

# Pharmacodynamic comparison of antibiotic activity against *Pseudomonas aeruginosa* in models of persistent infection (intracellular infection, biofilm)

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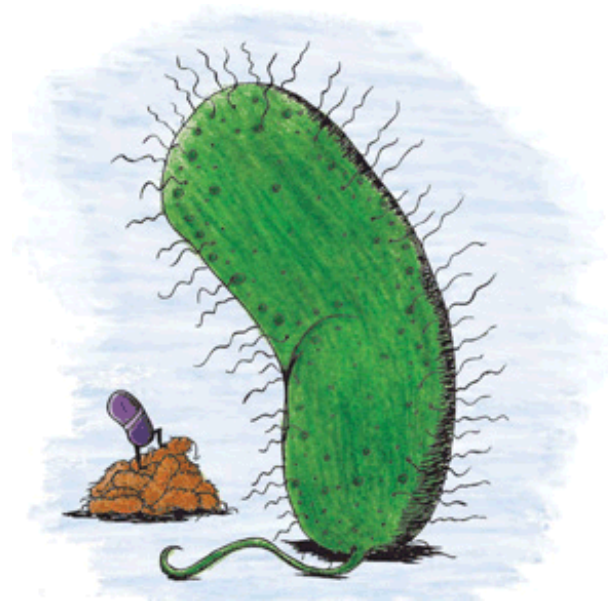
[www.facm.ucl.ac.be](http://www.facm.ucl.ac.be)

