Antimicrobial PK/PD Predictions

Considering PK Relative to MIC Works

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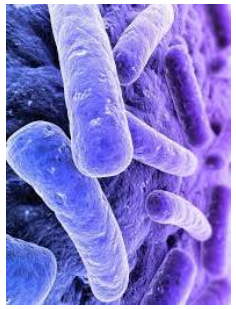
Why do we conduct PK-PD infection models?

Improving the Probability of Positive Outcome



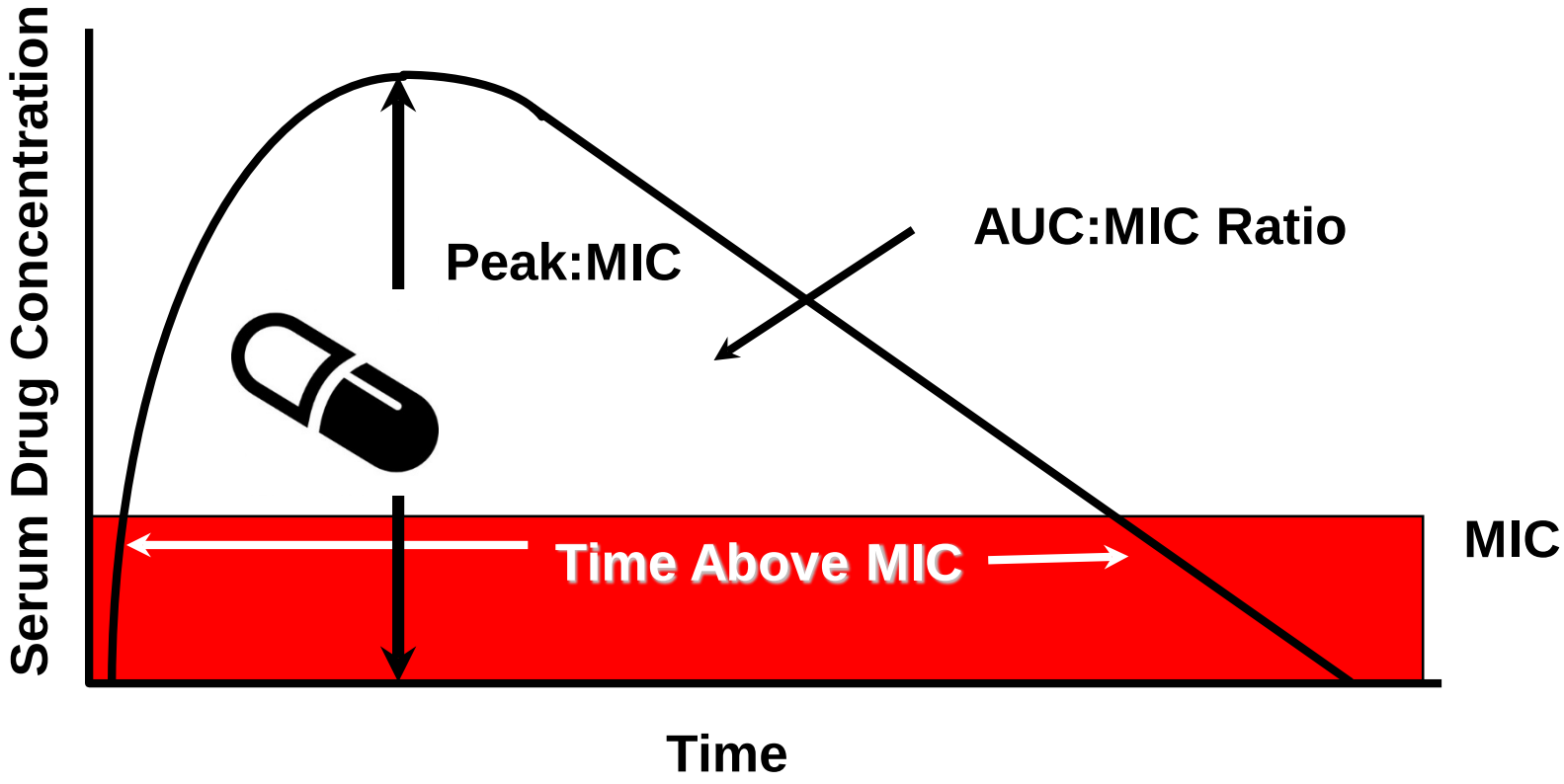
Bug

Host

Drug

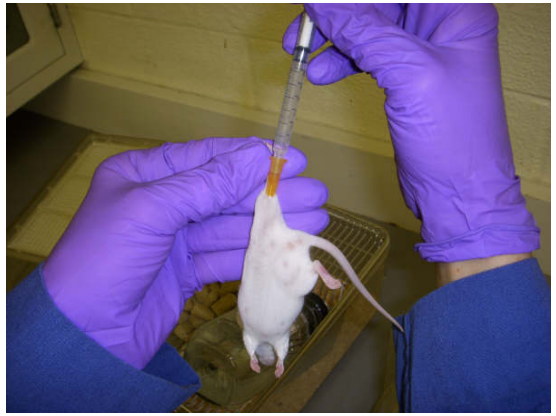
What do we do?

Tie Drug Potency to Antimicrobial Exposure = Pharmacodynamics



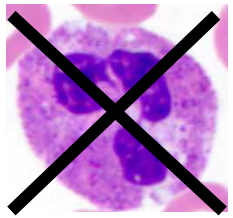
MIC = minimum inhibitory concentration; AUC = area under the curve; T = time

In vivo PK/PD Work Horse (Mouse)



