Animal models for the study of antibiotic PKPD against staphylococci

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Animal models for antibiotic acitivity against *S. aureus*

General screening models:

- Peritonitis/sepsis
  - mouse
- Thigh (myositis)
  - mouse
- Wax moth larva (Galleria mellonella)

Specialised infection models:

- Endocarditis
  - rabbit, rat
- Osteomyelitis
  - pig, rabbit, rat
- Skin infection
  - mouse
- Pneumonia
  - rat, mouse

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2007, p. 1633–1642 Vol. 51, No. 5
0066-4804/07/$08.00+0 doi:10.1128/AAC.01264-06

In Vivo Pharmacodynamic Activity of the Glycopeptide Dalbavancin[▽]

David Andes* and William A. Craig

Department of Medicine, University of Wisconsin, 600 Highland Ave., Room H4/572, Madison, Wisconsin 53792

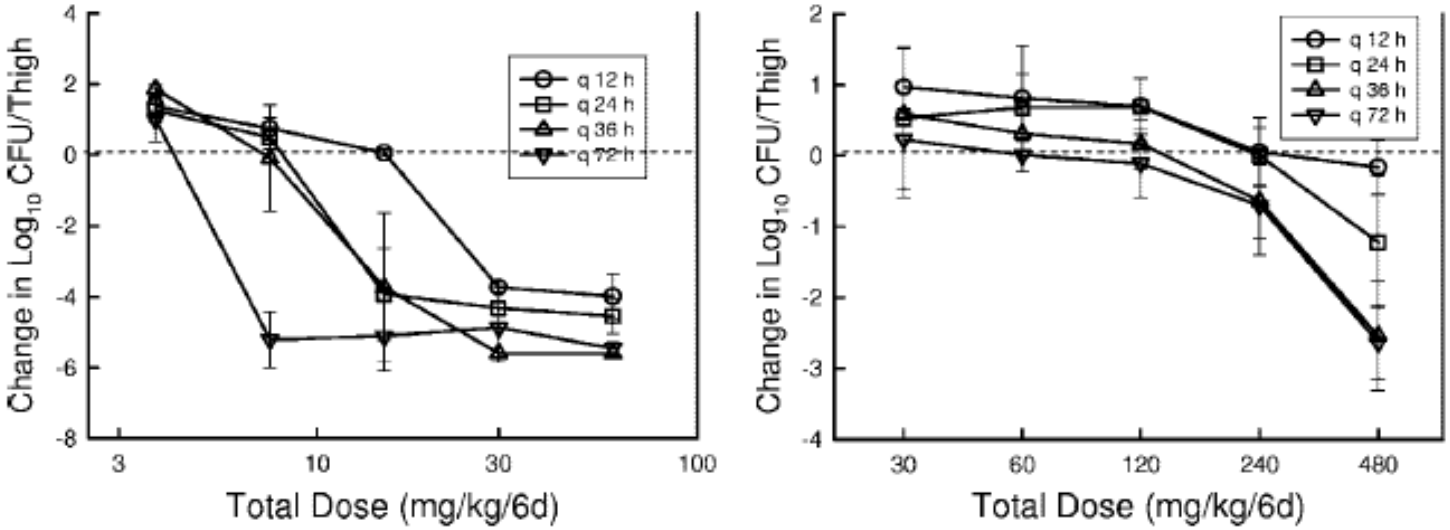

FIG. 3. Impact of dalbavancin dosing interval on the in vivo efficacy of dalbavancin against *S. pneumoniae* ATCC 10813 (left panel) or *S. aureus* ATCC 29213 (right panel) in neutropenic mice. Five total dose levels were fractionated over a 144-h study period. Each symbol represents one of four dosing intervals. Each datum point represents the mean and standard deviation $\log_{10}$ CFU/thigh for four thighs.

Pharmacodynamics of TD-1792, a Novel Glycopeptide-Cephalosporin Heterodimer Antibiotic Used against Gram-Positive Bacteria, in a Neutropenic Murine Thigh Model

Sharath S. Hegde,[a] Olanrewaju O. Okusanya,[b] Robert Skinner,[a] Jeng-Pyng Shaw,[a]* Glenmar Obedencio,[a] Paul G. Ambrose,[b] Johanne Blais,[a] and Sujata M. Bhavnani[b]

Theravance, Inc., South San Francisco, California, USA,[a] and Institute for Clinical Pharmacodynamics, Latham, New York, USA[b]

AAC 2012, 56: 1568-73

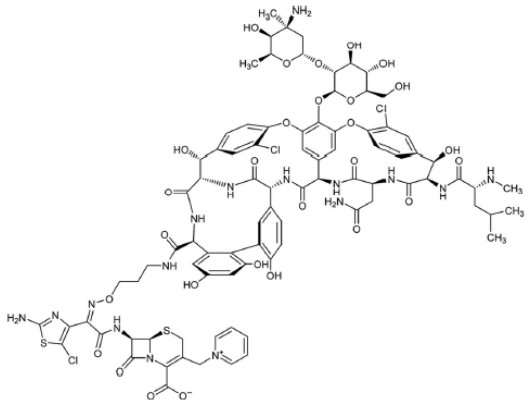

FIG 1 Chemical structure of TD-1792.

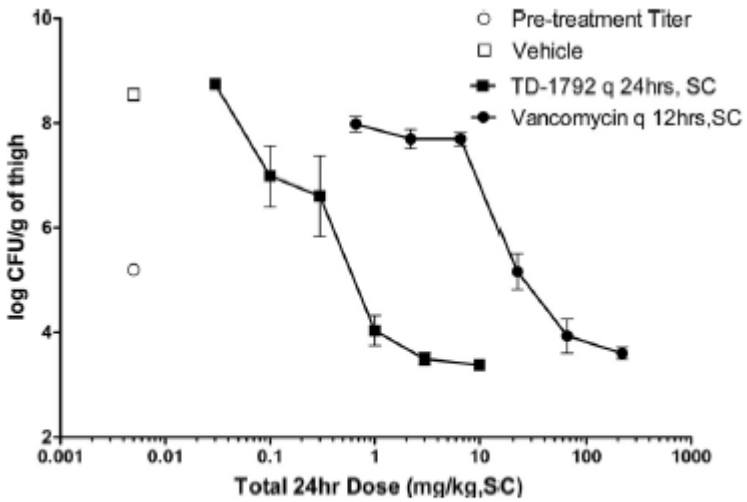

FIG 3 Efficacy of TD-1792 and vancomycin against MRSA ATCC 33591 in the neutropenic murine thigh model. The abscissa shows the total 24-h dosage in mg/kg, SC, and the ordinate shows the thigh bacterial burden in $\log_{10}$ CFU/g. Vehicle and TD-1792 were dosed every 24 h, whereas vancomycin was dosed every 12 h. Data are expressed as means ± standard deviations (SD) ($n = 5$ per group).

Pharmacodynamics of TD-1792, a Novel Glycopeptide-Cephalosporin Heterodimer Antibiotic Used against Gram-Positive Bacteria, in a Neutropenic Murine Thigh Model

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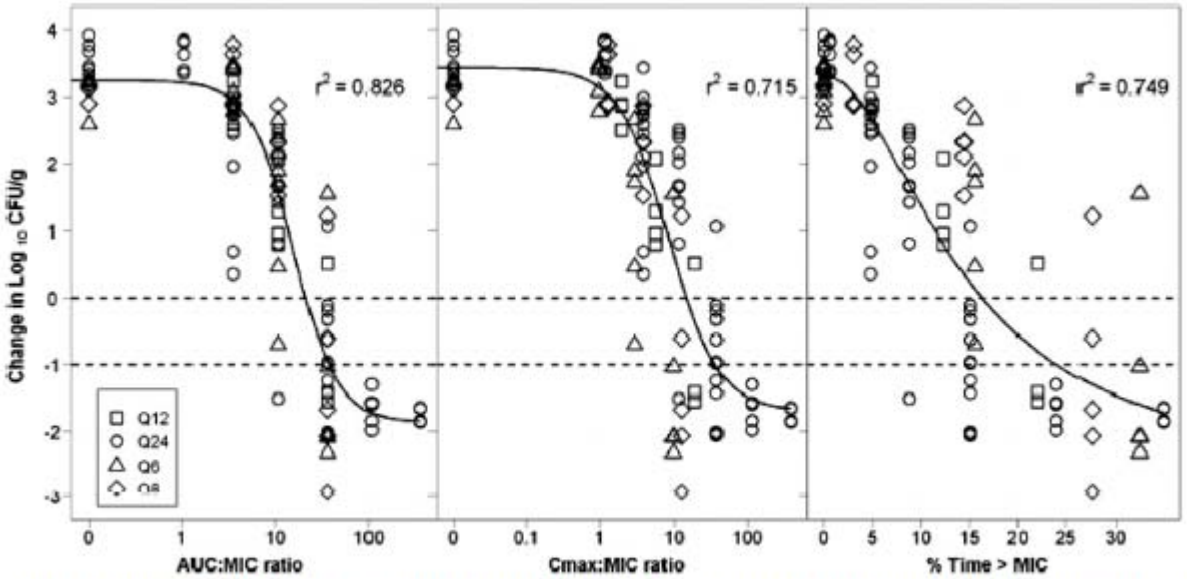


FIG 5 Relationship between AUC/MIC ratio (left), Cmax/MIC ratio (middle), %Time>MIC (right), and the change in $\log_{10}$ CFU/g from pretreatment values. Each point represents data from one mouse. The fitted line represents the Hill-type function.

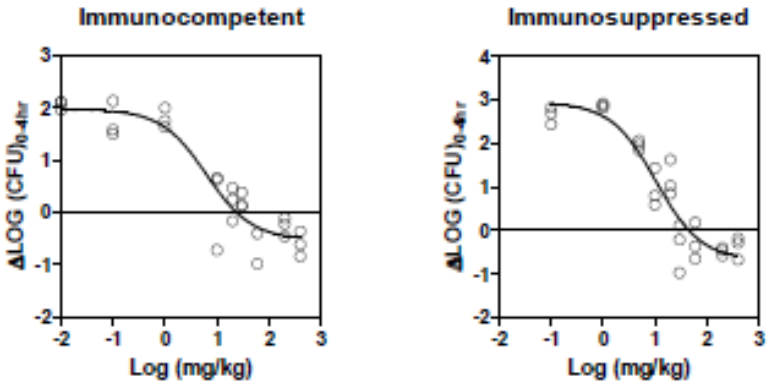
THE CHOICE OF MURINE INFECTION MODEL AND THE IMMUNE STATUS OF THE MICE HAS AN IMPACT ON THE PHARMACODYNAMICS OF DICLOXACILLIN AGAINST STAPHYLOCOCCUS AUREUS INFECTION

A Sandberg-Shaal, C Vingsbo Lundberg*, N Frimodt-Møller Statens Serum Institut, Copenhagen, Denmark

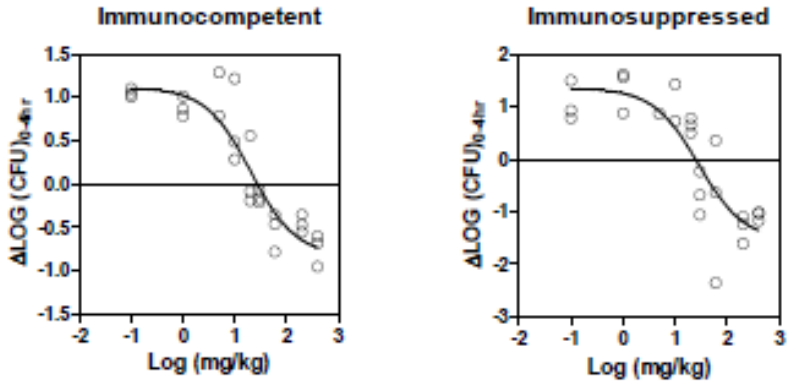
ECCMID 2009 Abs 2267

DOSE RESPONSE WITH DICLOXACILLIN AGAINST S.AUREUS

PERITONITIS MODEL



THIGH INFECTION MODEL



ED50 for Dicloxacillin in 4 different infection models:

PERITONITIS MODEL

Immunocompetent: **6.75 ± 1.6**
Immunosuppressed: **10.6 ± 1.3**

THIGH INFECTION MODEL

Immunocompetent: **20.6 ± 1.3**
Immunosuppressed: **28.2 ± 1.6**

TABLE 5. Impact of neutrophils on in vivo efficacy of dalbavancin against *S. pneumoniae*

Mouse group	Dose (mg/kg/6 days [95% CI])		
	Static dose	Dose associated with 1-log killing	Dose associated with 2-log killing
Healthy	2.03 (1.99–2.07)	2.35 (2.26–2.44)	2.66 (2.56–2.76)
Neutropenic	4.13 (0.23–8.0)	4.38 (0.28–8.50)	4.62 (0.32–8.90)

Andes & Craig AAC 2007

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2000, p. 1247–1254 Vol. 44, No. 5
0066-4804/00/$04.00+0

Pharmacodynamics of Glycopeptides in the Mouse Peritonitis Model of *Streptococcus pneumoniae* or *Staphylococcus aureus* Infection

JENNY DAHL KNUDSEN,[1]* KURT FUURSTED,[1] SUSAN RABER,[2] FRANK ESPERSEN,[1] AND NIELS FRIMODT-MØLLER[1]

Division of Microbiology, Statens Serum Institut, Copenhagen, Denmark,[1] and Providence Medical Center, Portland, Oregon[2]

TABLE 1. MICs and single-dose ED_{50}s of two glycopeptides against *S. aureus* (E-2371) and *S. pneumoniae* (I-1320)

Organism	Drug	MIC (μg/ml)	ED_{50}, mg/kg (95% CI; no. of mice)[a]
S. aureus	Vancomycin	1	3.82 (2.87–5.08;122)
	Teicoplanin	1	2.96 (2.38–3.69;136)
S. pneumoniae	Vancomycin	0.125	0.65 (0.62–0.69; 85)
	Teicoplanin	0.062	0.45 (0.45–0.46;115)

[a] CI, confidence interval.