# Infectious diseases: No ESKAPE !

*E. faecium*

*E. aerogenes*

*S. aureus*



*P. aeruginosa*

*K. pneumoniae*

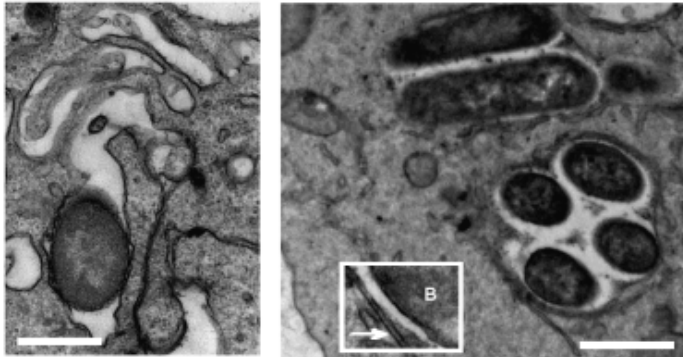
*A. baumannii*

# Beside resistance ... persistent forms of infections

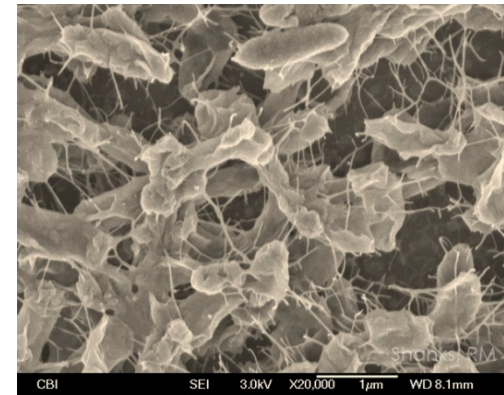


Intracellular survival

Biofilms



*Buyck & Van Bambeke*



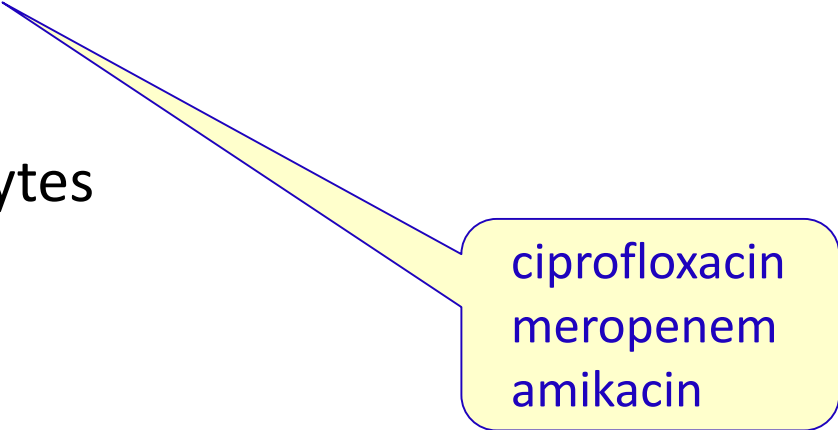
<http://eyemicrobiology.upmc.com>

→ Protection against host defenses and antibiotics

# Aim of the study

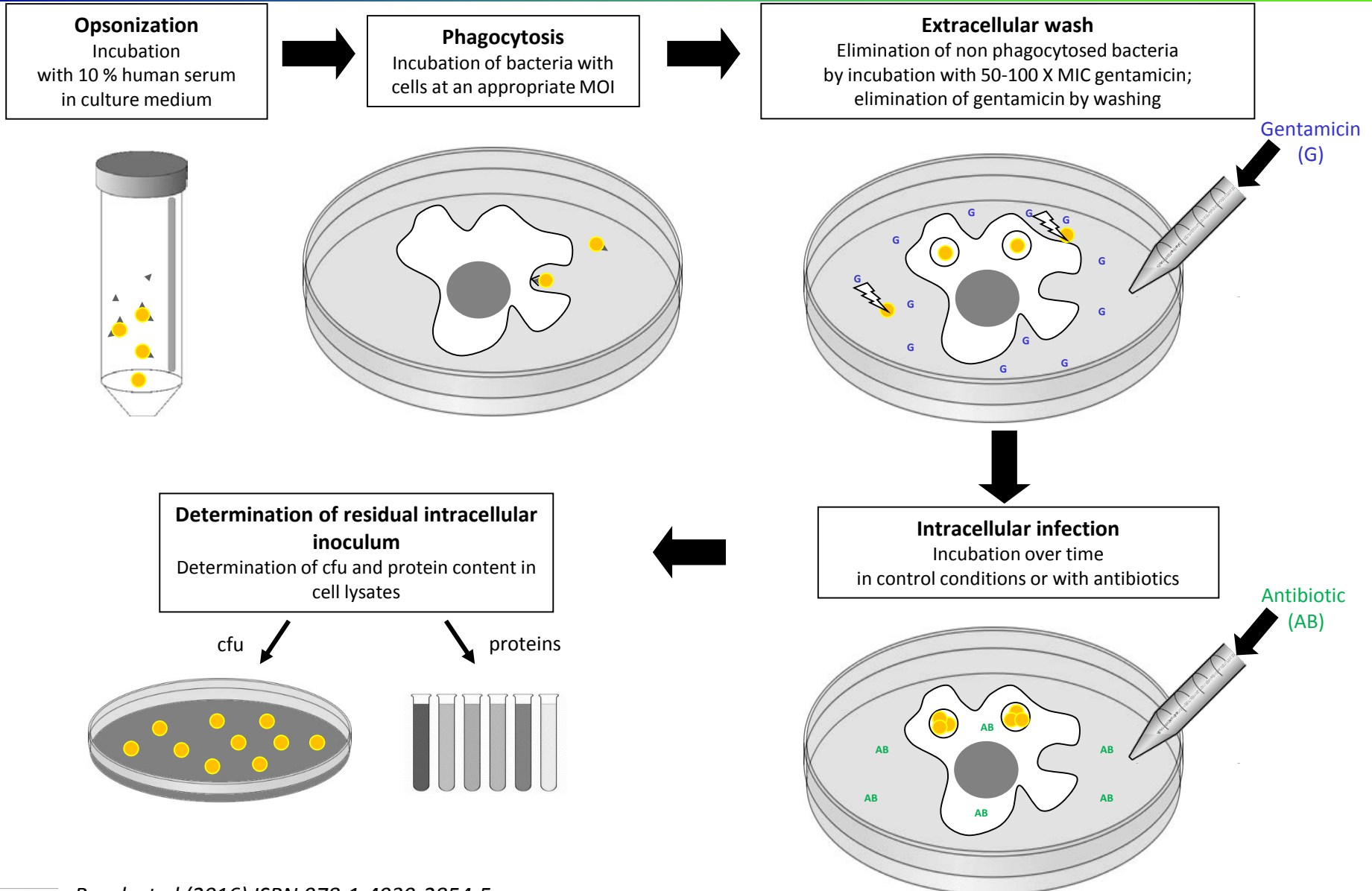
to study antibiotic activity against the reference strain PAO1  
in in-vitro models of

