P. aeruginosa : *resistance and therapeutic options*

Are there new molecules for *Pseudomonas* in the pipeline ?

UCL
Université catholique de Louvain

Unité de Pharmacologie cellulaire et moléculaire

F. Van Bambeke

Is there a need for new drugs against Pseudomonas ?

BIOCHEMICAL PHARMACOLOGY 71 (2006) 991–995

Unmet medical needs in antibacterial therapy

Louis B. Rice

Evolving and persistent unmet needs in antibacterial therapy

Evolving needs	Persistent need
Multi-resistant Gram-negative bacteria *Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Stenotrophomonas maltophilia*, Community-acquired (CA) UTI	Antibiotics for biofilm-related infections *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumonia*, *Enterobacter* spp., *Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Stenotrophomonas maltophilia*
Escherichia coli CA- and hospital-acquired pneumonia *Staphylococcus aureus*	

Is there a need for new drugs against Pseudomonas ?

BIOCHEMICAL PHARMACOLOGY 71 (2006) 1073–1084

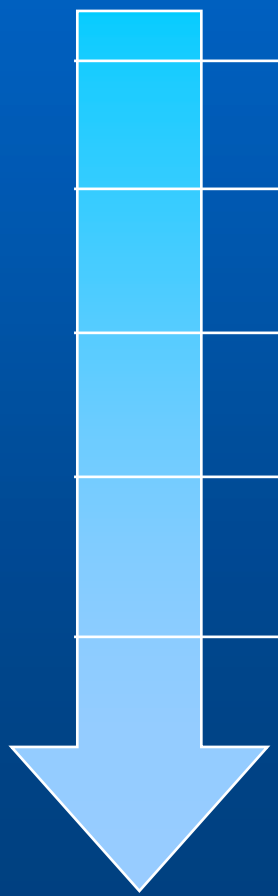
The forgotten Gram-negative bacilli: What genetic determinants are telling us about the spread of antibiotic resistance

Thomas D. Gootz

Resistance mechanisms to some antibiotics

Antibiotic class	Resistance mechanism	Determinants
Aminoglycosides	Compound modification	Adenyltransferases, acetyltransferases phosphotransferases
Streptomycin	Target modification	Mutation in small ribosomal proteins
Cephalosporins	PBP changes Beta-lacatamases Efflux systems/Omp mutations	Rare in Gram-negatives Ambler classes A–D[a] RND–MFP–OMF[b]/ΔOmpF, OmpC
Carbapenems	PBP changes Beta-lactamases Efflux/Omp changes	Rare Ambler classes A, B, D[a] RND–MFP–OMF[b]/ΔOprD
Fluoroquinolones	Target mutation Target rescue Efflux/Omp mutations	Gyrase primary Topoisomerase IV secondary qnr RND–MFP–OMF[b]/ΔOmpF and OmpC

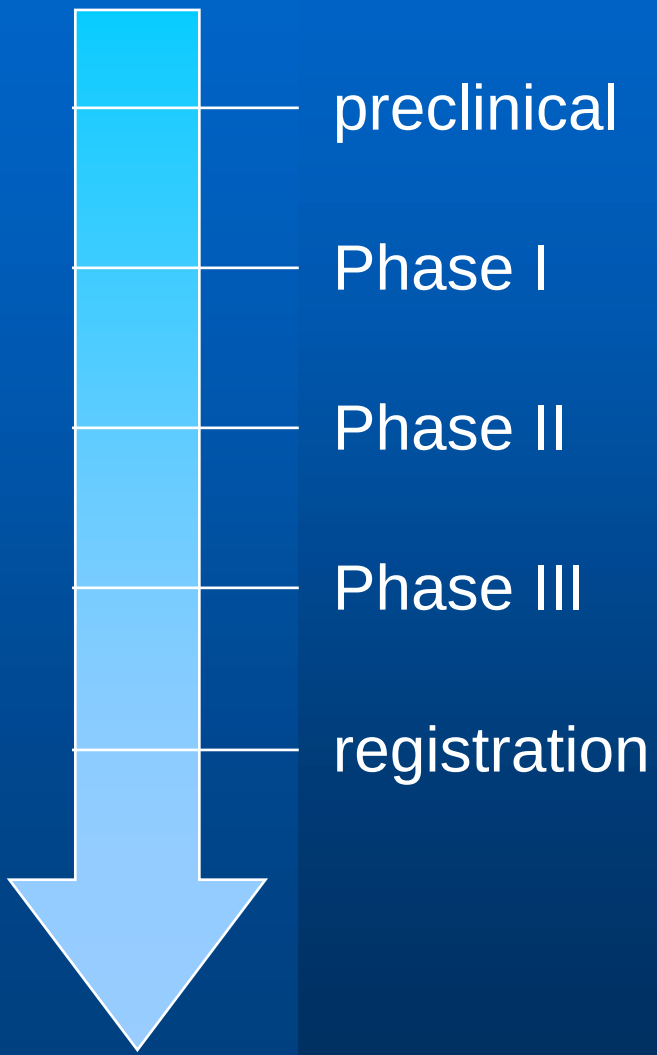
What is new over the last years ?



