

**Daptomycin:  
a new-old antibiotic**

*or*

**how did pharmacodynamics  
bring back to life  
a disappointing drug ?**

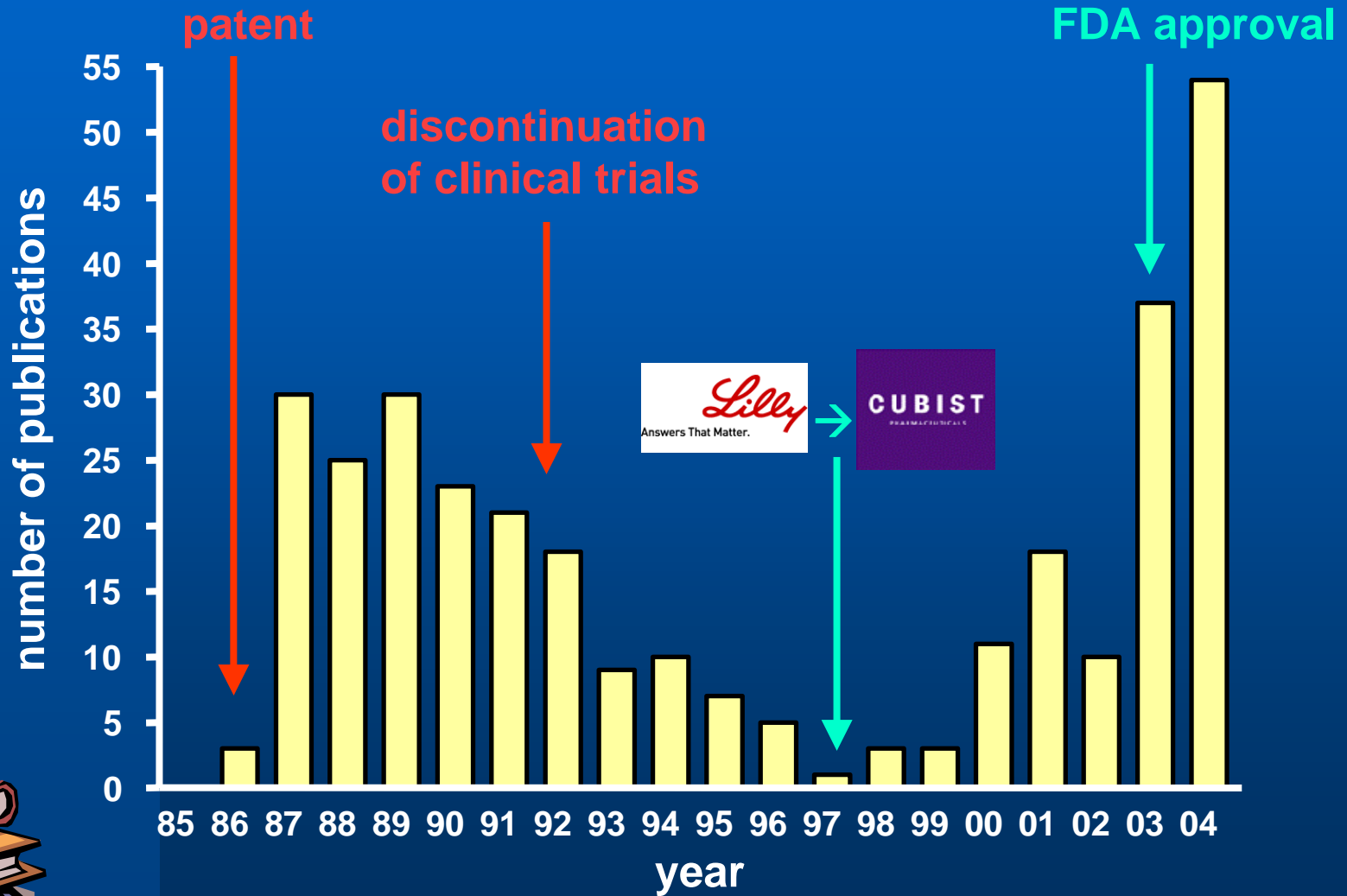


Unité de Pharmacologie  
cellulaire et moléculaire

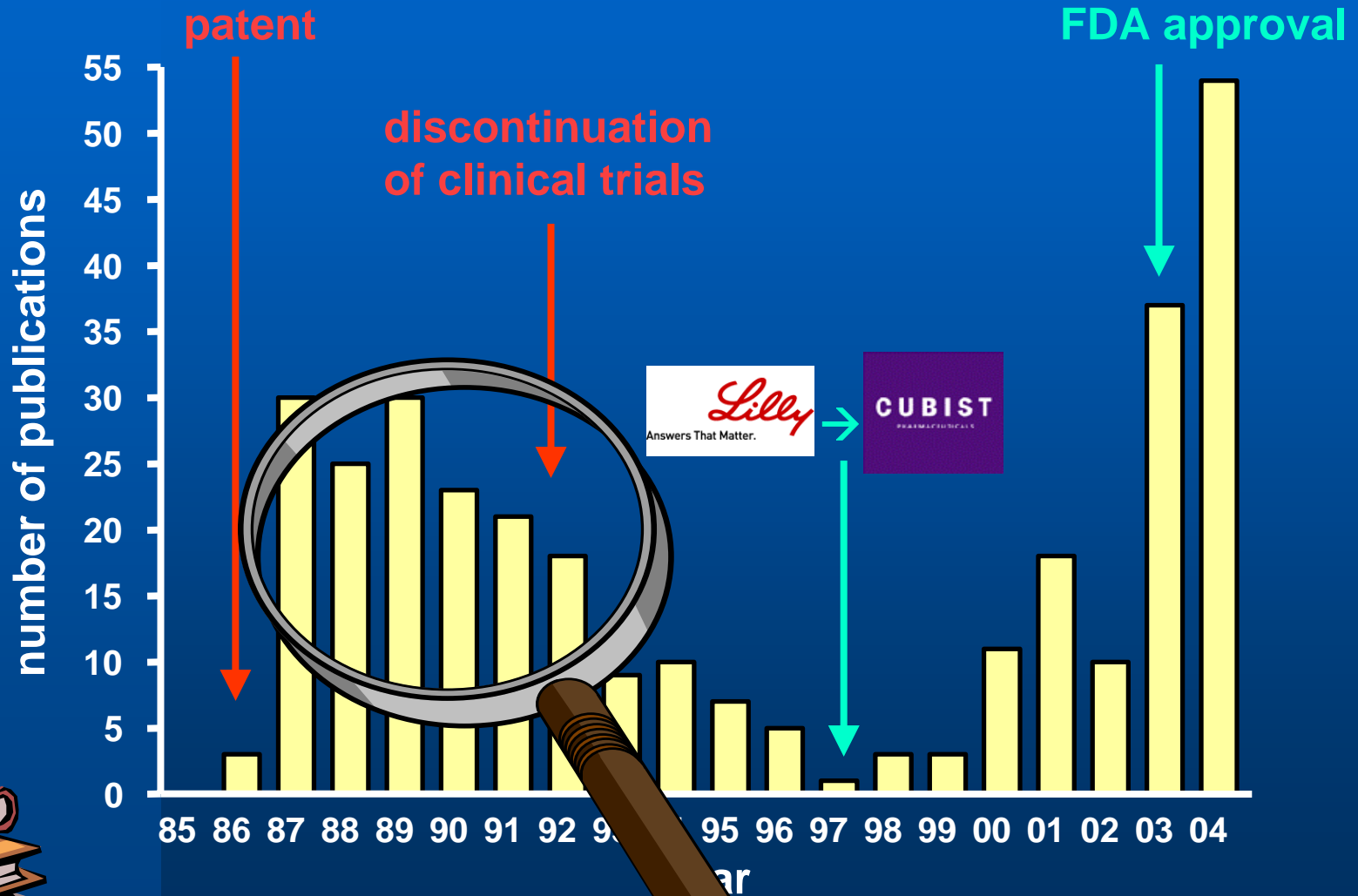
