"PK/PD" type of modelling approach to support time-kill data interpretation of cefoxitin for the treatment of *Mycobacterium abscessus*

Mycobacteria, Angers, 27th June 2019

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Mycobacterium abscessus

- ✓ Non Tuberculosis Mycobacteria
- ✓ Pulmonary infections

- General treatment:
  Tri-antibiotic combination:
  one **macrolide** (clarithromycin) +
  two antibiotics (amikacin, cefoxitin, imipenem or linezolid (by ATS))

- Treatment: long, costly, often associated with drug related toxicity and rapid development of drug resistance

- High treatment failure

Koh W *et al*. 2002
Griffith *et al.* 2007

Cefoxitin

- ✓ β-lactam antibiotic
- ✓ Time-dependent activity

Few challenges during *in vitro* experiments against *M. abscessus*

- ✓ not stable over time
- ✓ MIC determination after 3 days – misleading !
- ✓ Time-kill kinetics assay for long durations

Rominski *et al.* 2017

Study *in vitro* pharmacodynamics of FOX

1. Characterize FOX degradation over time

→

2. Develop a PK/PD type modeling approach to correct for degradation

Rominski *et al.* 2017

Why Regrowth?

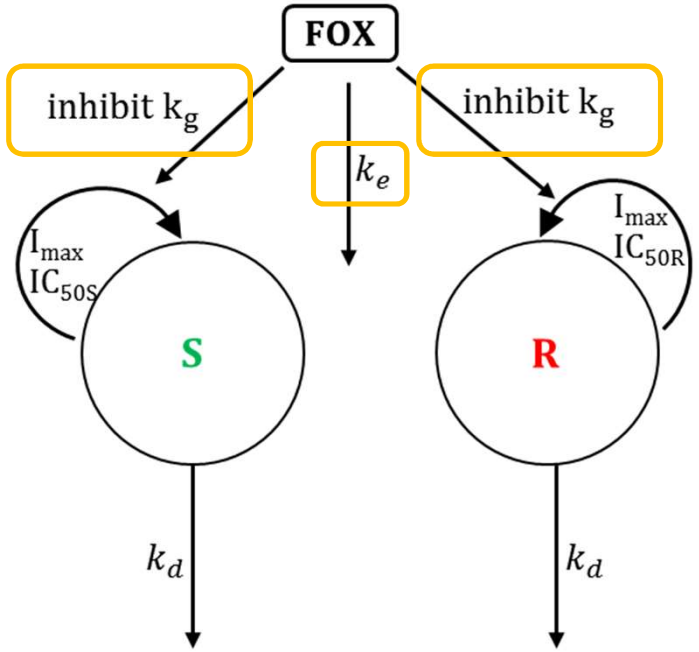
Experimental Design

Ferro *et al.* Identified a FOX resistant (R) subpopulation pre-existing at time 0

Growth inhibition model with single homogeneous bacterial population (S)

