Mouse Models for Antibacterial PK/PD

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Disclosures

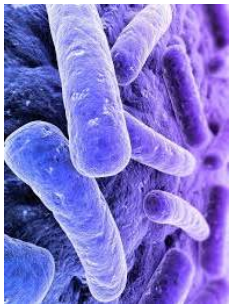
- Research grants and/or consulting: Astellas, Merck, GSK, Scynexis, Cubist, Forrest, Rempex, Dipexium, Nexcida, Durata, Actelion, Zavante, Paratek, Meiji, Geom, Cidara, Melinta, Theravance, Iterum, Sentinella, Kalidex, Novozymes, Trius, Taxis
- Member ABIM

Outline

- What PK/PD questions can the models address?
- What study variables impact PK/PD answers?
- Can the model PK/PD results predict clinical efficacy?

Why do we conduct PK-PD infection models?

Improving the Probability of Positive Outcome



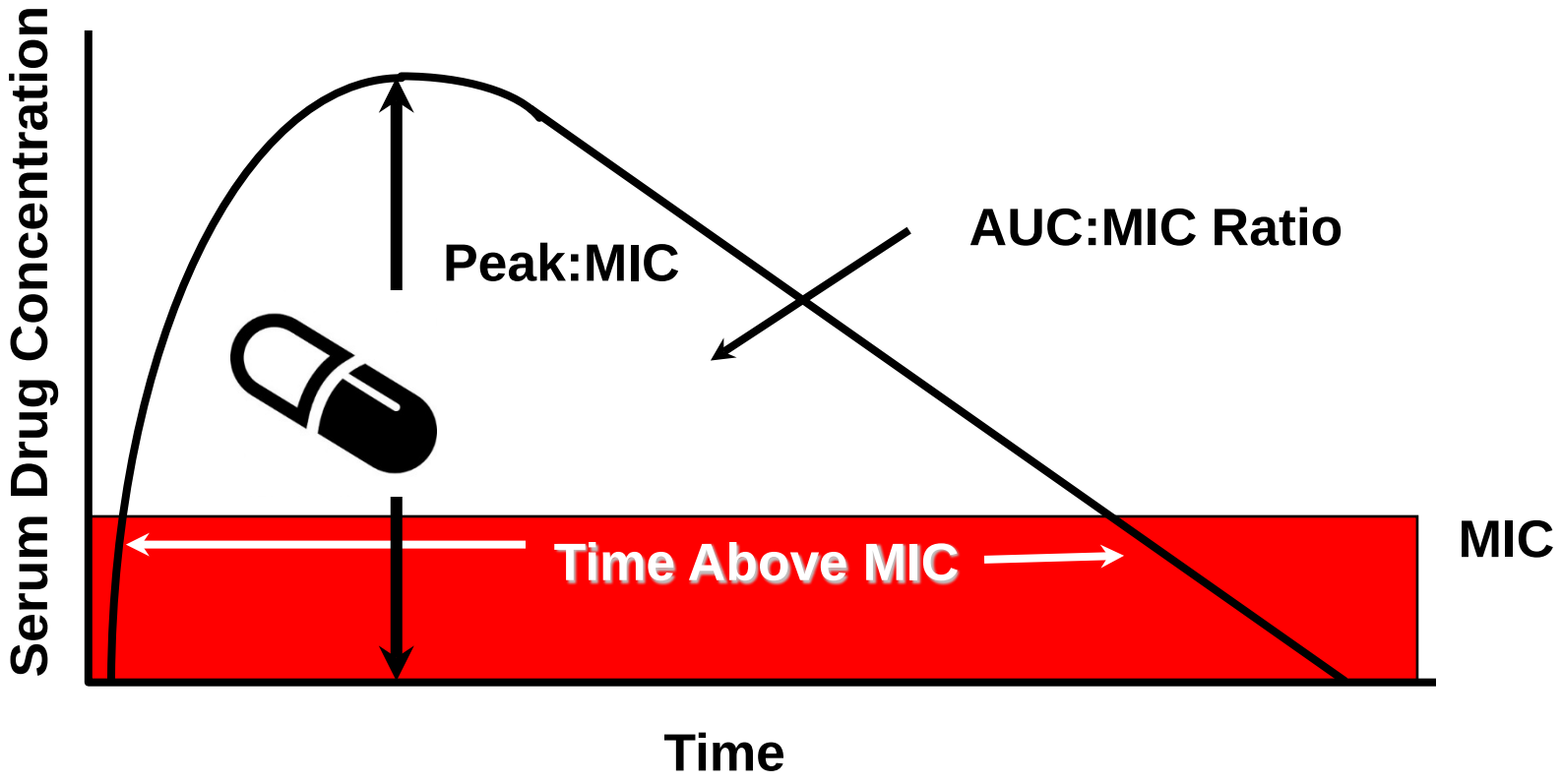
Bug

Host

Drug

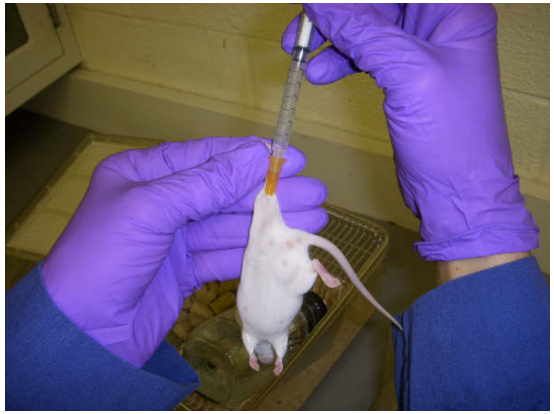
What do we do?

Tie Drug Potency to Antimicrobial Exposure = Pharmacodynamics



MIC = minimum inhibitory concentration; AUC = area under the curve; T = time

In vivo PK/PD Work Horse(s)



- Murine thigh and lung models
  - Mimics soft tissue/sepsis and pneumonia, respectively
  - Neutropenic
  - Organism burden primary endpoint
  - Supports growth of most bacteria
  - Multiple drug administration routes
  - Large group of comparator antibacterial agents
  - Outcomes correlated with treatment success in patients
  - Useful for trial dosing regimen selection and susceptibility breakpoint development

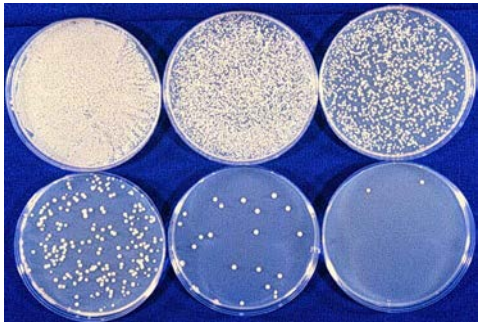
Study Design

Infect

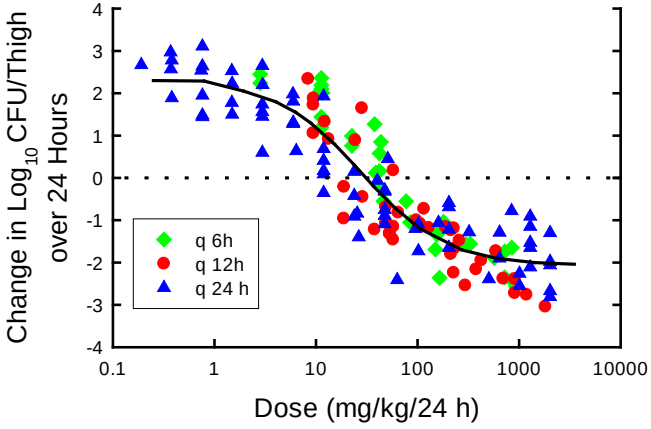
-2 hr

Antibiotic Therapy

24 hr



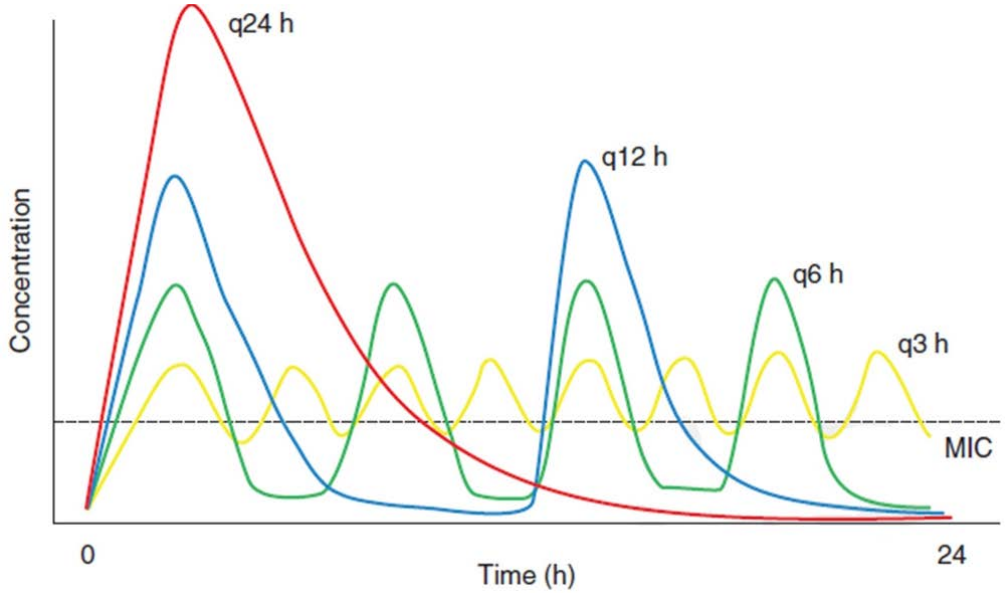
Bacterial Burden Assessment



Pharmacodynamic Analysis

How do we determine how much and how often to administer an antibiotic?