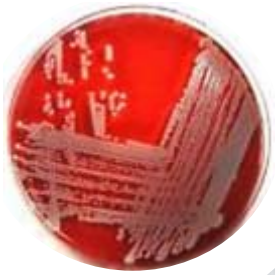
TABLE 2. Survival of mice treated with doses close to the ED_{50}s, given in one or two doses beginning 1 h after challenges[a]

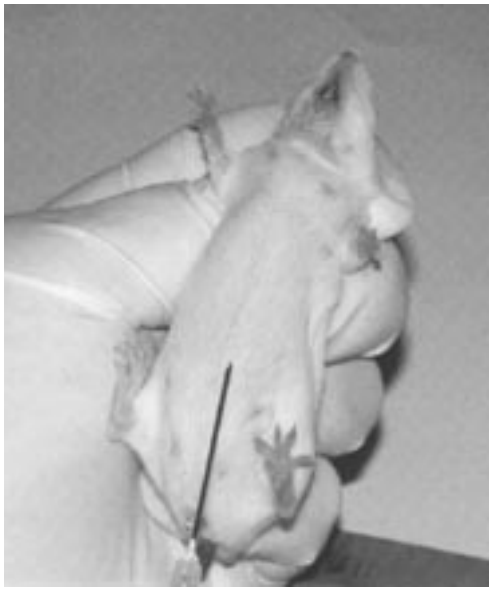
Organism	Drug regimen	Dosing regimen		No. of mice surviving/total no. of mice tested (%)	*P* value determined by Mantel-Haenszels test[b]	PK-PD parameters				
		Dose (mg/kg)	No. of times given			C_{max}/MIC	$T_{>MIC}$ (h)	AUC[c]/MIC (h)	$C_{max\text{-}free}$[d]/MIC	$T_{>MIC\text{-}free}$[e] (h)
S. aureus	Control	0		8/58 (13.8)		0.00	0.00	0.00	0.00	0.00
	Vancomycin	4.73	1	15/24 (62.5)	0.04	7.57	1.56	6.40	5.68	1.34
		2.37	2	9/24 (37.5)		4.07	2.04	6.40	3.05	1.60
	Teicoplanin	2.70	1	15/24 (62.5)	0.37	8.10	7.61	29.51	0.81	0.00
		1.35	2	11/24 (45.8)		4.24	10.18	29.51	0.42	0.00
S. pneumoniae	Control	0		0/20 (0.0)		0.00	0.00	0.00	0.00	0.00
	Vancomycin	0.67	1	17/30 (56.7)	<0.01	8.56	1.65	6.96	6.40	1.43
		0.33	2	5/30 (17.7)		4.56	2.22	6.96	3.44	1.80
	Teicoplanin	0.38	1	6/30 (20.0)	0.05	18.39	10.59	65.00	1.77	2.09
		0.19	2	4/30 (13.3)		9.68	16.14	65.00	0.97	0.00
	Teicoplanin	0.60	1	27/30 (90.0)	<0.01	29.03	12.25	104.52	2.90	3.88
		0.30	2	4/30 (13.3)		15.16	19.46	104.52	1.45	2.72

[a] The second doses were given 2 h later for vancomycin and 12 h later for teicoplanin. Mice were observed for 6 days.

The mouse peritonitis model

Intra- and extracellular activity of antibiotics against *S. aureus*





Inoculation:

- Intraperitoneal injection of *S.aureus*

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

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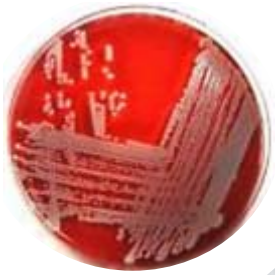
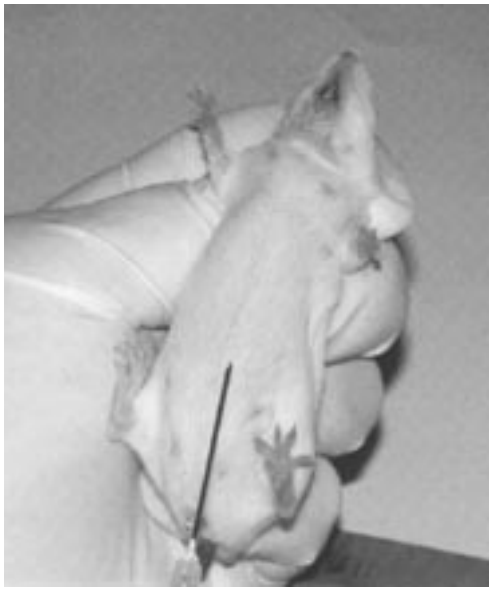


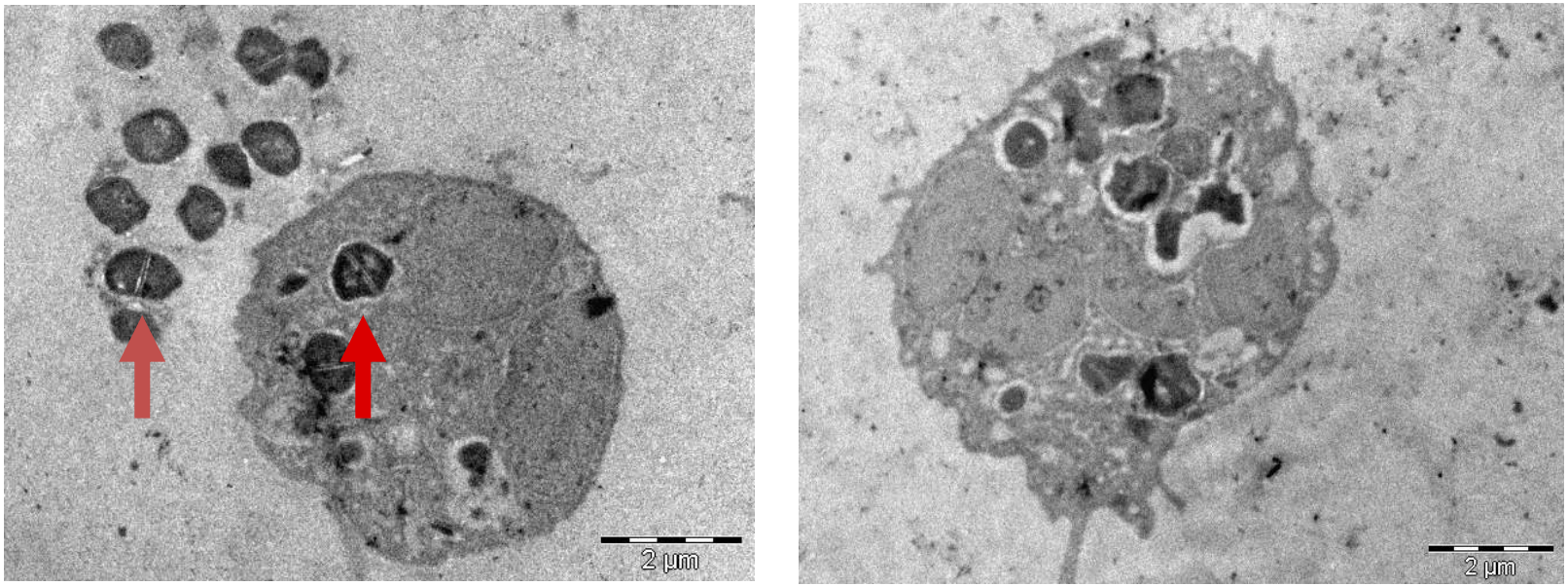


Inoculation:

- Intraperitoneal injection of *S.aureus* ⟶ peritonitis (2 hr)

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

The mouse peritonitis model



Electron microscopy of peritoneal fluid post infection with *S. aureus*

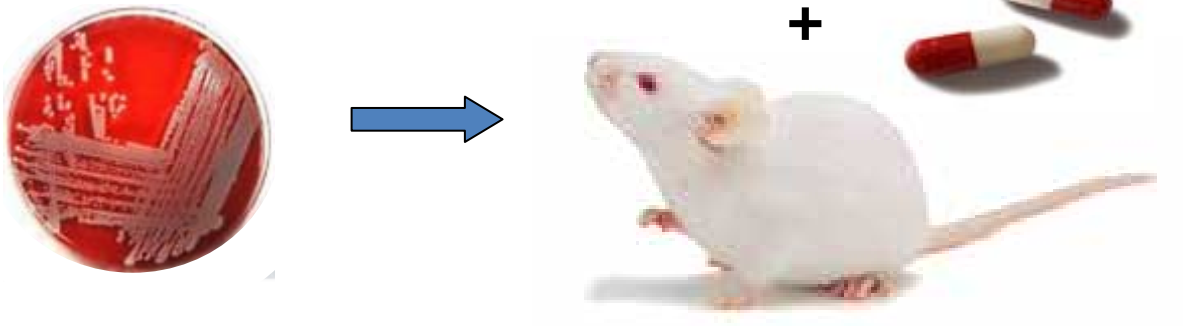
Extracellular *S. aureus*

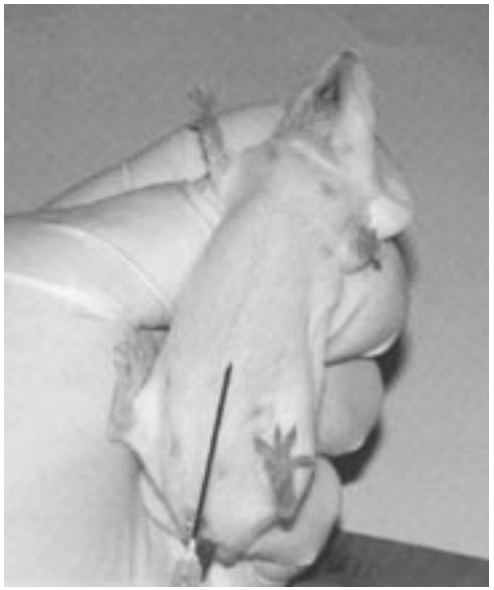
Intracellular *S. aureus*

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

The mouse peritonitis model

Intra- and extracellular activity of antibiotics against *S. aureus*





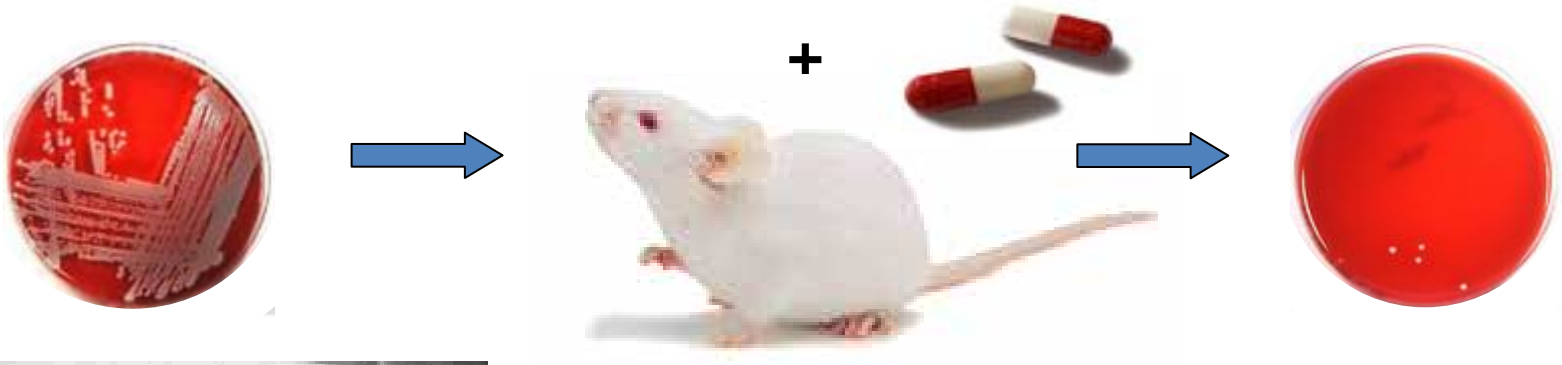
Antibiotic treatment

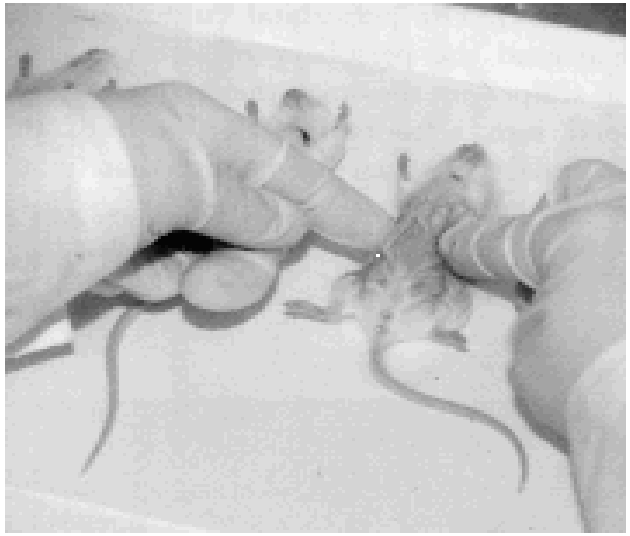
- Intraperitoneal injection of *S.aureus*
- Subcutaneous injection of antibiotic