- infected THP-1 monocytes
- mature biofilms

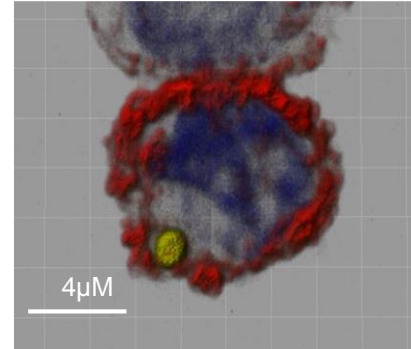
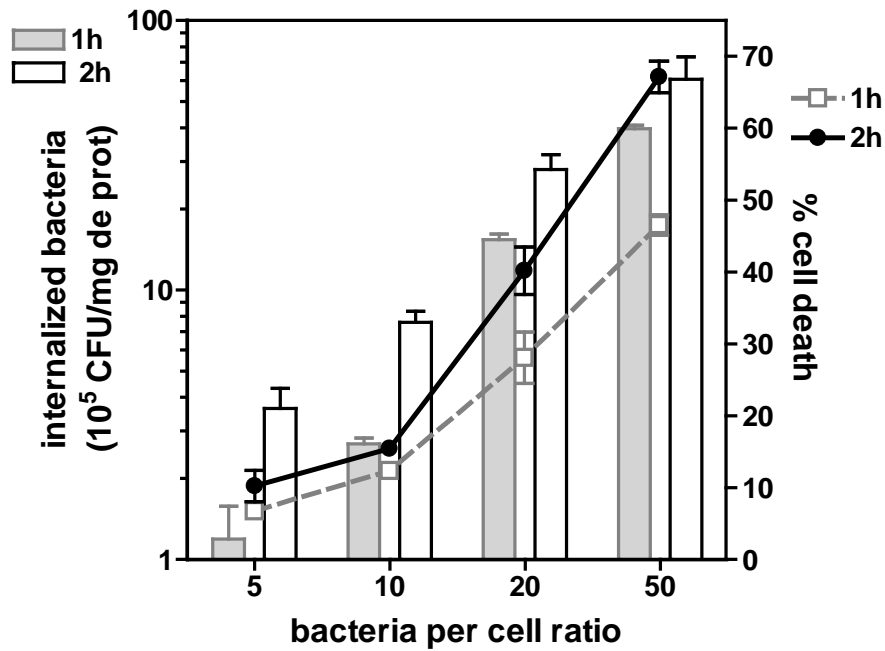


ciprofloxacin  
meropenem  
amikacin

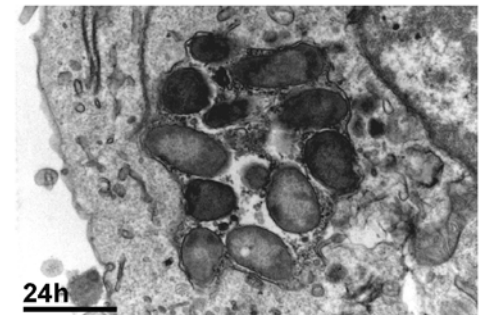
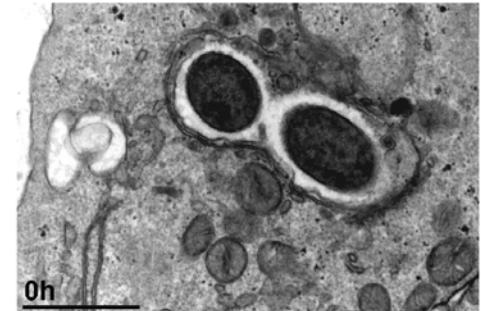
# In vitro model of intracellular infection



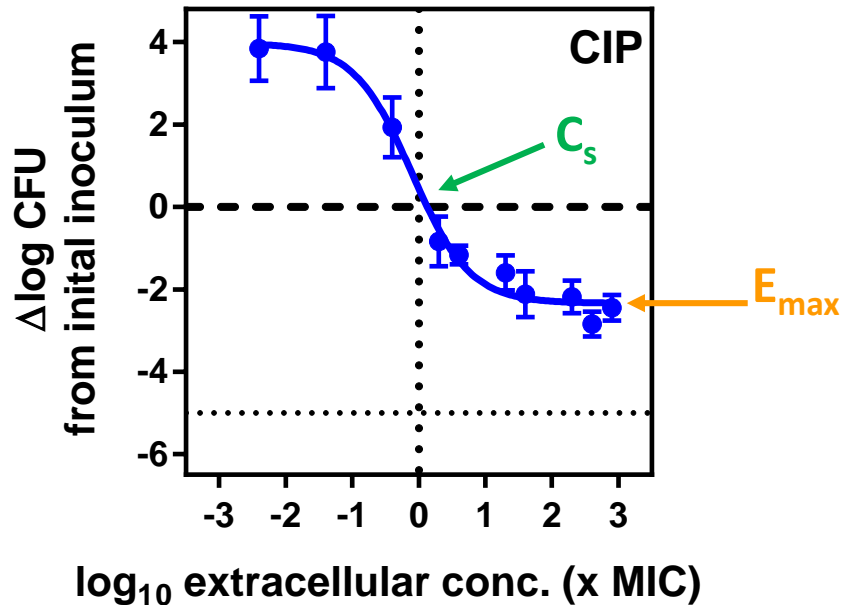
# Setting up the model of intracellular infection