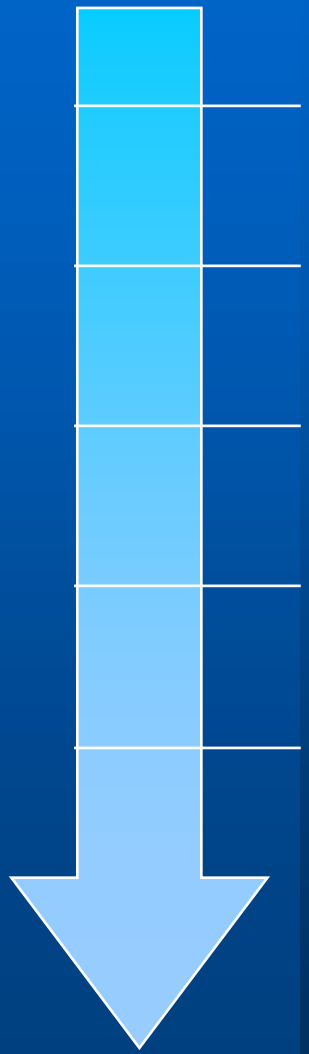
		Gram(+)	Gram(-)
2001	moxifloxacin	●	
	linezolid	●	
2002	ertapenem	●	●
2003	gemifloxacin	●	
	daptomycin	●	
2004	telithromycin	●	
2005	tigecycline	●	●

But no anti-Pseudomonas agent …

What is in the pipeline for Pseudomonas ?



Anti - Pseudomonas cephalosporins ?