F. Van Bambeke



# A drug with bimodal popularity ...



# A drug with bimodal popularity ...



# First life of daptomycin

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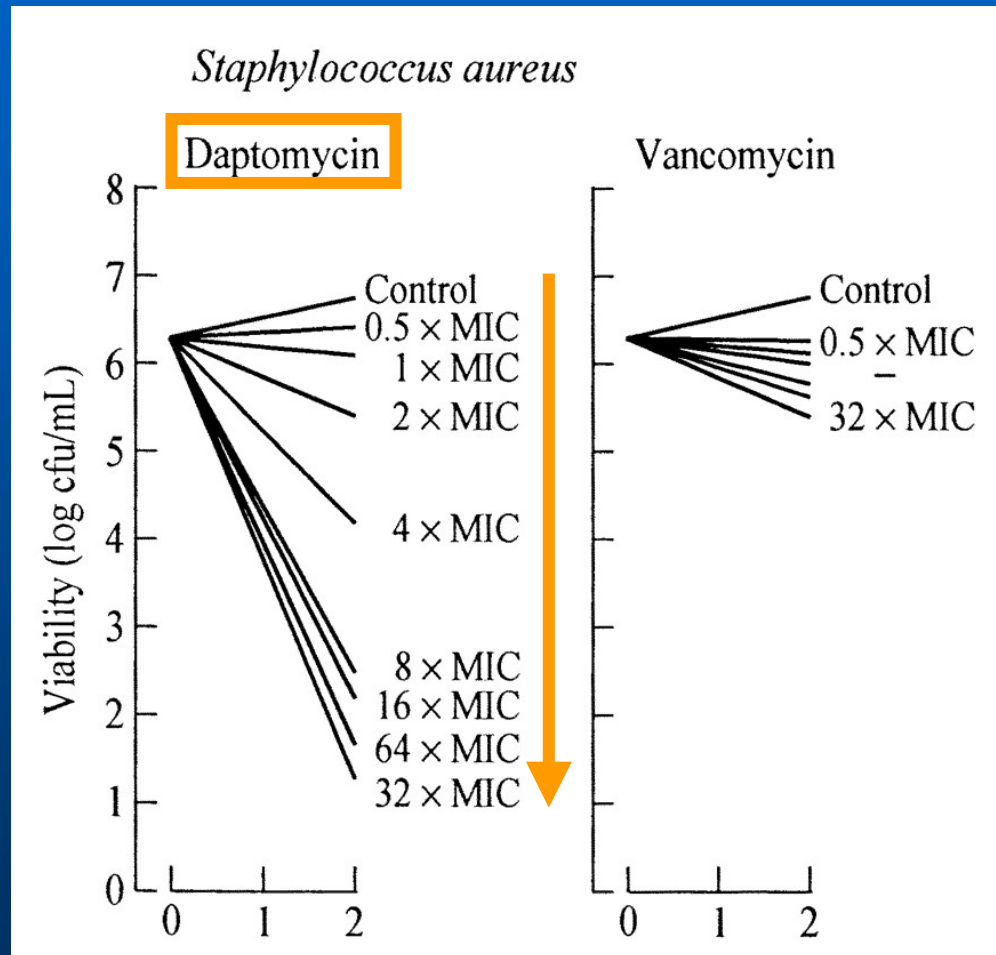


Discovery of a promizing drug ....