- 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

Typical Study Design



Immunosupress
D-4, D-1

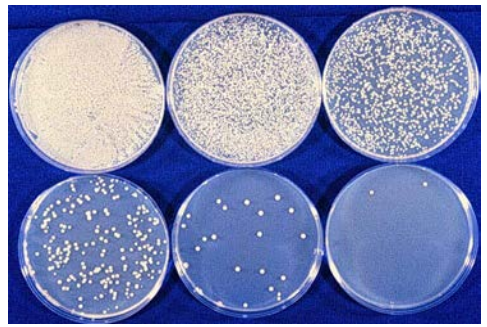
Organism
Preparation
D-1, H-12

Infect,
100 µl thigh
50 µl lung

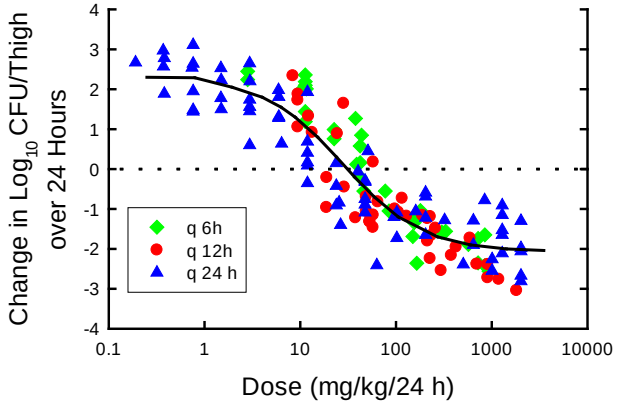
-2 hr

Antibiotic
Therapy

24 hr



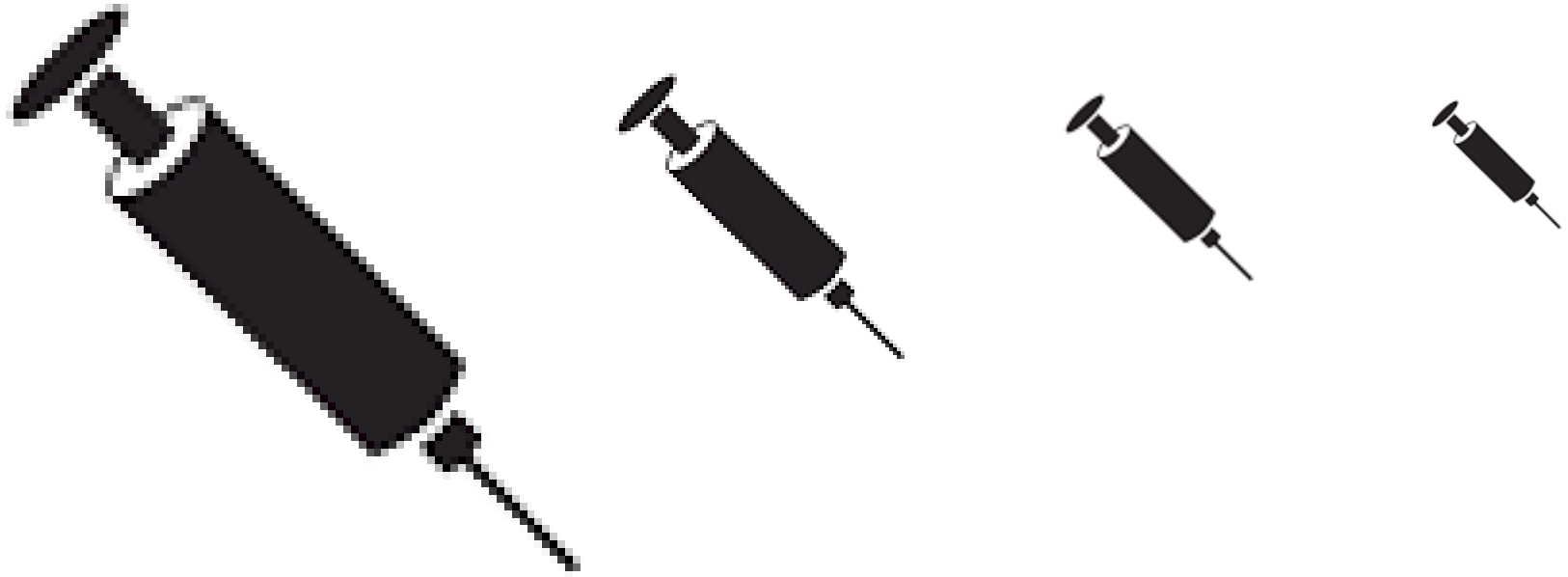
Bacterial Burden Assessment



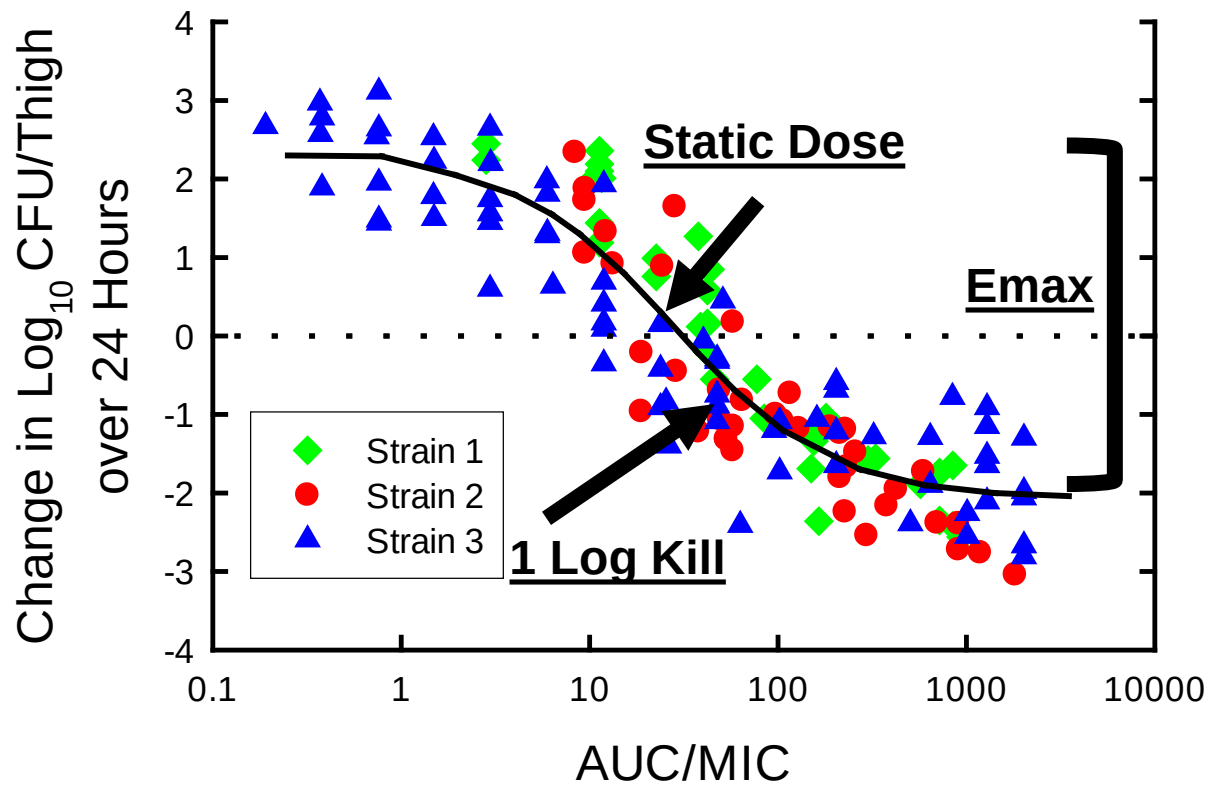
Pharmacodynamic Analysis

How do we define the PK/PD target?