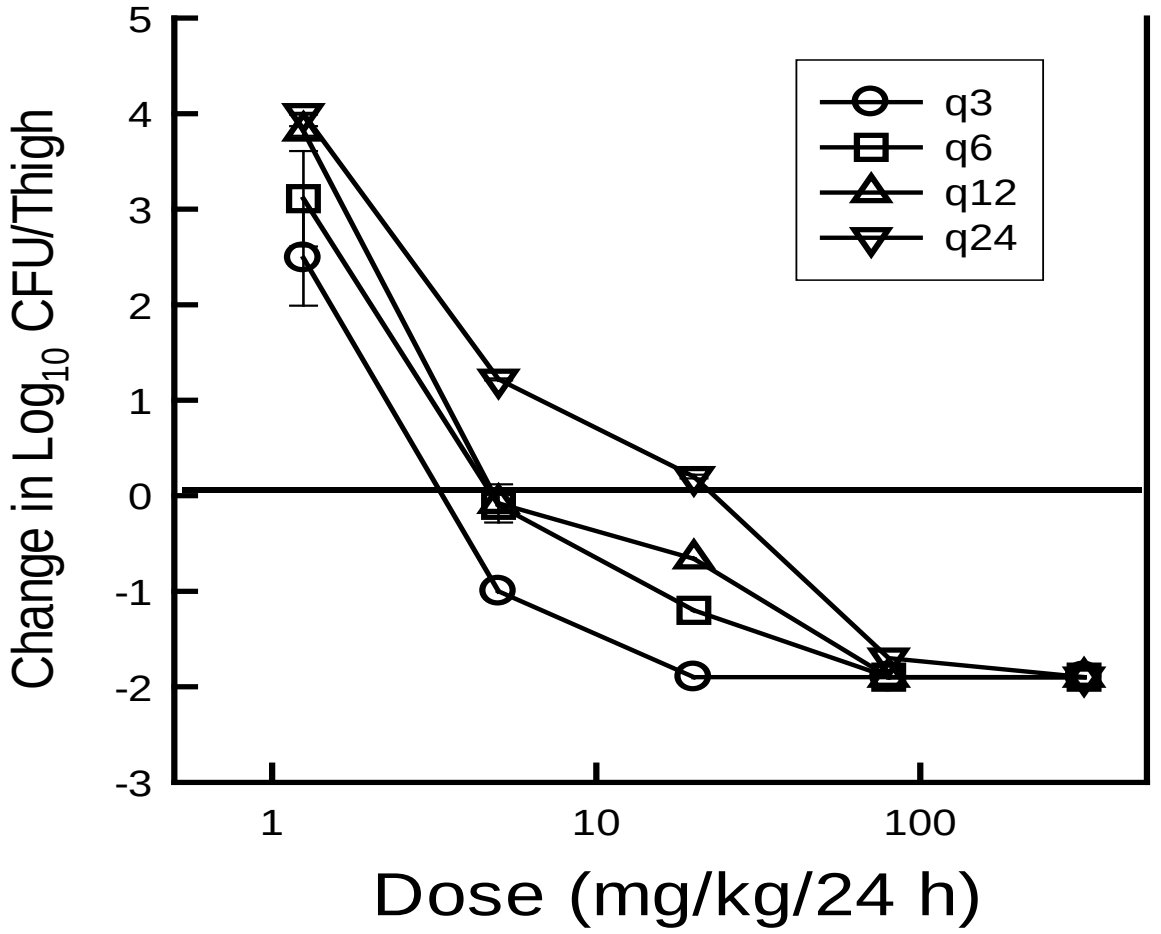
PK/PD Driver – Dose or Interval



Dose Level

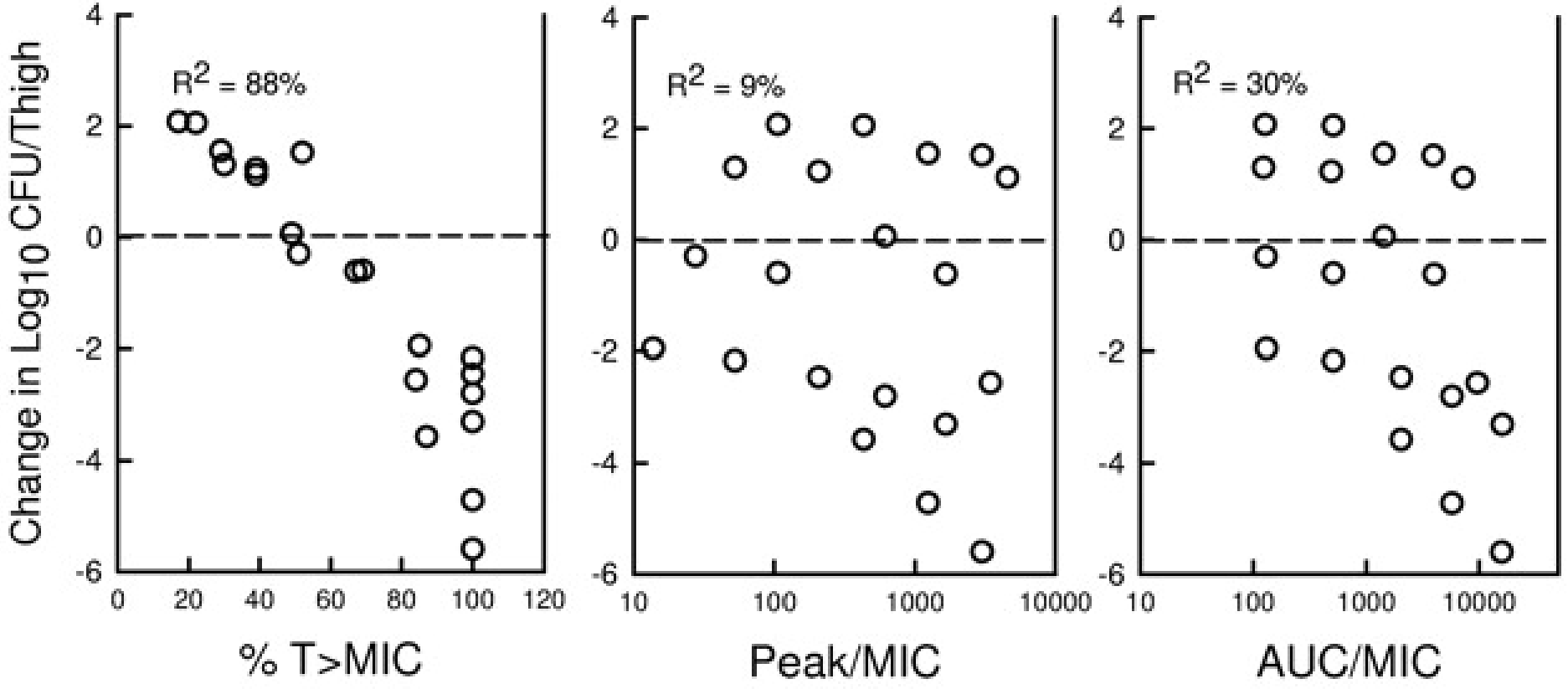
Dosing Frequency

Dose Fractionation Design



Andes and Craig. Antimicrob. Agents Chemother. 2006;50:1376-1383

Dose Fractionation Analysis



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PK/PD Patterns Activity

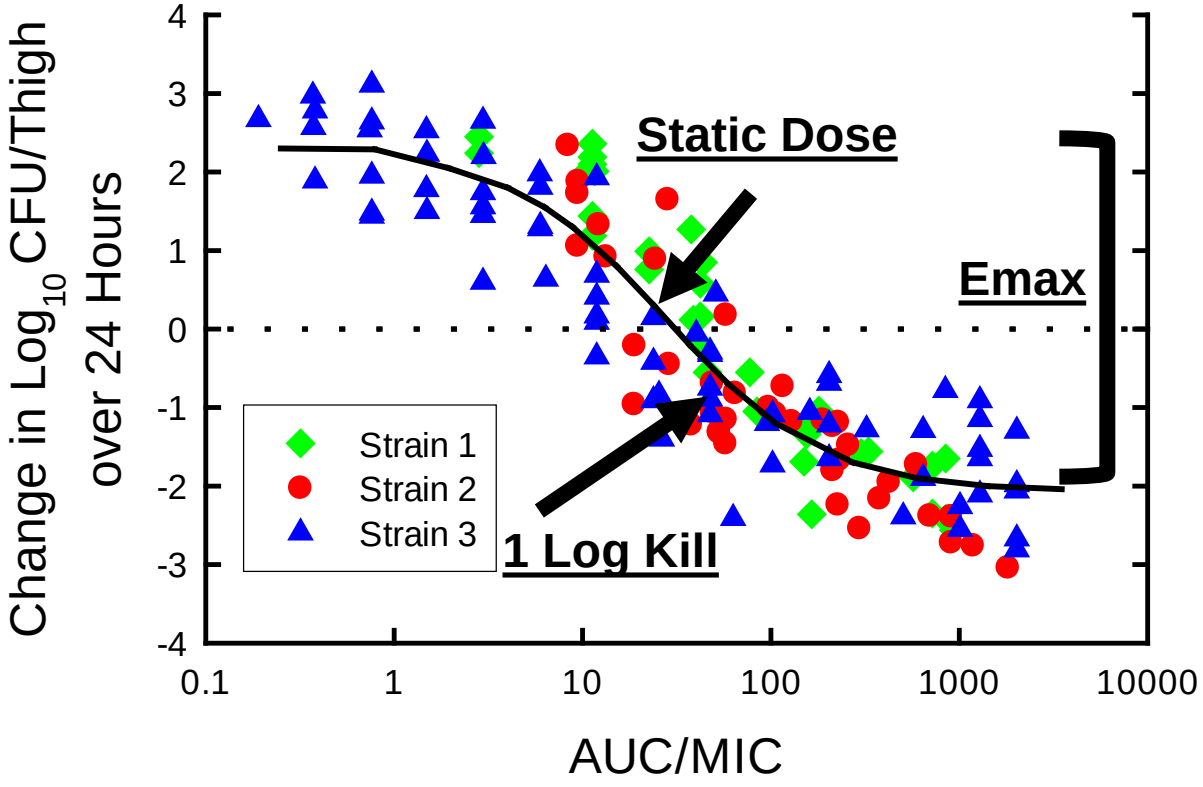
Pattern	Antibacterial	Dosing Goal
Concentration-dependent killing and prolonged persistent effects	Quinolones, Aminoglycosides, Ketolides, and Daptomycin	Maximize concentrations; Cmax/MIC or AUC/MIC
Time-dependent killing and minimal or no persistent effects	Beta-lactams	Optimize duration of exposure; %T>MIC
Time-dependent killing and moderate to prolonged persistent effects	Macrolides, Azithromycin, Clindamycin, Tetracyclines, Glycylcyclines, Streptogramins, Glycopeptides, Oxazolidinones	Optimize amount of drug; AUC/MIC

Dose fractionation in the mouse models reliably defines the PK/PD driver

How do we define the PK/PD target?