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

The mouse peritonitis model

Intra- and extracellular activity of antibiotics against *S. aureus*





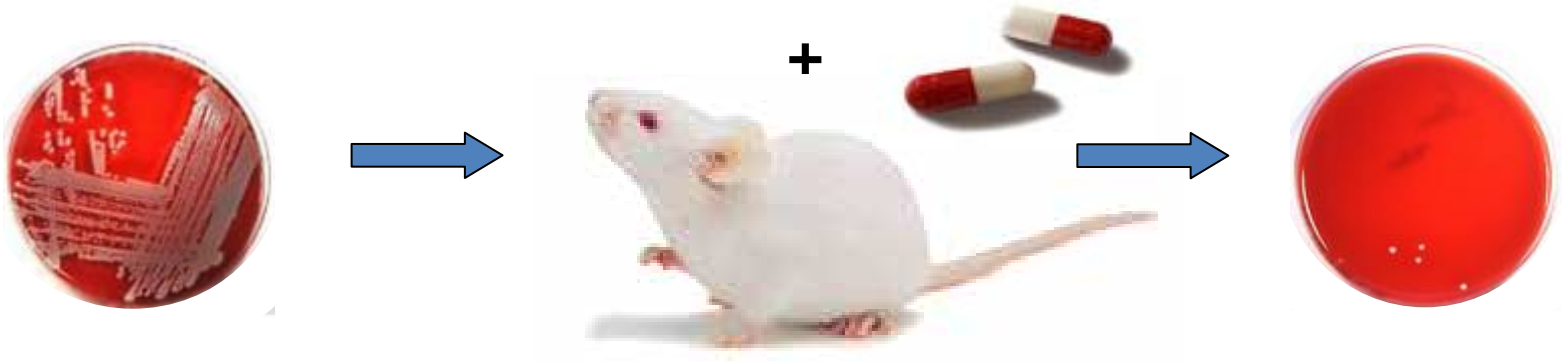
Sampling:

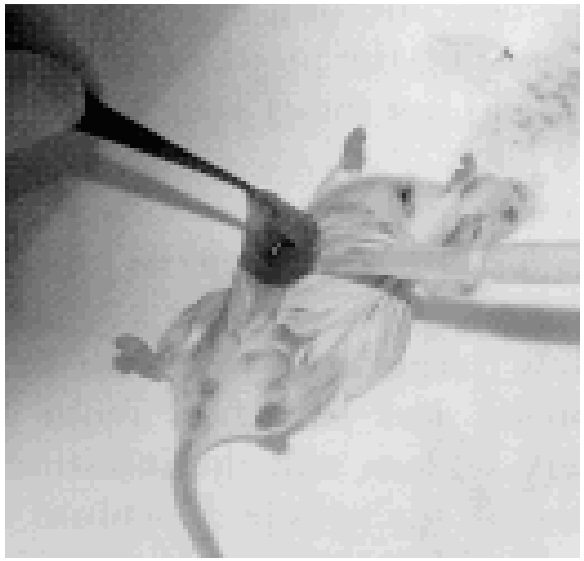
- Euthanasia
- Intraperitoneal injection of HBSS (2 ml) and mix

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

The mouse peritonitis model

Intra- and extracellular activity of antibiotics against *S. aureus*



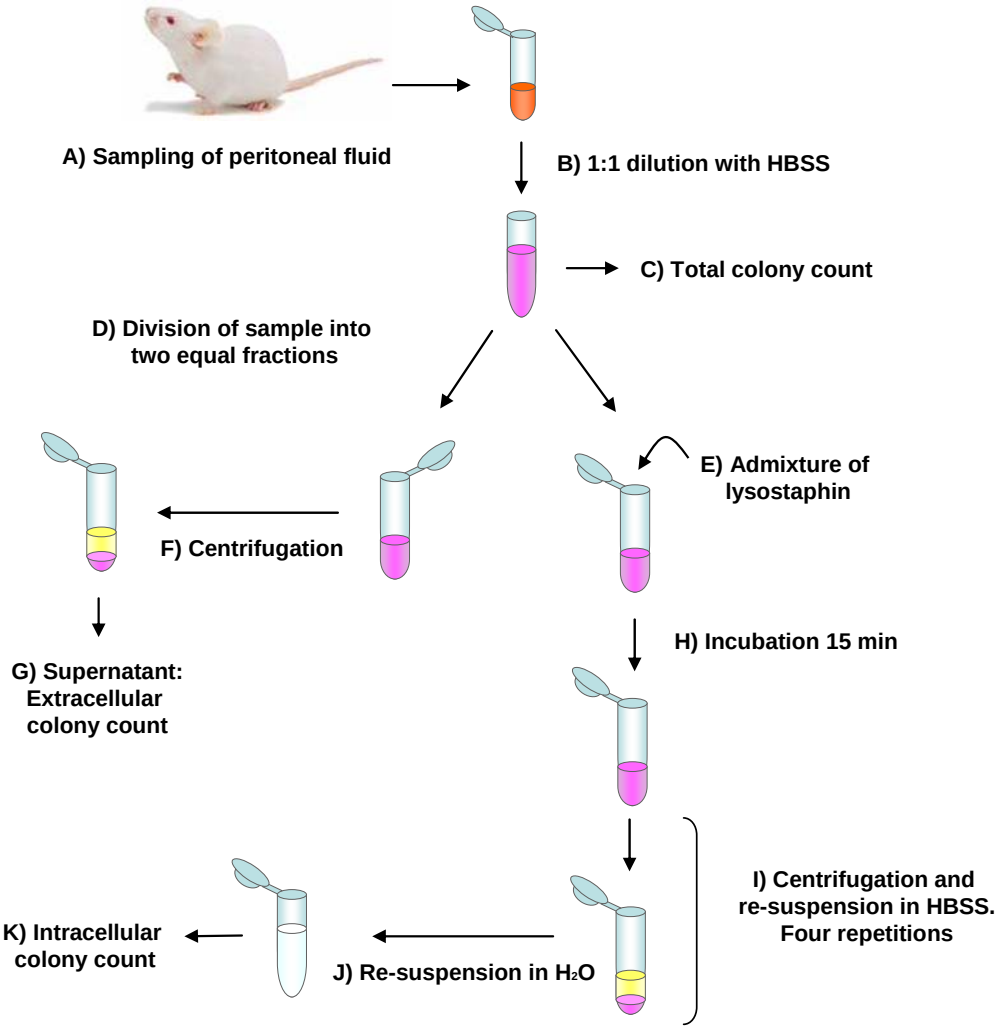


Sampling:

- Euthanasia
- Intraperitoneal injection of HBSS (2 ml) and mix
- Collection of peritoneal fluid through incision

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

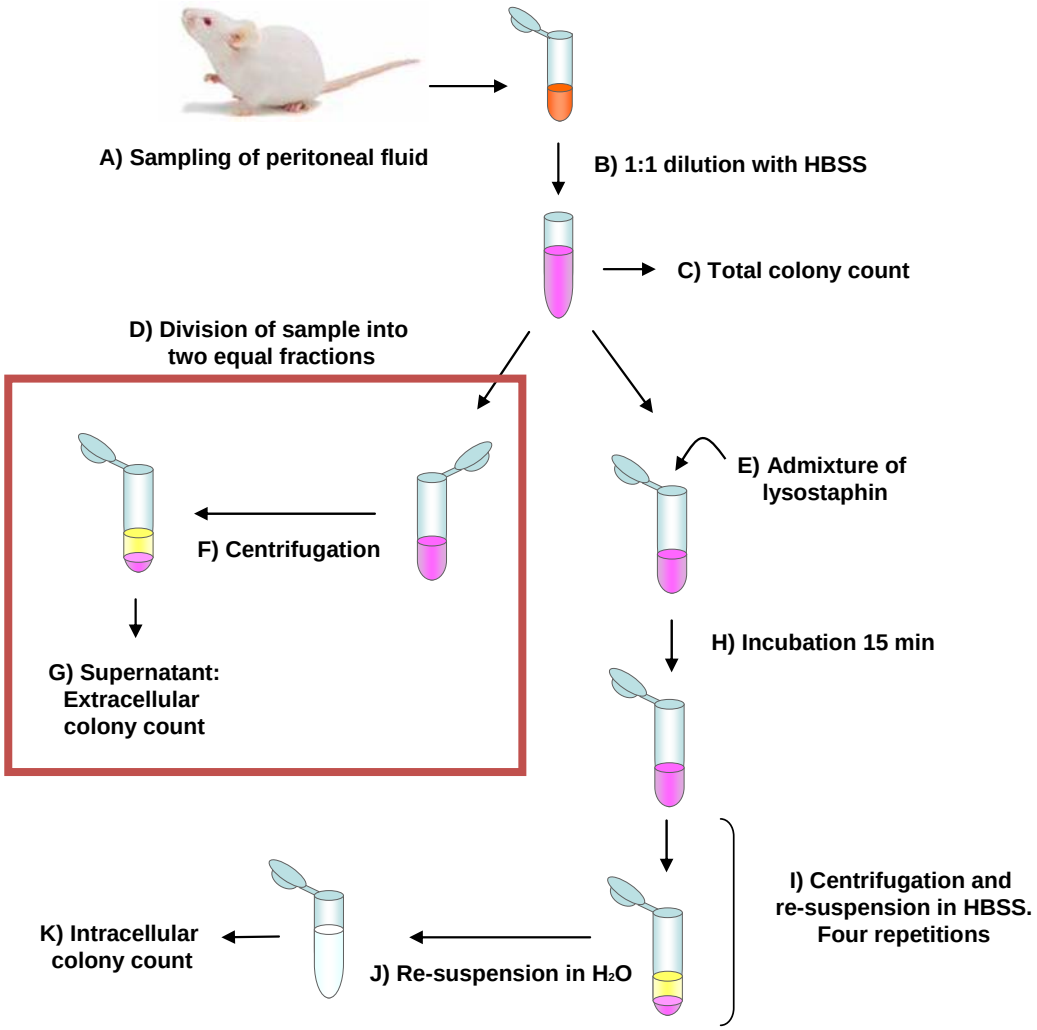
Separation of intra- and extracellular bacteria



Division of sample into two equal fractions

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

Separation of intra- and extracellular bacteria

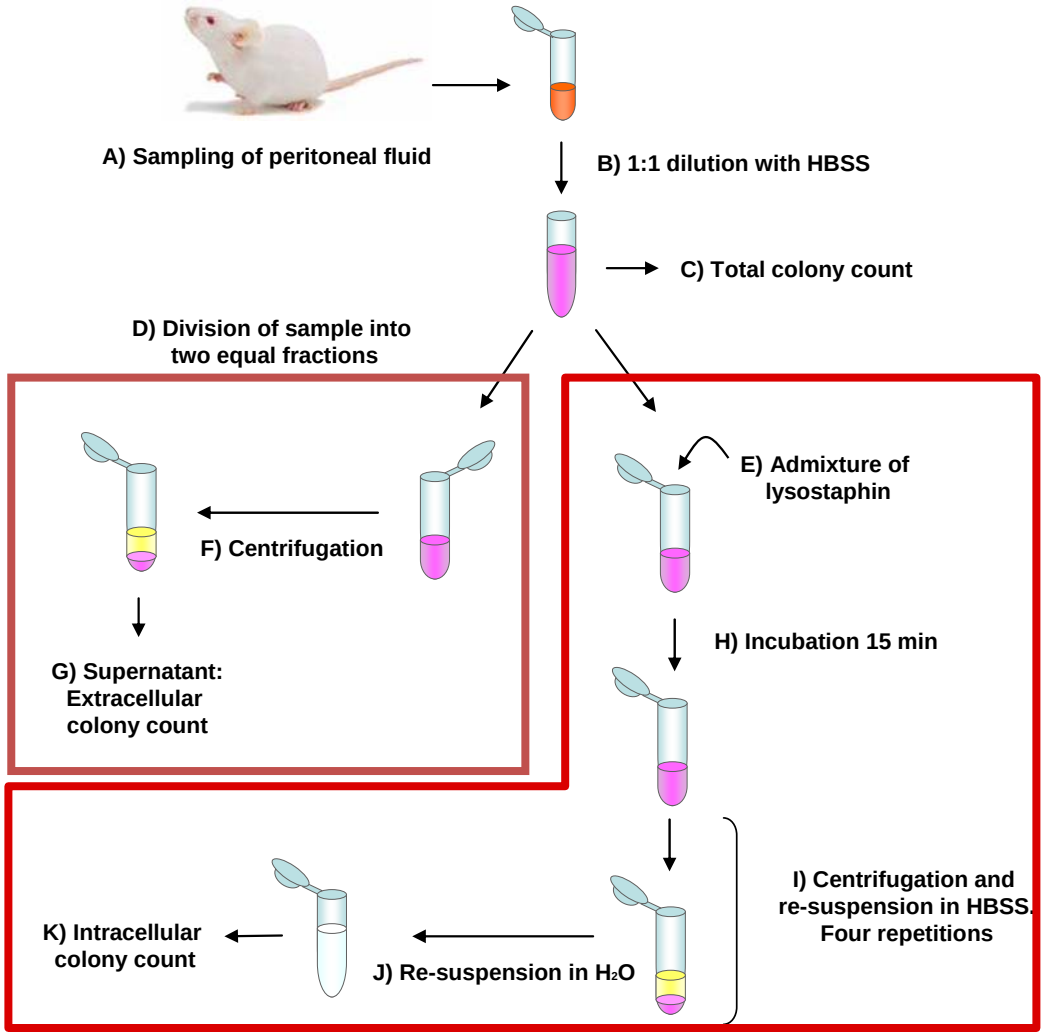


Division of sample into two equal fractions

Fraction A:
Extracellular *S. aureus* estimated from supernatant after centrifugation