Dose Level



PK/PD Target Design



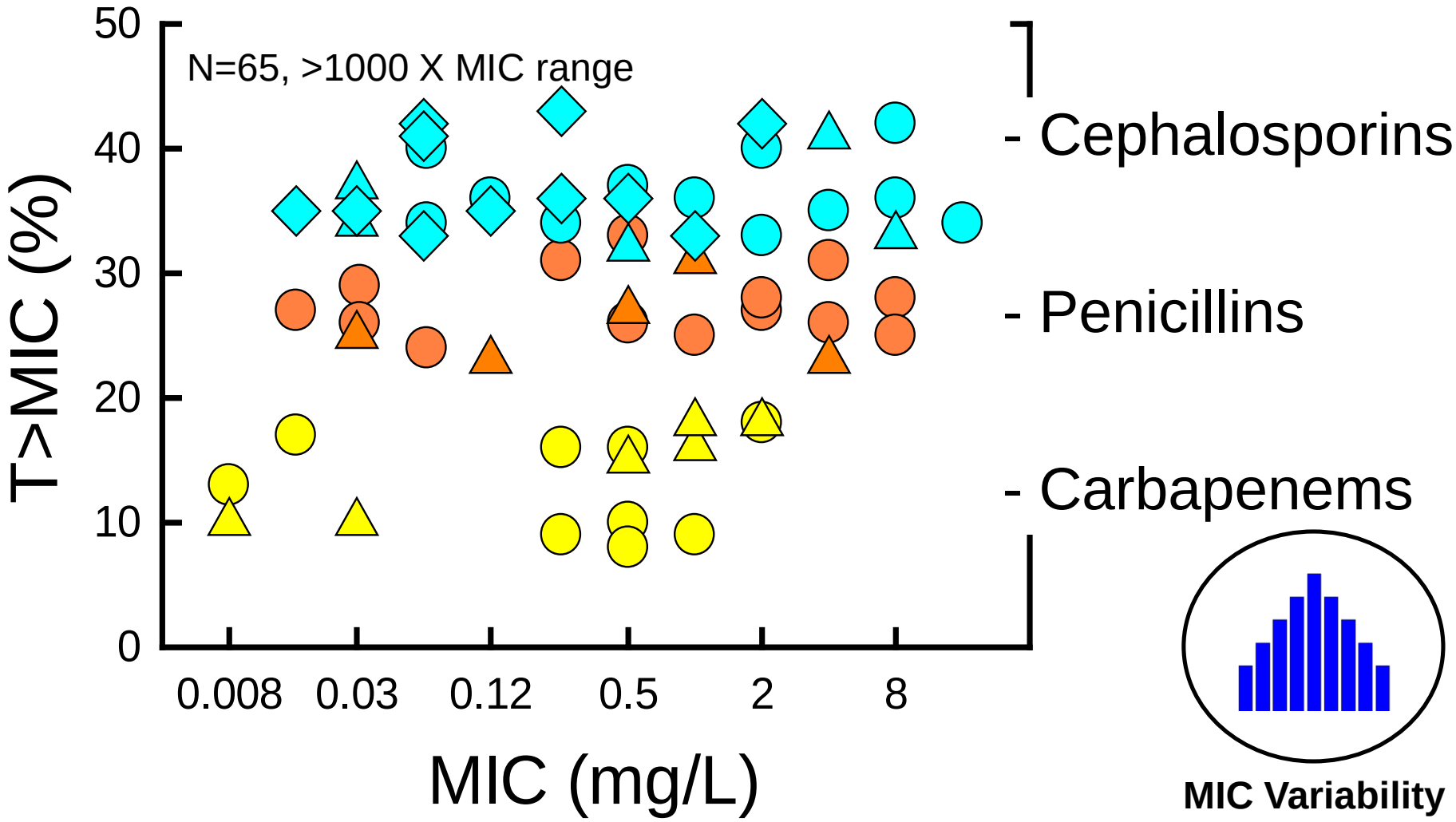
Nonlinear regression and Hill equation to estimate Emax (difference from untreated control), P_{50} (dose giving 50% of Emax) and slope (N) of the dose-response relationship

