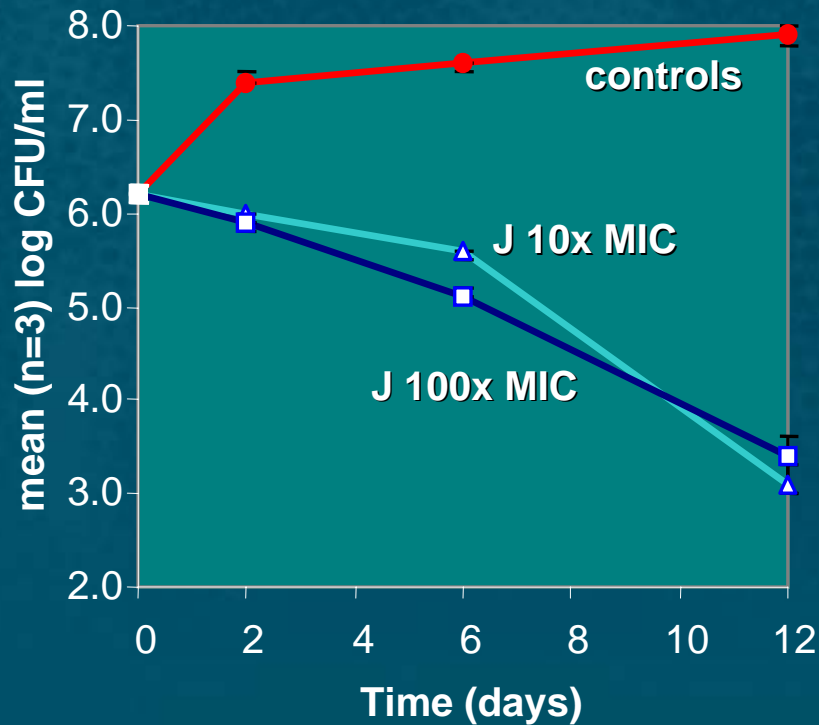
LFC LMVAFLI

H. sapiens

**Mutations in resistant
 mycobacteria**

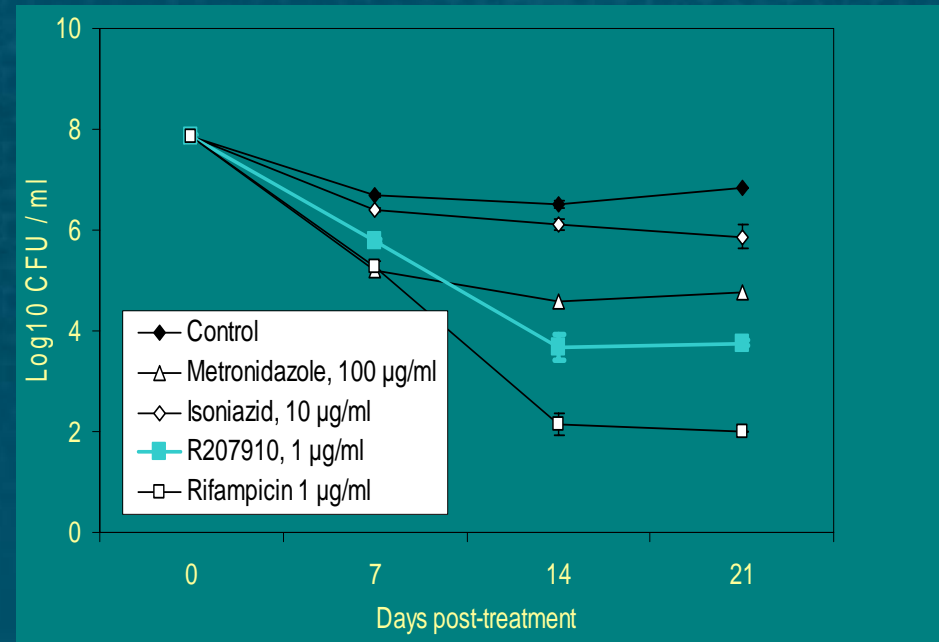
Andries et al, Science 2005, 307,223
 Petrella et al, AAC, 2006, 50, 2853