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

Separation of intra- and extracellular bacteria



Division of sample into two equal fractions

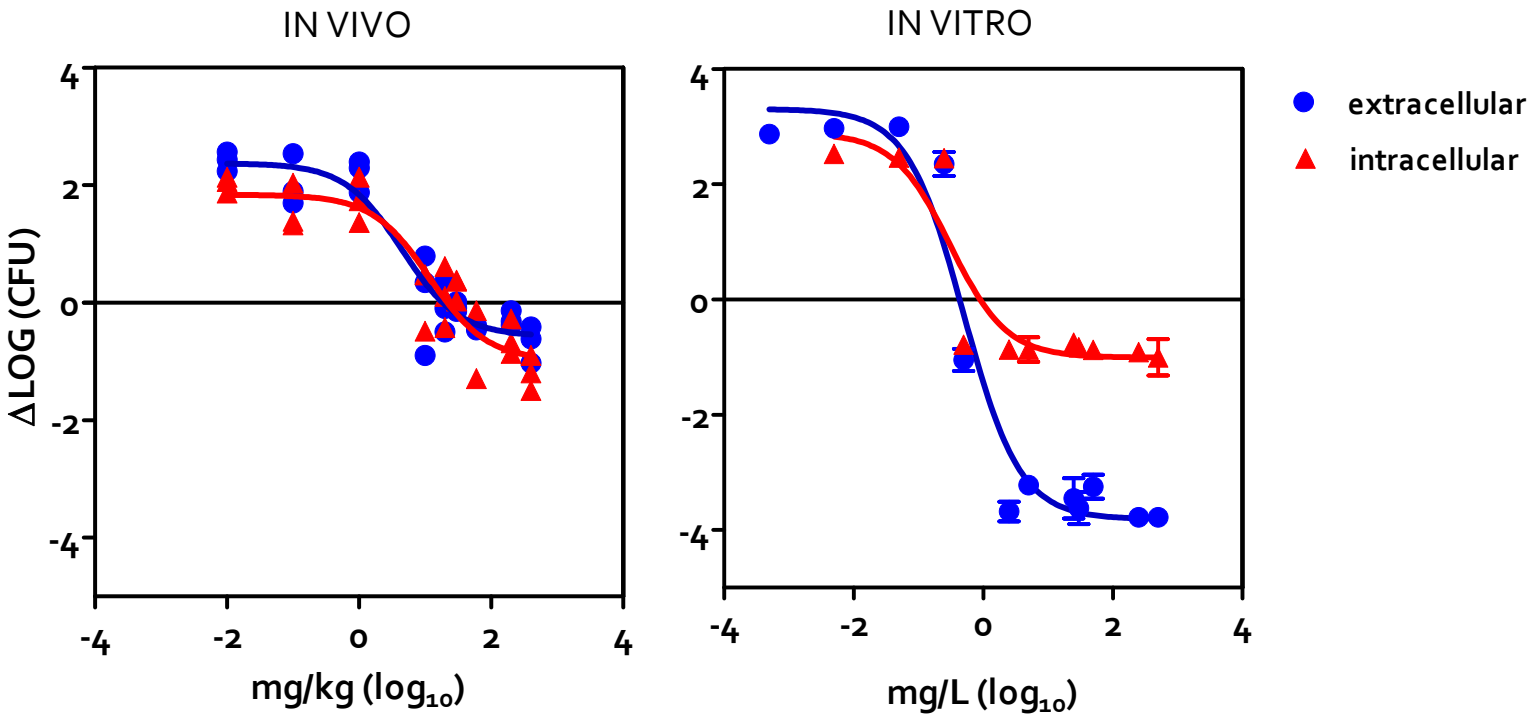
Fraction A:
Extracellular *S. aureus* estimated from supernatant after centrifugation

Fraction B:
Intracellular *S. aureus* estimated after incubation with lysostaphin, lysostaphin wash-out, and lysis with H_2O

Sandberg et al., Antimicrob Agents Chemother (2009) 53:1874-1883

Dose-response studies

DICLOXACILLIN vs. *S. aureus*

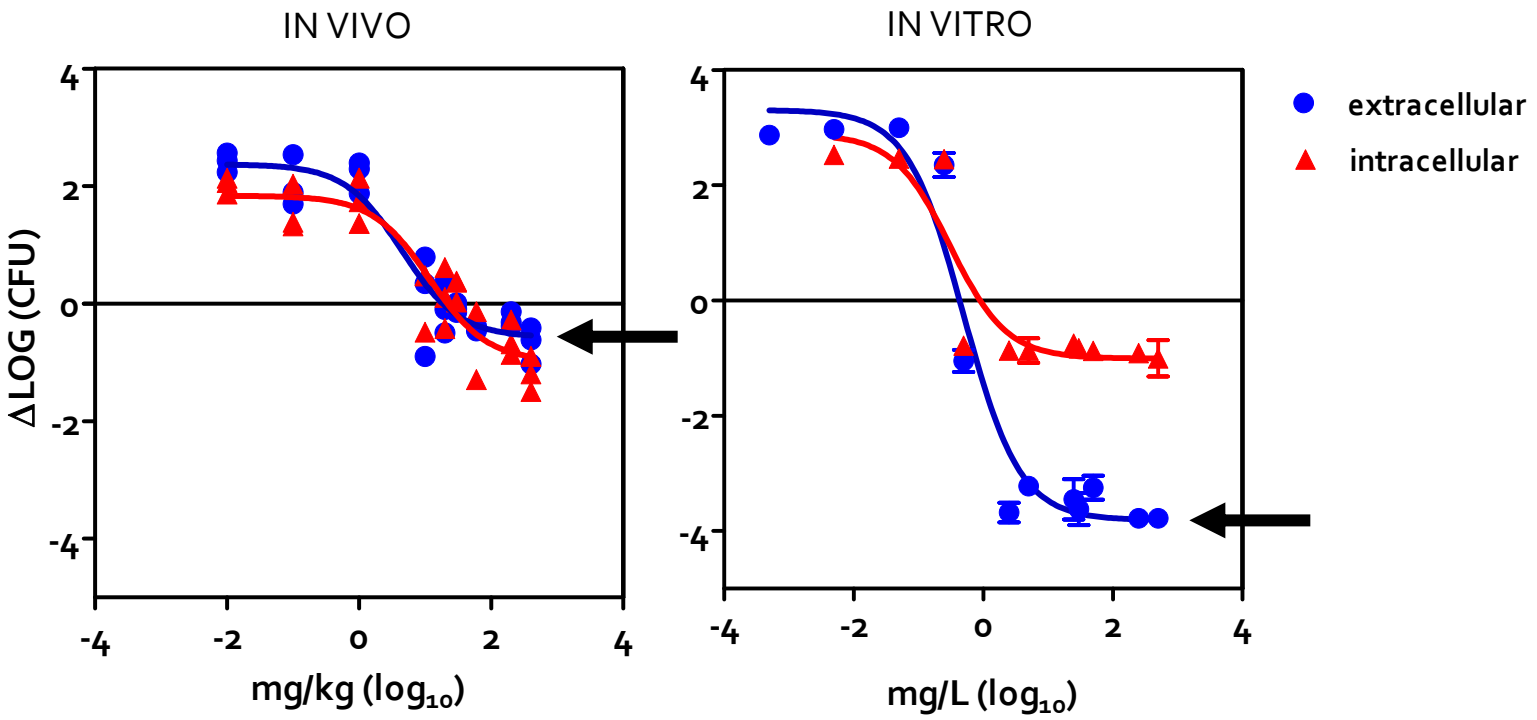


Δlog(CFU) = changes in colony counts compared to the original inoculum (treatment outcome)