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

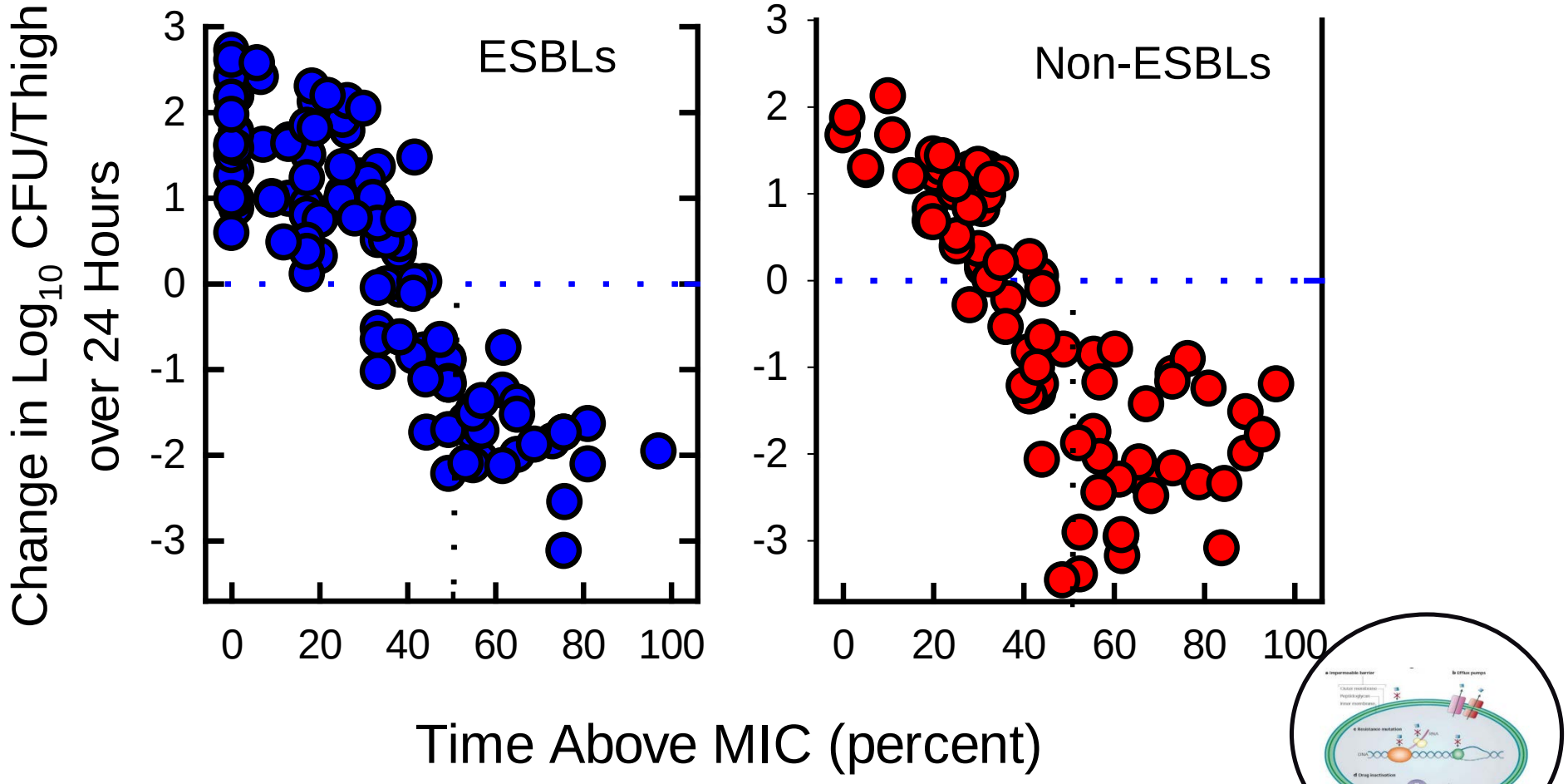
Introduce additional isolates, preferably with MIC variation