Dose Level

PK/PD Target Design

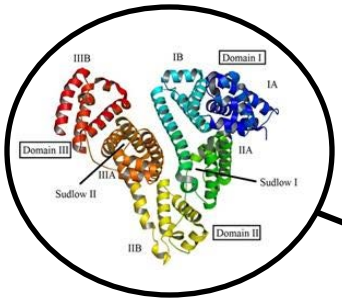


Nonlinear regression and Hill equation to estimate Emax (difference from untreated control), P_{50} (dose giving 50% of Emax) and slope (N) of the dose-response relationship

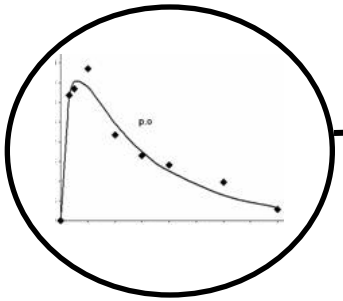
$$\Delta CFU = \frac{(Emax)\ Dose^N}{Dose^N + P_{50}{}^N}$$

Introduce additional isolates, preferably with MIC variation

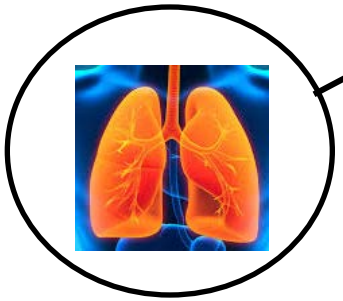
PK/PD Target Variables



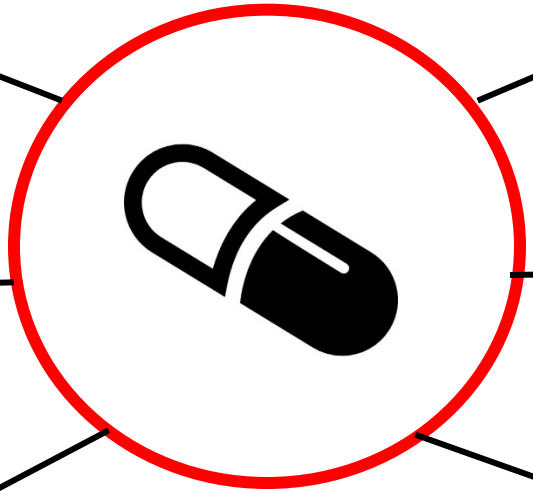
Protein Binding



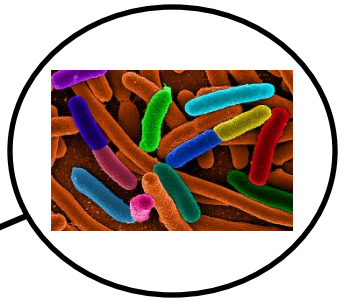
Pharmacokinetics



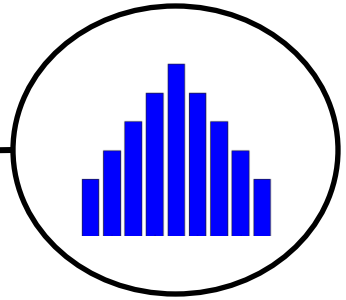
Infection Site



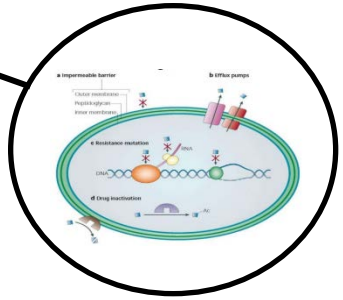
Right Dose
PK/PD Target



Strain Variability

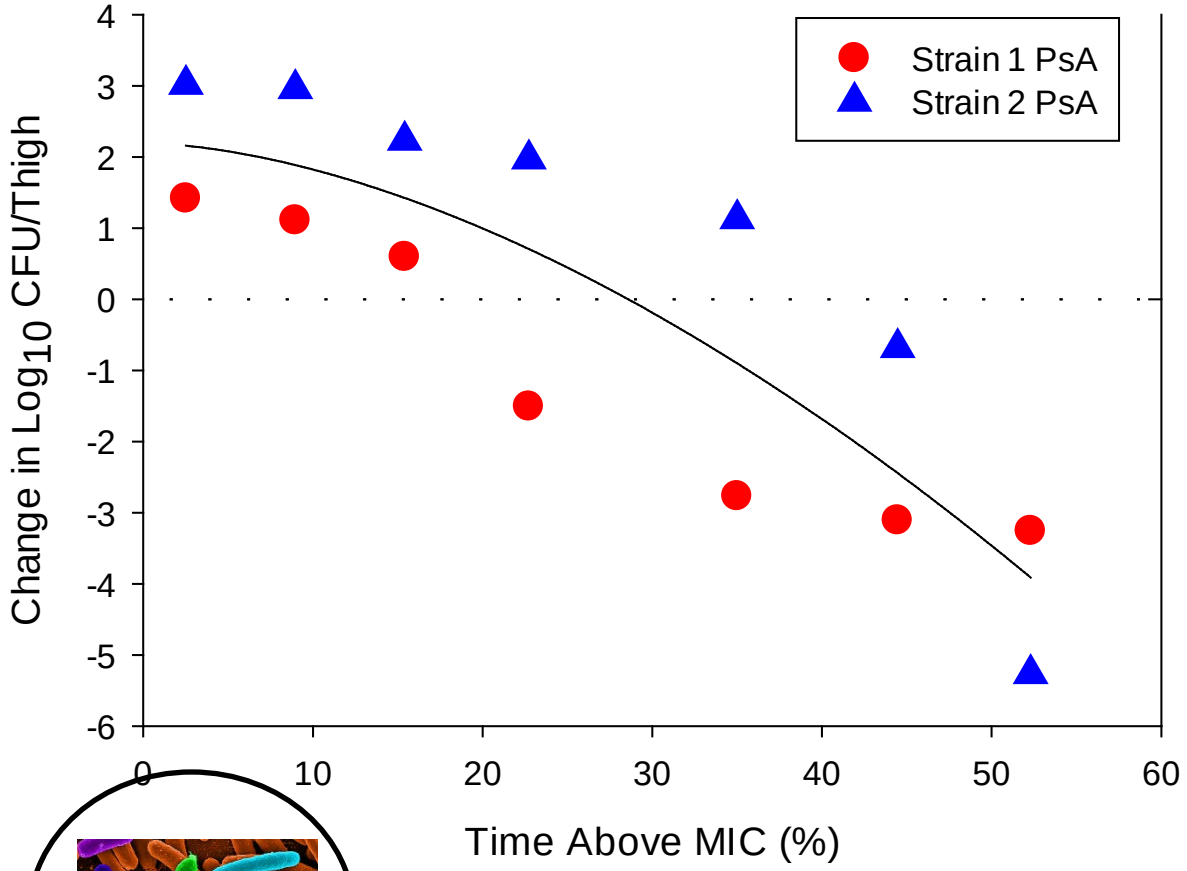


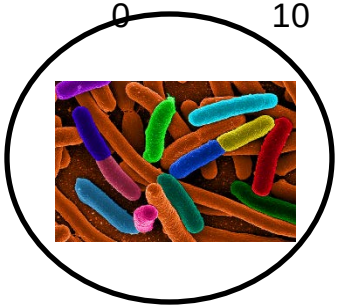
MIC Variability



Resistance Mechanism

Impact of Strain to Strain Variation on the PK/PD Target

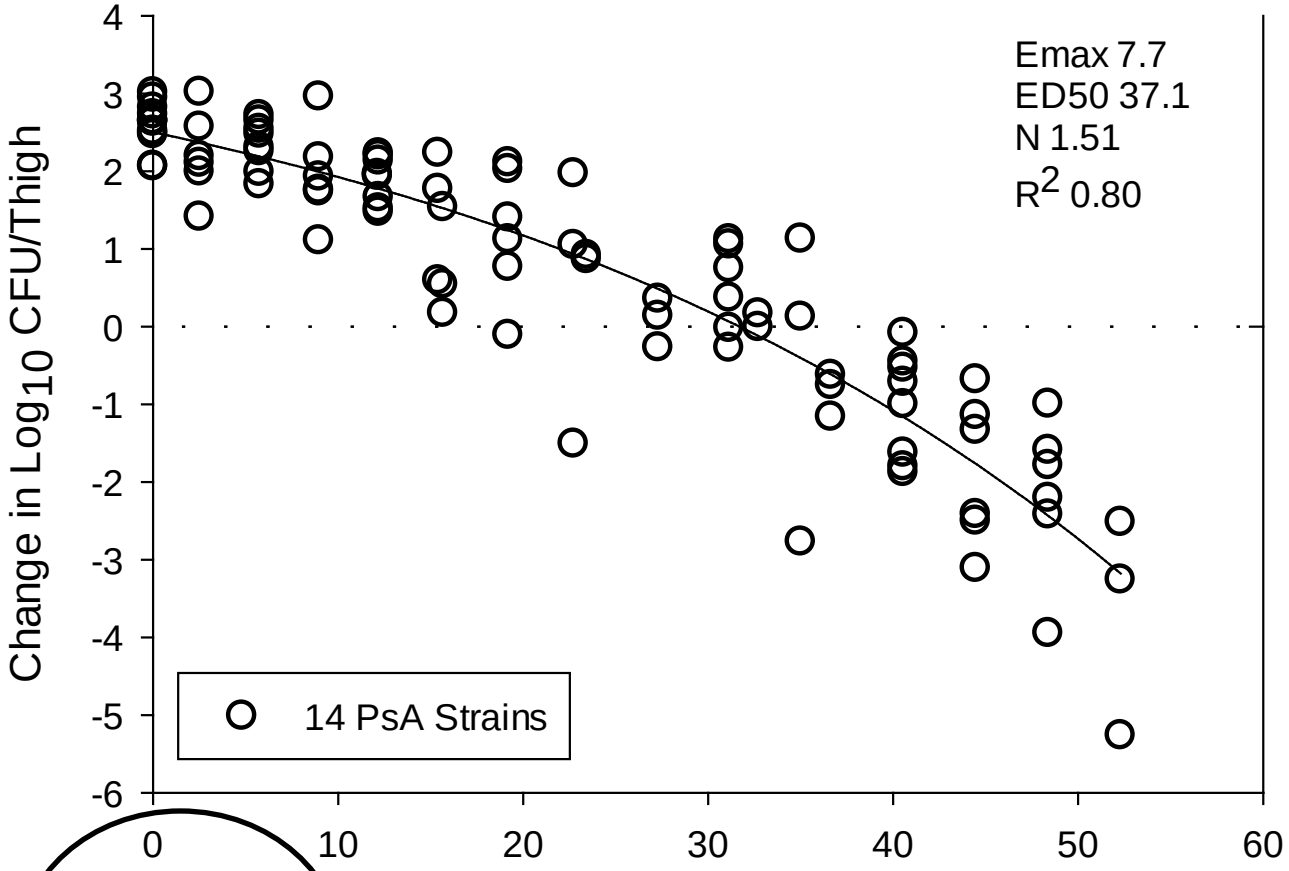


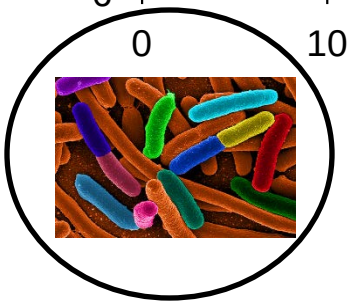


Strain Variability

	Mouse	Stasis %T>MIC	1 log Kill %T>MIC
Strain 1	1	15	21
	2	15	21
	3	16	22
	4	16	20
	Mean	**16**	21
	SD	0.6	0.8
Strain 2	1	39	42
	2	40	43
	3	39	43
	4	39	42
	Mean	**39**	43
	SD	0.5	0.6