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

Dose-response studies

DICLOXACILLIN vs. *S. aureus*

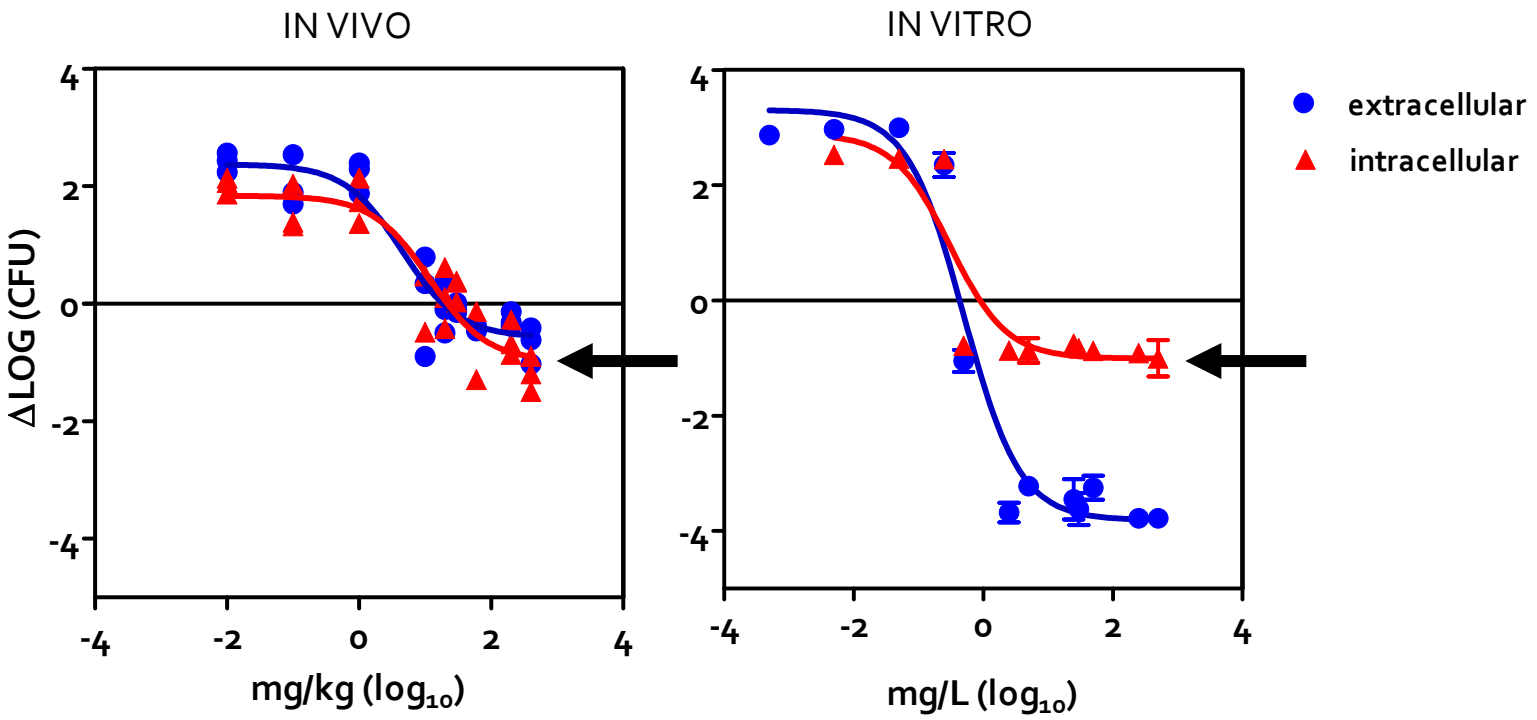


Extracellular activity: dissimilar results were obtained in vitro and in vivo

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

Dose-response studies

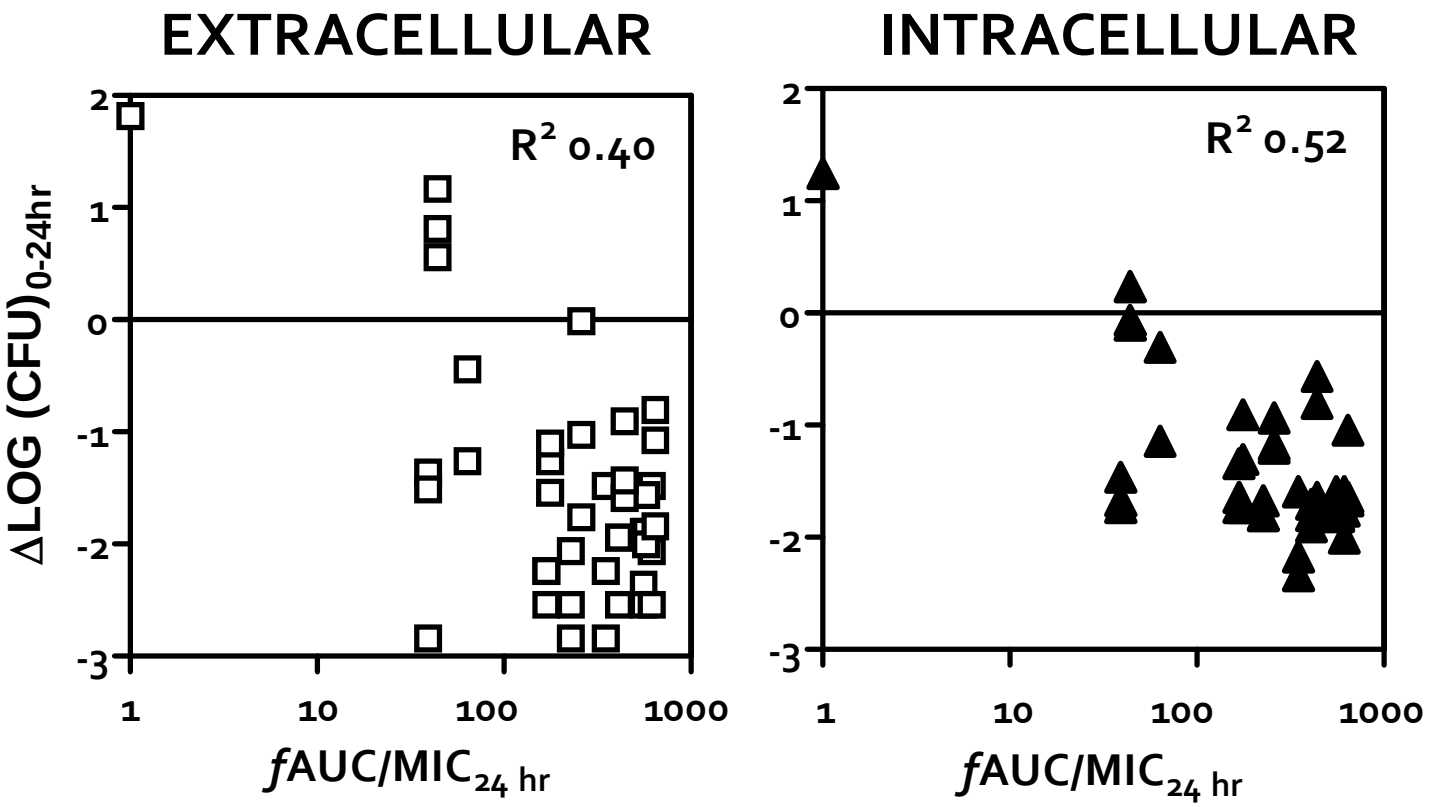
DICLOXACILLIN vs. *S. aureus*



Intracellular activity: similar results were obtained in vitro and in vivo

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

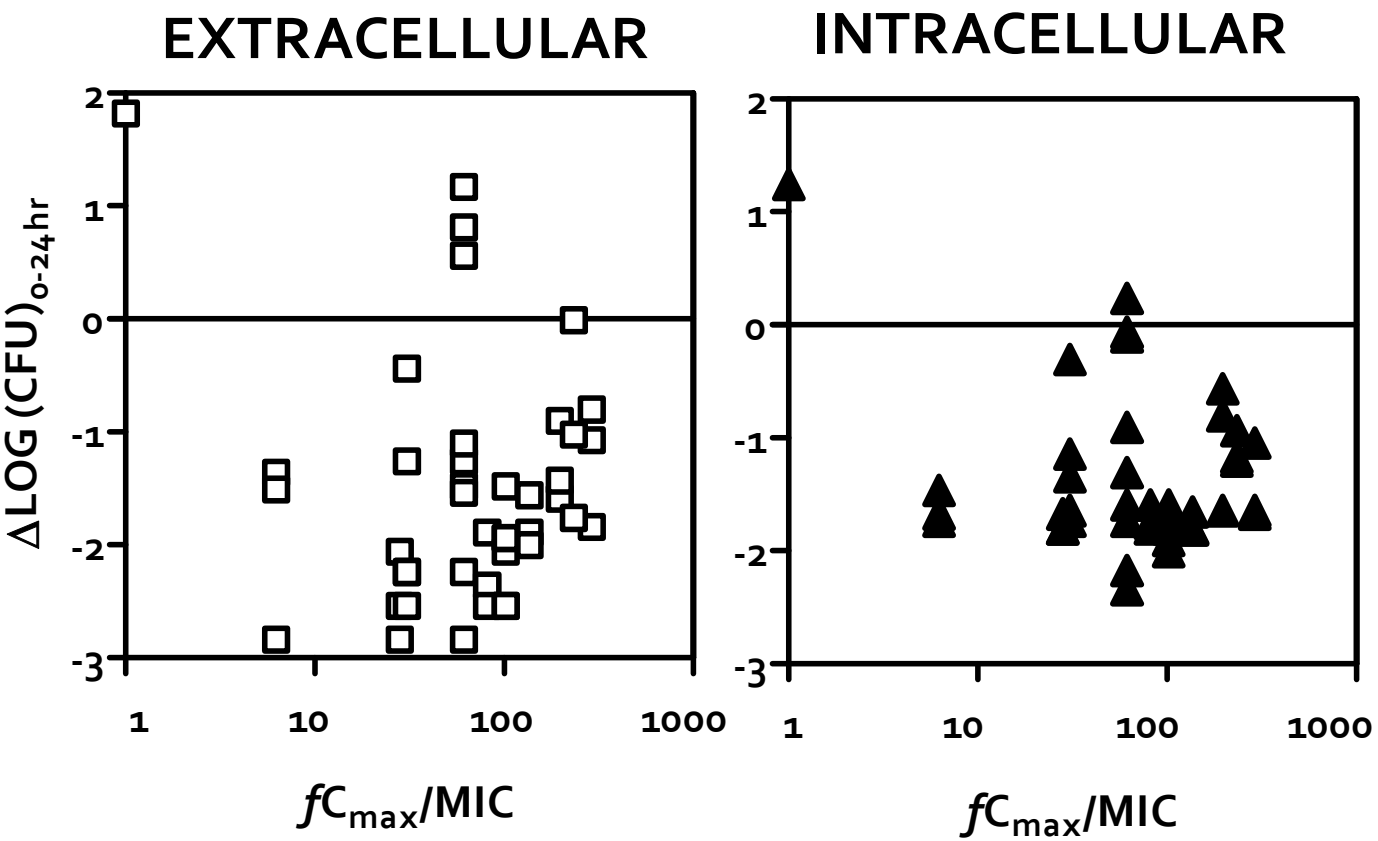
PK/PD studies: Dicloxacillin vs *S. aureus*



No correlation between treatment outcome and the AUC/MIC index

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

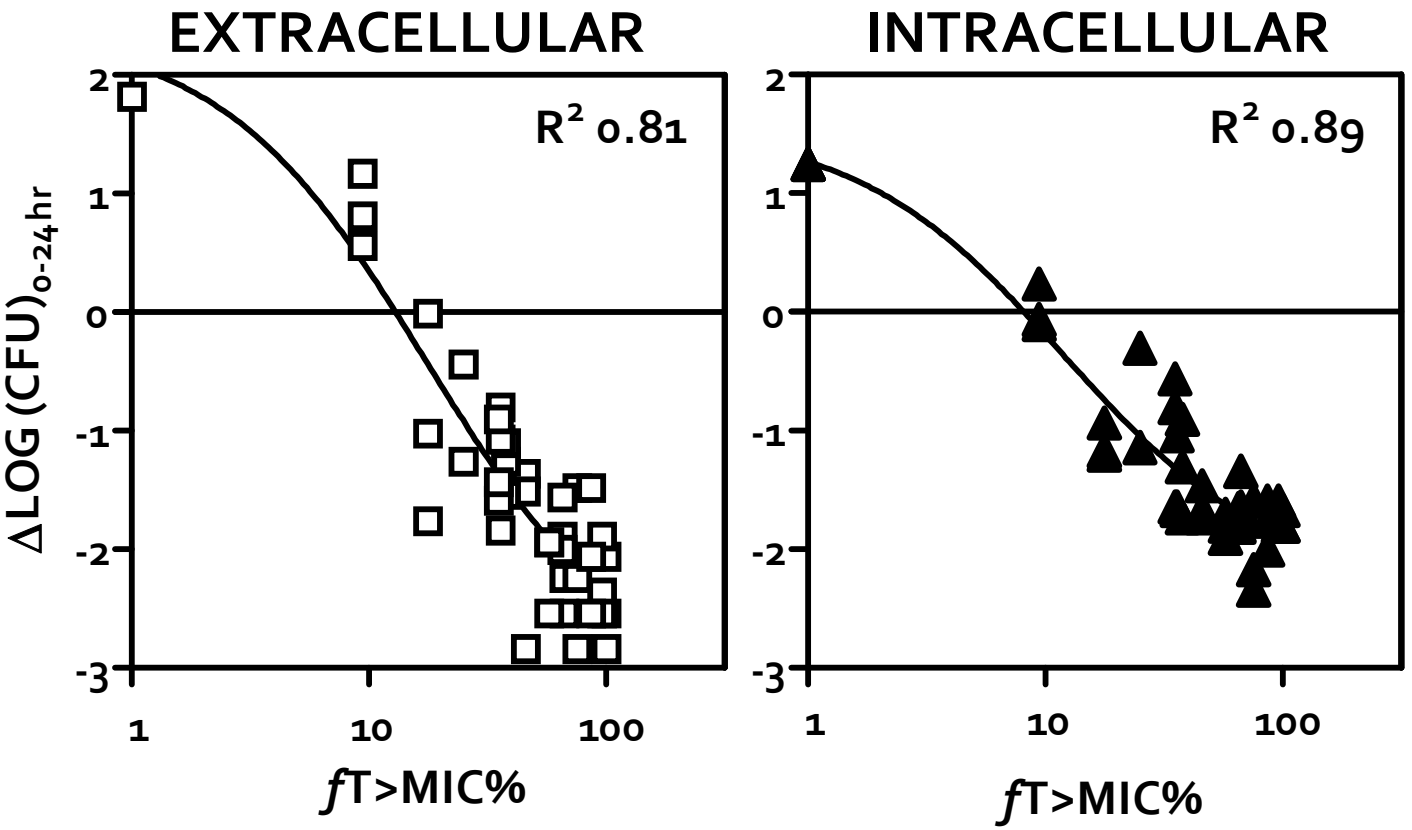
PK/PD studies: Dicloxacillin vs *S. aureus*



No correlation between treatment outcome and the C_{max} /MIC index

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

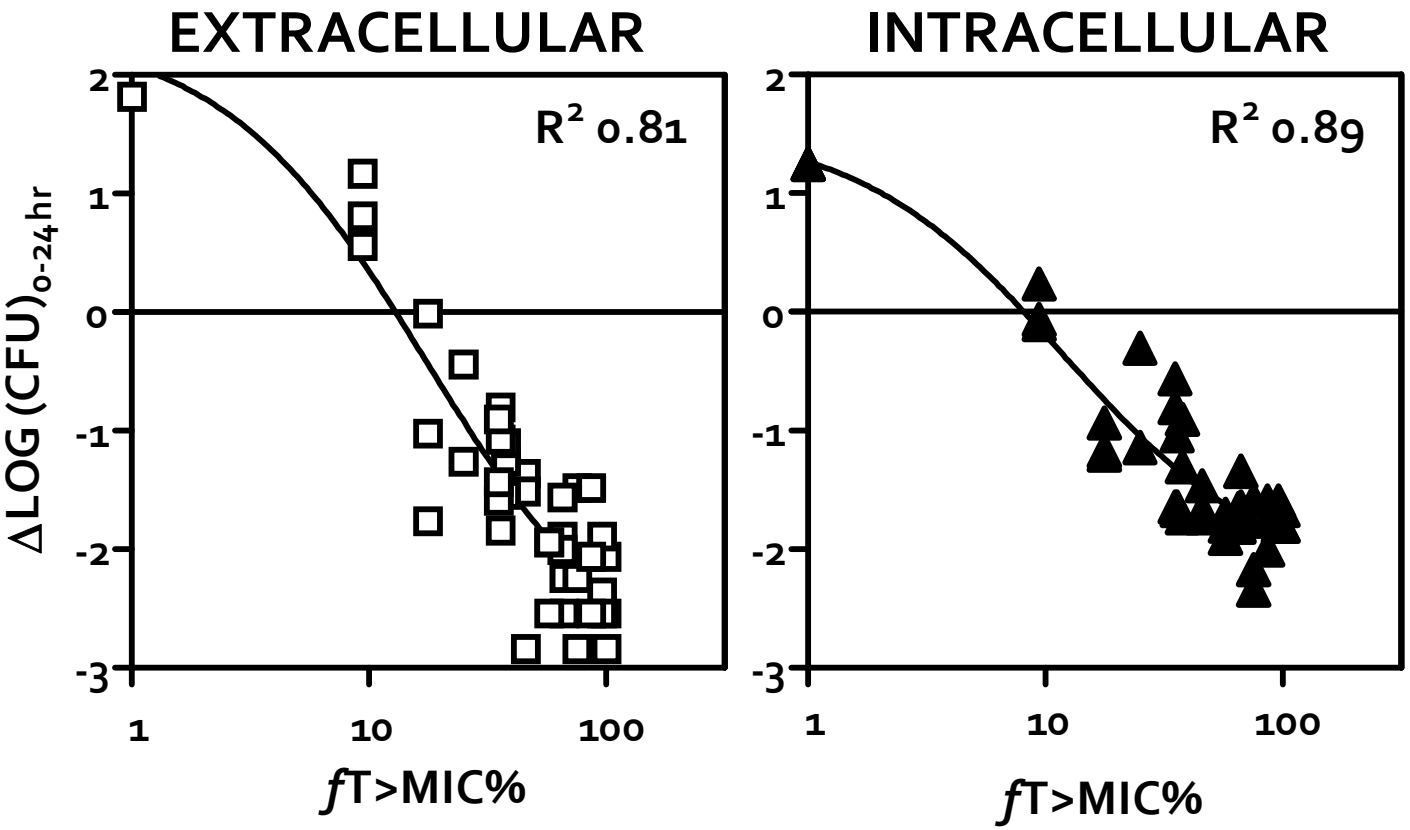
PK/PD studies: Dicloxacillin vs *S. aureus*