Blue: nucleus  
Red: Actin  
Green: Bacteria



# Activity of antibiotics against intracellular *P. aeruginosa*



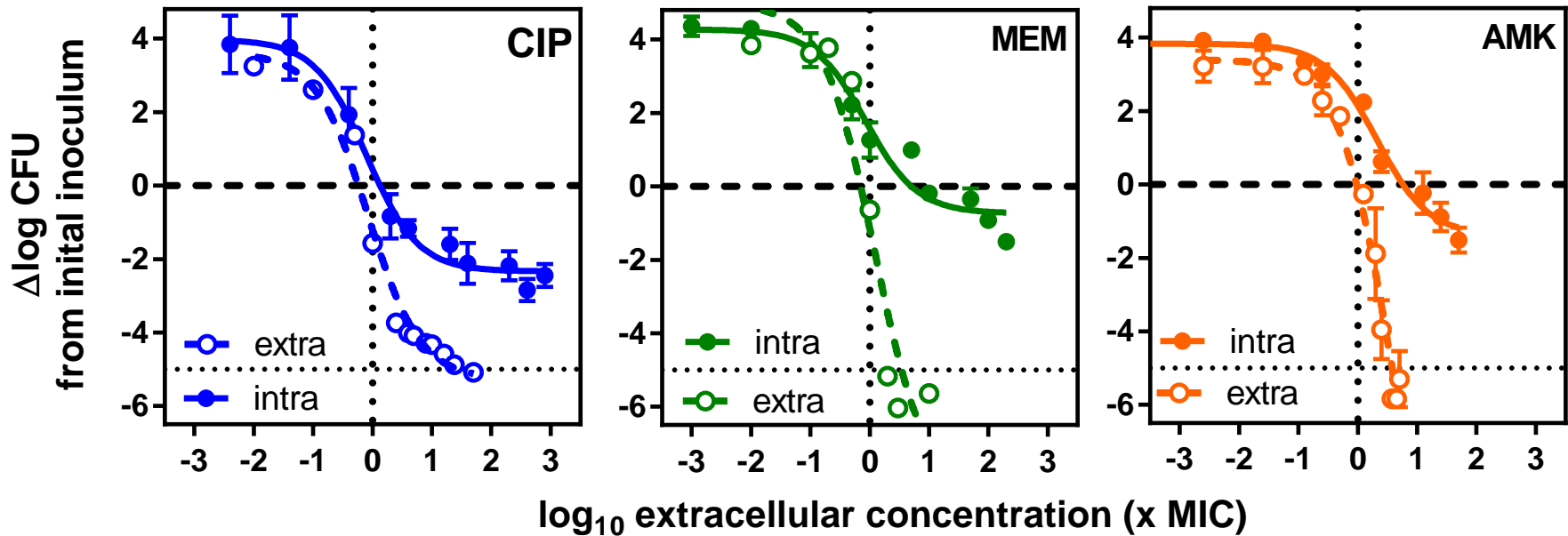
## $C_s$ (static concentration): relative potency

- Estimation of the concentration needed to reach a specified effect
- Measure of the « intracellular MIC »

## $E_{max}$ (maximal efficacy)

- Estimation of the maximal reduction in inoculum for an infinitely large concentration
- Measure of the killing capacity