... Bactericidal for replicating **AND** non-replicating bacilli



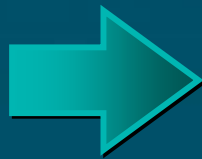
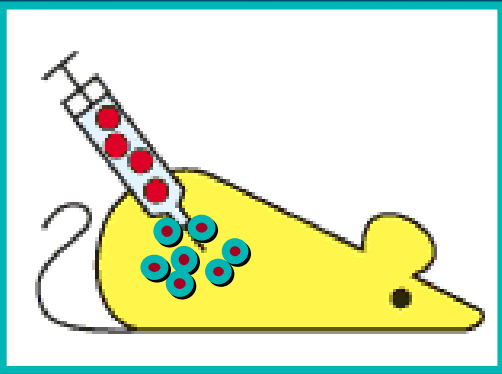
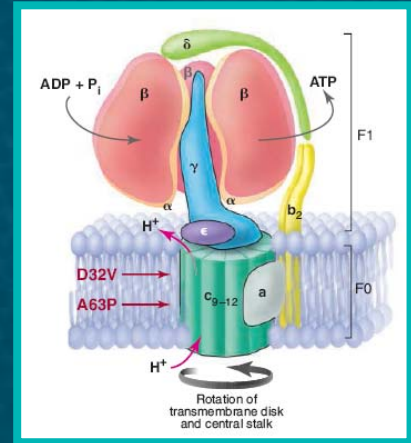
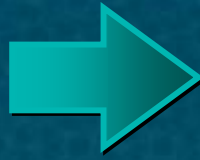
M. tuberculosis - replicating bacilli

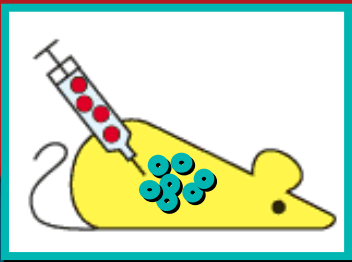
Andries et al., *Science* 2005, 307, 223



M. tuberculosis - non-replicating bacilli

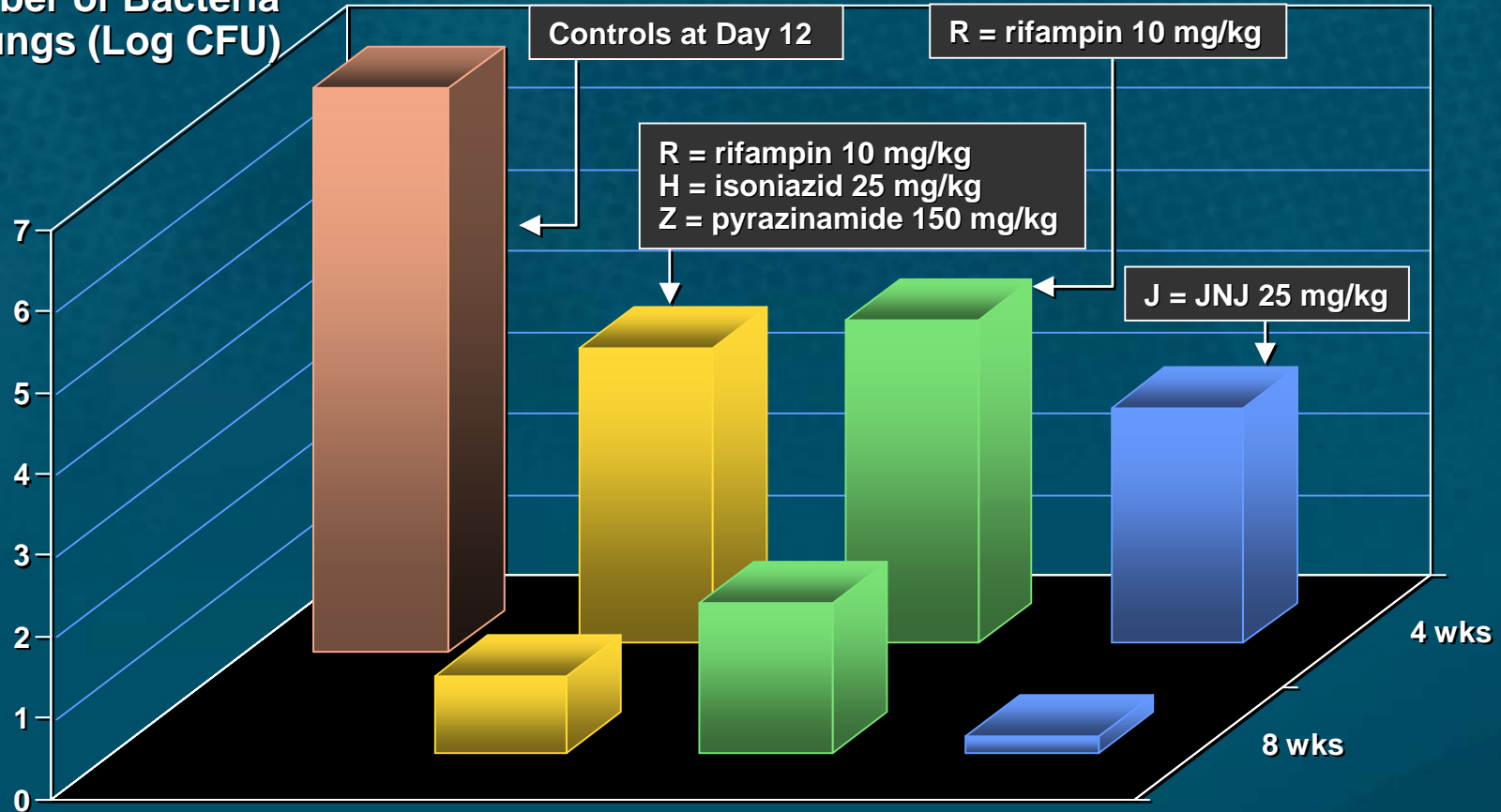
Koul et al., *JBC* 2008, 283, 25273



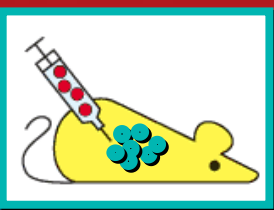


TMC207 (J) Is Sterilizing (Treatment 4 Weeks or 8 Weeks)