Does MIC Help Define the the PK/PD Target

Impact of MIC Variation on the PK/PD Target



Impact of Resistance and ESBL Production



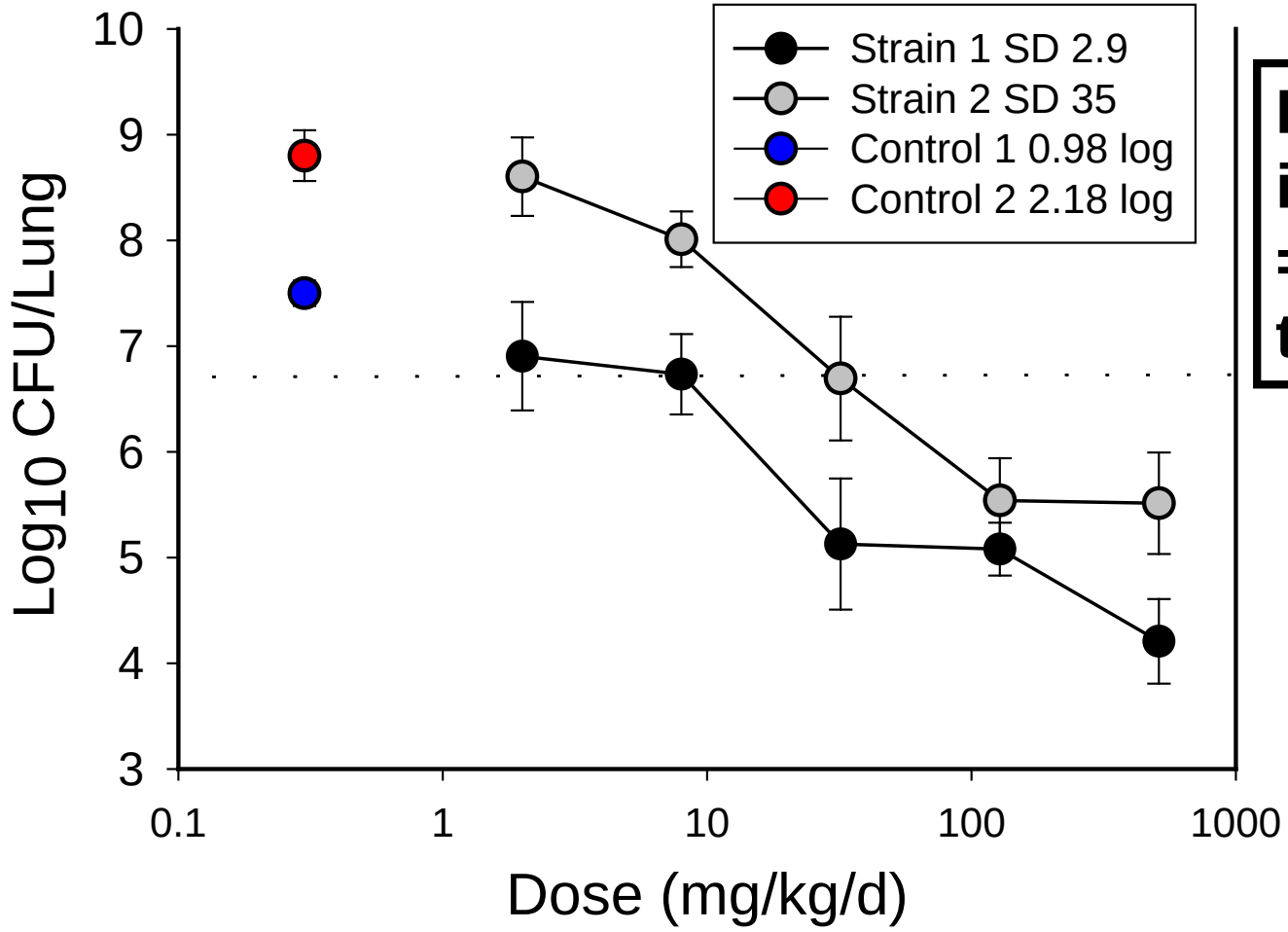
N=20 organisms, 4 cephalosporins

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

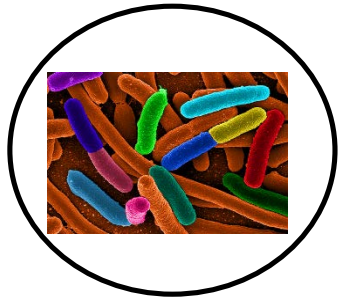
Resistance Mechanism

MIC is Helpful for Defining the PK/PD Target - EXCEPT

Impact of Organism Fitness



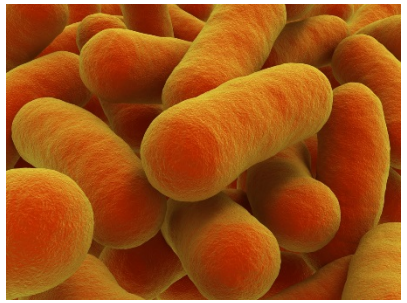
Less than 1 log Δ in growth = 10-fold Δ in PD target