FOX is bacteriostatic against *M. abscessus*

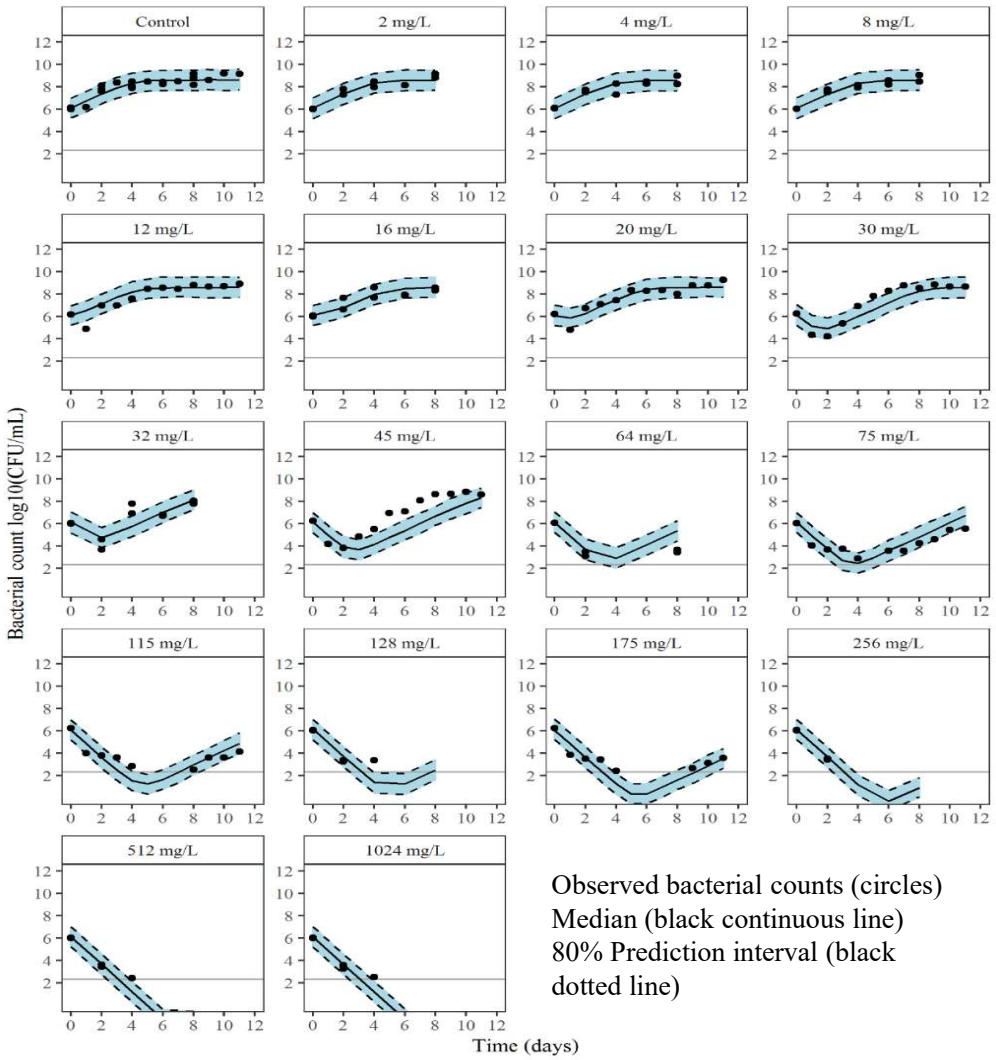
Growth inhibition model, **two subpopulations S & R** and **FOX degradation (k_e)** PK/PD type modeling approach using NONMEM