Impact of Strain to Strain Variation on the PK/PD Target

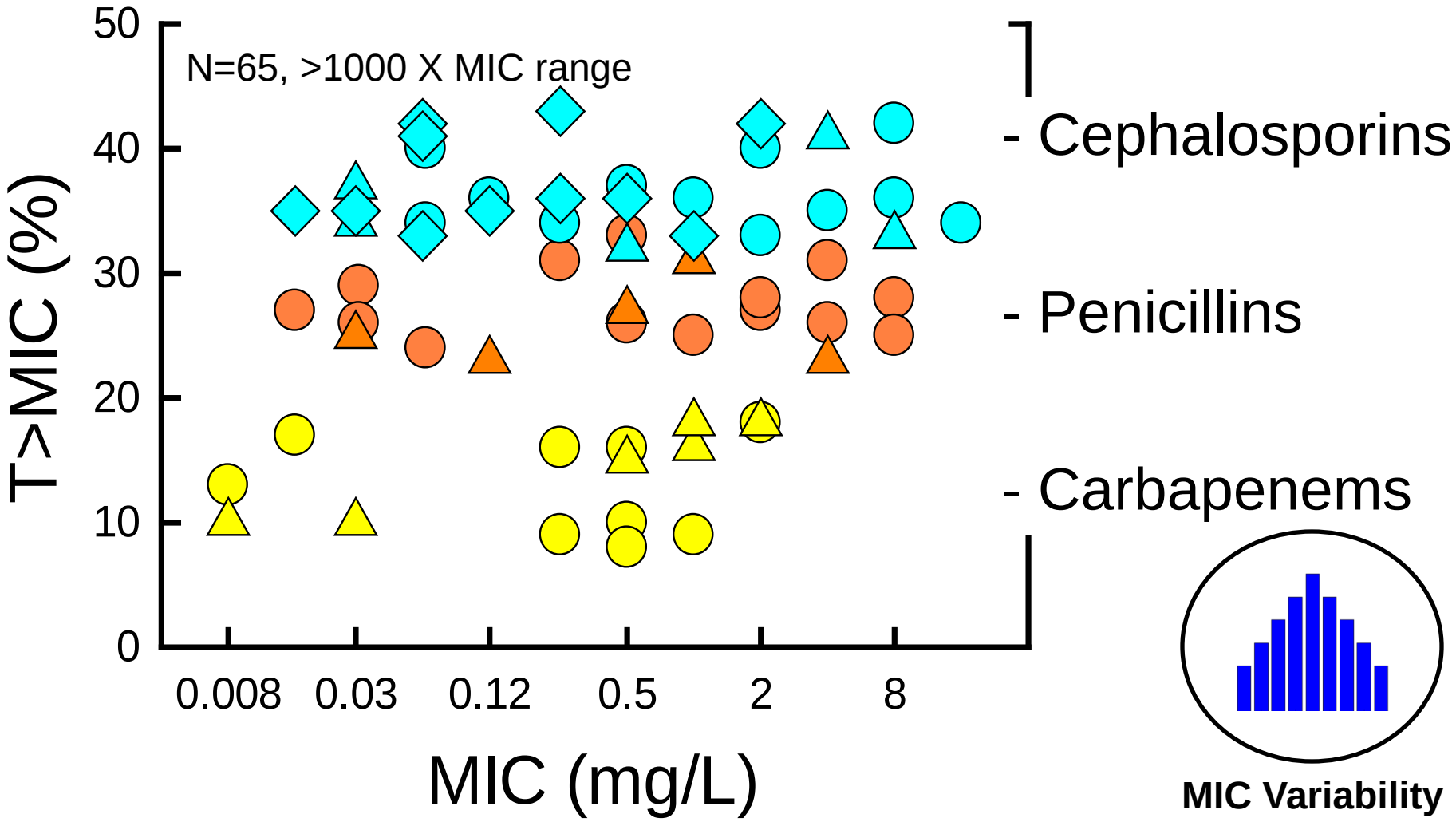




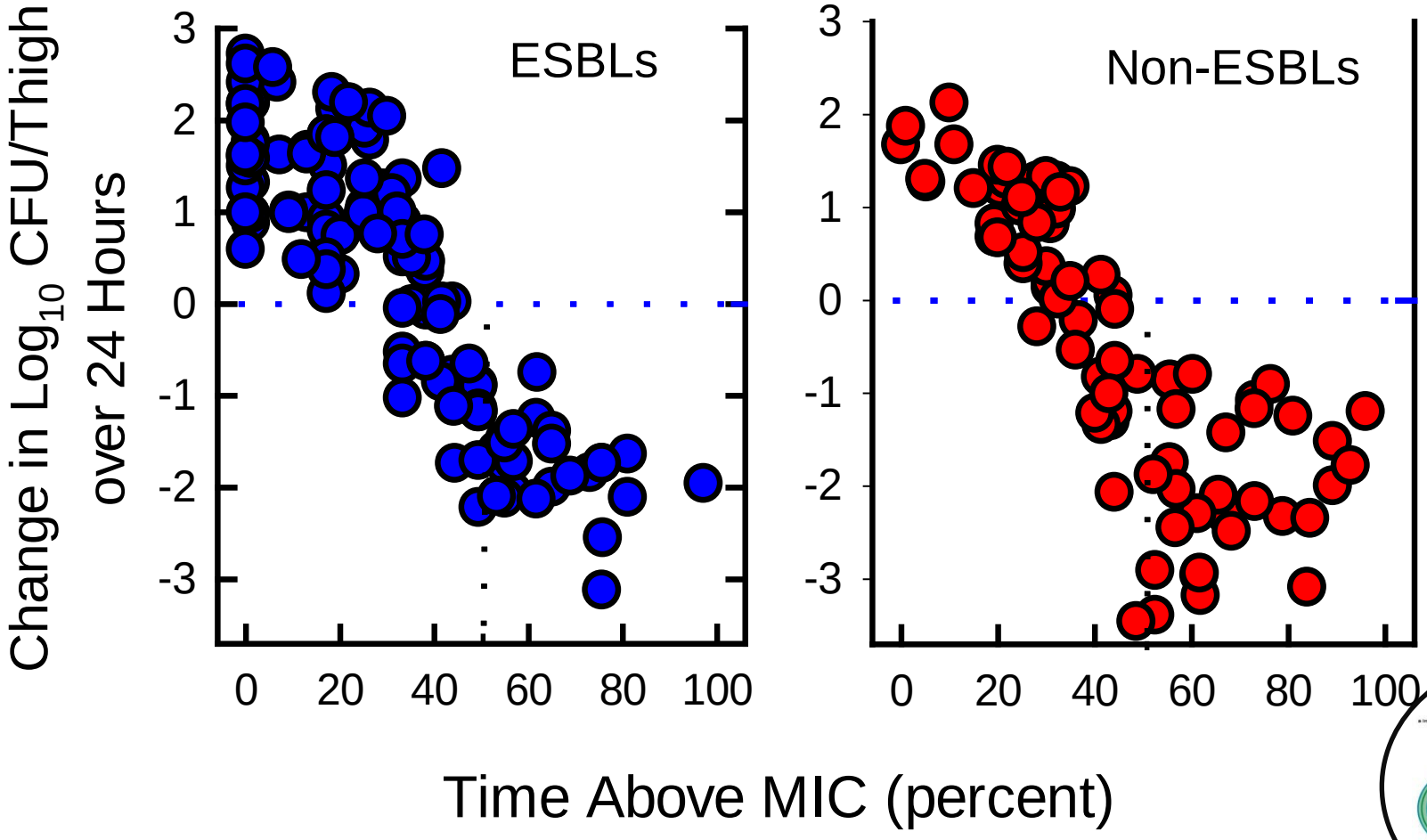
Strain Variability

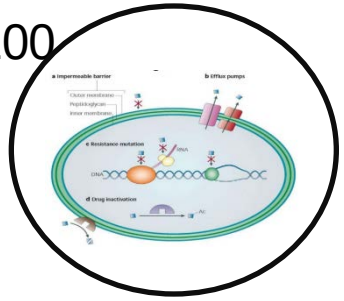
Organism	Stasis % T > MIC	1 log kill %T>MIC
1	16	21
2	37	45
3	35	46
4	30	38
5	36	47
6	37	43
7	35	
8	40	43
9	29	
10	28	43
11	22	34
12	30	37
13	32	39
14	27	37
Mean	**31**	**39**
Median	**31**	**41**
SD	**6**	**7**
%CV	**0.19**	**0.18**

Impact of MIC Variation on the PK/PD Target



Impact of Resistance and ESBL Production





Resistance Mechanism

N=20 organisms, 4 cephalosporins

Andes D, Craig WA. Clin Microbiol Infect 2005;11:10-17.