Correlation between treatment outcome and the T>MIC index

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

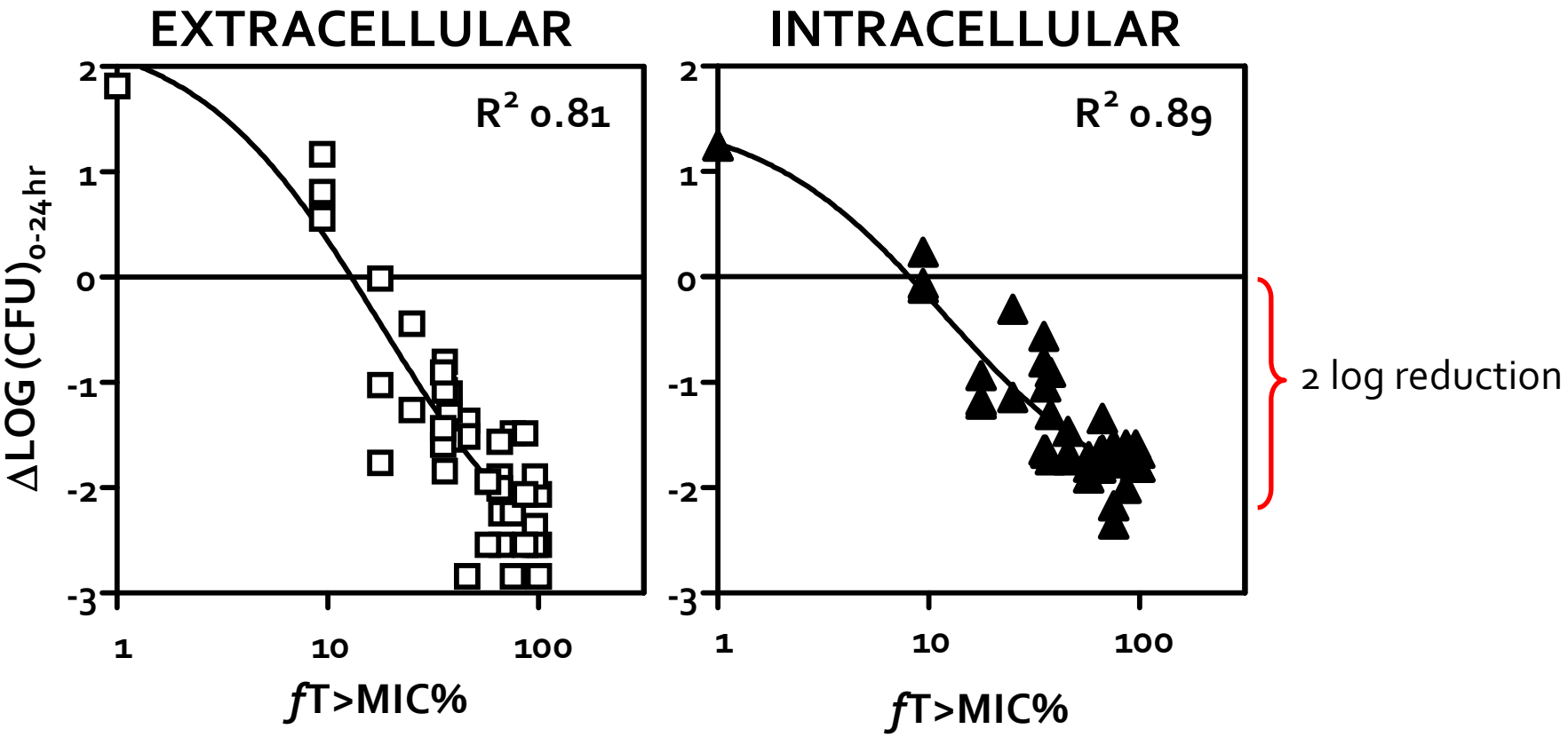
PK/PD studies: Dicloxacillin vs *S. aureus*