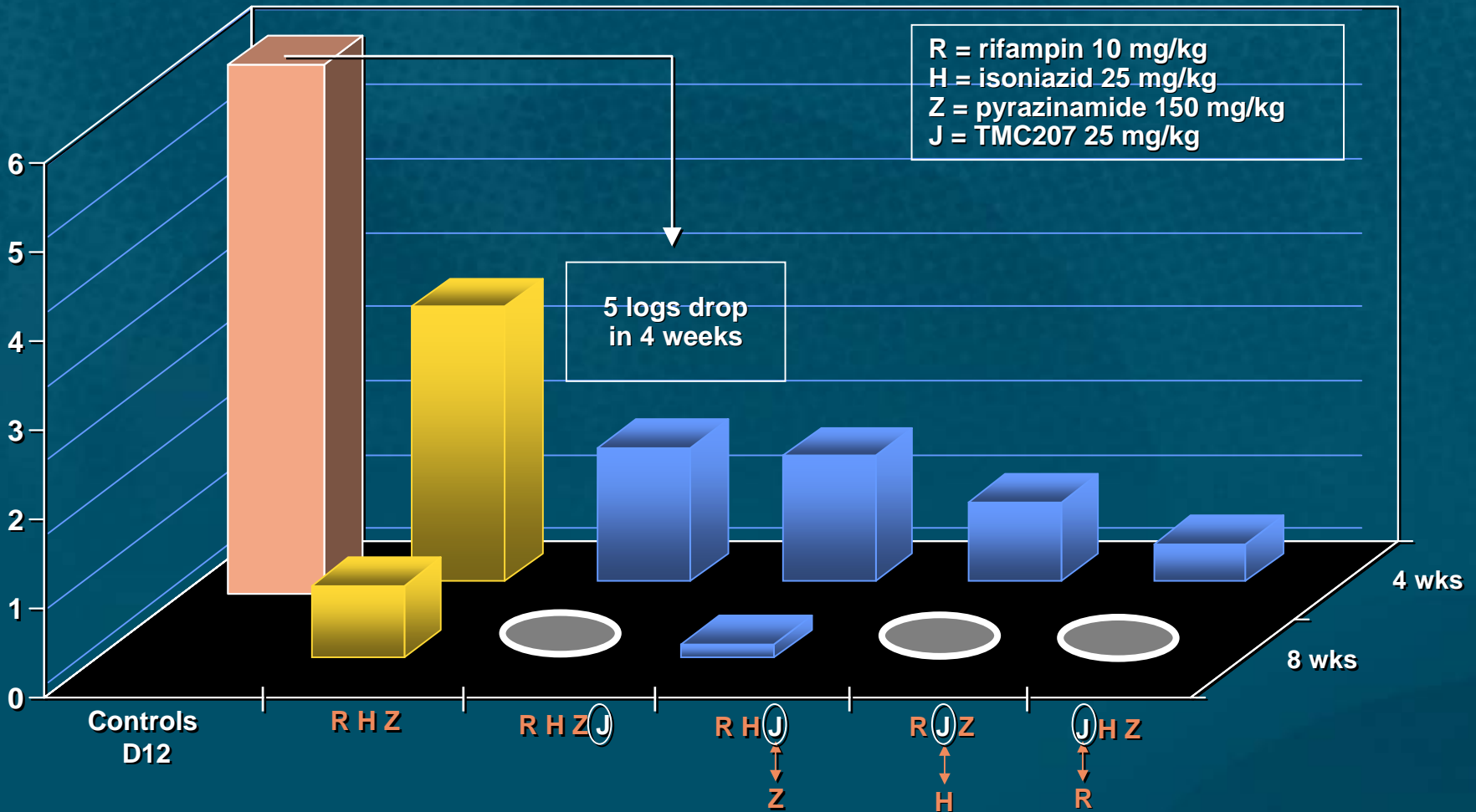
Number of Bacteria
in Lungs (Log CFU)