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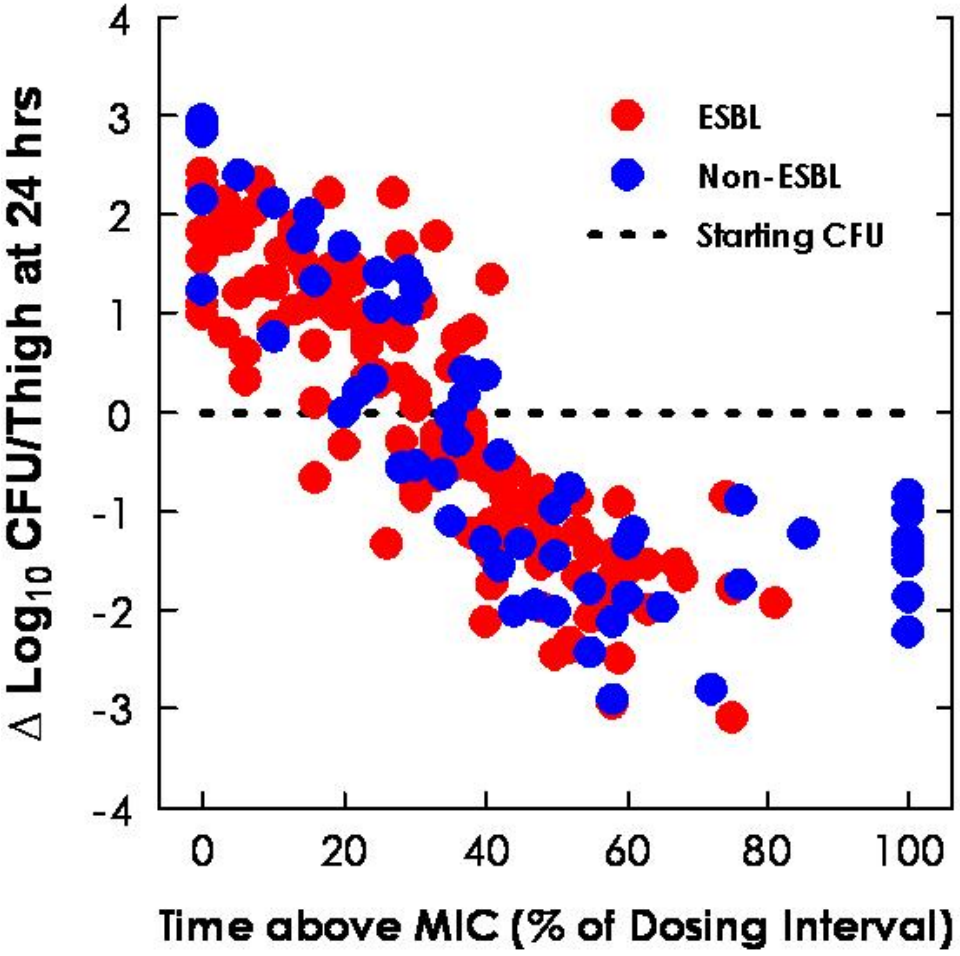

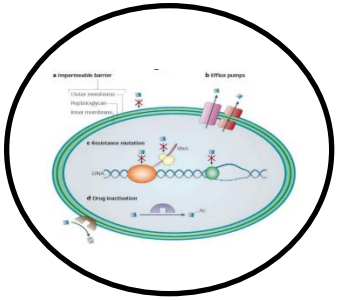

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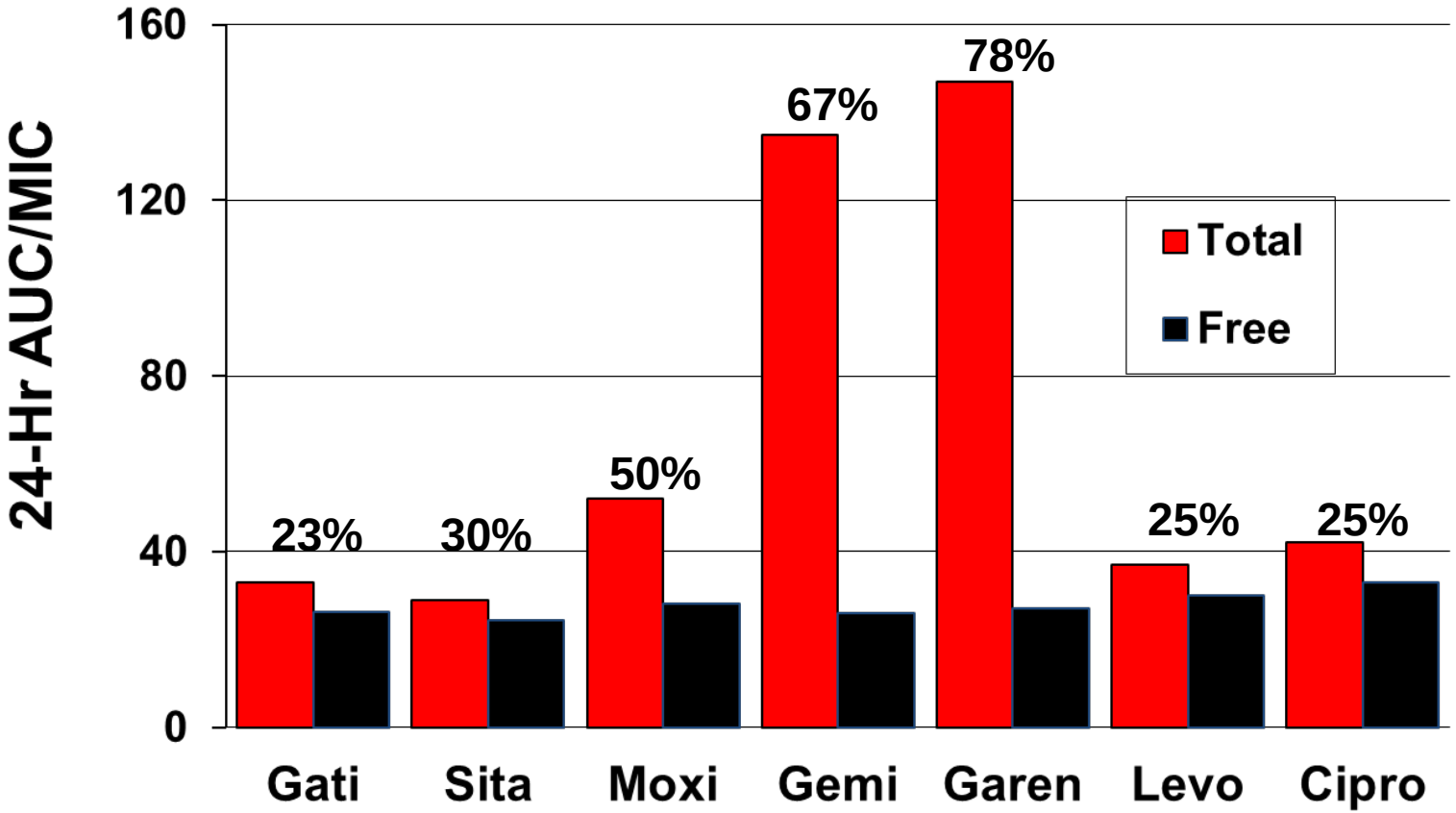
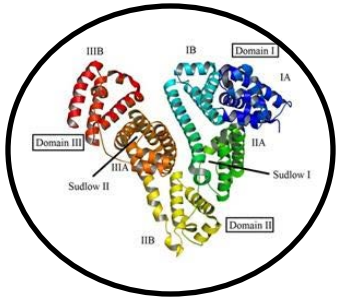
Impact of Protein Binding