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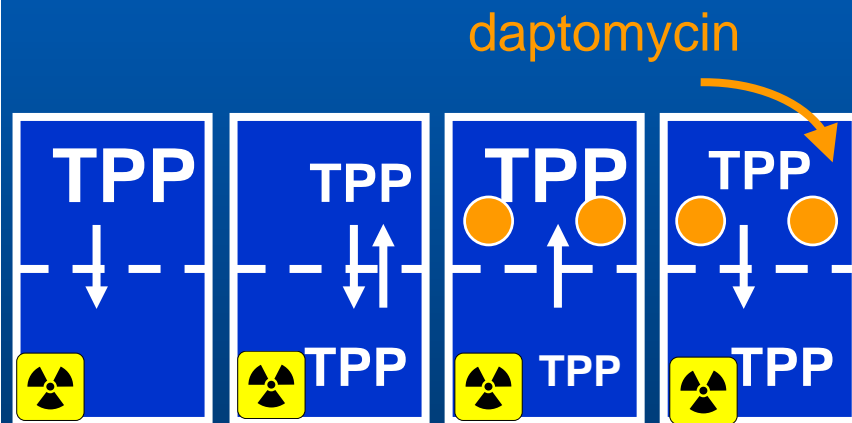
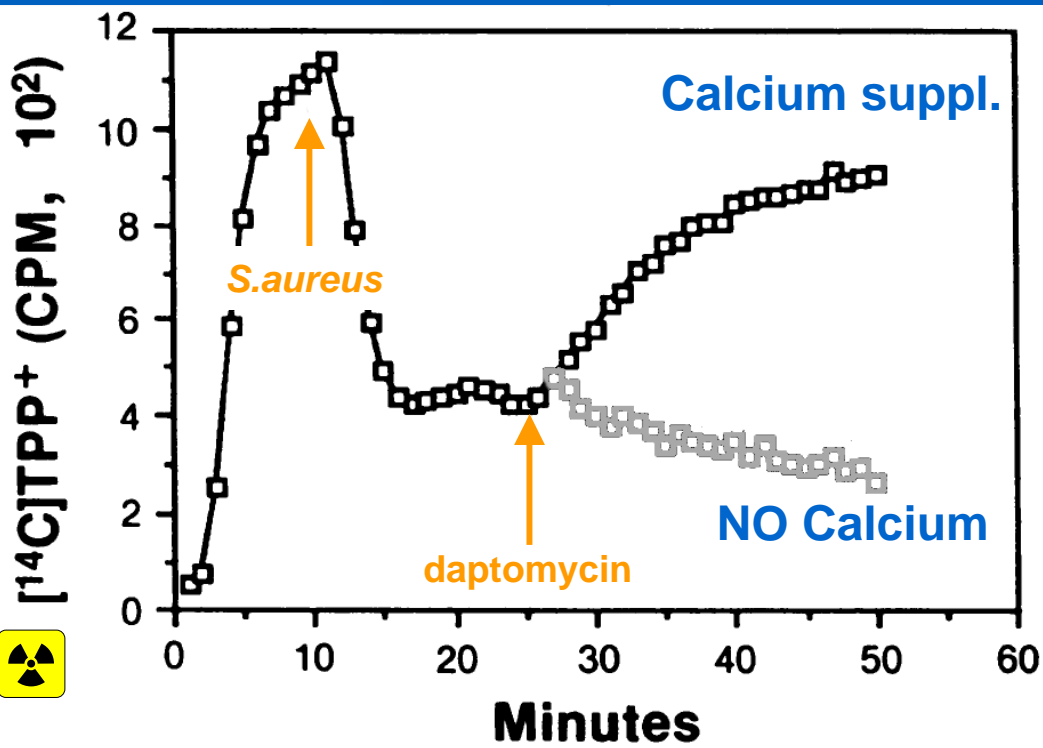
# In vitro pharmacodynamic profile

concentration-dependent, bactericidal activity on Gram (+)



# Bacterial killing due to alteration of membrane integrity

calcium-dependent disruption of membrane potential



TPP: tetraphenylphosphonium bromide

# Encouraging preclinical data

## Efficacy demonstrated in animal models of difficult-to-treat Gram (+) infections

- ***Staphylococcus aureus* endocarditis**

- Kaatz *et al*, AAC (1990) 34, 2081–5

- **Gentamicin-resistant,  $\beta$ -lactamase-producing *Enterococcus faecalis* endocarditis**

- Hindes *et al*, AAC (1989) 33, 1019–22.

- **Methicillin-resistant *Staphylococcus aureus* pneumonia.**

- Kephart & Esposito, JAC (1988) 21, 33–9.

- ***Staphylococcus aureus* osteomyelitis**

- Luu *et al*, *Eur. J. Clin. Microbiol. Infect. Dis.* (1989) 8, 562–3.

- **Enterococcal pyelonephritis**

- Minitzer *et al*, AAC (1987) 31, 1199–203.

- ***Clostridium difficile* colitis**

- Dong *et al* AAC (1987) 31, 1135–6.



# What went wrong with daptomycin ?

- “Nineteen Phase 1 and two Phase 2 clinical studies involving more than 370 subjects were conducted in the 1980s and early 1990s.

The results in skin and soft tissue infections and bacteraemia were encouraging, and clinical results with endocarditis suggested the potential for efficacy at higher doses.”

- “However, Lilly was not satisfied with the overall clinical results observed with the **twice-daily** dosing regimen utilized in these studies”