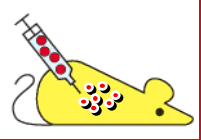


... and its sterilizing activity is better than that of rifampin

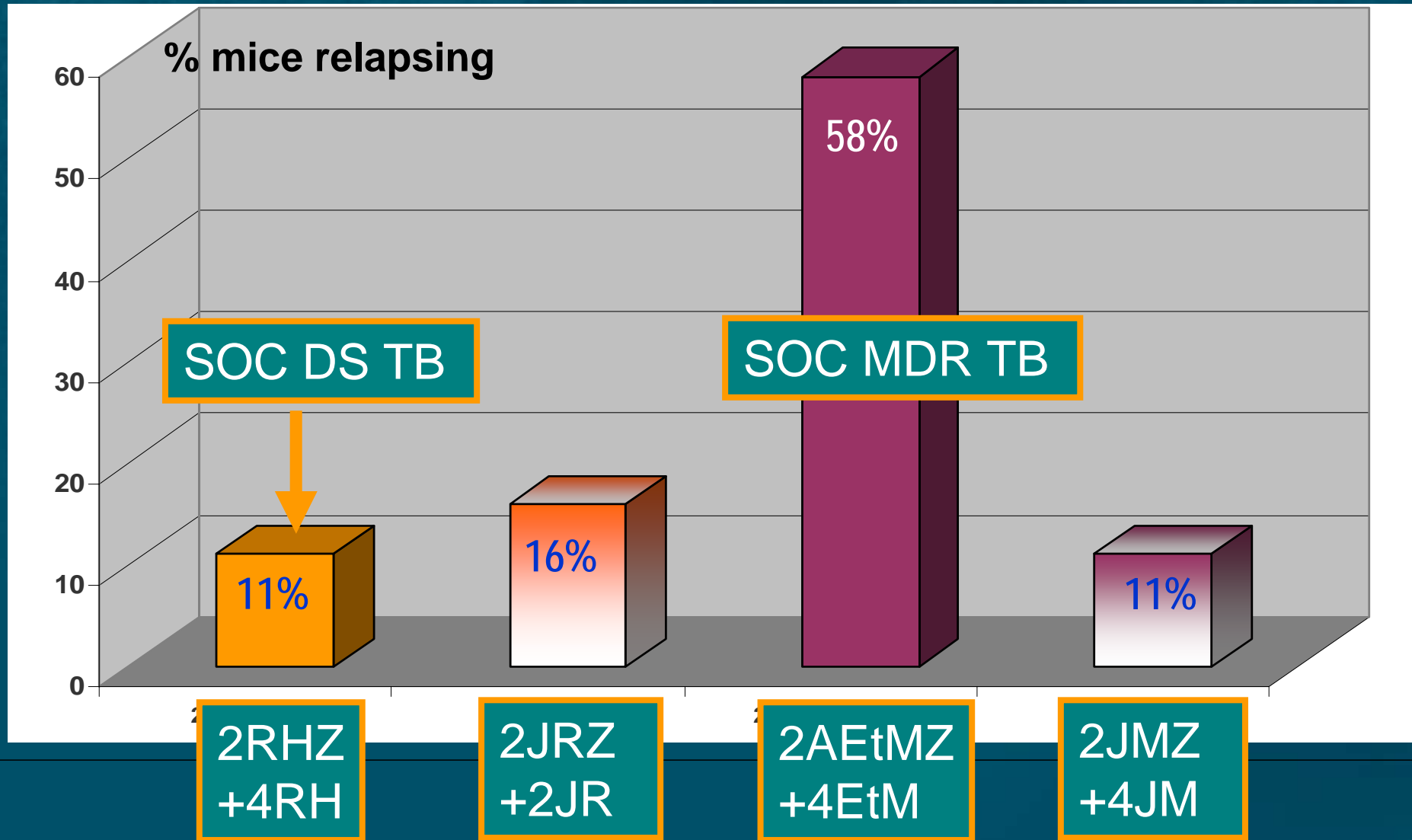


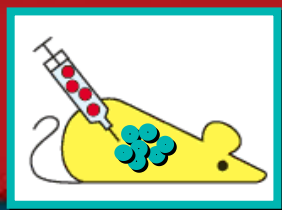
TMC207 (J) in Combination Therapy: Accelerated Drop in Bacterial Load