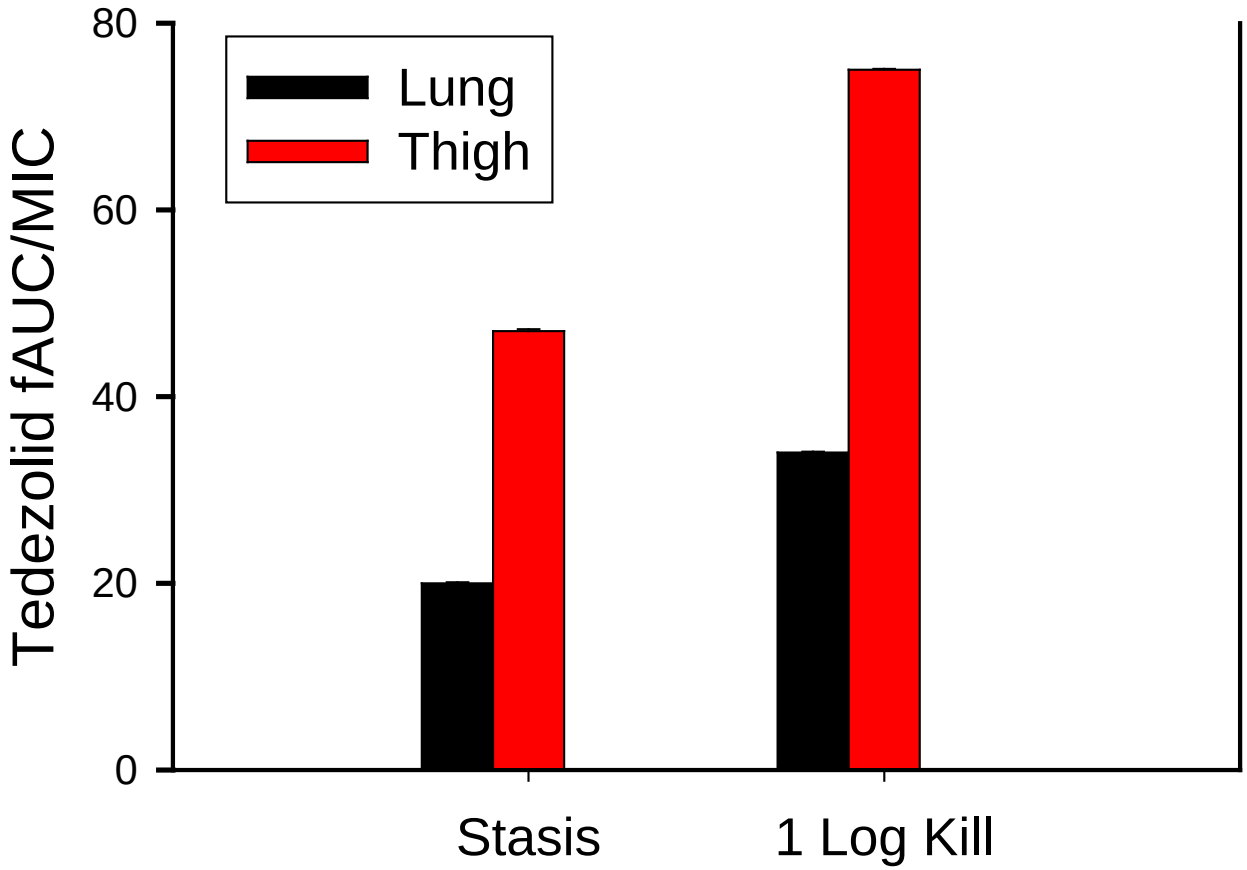




Protein Binding

Andes & Craig 40th and 41st ICAAC, 2000 and 2001

Impact of Infection Site



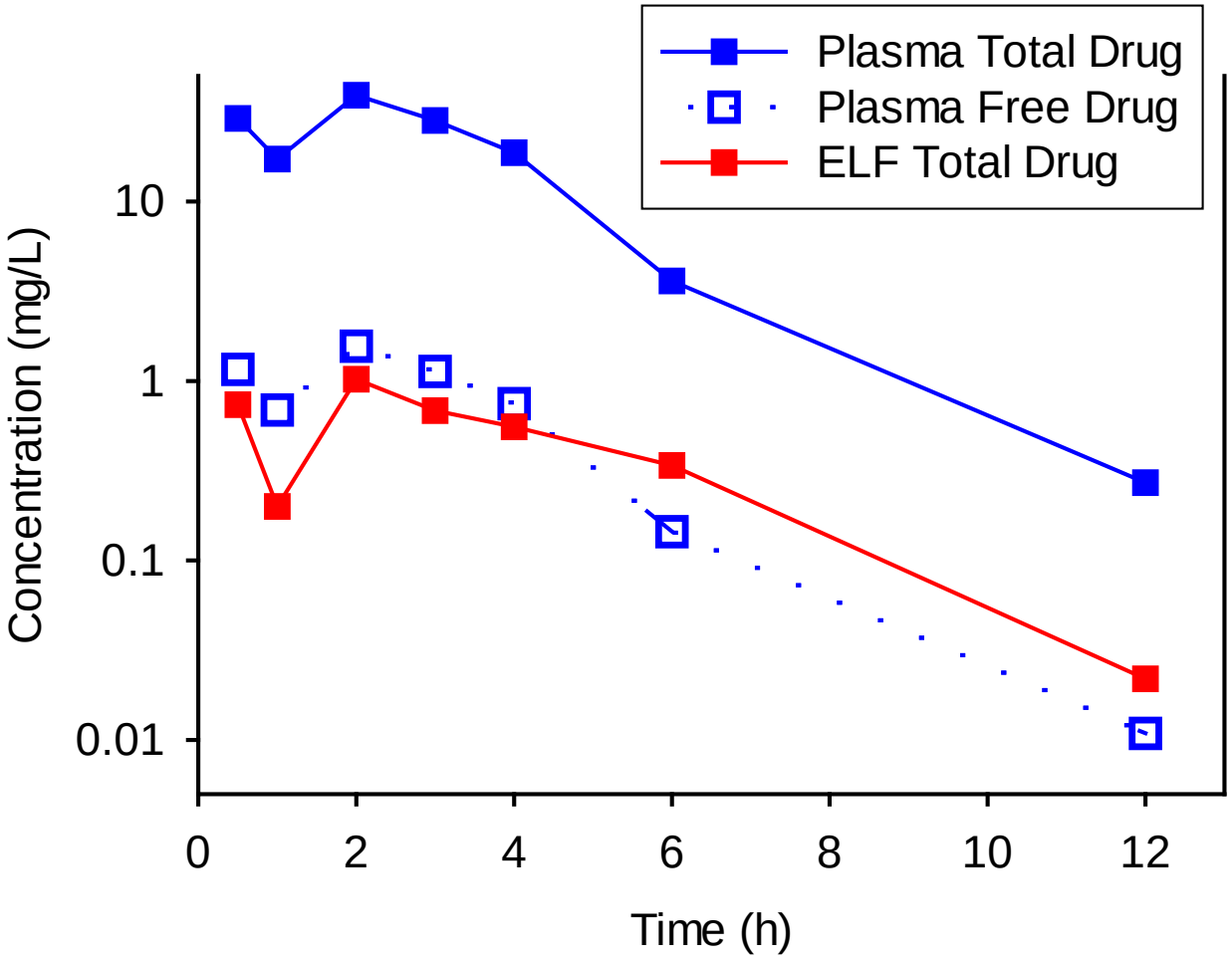
Oxazolidinone and MRSA

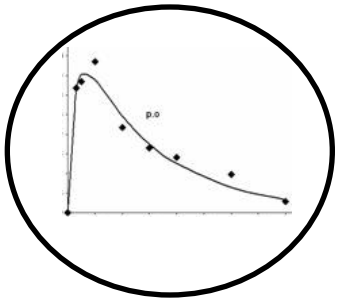
Infection Site

Lepak AAC 2012;56:5916
Louie AAC 2011;55:3453

Mouse ELF:Blood Penetration > 10

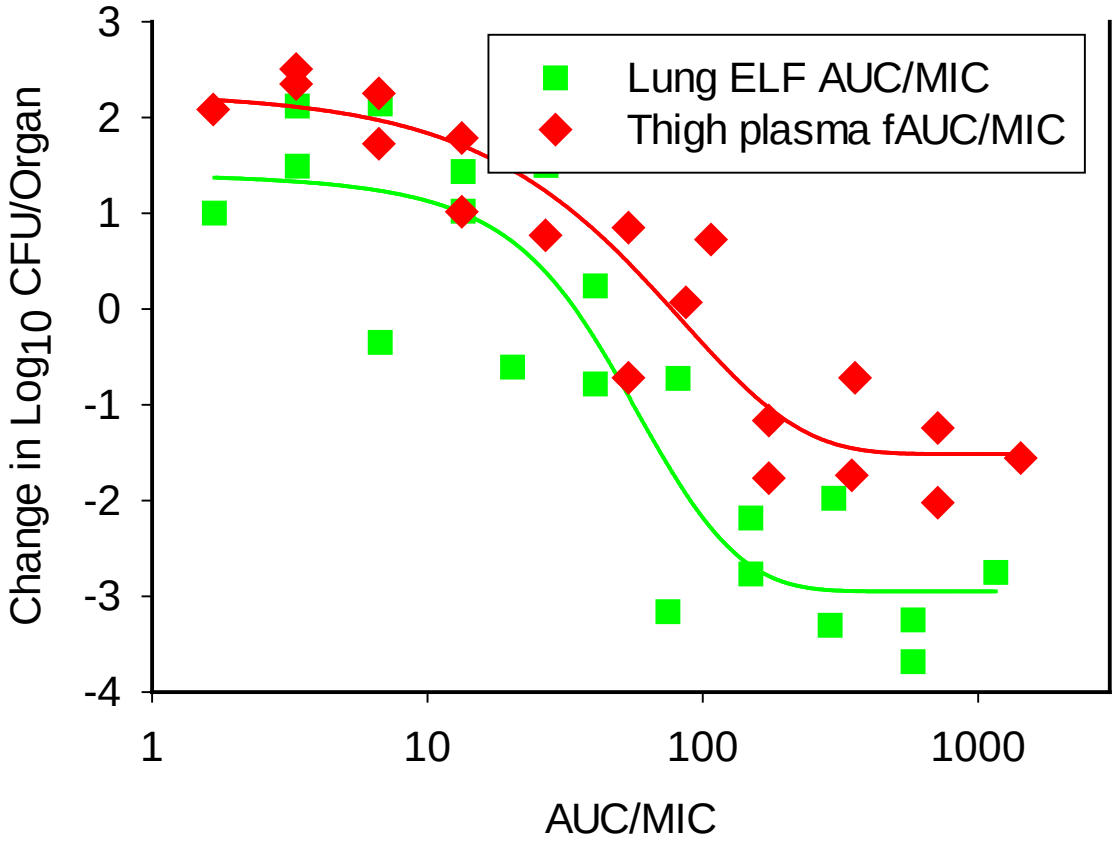
Impact of Infection Site

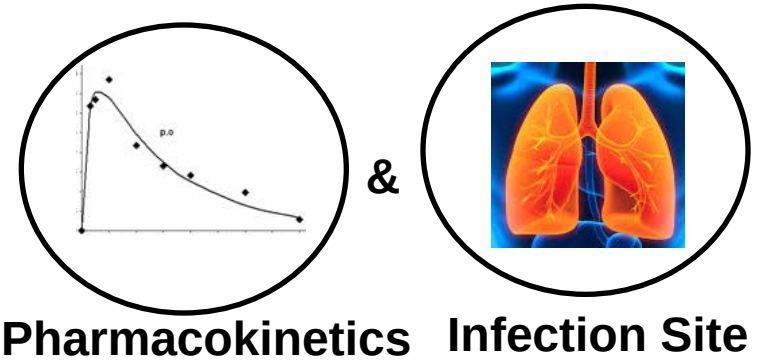




Pharmacokinetics

Impact of Infection Site





ELF/Plasma Penetration: Mouse and Man

Drug	Mouse ELF:Plasma Ratio	Man ELF:Plasma Ratio
Ceftibiprole	0.69	0.26
Meropenem	0.60	0.80
Levofloxacin	0.77	1.16
Tedezolid	10	2-4
Tigecycline	10-20	1.12
Vancomycin	0.50	0.50
Gentamicin	1.0	0.30-0.85

In vivo PK/PD Target Identification
(>100 individual drugs)

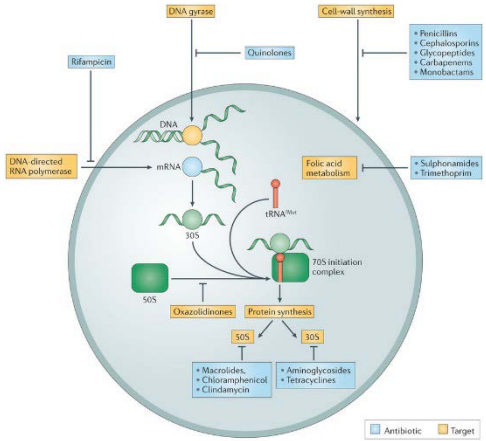
Penicillins
Cephalosporins
Carbapenems
Aztreonem
Flucytosine
Echinocandins
Azithromycin
Streptogramins
Vancomycin
Tetracyclines
Glycylcyclines
Glycopeptides

Aminoglycosides
Fluoroquinolones
Metronidazole
Ketolides
Polyenes
Plectasins
Macrolides
Oxazolidinones
Clindamycin
Triazoles
Beta peptides
Pleuromutalins

Mouse models can define the PK/PD target, but there are important variables to consider

Let’s put this pre-clinical PK-PD in context with clinical efficacy

Why Does This Work?



Despite:

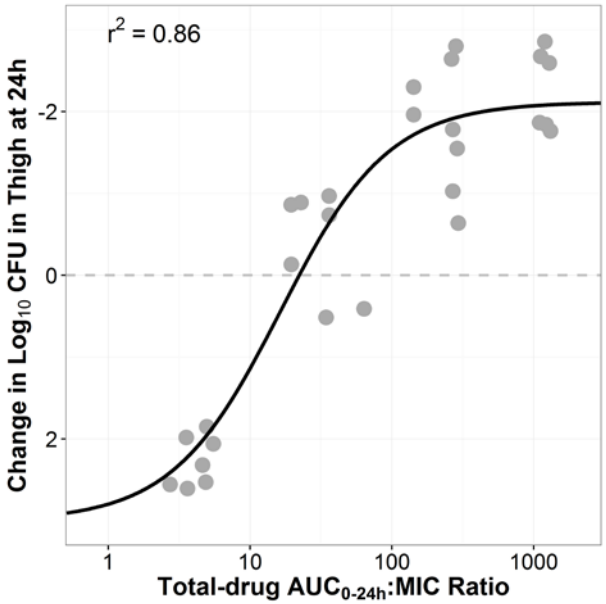
- **Different doses (mg/kg)**
- **Faster half-life in small animals**

BUT:

- **Drug target is in the organism and NOT the host**
- **Exposure relative to MIC is the determinant**

PK-PD INFECTION MODELS

Do They Forecast Success?