# What went wrong with daptomycin ?

## 4 mg/kg bid

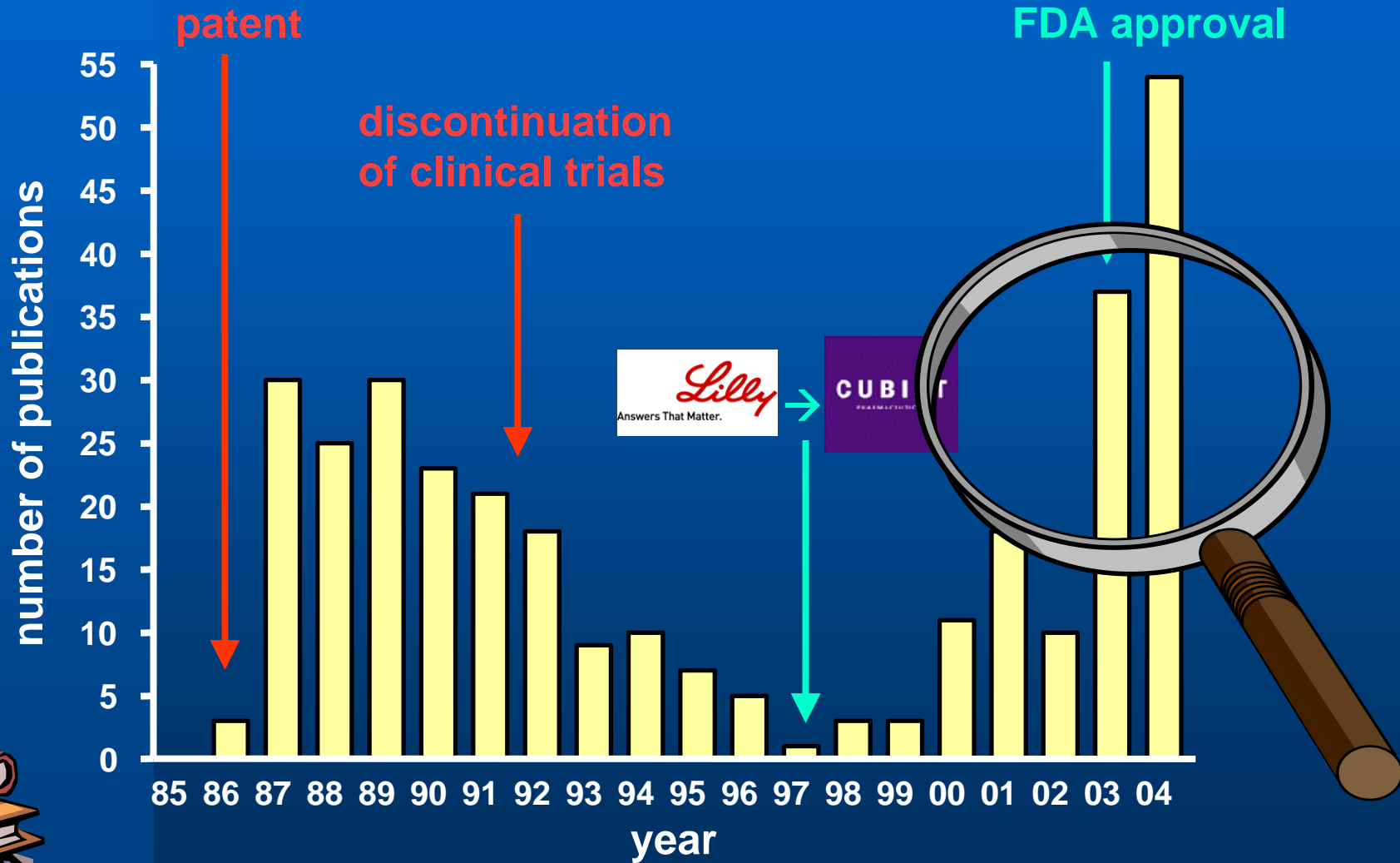
- forearm weakness
- myalgia
- elevated creatine kinase



Tedesco *et al*, *Pharmacotherapy* (2004) 24:41-57

- “However, Lilly was not satisfied with the overall clinical results observed with the **twice-daily** dosing regimen utilized in these studies”

# A drug with bimodal popularity ...



# Second life of daptomycin

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**Renewing confidence in the drug**

Showing its potential interest in the clinics

Further exploring its antibacterial activity

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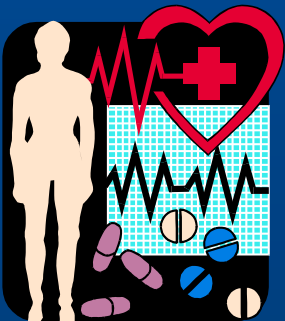
# Where pharmacodynamics is helpful ...

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## Modification of the therapeutic scheme