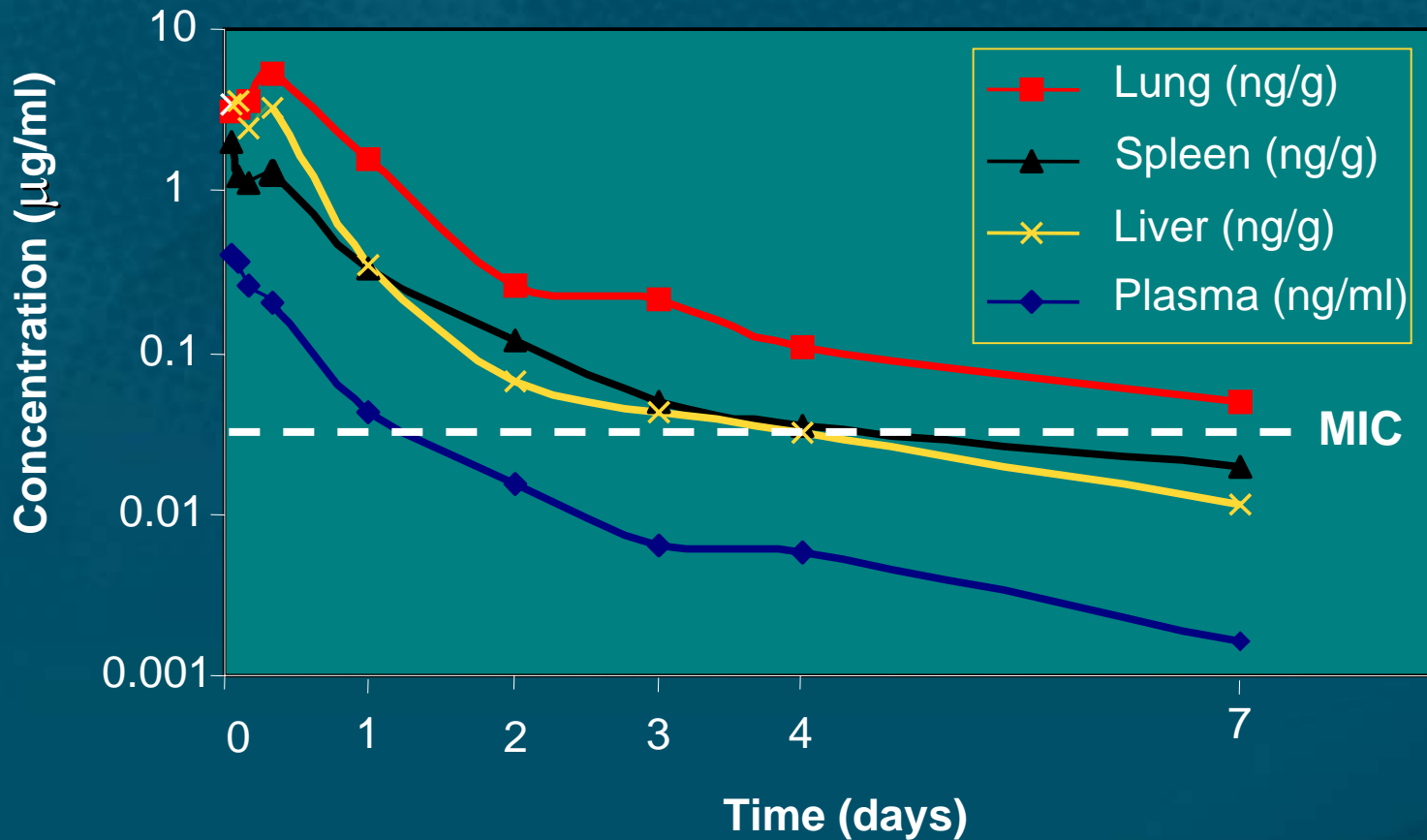


Confirmation of sterilizing activity in mice





Unique PK properties

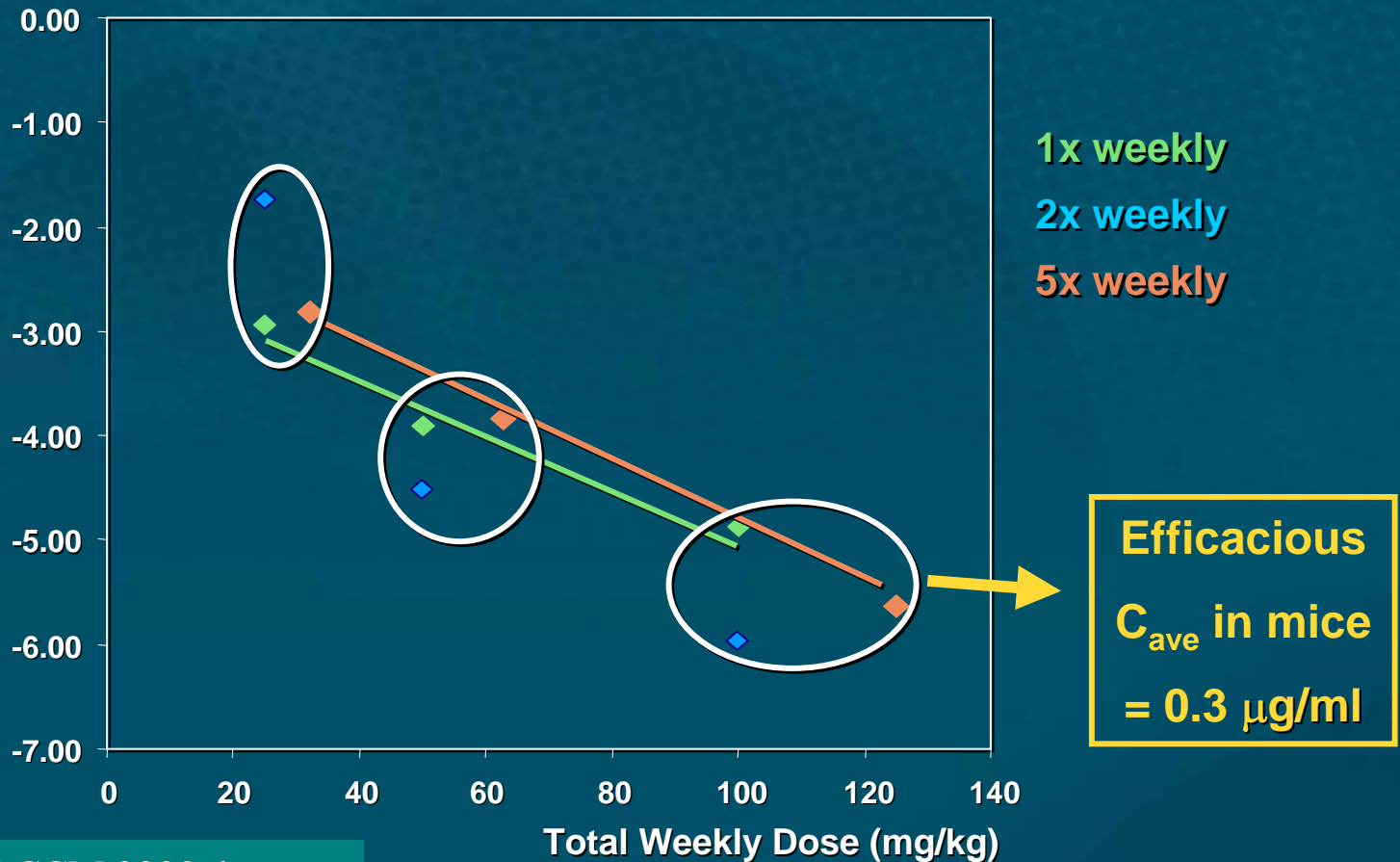


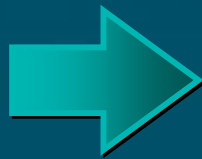