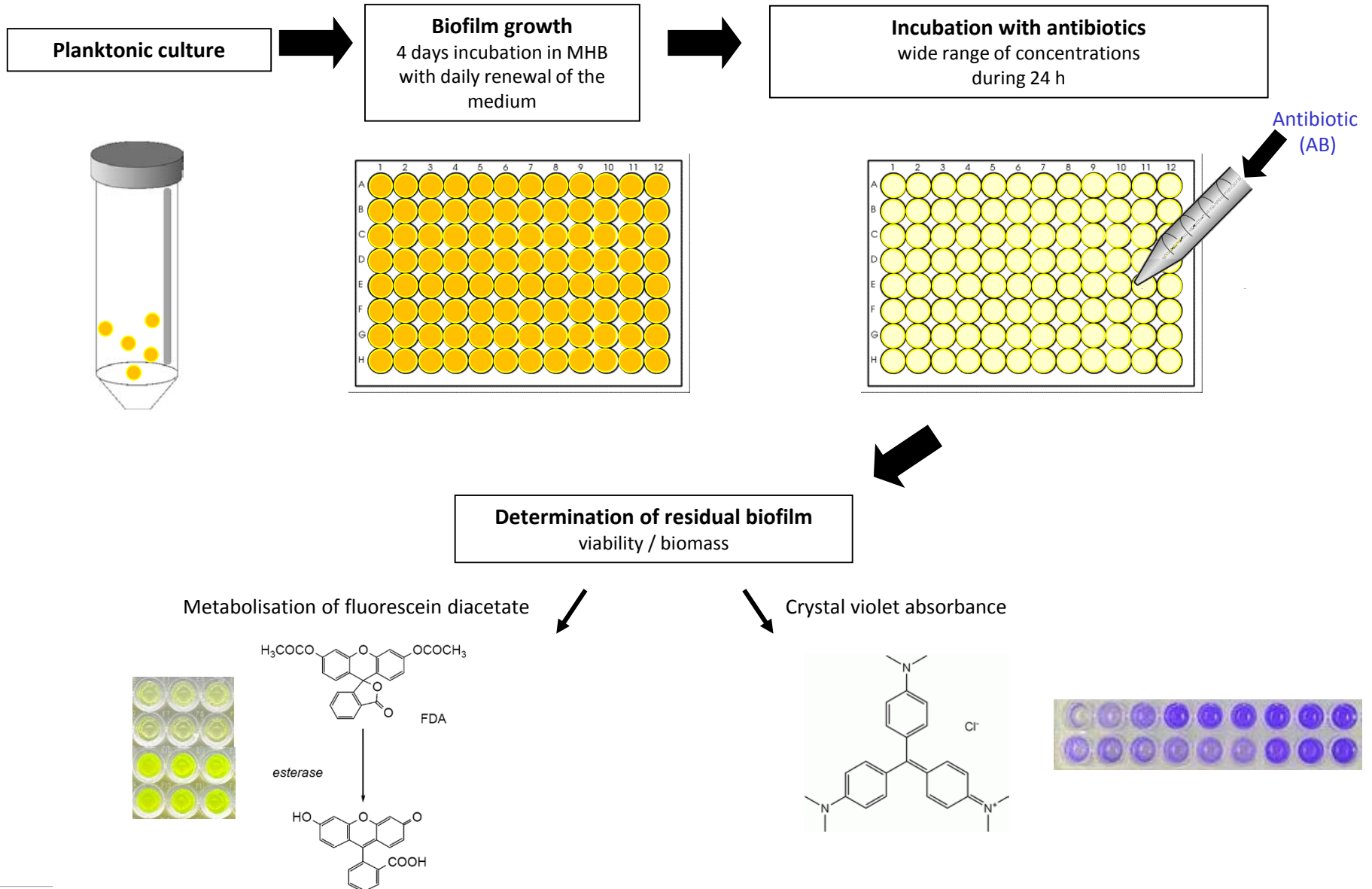
# Activity of antibiotics against intracellular *P. aeruginosa*



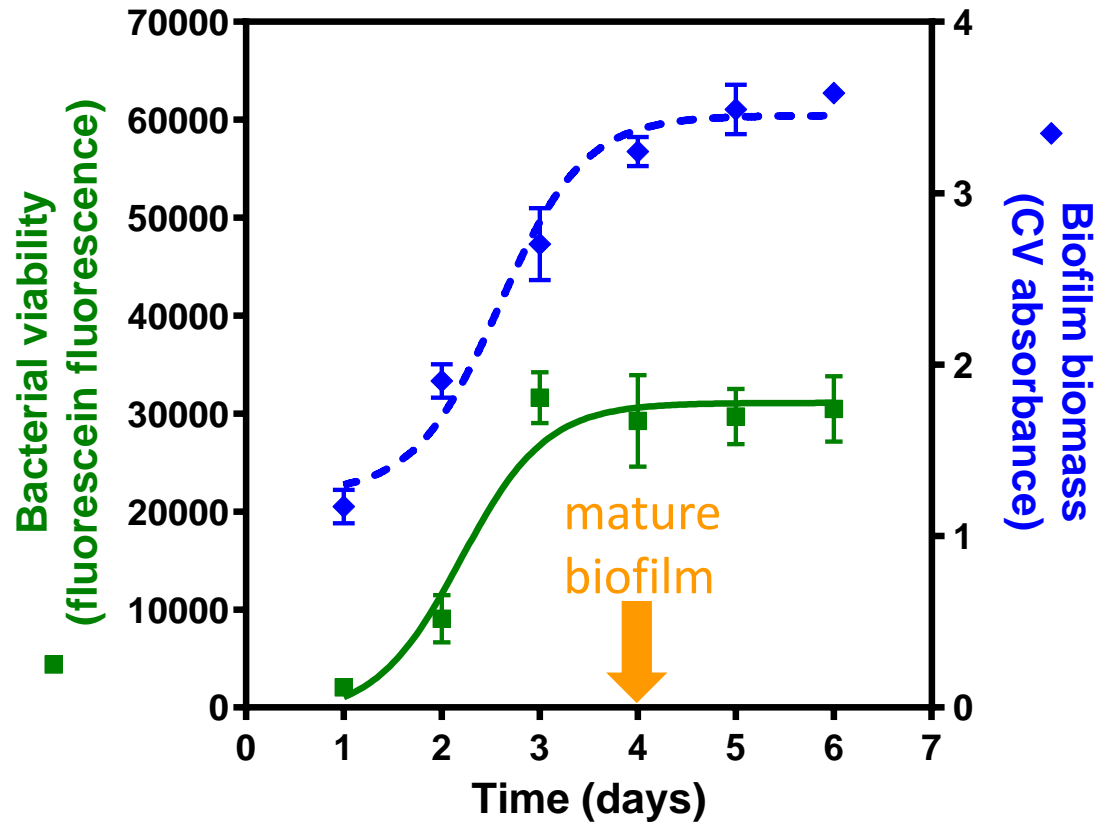
- $E_{\max}$  (efficacy): intracellular  $\ll$  extracellular
- $C_s$  (relative potency): intracellular  $\sim$  extracellular