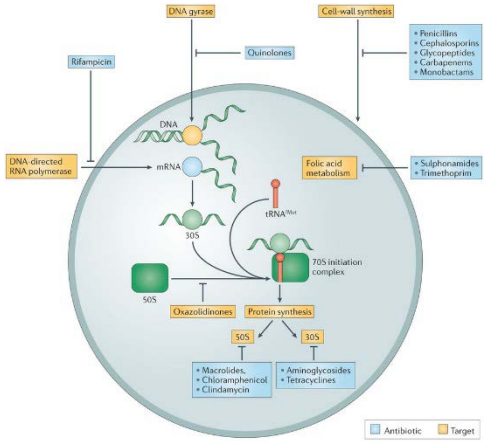


Strain Fitness

Murine infection model PK/PD can be used to forecast effective regimens in patients

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**

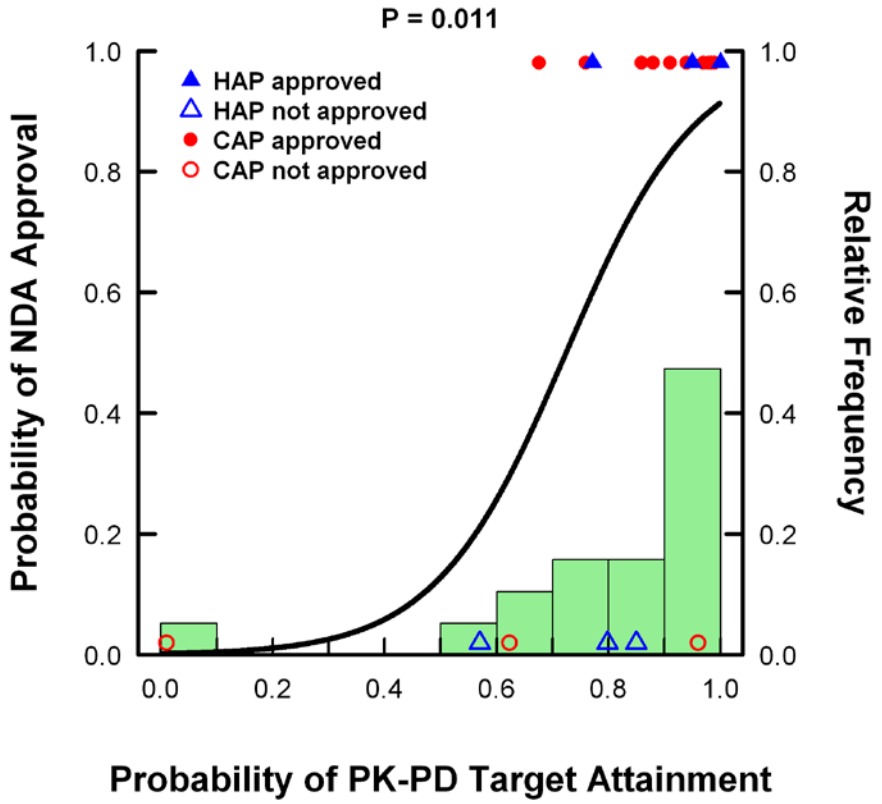
PK-PD INFECTION MODELS
Do They Forecast Success?

- 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

PK-PD INFECTION MODELS

Do They Forecast Success?