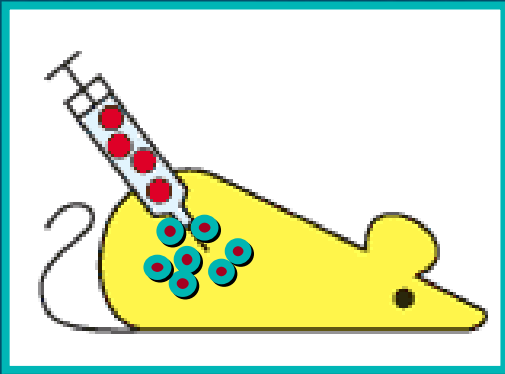
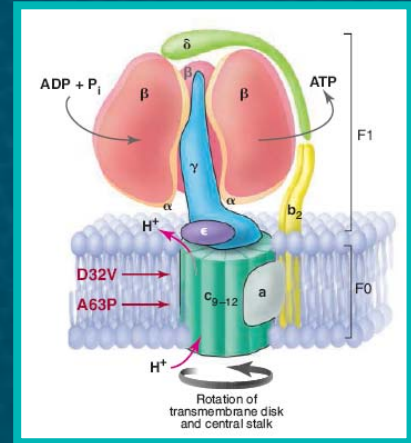
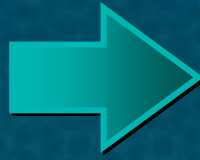
6.25 mg/kg PO in mice

The Weekly Dose Drives Efficacy!