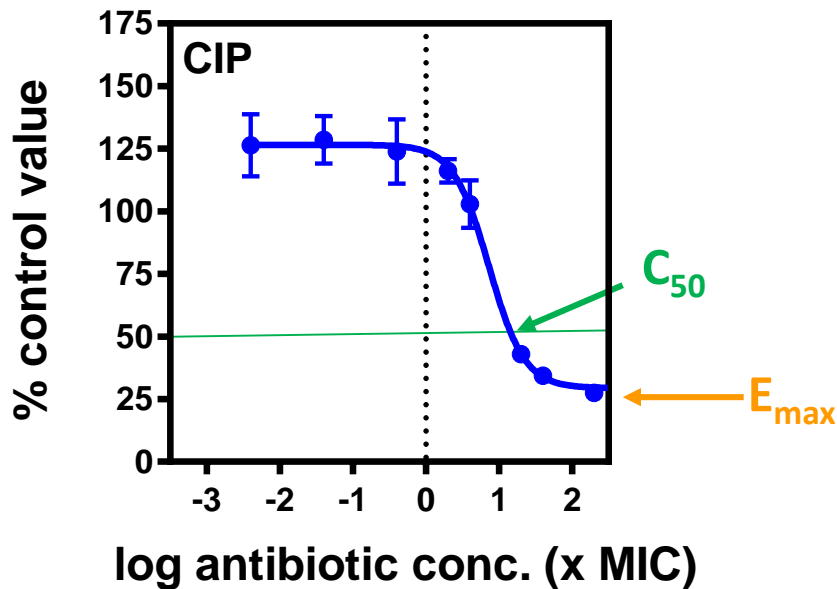
# In vitro model of biofilm



# Setting up the model of biofilm



# Activity of antibiotics against biofilms of *P. aeruginosa*



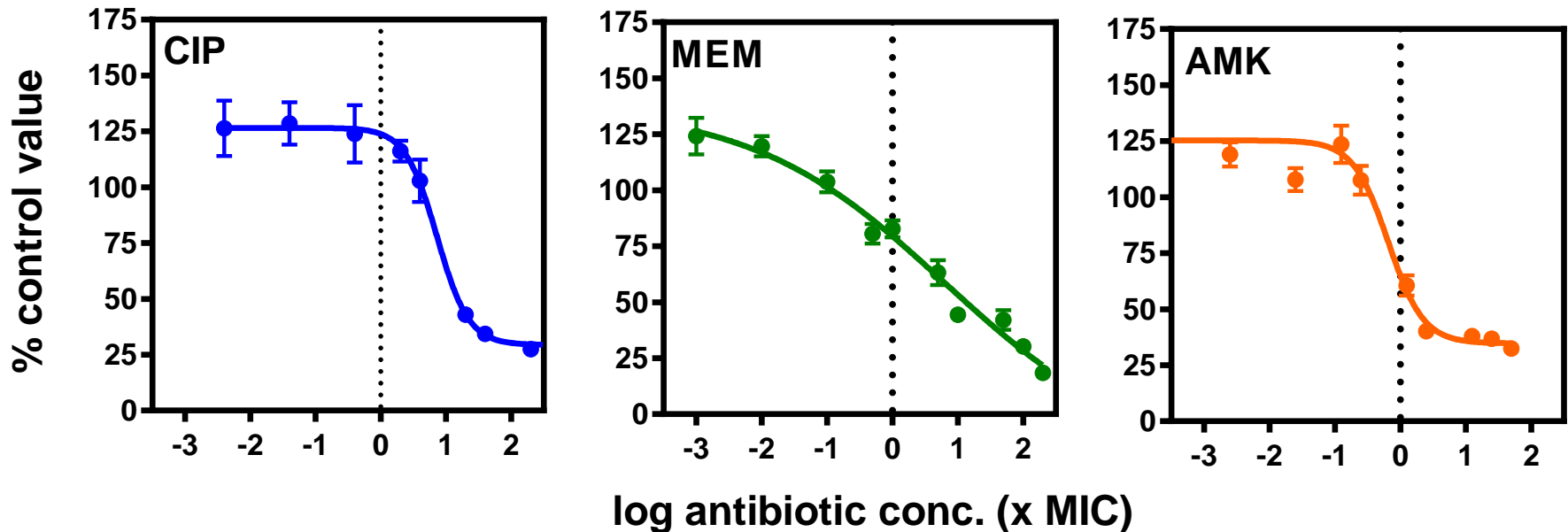
## $C_{50}$ (conc. reducing viability of 50%): relative potency