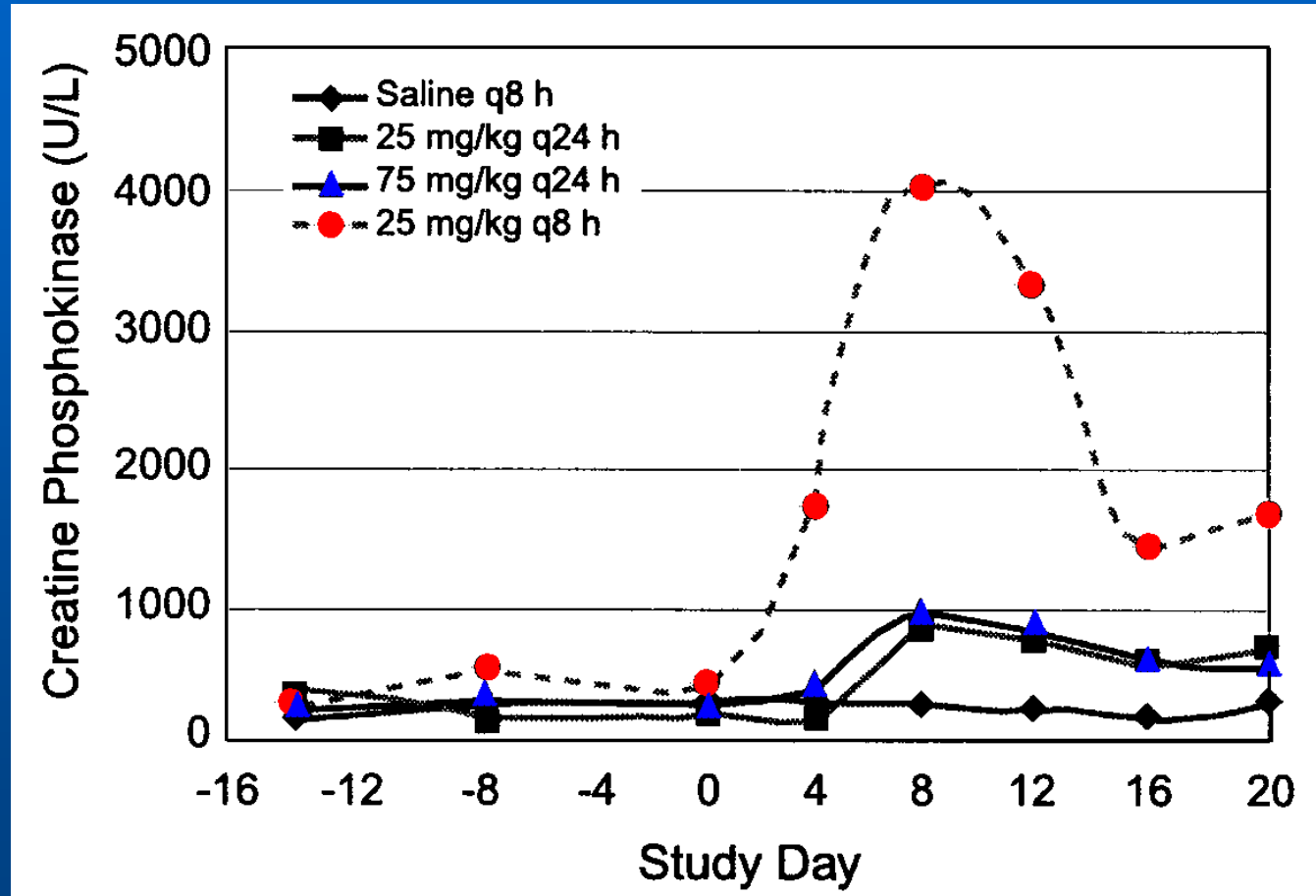
→ lower toxicity

→ improved activity



# Where pharmacodynamics is helpful ...

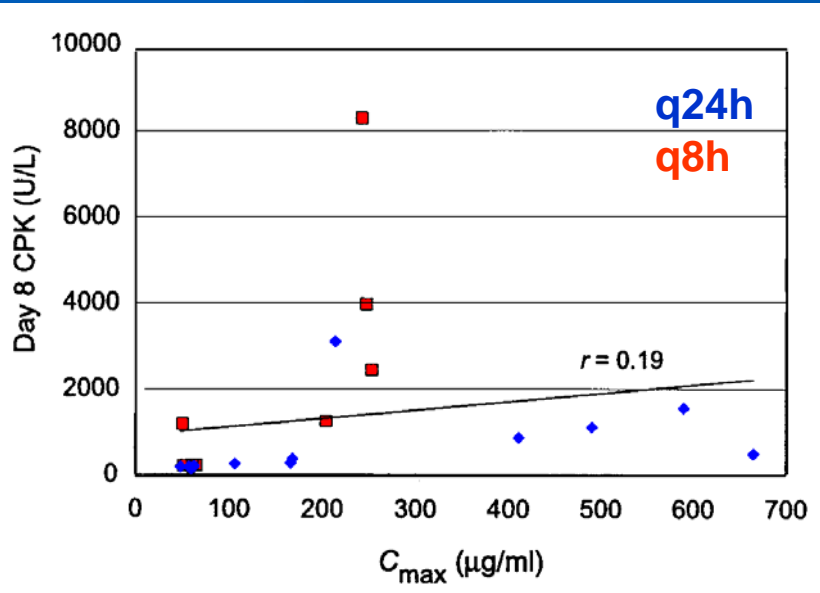
longer dosing interval → less musculo-skeletal side effects