Preclinical data: Craig/Andes

Clinical data: Bhavnani SM et al. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. *Antimicrob Agents Chemother.* 2012; 56:1065-1072

Rubino CM, et al.. Evaluation of tigecycline penetration into colon wall tissue and epithelial lining fluid using a population pharmacokinetic model and Monte Carlo simulation. *Antimicrob Agents Chemother*, 2007 November; *51*(11), 4085-4089.

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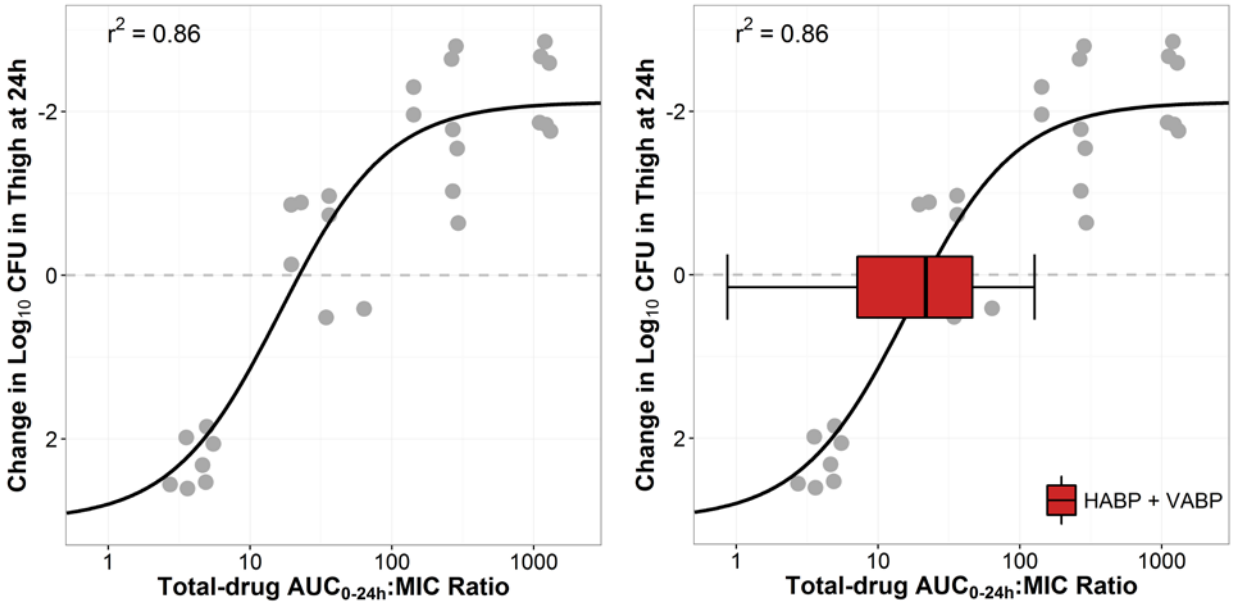

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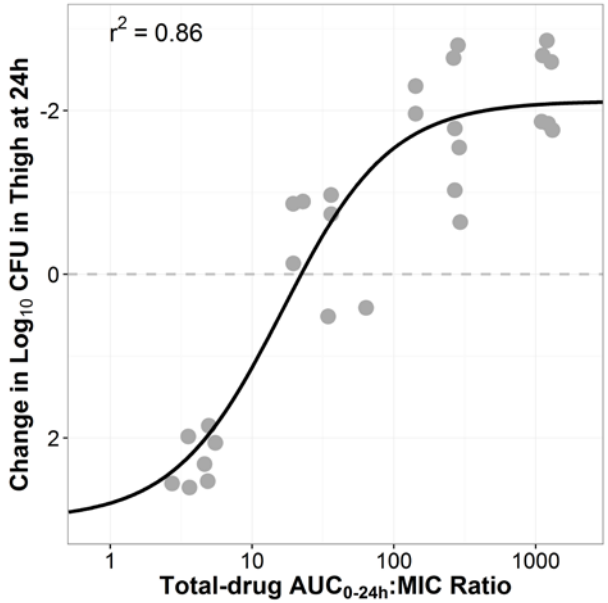
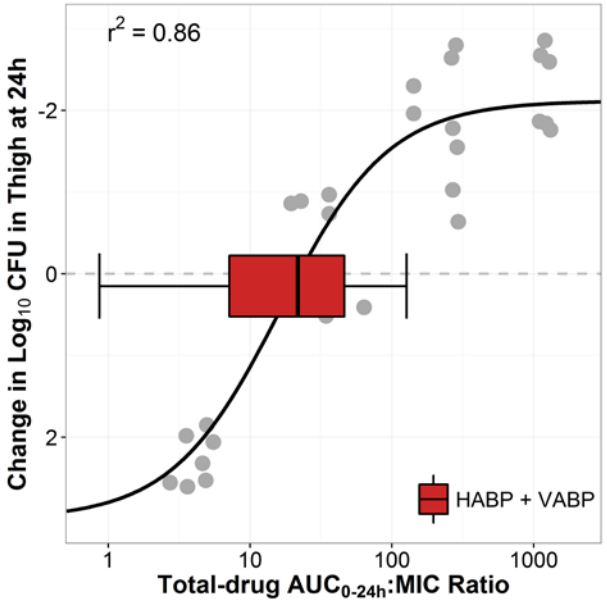
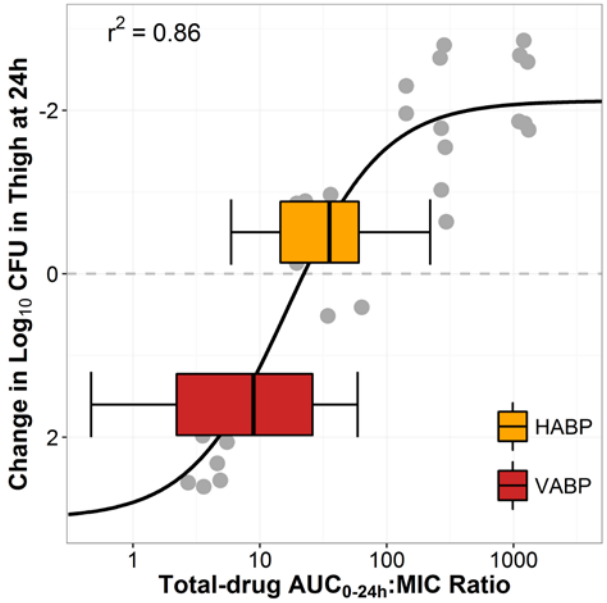
PK-PD INFECTION MODELS

Do They Forecast Success?

From ICPD







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PK-PD INFECTION MODELS
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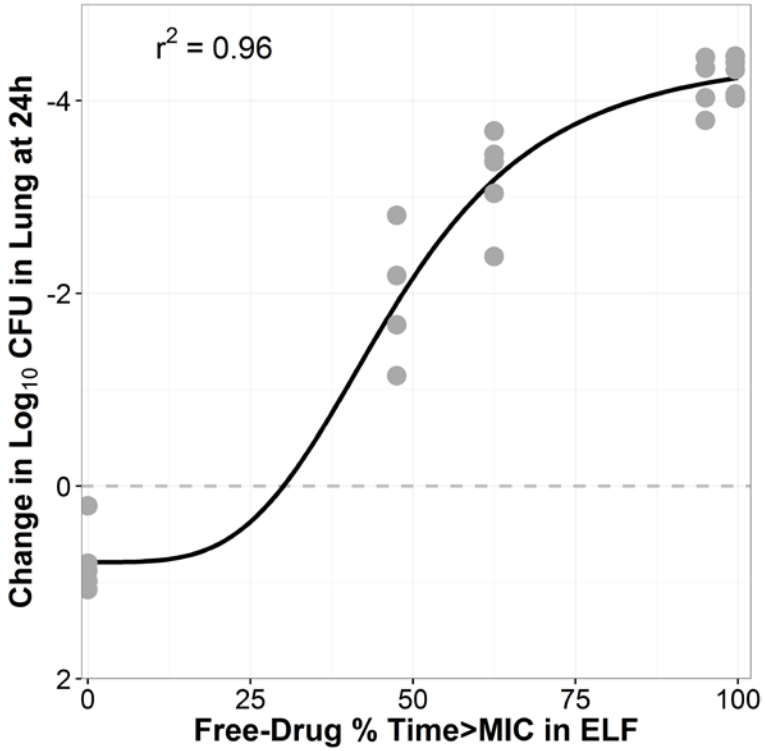

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Surveillance data: EUCAST (2016).MIC distributions and ECOFFs.

Clinical data: Mattioli F, et al. Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. *European journal of clinical pharmacology*, 2013;1-10.

Lodise TP, et al. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother*. 2011 April; *55*(4), 1606-1610.