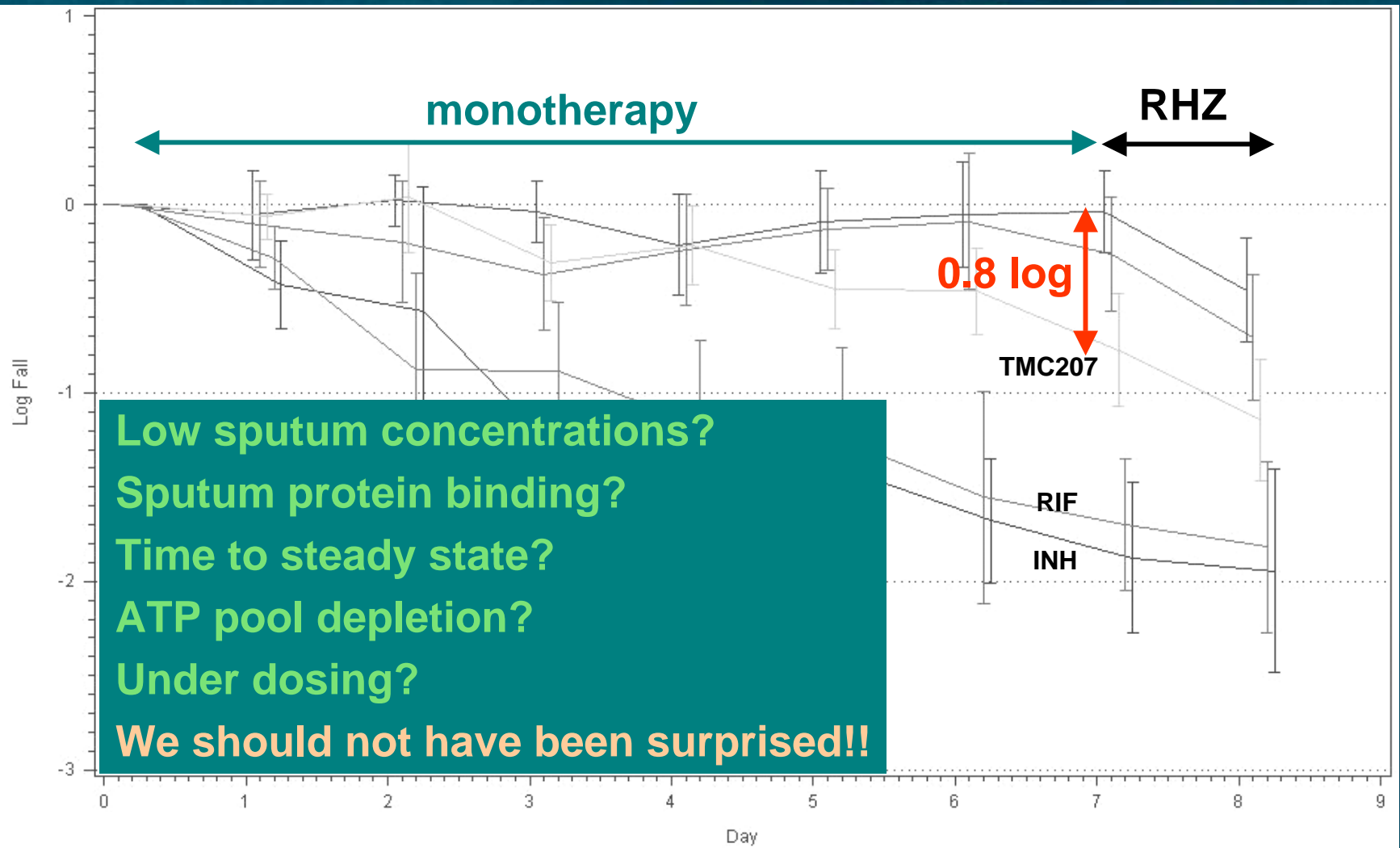


Drop in Bacteria After Two Months Treatment (Log CFU)





C202: Bactericidal effect in patients

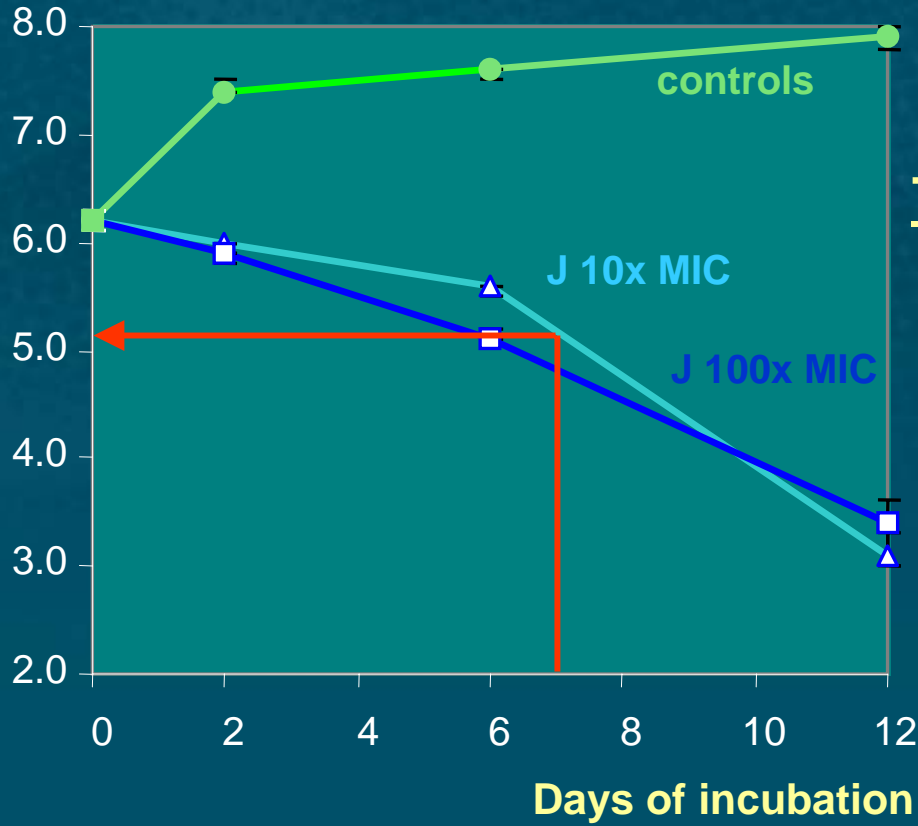




“in vitro EBA”