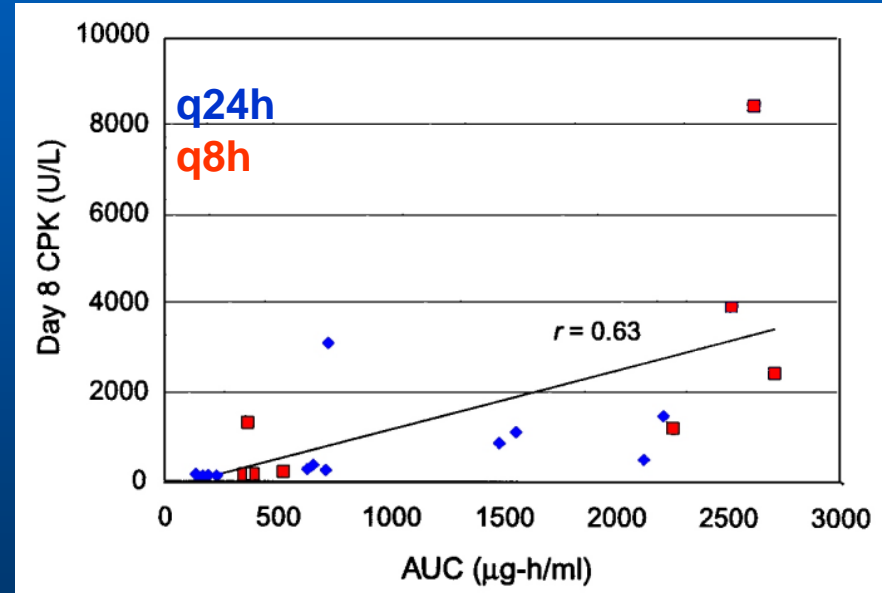
*dog model*

# Where pharmacodynamics is helpful ...

## No correlation with peak

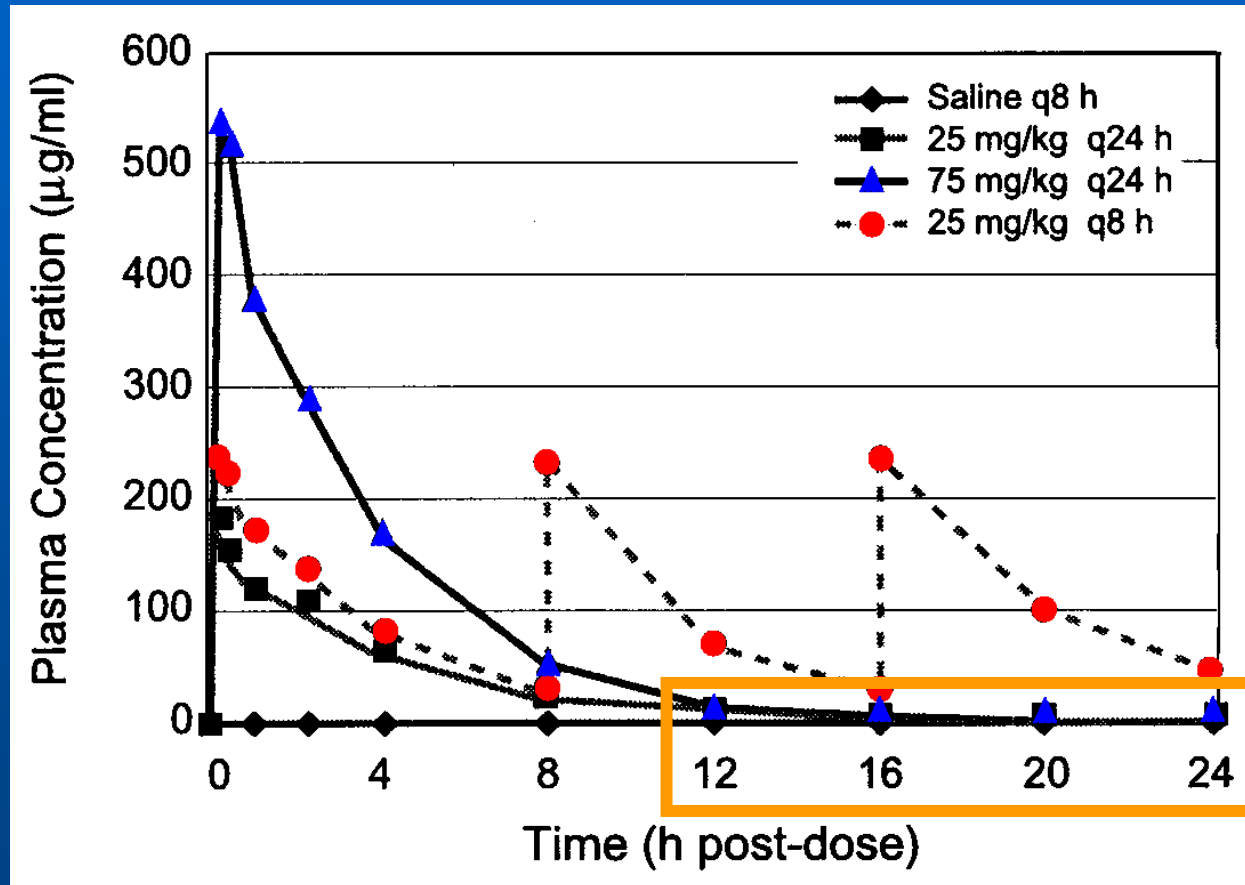


## Bad correlation with AUC



# Where pharmacodynamics is helpful ...

more time at lower concentrations → more time for repair





# Where pharmacodynamics is helpful ...

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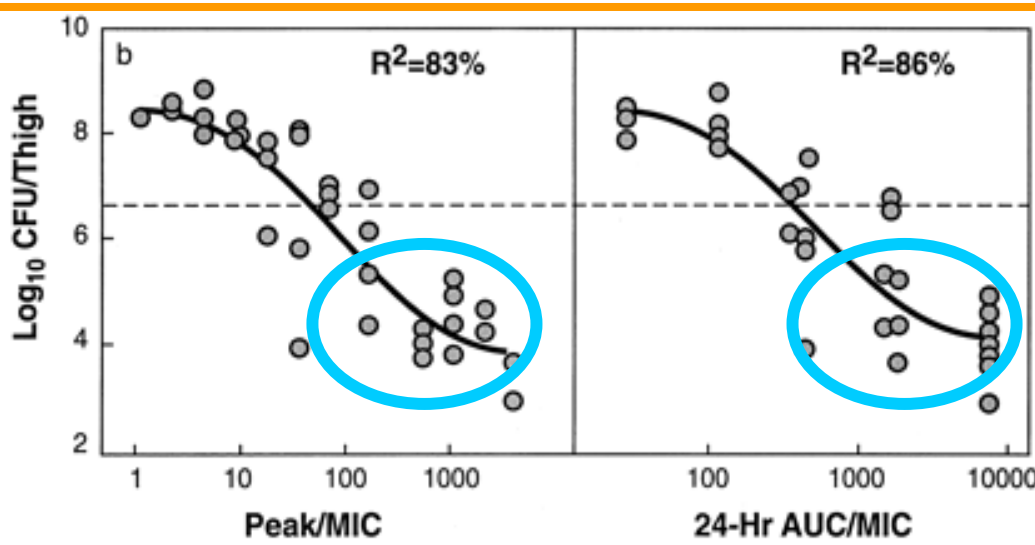
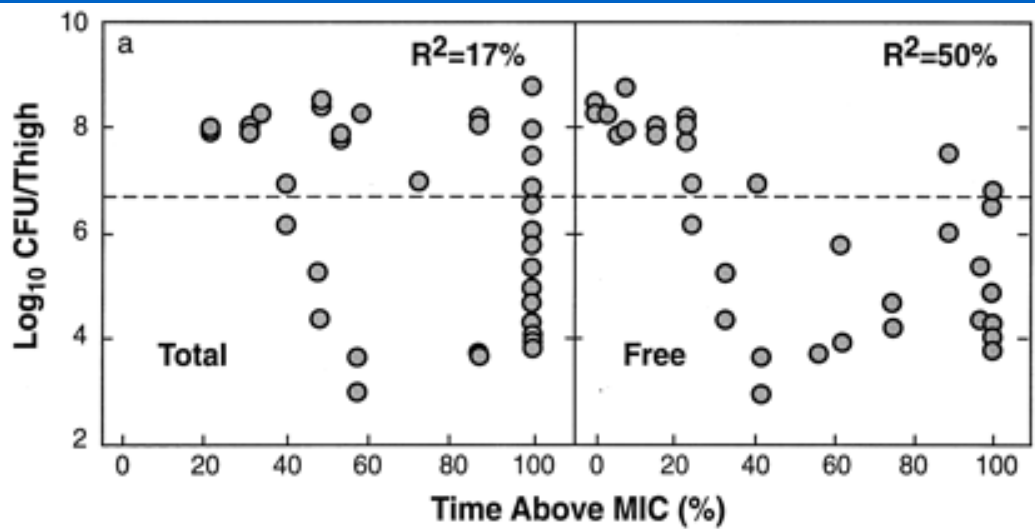
## Modification of the therapeutic scheme

→ lower toxicity

→ improved activity



# Where pharmacodynamics is helpful ...



conc-dependent activity

efficacy correlated with Peak/MIC and AUC/MIC ratios

Peak/MIC > 60-100  
AUC/MIC > 400-550

for *S. aureus*

calculated for TOTAL drug (free+ prot. bound)

Safdar et al, AAC (2004) 48:63

# Where pharmacodynamics is helpful ...

## Optimizing doses in humans based on PK/PD

Dose (mg/kg)	C <sub>max</sub>	MIC for C <sub>max</sub> /MIC = 60	AUC	MIC for AUC/MIC = 400	MIC MRSA
4	58	~ 1	500	~ 1	
6	100	~ 1.5	750	~ 2	0.06 - 0.5
8	133	~ 2	1130	~ 3	

# Where pharmacodynamics is helpful ...

## Optimizing doses in humans based on PK/PD

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MIC  $\ll$  PK/PD breakpoint ...