Schematic representation of final PK/PD type model

Lefebvre *et al.* 2016
Ferro *et al.* 2016

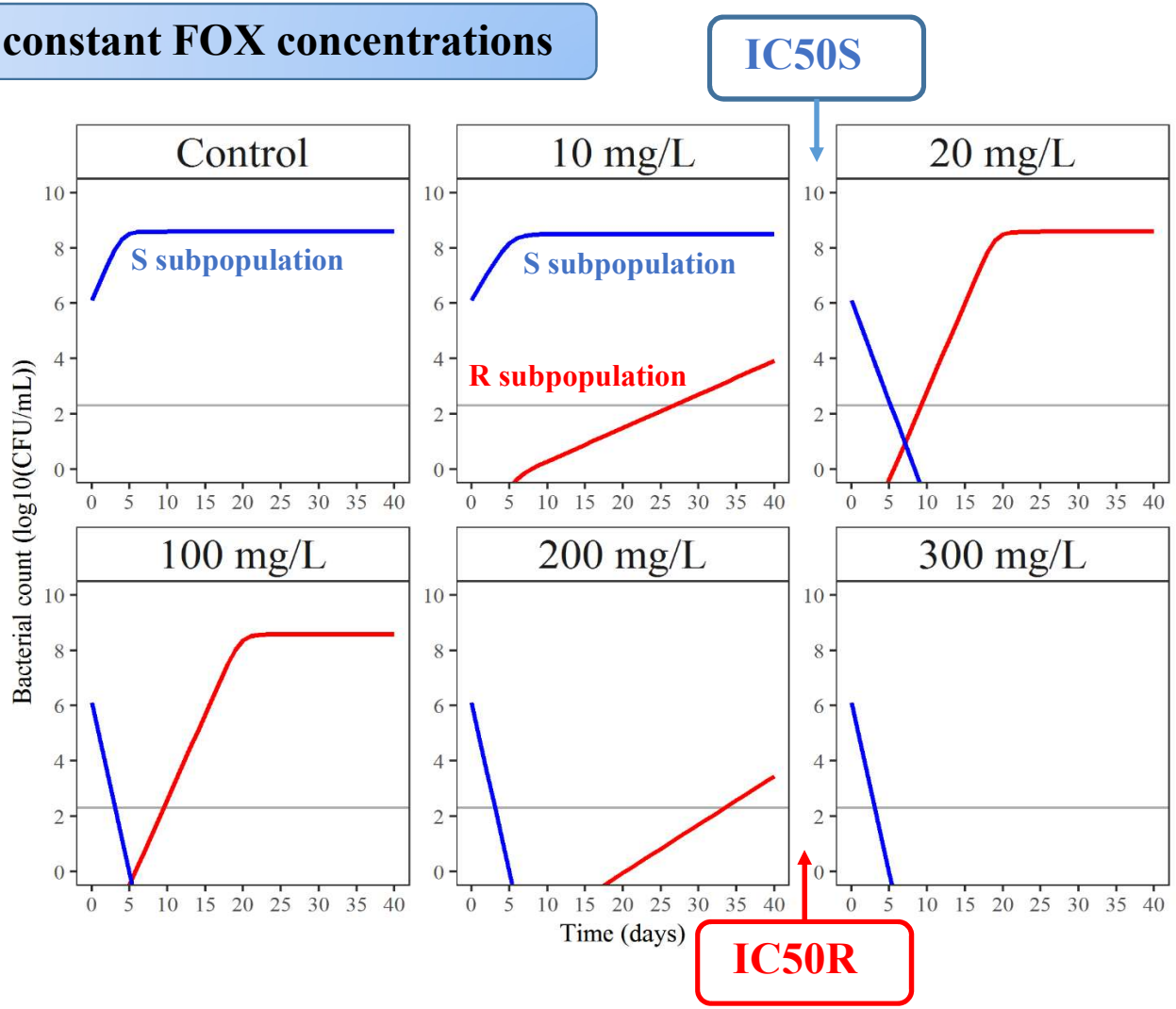
Results



Observed bacterial counts (circles)
Median (black continuous line)
80% Prediction interval (black dotted line)

Parameter (units)	Estimation (%RSE)
LGINOC (Log_{10}CFU/mL)	6.1 (1%)
K_g (day^{-1})	4.3 (6%)
B_{max} (Log_{10}CFU/mL)	9.05 (1%)
K_d (day^{-1})	2.83 (7%)
I_{max}	1 (fixed)
IC_{50S} (mg/L)	16.2 (11%)
IC_{50R} (mg/L)	252 (20%)
K_e (day^{-1})	0.438 (fixed)
MUTF	-9.66 (6%)
γ	4.8 (39%)

Simulations with constant FOX concentrations



Conclusion

- ✓ A PK/PD type model allows to accurately characterize FOX anti-microbial efficacy by taking into account its degradation during *in vitro* study