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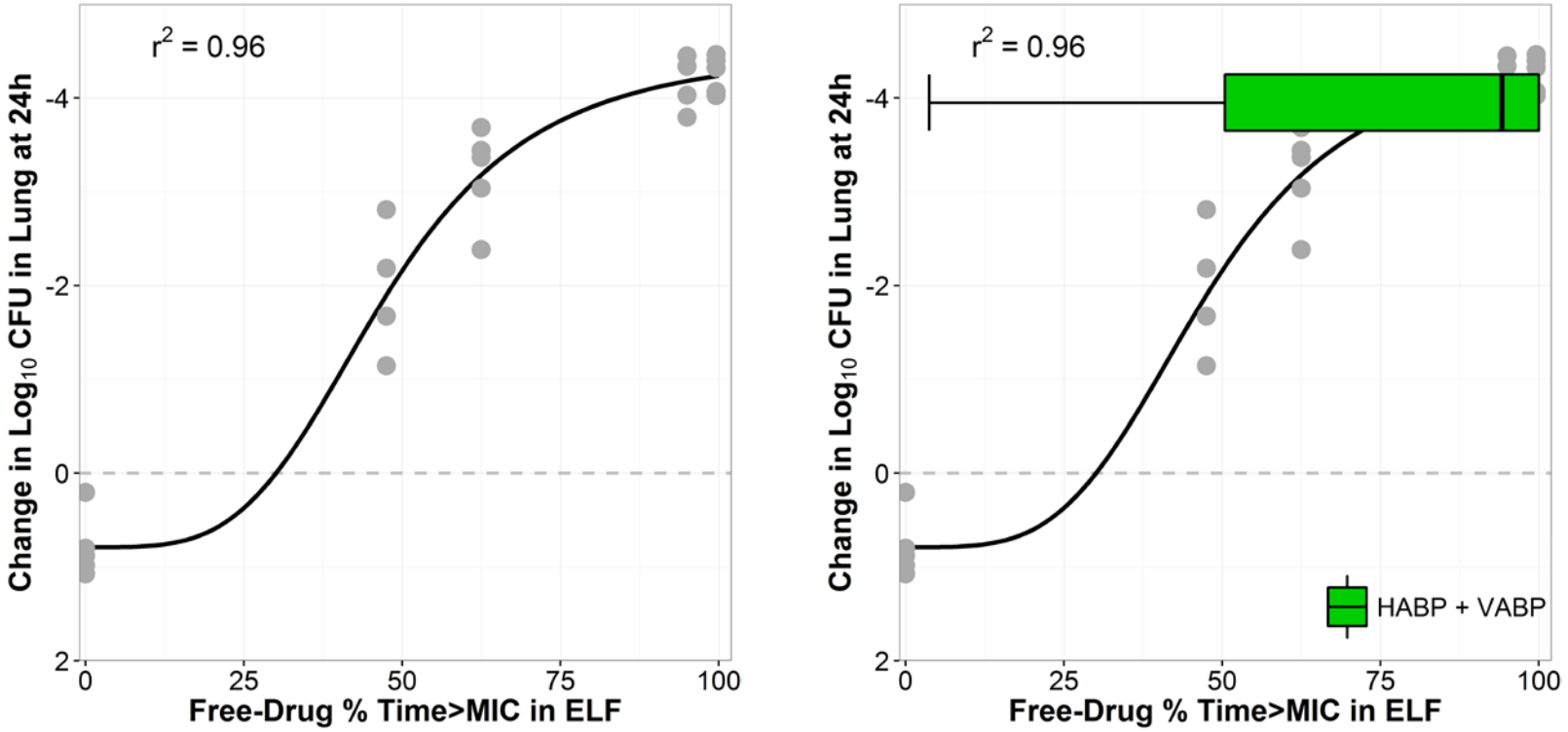

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PK-PD INFECTION MODELS
Do They Forecast Success?

From ICPD

- Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment
  - The study period was December 1996 through 2011
- Indications included community- and hospital-acquired pneumonia
  - For CAP, *S. pneumoniae* was the index pathogen
  - For HAP, the index pathogen was antibiotic spectrum dependent
  - 14 antibiotics that gained regulatory approval and 6 that failed to gain approval

- Cefditoren
- Ceftaroline
- Ceftobiprole
- Daptomycin
- Doripenem
- Ertapenem
- Faropenem
- Garenoxacin
- Gatifloxacin
- Gemifloxacin
- Levofloxacin
- Linezolid
- Moxifloxacin
- Televancin
- Teilithromycin
- Tigecycline
- Trovafloxacin

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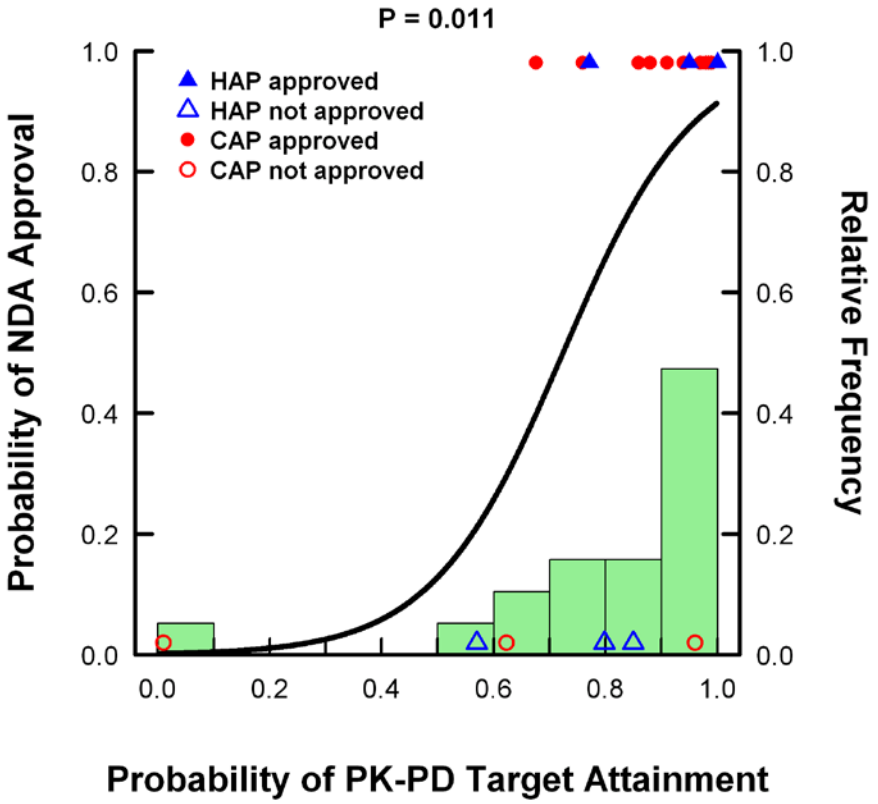


Quartile	Target Attainment Median	% NDA Approval (n/N)
1	0.62	40% (2/5)
2	0.85	60% (3/5)
3	0.94	80% (4/5)
4	0.985	100% (5/5)

The Answer: Yes! The probability of regulatory approval increases with the probability of PK-PD target attainment

Note: PK-PD target was net-bacterial stasis in neutropenic mice for CAP agents and 1-2 $\log_{10}$ unit reduction in bacterial burden for HAP agents

But, A Mouse is Not a Human

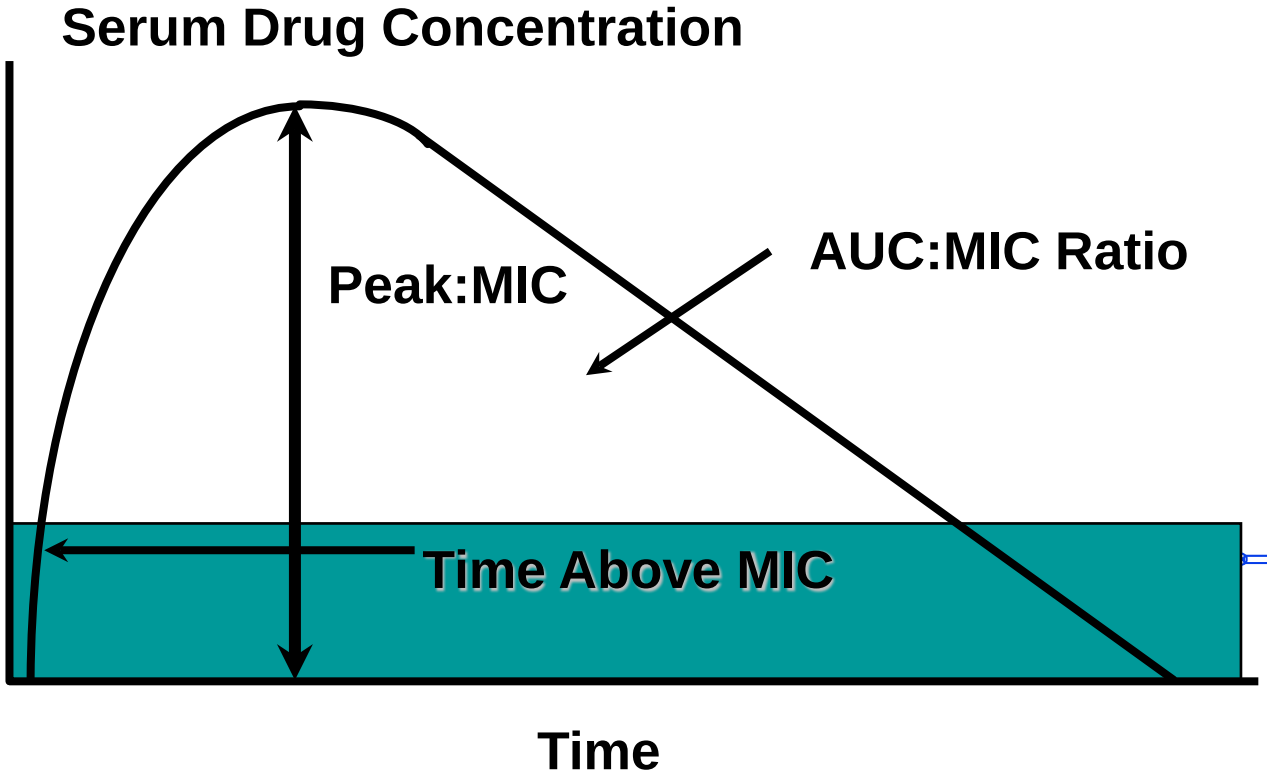
- Host susceptibility
  - Difference in lung anatomy
  - Different pattern recognition receptors
  - Lower pulmonary WBC and no defensins

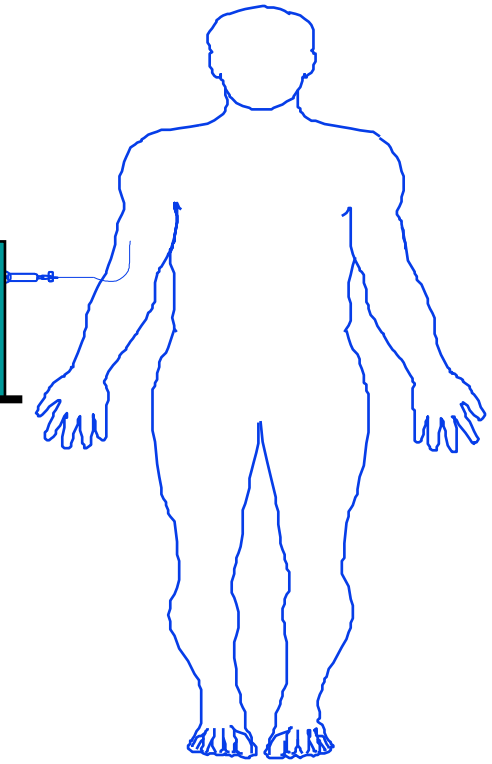
  RESULT
  - Variable susceptibility to human lung pathogens

- Pharmacokinetics
  - Penetration into AM and ELF sometimes, but not often same as humans

Murine infection models can be used to forecast effective regimens in patients

THANK YOU





"It all started with a mouse."
- Walt Disney