T>MIC is the predicting PK/PD index both intra- and extracellularly

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

PK/PD studies: Dicloxacillin vs *S. aureus*

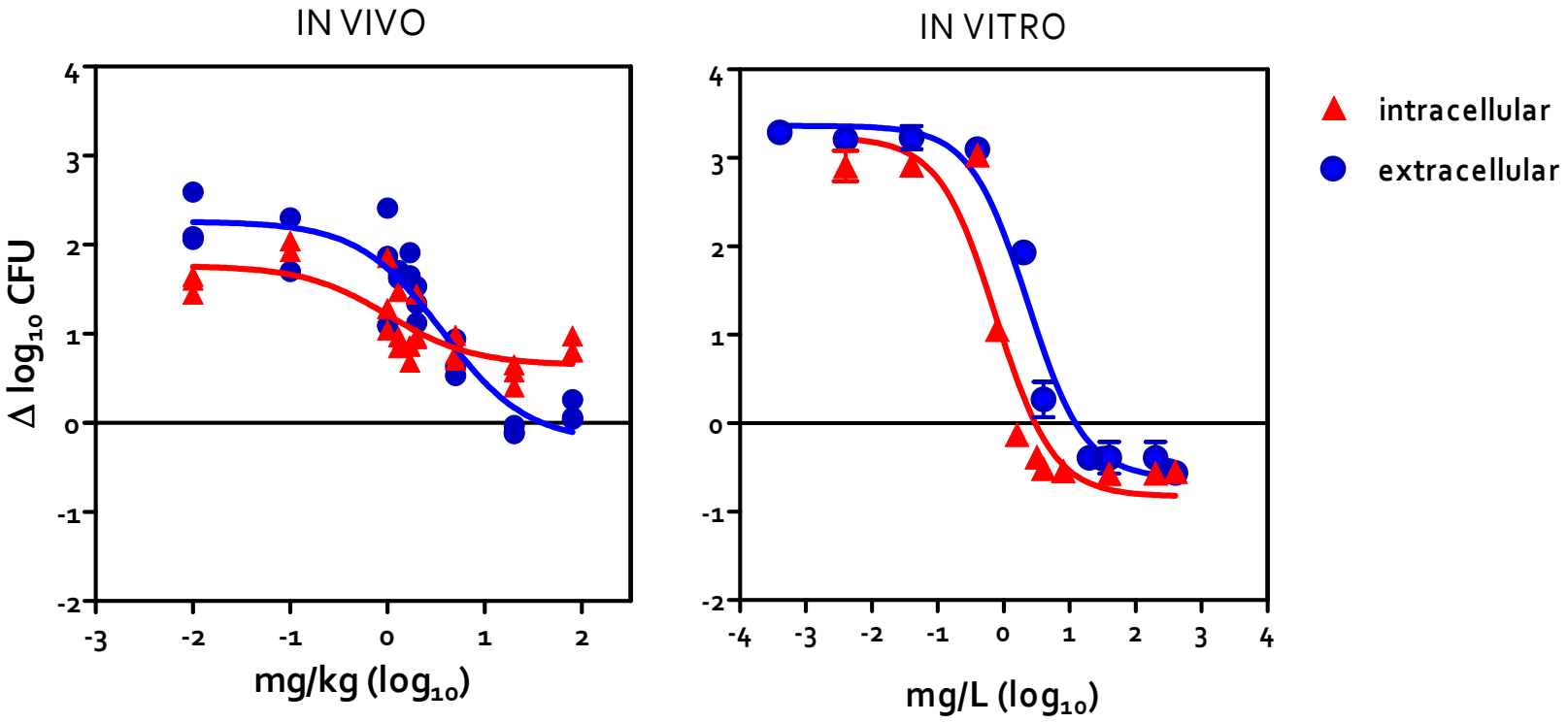


A reduction of 2 logs was obtained intracellularly with optimal dosing

Sandberg et al., Antimicrob Agents Chemother (2010) 54:2391-2400

Dose-response studies

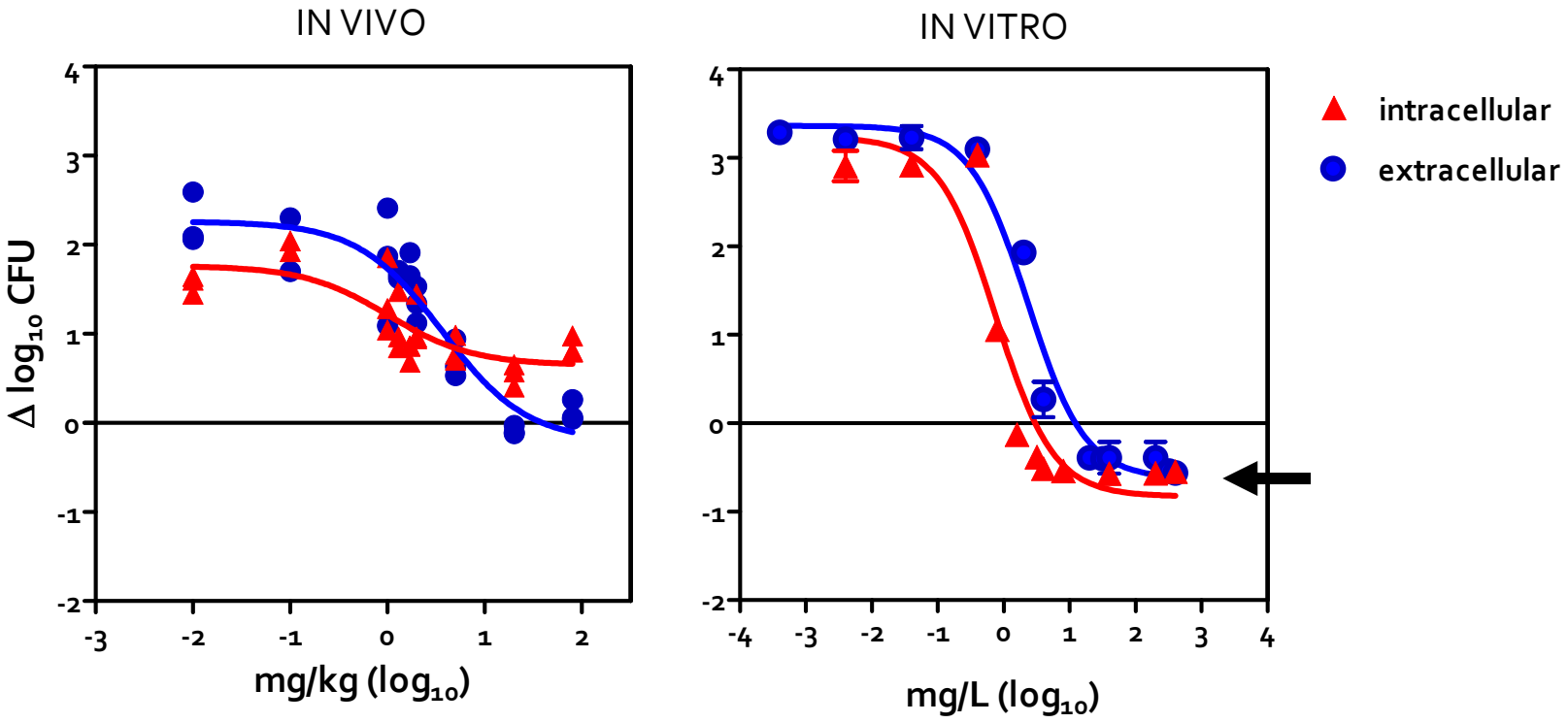
LINEZOLID vs. *S. aureus*



Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

Dose-response studies

LINEZOLID vs. *S. aureus*

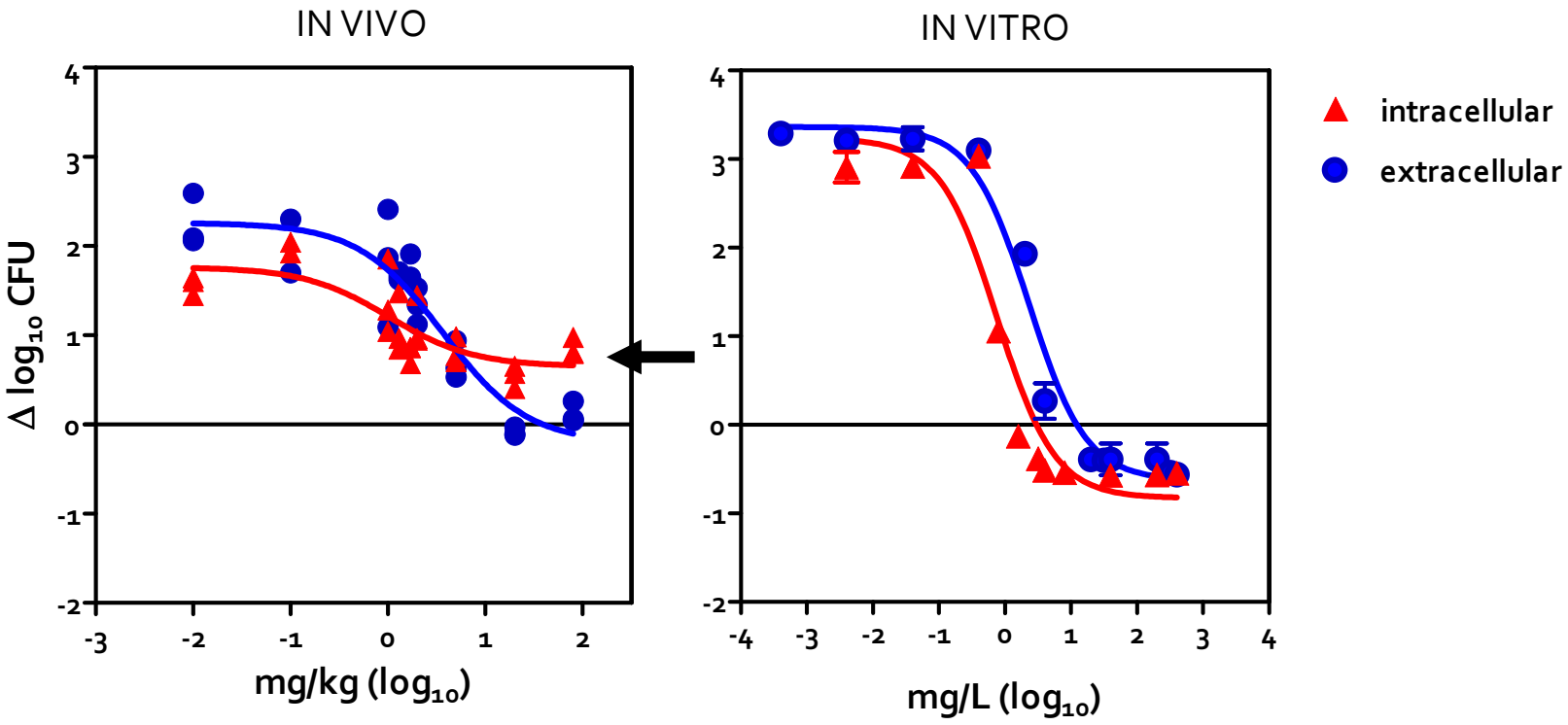


No decreased intracellular activity in vitro

Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

Dose-response studies

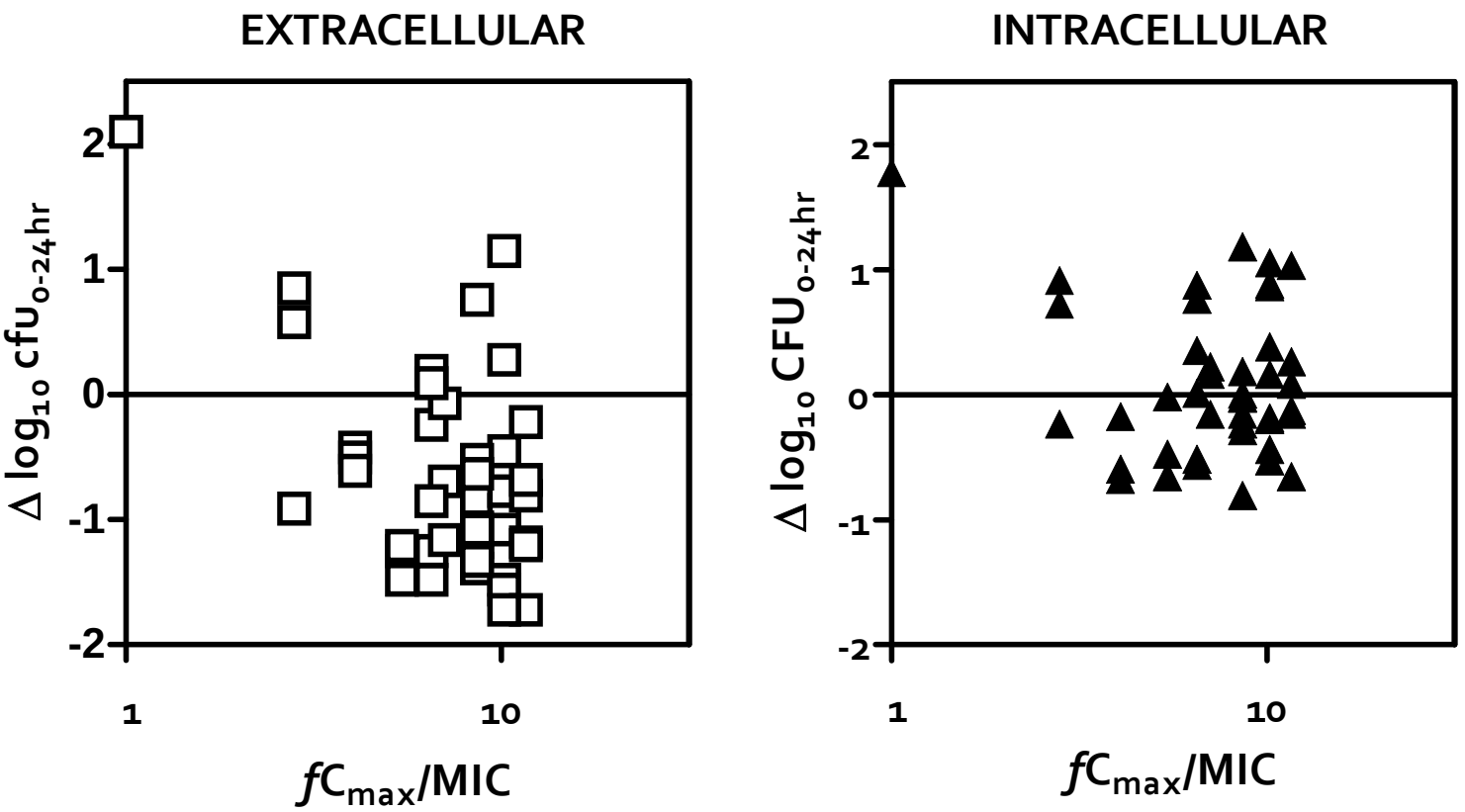
LINEZOLID vs. *S. aureus*



No reduction of the original intracellular inoculum in vivo

Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

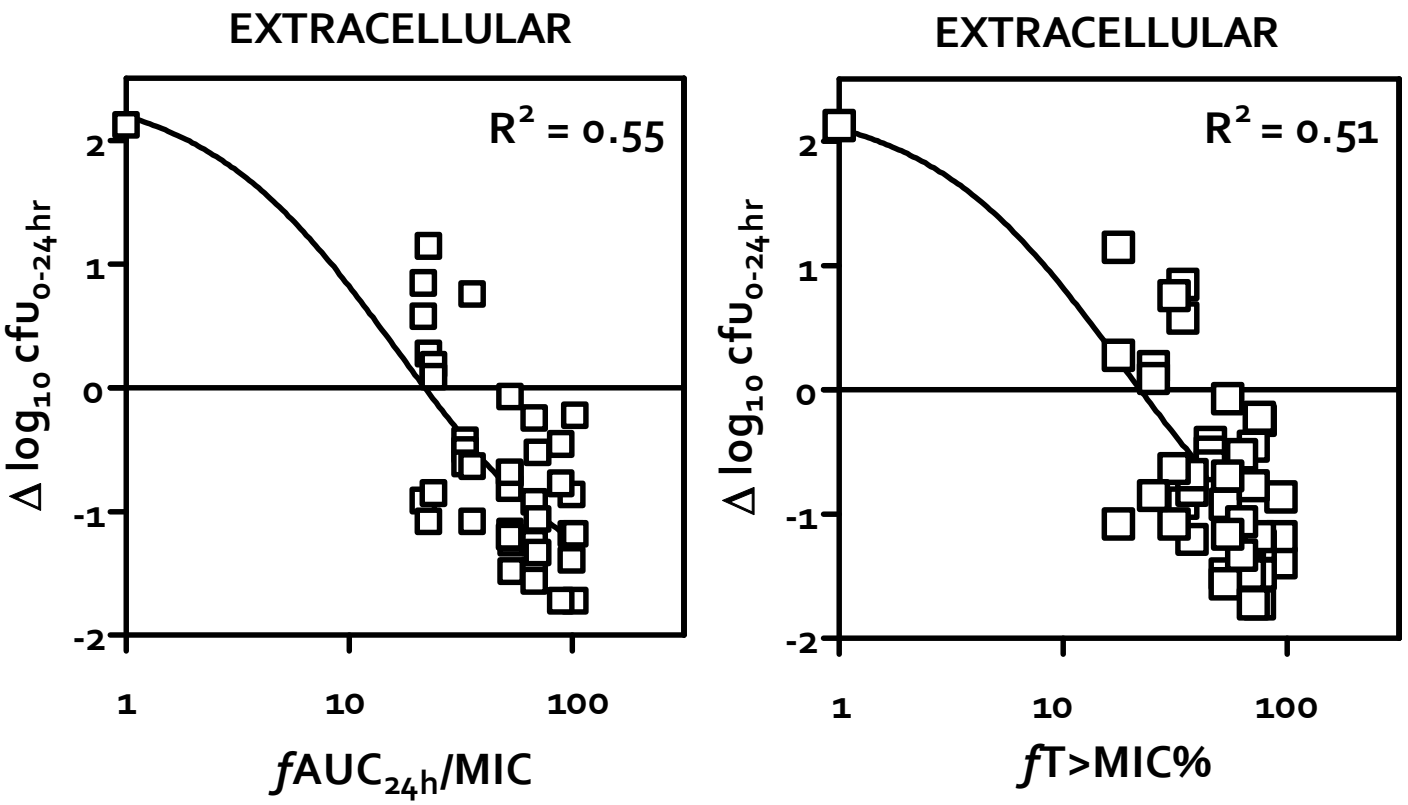
PK/PD studies: Linezolid vs *S. aureus*



No correlation between treatment outcome and the C_{max} /MIC index

Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

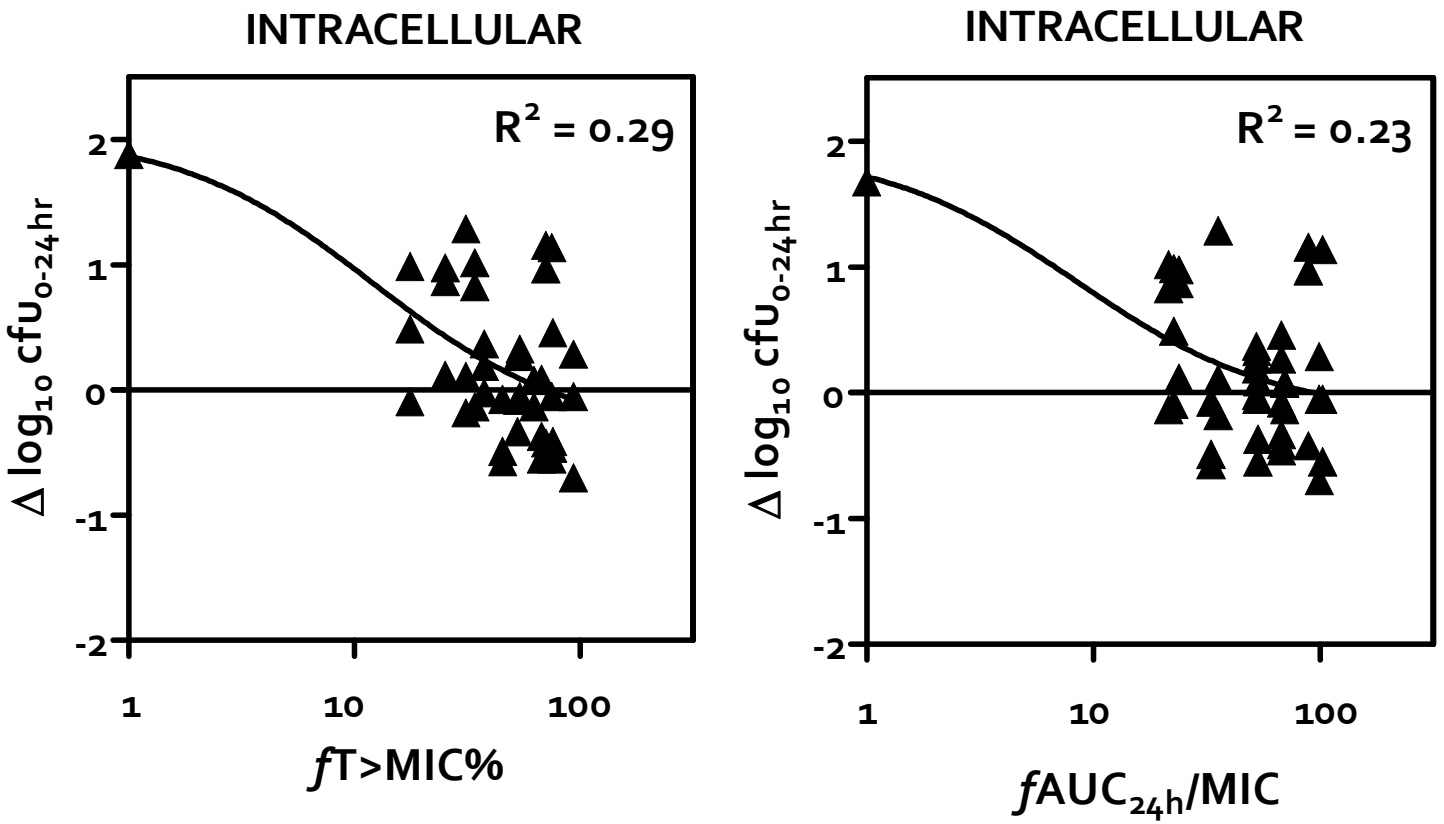
PK/PD studies: Linezolid vs *S. aureus*