- Estimation of the concentration needed to reach a specified effect
- Measure of the relative potency

## $E_{max}$ (maximal efficacy)

- Estimation of the maximal reduction in viability for an infinitely large concentration
- Measure of the killing capacity

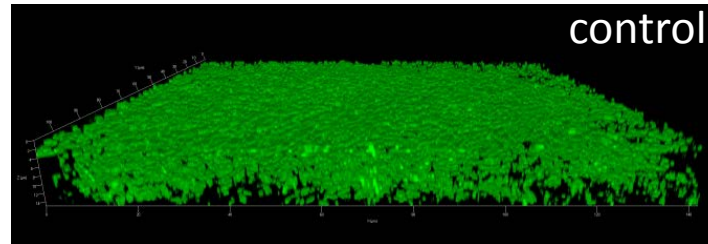
# Activity of antibiotics against biofilms of *P. aeruginosa*



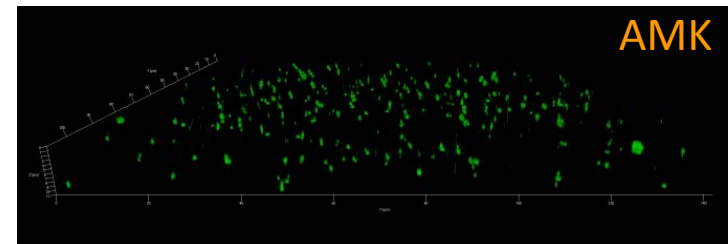
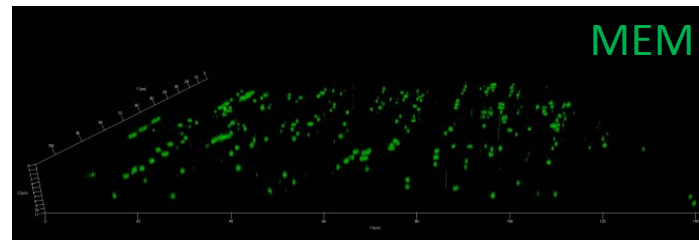
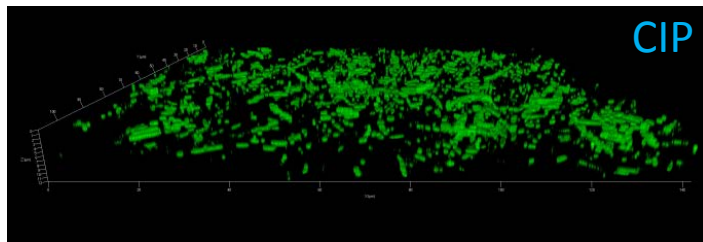
- $E_{max}$  (efficacy): biofilm  $\lll$  broth (no complete eradication)
- $C_{50}$  (relative potency): biofilm  $\lll$  broth (low effect at the MIC)