# Second life of daptomycin

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Renewing confidence in the drug

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# Clinical trials



safety and efficacy of daptomycin  
for the treatment  
of complicated skin and skin-structure infections

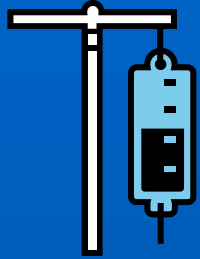
**daptomycin**  
4 mg/kg q24h,  
7-14 days  
534 pts

versus

**vancomycin**  
1 g q12h,  
7-14 days  
221 pts

**penicillinase-resistant  
penicillin**  
4-12 g in divided doses,  
7-14 days  
337 pts

# Clinical trials: efficacy



**Success rate with daptomycin : ~ 85 %**

no differences according to

- comparator (vancomycin, PRP)
- infection type (abscess, wound, ulcer)
- infecting organism

	<b>daptomycin</b>	<b>comparator</b>
<b>MSSA</b>	<b>86 %</b>	<b>87 %</b>
<b>MRSA</b>	<b>75 %</b>	<b>69 %</b>
<b><i>S. pyogenes</i></b>	<b>94 %</b>	<b>91 %</b>
<b><i>S. agalactiae</i></b>	<b>85 %</b>	<b>76 %</b>
<b><i>E. faecalis</i></b>	<b>73 %</b>	<b>76 %</b>

# Clinical trials: safety



**No difference between treatment groups**

	<b>daptomycin</b>	<b>comparator</b>
<b>Adverse effects</b>	<b>18.0 %</b>	<b>21.0 %</b>
<b>Severe adverse effects</b>	<b>10.9 %</b>	<b>8.8 %</b>
<b>Treatment discontinuation</b>	<b>2.8 %</b>	<b>2.8 %</b>
<b>elevated serum creatin phosphokinase level</b>	<b>2.8 %</b>	<b>1.8 %</b>



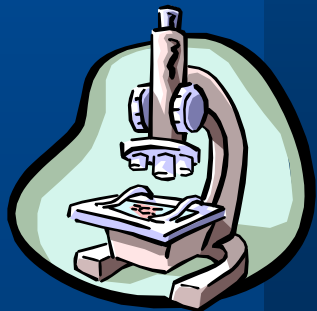
# Second life of daptomycin

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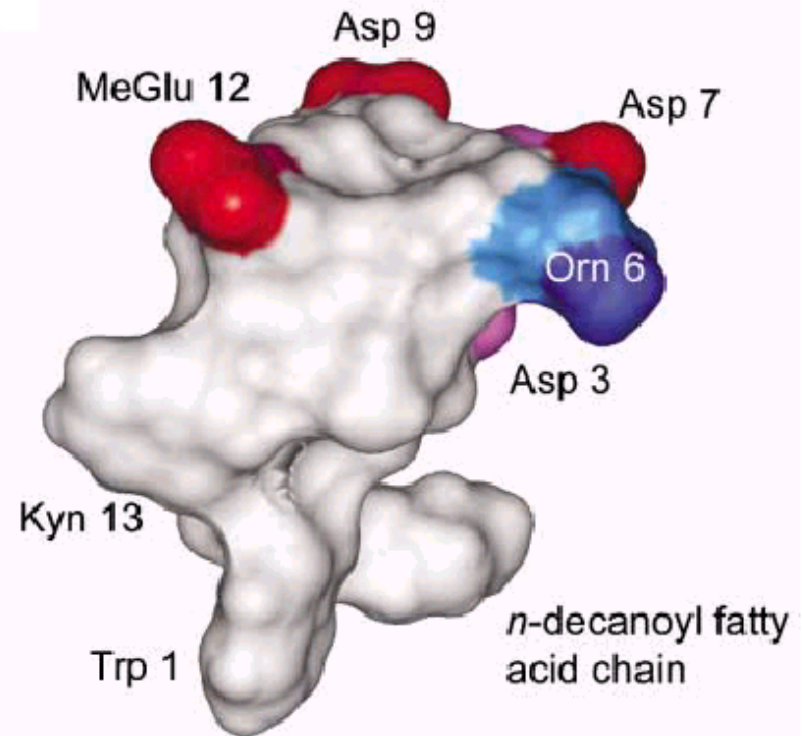
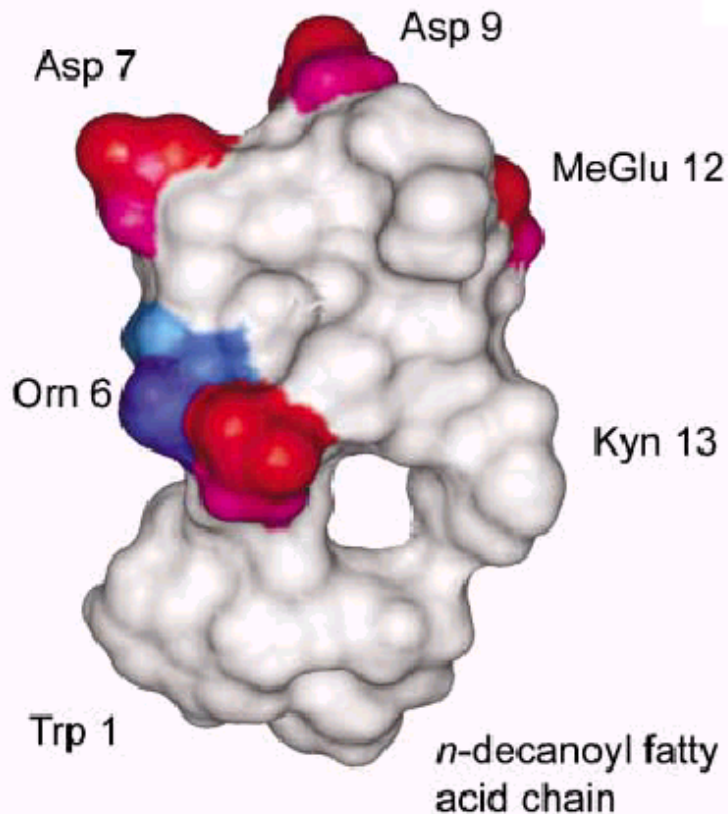