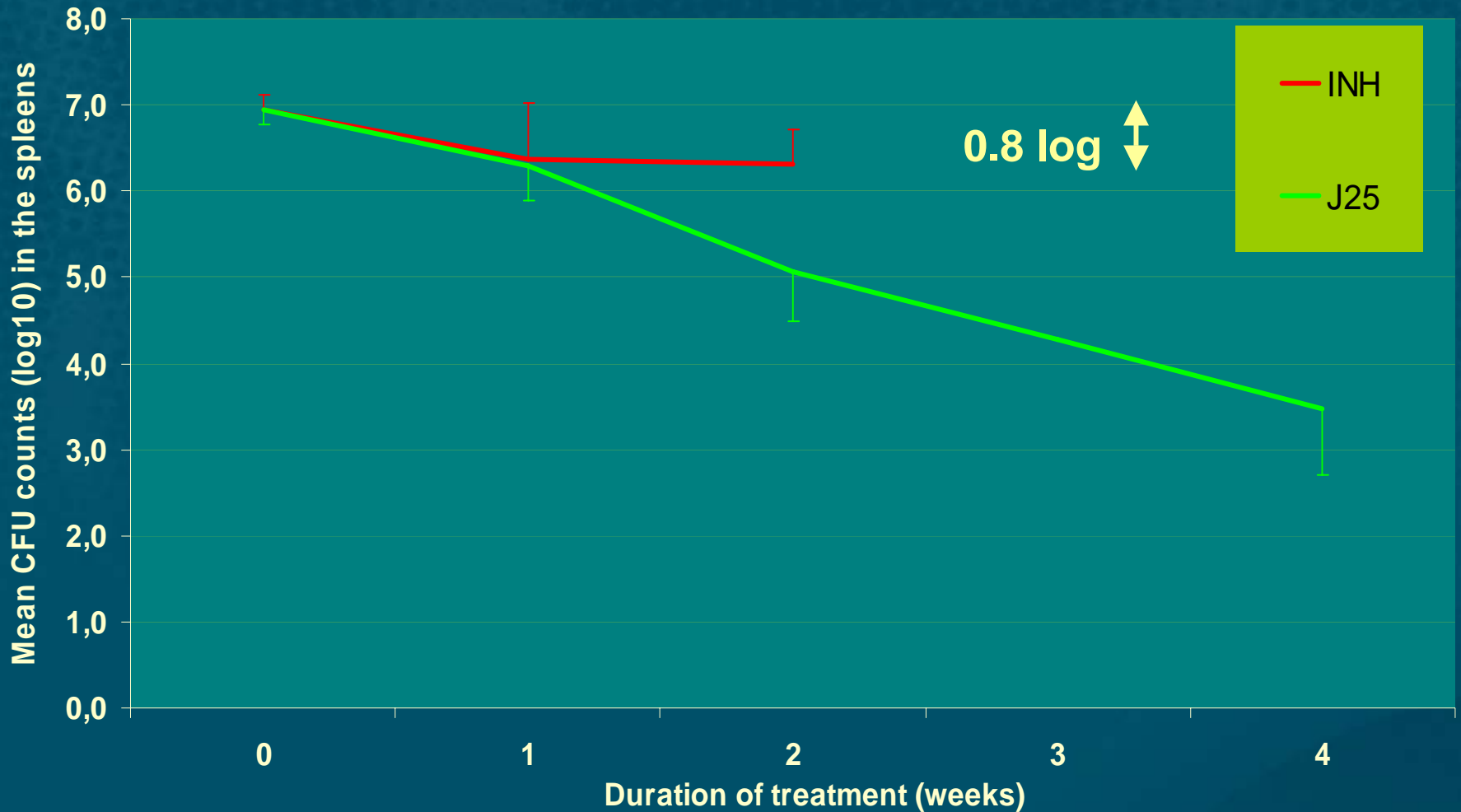
Log CFU
M. tuberculosis

1.0 log



Time-dependent killing!
...unlike INH, RIF, MOXI

Mouse EBA: killing kinetics of INH and J



C208: Trial Design

- Phase II, placebo-controlled, double-blind
- Patients with newly diagnosed MDR-TB
- Two-stage trial design
 - Stage 1 - Safety and dose determination
 - 8 weeks dosage TMC207/placebo and BR, then BR and 24 months follow-up
 - Dose regimen: 400 mg qd for 2 weeks followed by 200 mg three times weekly for 6 weeks
 - Stage 2 - Recruiting - full 6 month dosage

A pre-planned analysis of the Stage 1 results after 8 weeks of treatment is now available

Microbiological efficacy

- **Percentage patients converted**
(= 2 consecutive *negative* results in liquid media)
after 2 months of therapy

- **Drop in bacterial load**
(TB Colony Forming Units on solid media)

TMC207 could dramatically change the current treatment paradigm...



- Bactericidal properties
- Sterilizing properties
- Activity on MDR-TB
- PK profile
- Activity on dormant bacilli

.... and has the potential to address one of the biggest medical needs in history