# Activity of antibiotics against biofilms of *P. aeruginosa*

GFP-expressing  
*P. aeruginosa*

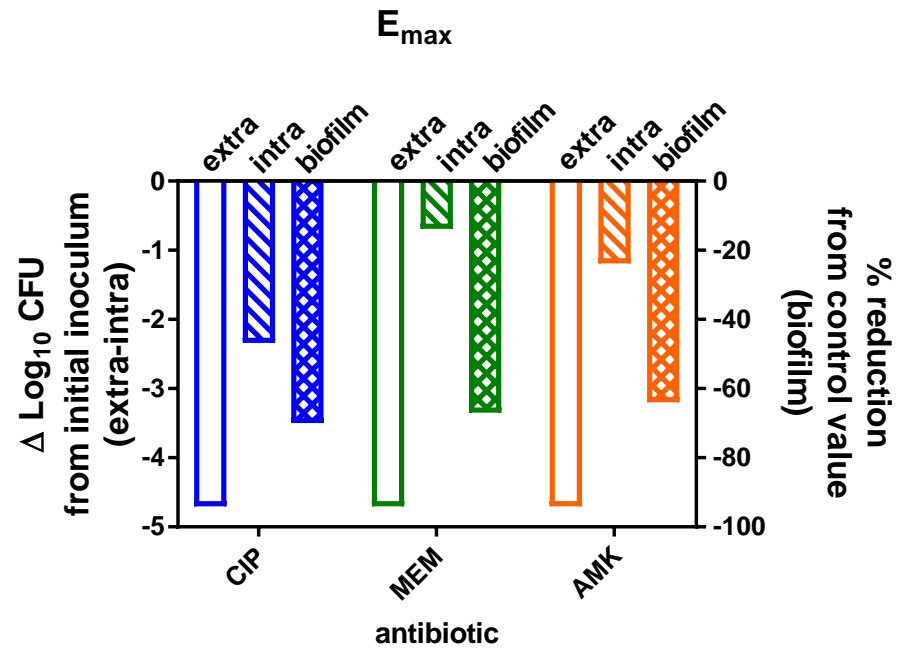
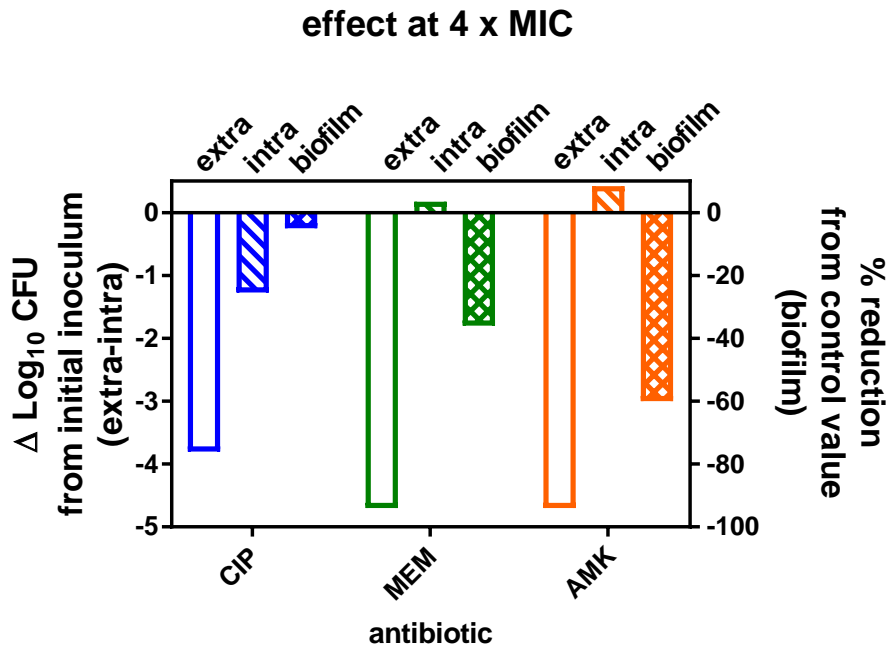


Antibiotics at 50 x MIC



confirmation of incomplete  
eradication of living bacteria

# Comparison of PD parameters in these models

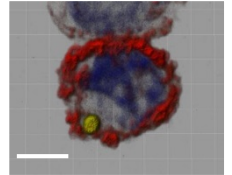


- Lower activity at equipotent concentration
  - Lower E<sub>max</sub>
- } intracellularly and in biofilm vs. extracellularly

# Conclusions

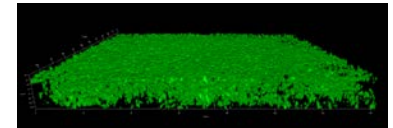
## ■ Intracellularly

- Antibiotics equipotent as extracellularly  
→ intracellular bioavailability similar for all classes
- Antibiotics much less efficacious than extracellularly  
→ intracellular bacterial less responsive to antibiotics



## ■ In biofilms

- Antibiotics less potent than in planktonic cultures  
→ low bioavailability in biofilms
- Antibiotics much less efficacious than extracellularly  
→ bacteria less responsive to antibiotics



- ## ■ Innovative strategies needed to act upon these persistent forms of infections !