# Role of calcium in daptomycin activity

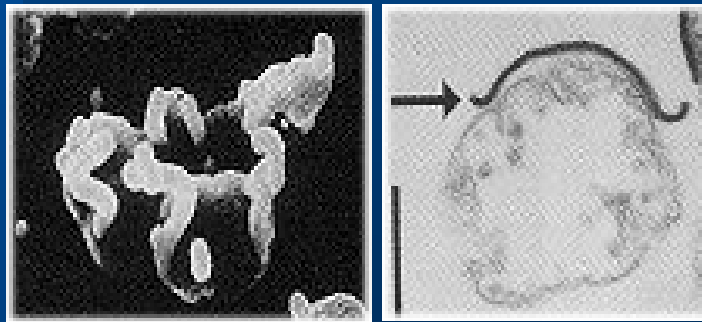
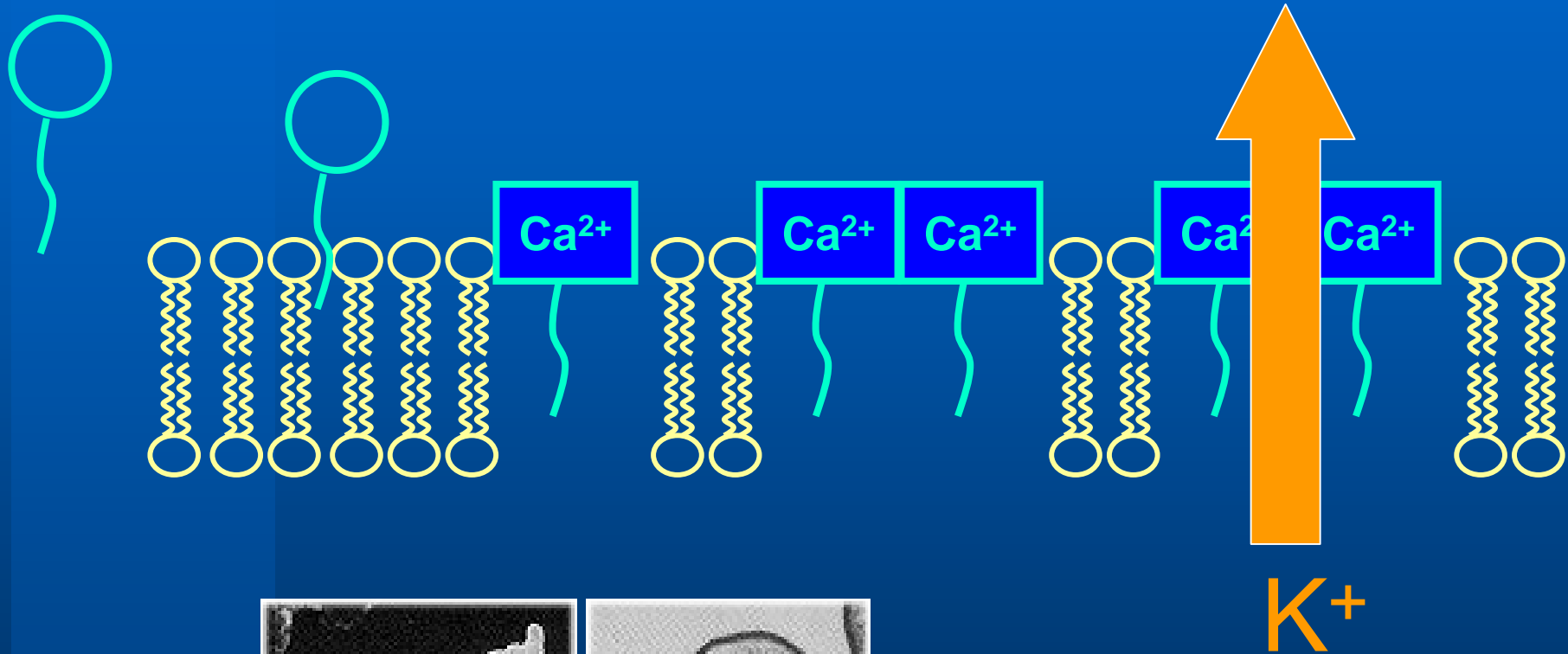
Calcium induces a conformational change increasing daptomycin amphiphilicity

**NO calcium**

**calcium**



# Mode of action of daptomycin revisited



# Weighing pros and cons ....

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- 
- bactericidal
  - no cross-resistance
  - MIC < PK/PD breakpoint
  - no drug interaction (CYP)
  - daily administration

**PROS**

- resistance already selected
- high price
- no oral route
- safety / efficacy not studied in < 18 years

**CONS**

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# Questions for future research

- **Specificity to bacterial cells ?**
  - Interaction with “daptomycin binding proteins” ?
    - Boaretti *et al*, New Microbiol. (2000) 23:305-17
- **Emergence of resistance ?**
  - Selected *in vitro* ( $10^{-10}$ )
    - Silverman *et al*, AAC (2001) 45:1799-802
  - Observed *in vivo* (2/1000 subjects)
    - Cubicin® Package Insert
  - Case reports with
    - MRSA
      - Rezai *et al* ICAAC (2004) K97a
    - VRE
      - Sabol *et al* AAC (2005) 49:1664-5



# Questions for future research

## ● Other indications ?

- Disappointing efficacy in community acquired pneumonia (inferiority to ceftriaxone); due to binding to PC in surfactant
- Efficacy in complicated urinary tract infections (small trial - 60 patients)
- Ongoing studies for bacteriemia and endocarditis by *S. aureus*

## ● Safety issues ?

- Populations at higher risk (statins ?)
  - Cubicin<sup>®</sup> Package Insert