Both AUC and T>MIC correlated equally to the extracellular outcome

Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

PK/PD studies: Linezolid vs *S. aureus*

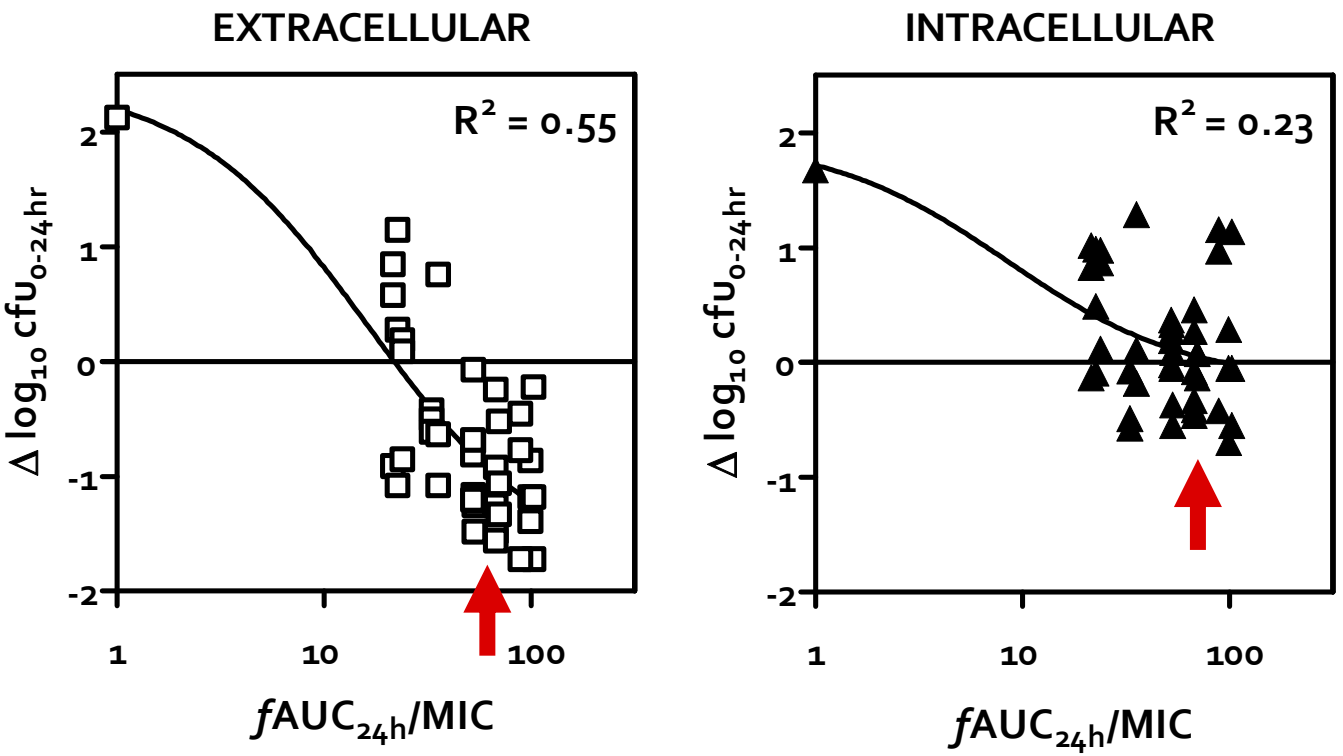


Poor correlation between PK/PD indices and the intracellular outcome

Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

PK/PD studies: Linezolid vs *S. aureus*

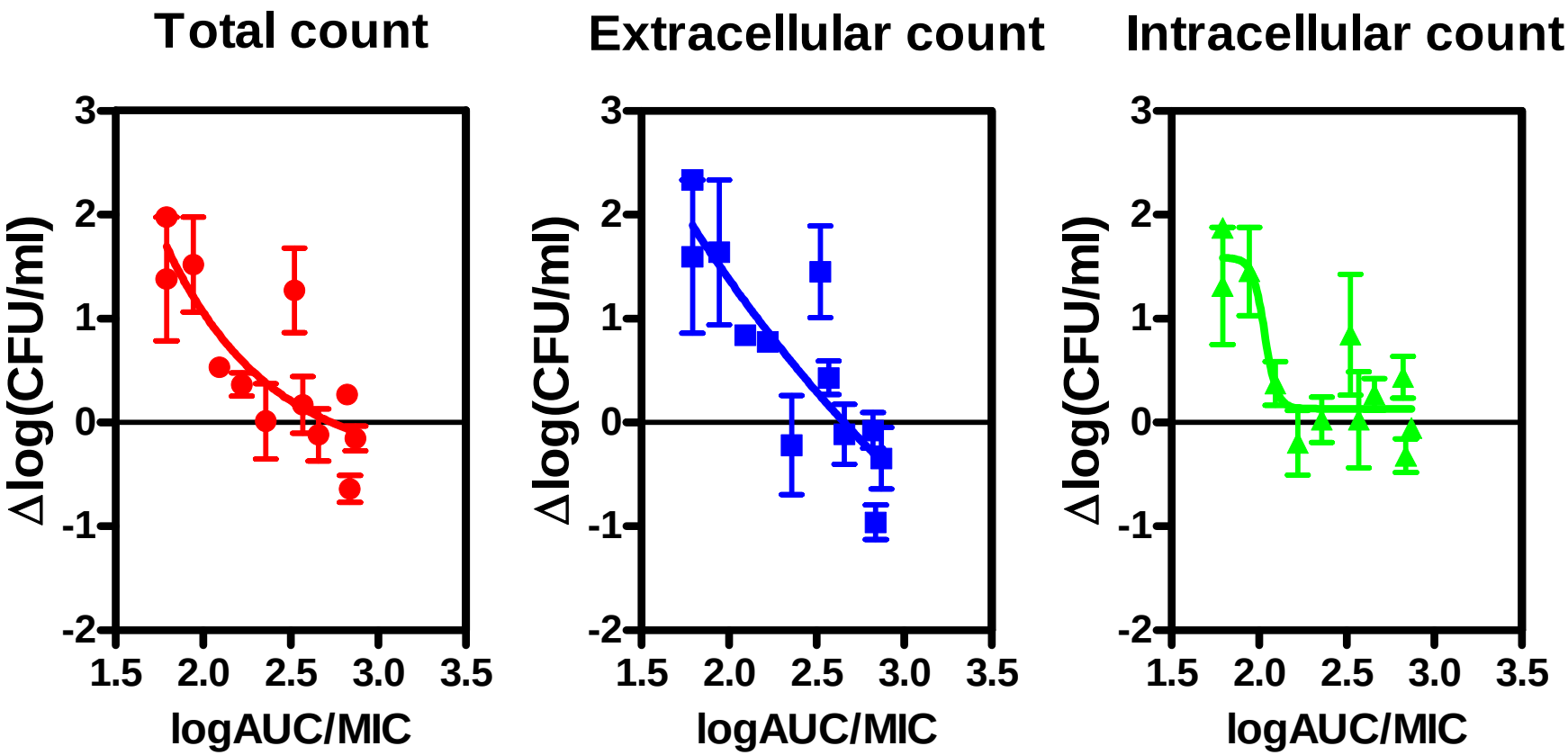
Conventional dose: 600 mg twice daily ⟶ AUC/MIC = 80



Acceptable extracellular effect but questionable intracellular effect with conventional dose

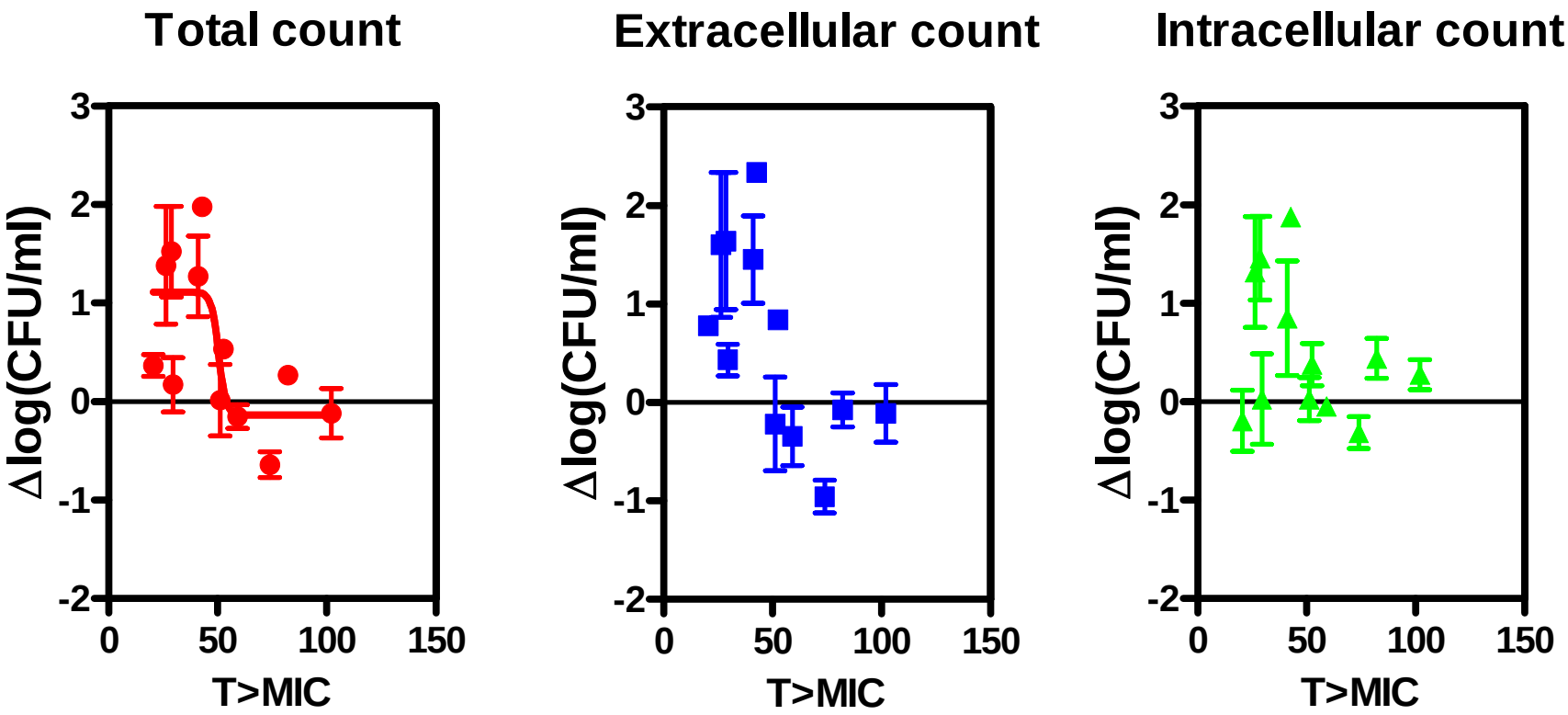
Sandberg et al., J. Antimicrob. Chemother (2010) 65:962-973

Intracellular peritonitis mouse model: Fusidic acid



Sandberg et al. unpublished

Intracellular peritonitis mouse model: Fusidic acid



Sandberg et al. Unpublished

Conclusion

- *S. aureus* infection primarily intracellularly
- Still, antibiotic effect better (lower doses) in normal (non-neutropenic) mice
- PKPD studies of antibiotics against S. aureus should include both intra- and extracellular compartments
- Surprisingly, dicloxacillin best effect in vivo (vs. linezolid, fusidic acid, macrolides)