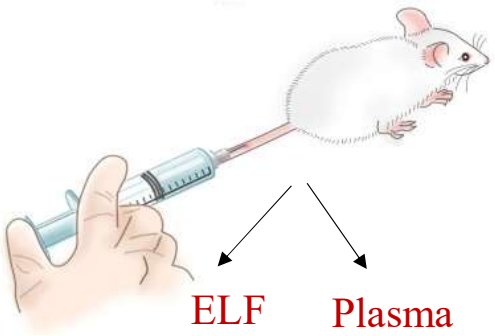
Perspective

- ✓ Use nebulization to achieve high concentrations at infection site

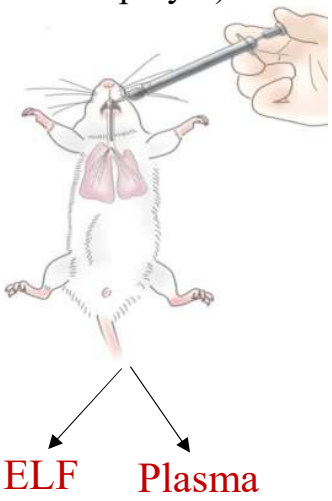
Experimental Design

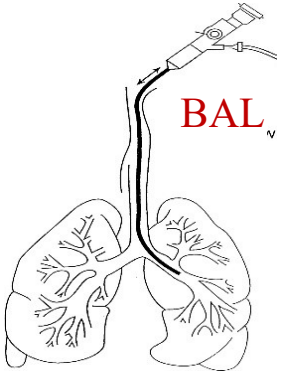
healthy Sprague-Dawley rats
Dose: 90 mg/kg, 5 groups (n=49)

IV bolus: 1 mL
(In tail vein by syringe)



Intratracheal: 100µL
(by microsprayer)