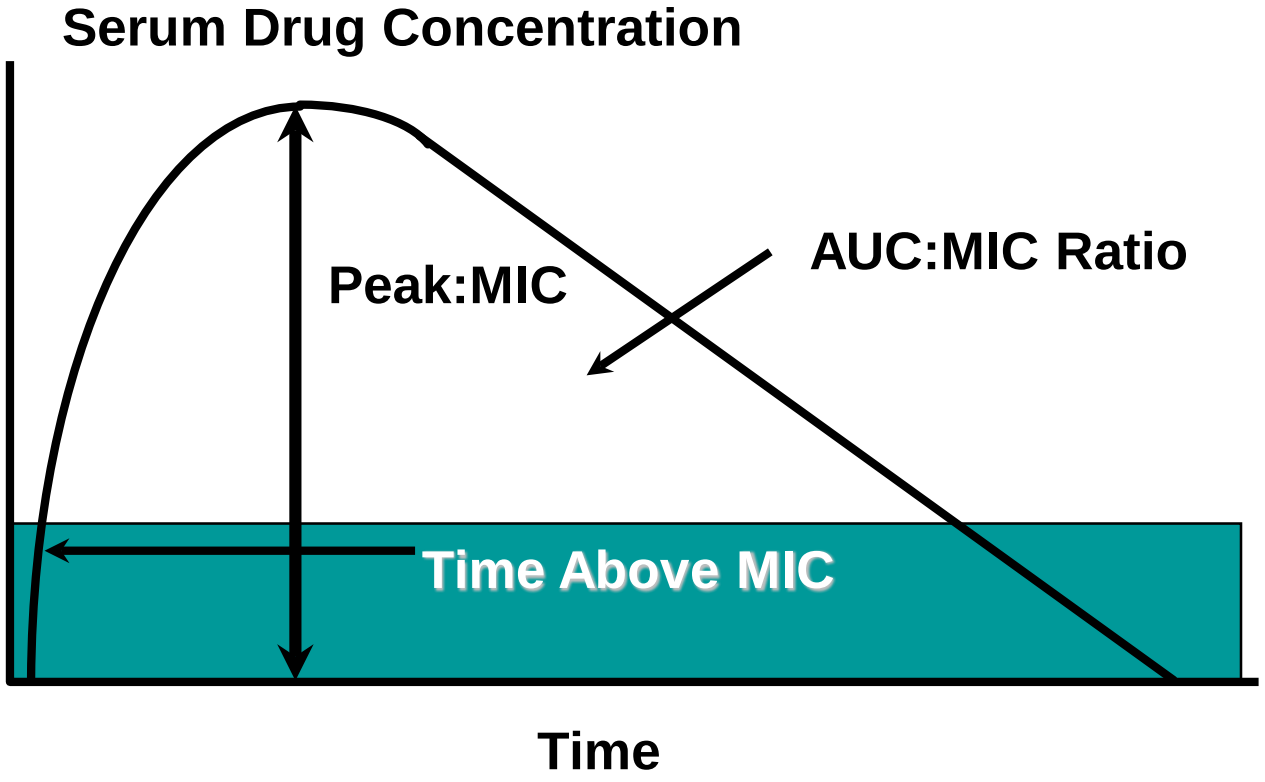


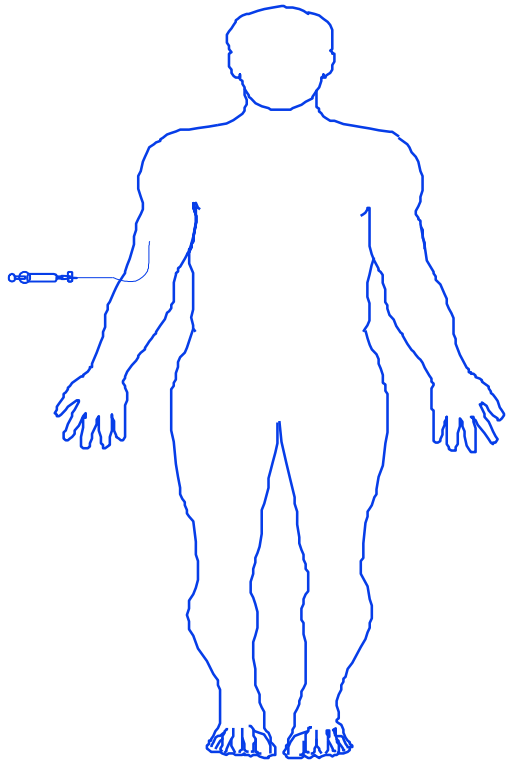
Quartile	Target Attainment Median	% NDA Approval (n/N)
1	0.62	40% (2/5)
2	0.85	60% (3/5)
3	0.94	80% (4/5)
4	0.985	100% (5/5)

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

THANK YOU





“It all started with a mouse.” ***AND AN MIC***

- Walt Disney and Bill Craig