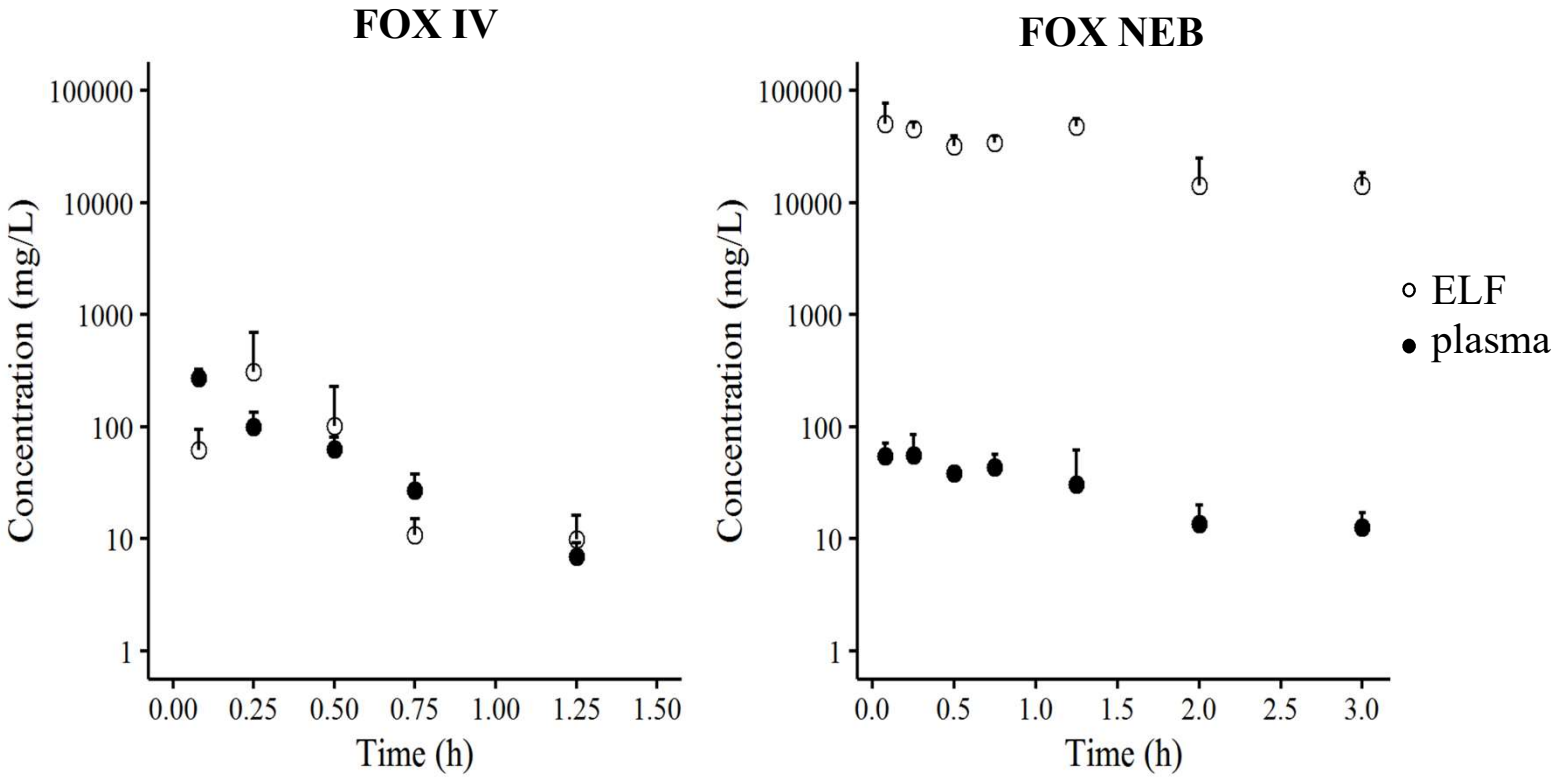


ELF → 

Plasma → By puncturing heart

Samples:
- For cefoxitin: 0.08h, 0.25h, 0.5h, 0.75h & 1.25h
- Urea measurement

Noncompartmental analysis using Phoenix NLME



✓ $C_{ELF} > C_{plasma}$ after NEB

Conclusion

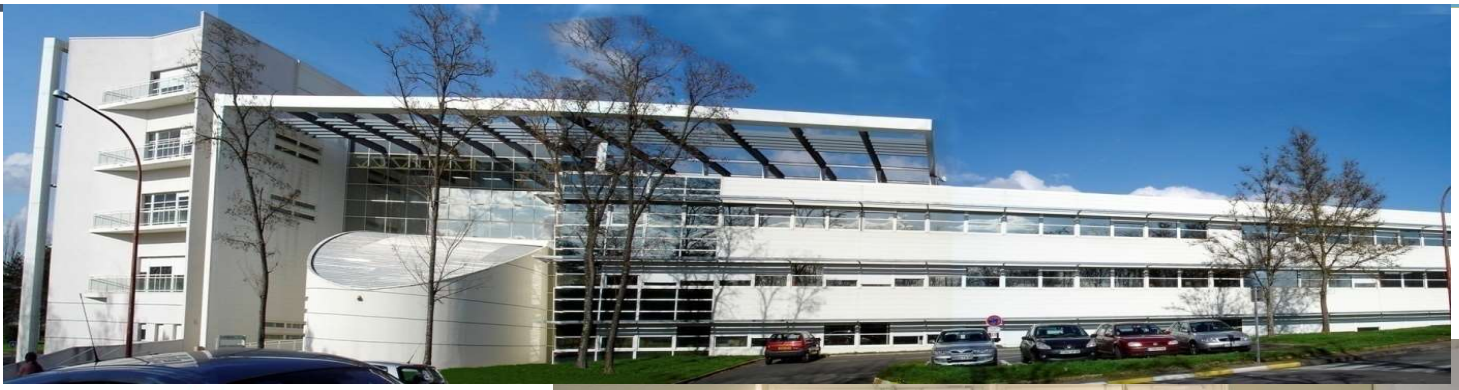
- ✓ A PK/PD type model allows to accurately characterize FOX anti-microbial efficacy by taking into account its degradation during *in vitro* study

Perspective

- ✓ Use nebulization to achieve high concentrations at infection site
- ✓ Extend PK/PD characterization of FOX in combination with other antibiotics

Acknowledgements

Pre-clinical pharmacokinetic and pharmacodynamic data to support cefoxitin nebulization for the treatment of *Mycobacterium abscessus.*
Mehta S, Aranzana-Climent V, Rammaert B, Grégoire N, Marchand S, Couet W, Buyck J.M.
Antimicrobial Agents and Chemotherapy, June 2019 63:e02651-18, doi:10.1128/AAC.02651-18



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