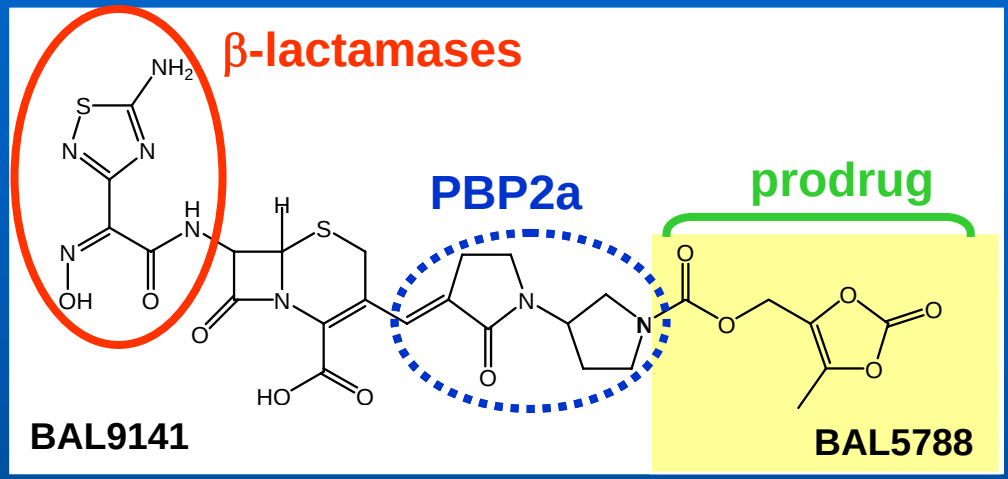
preclinical

Phase I

Phase II

Phase III

registration



ceftobiprole

basilea PHARMACEUTICA

Johnson&Johnson

BAL9141

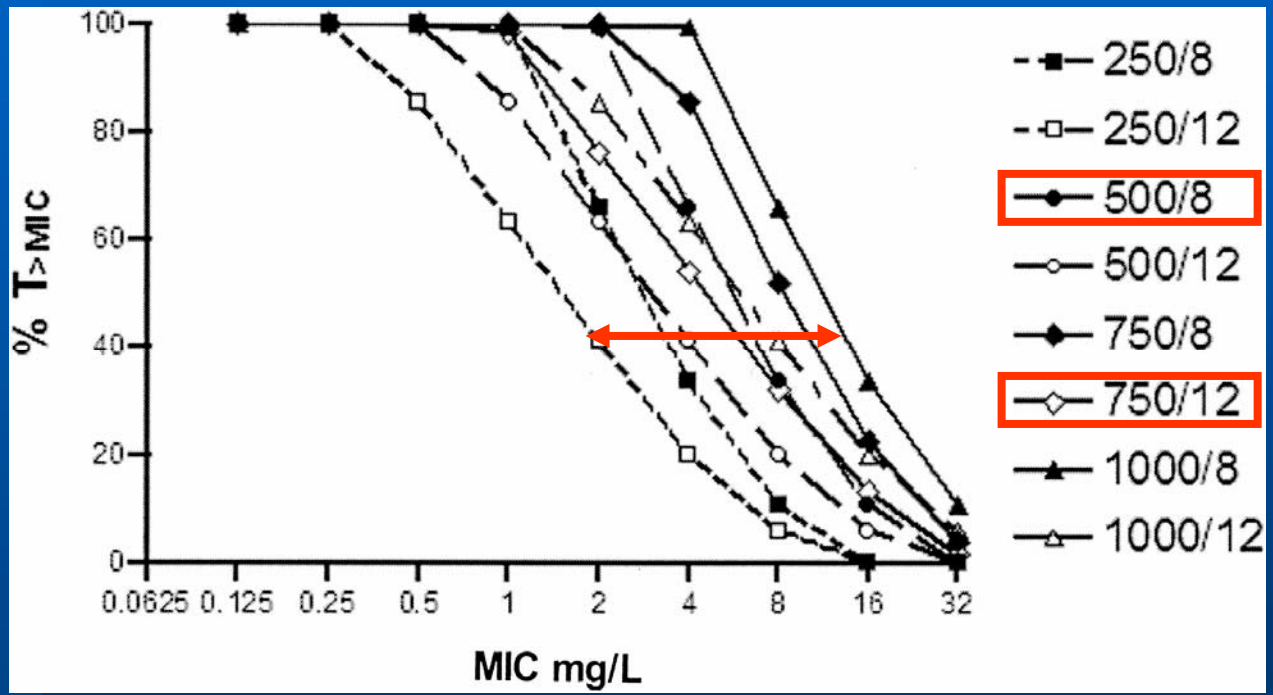
As active as cefepime

cephalosporine	MIC range (mg/L)	MIC 50	MIC 90
BAL9141	0.5 - 16	2	8
ceftriaxone	1 - 128	16	128
cefepime	0.5 – 32	2	8

Issa *et al.*, Diagn Microbiol Infect Dis. (2004) 48:73-5

BAL5788

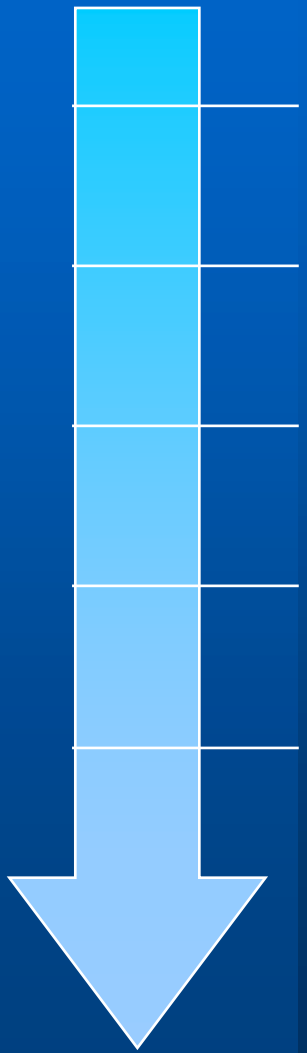
Which dose for which bug ?



MIC 8

Mouton *et al*. AAC (2004) 48:1713-8

Anti - Pseudomonas carbapenems ?



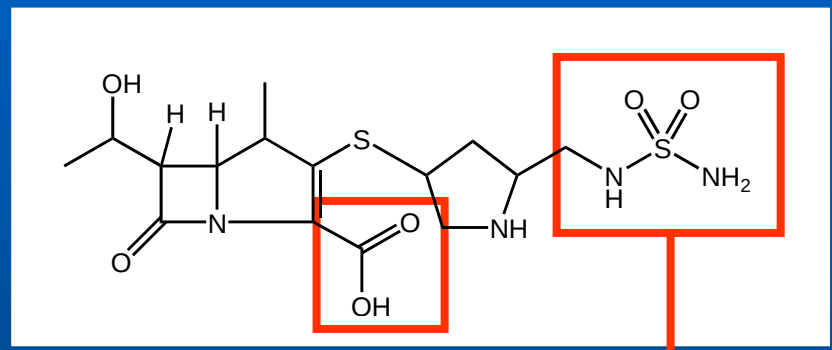
preclinical

Phase I

Phase II

Phase III

registration



doripenem

Peninsula pharmaceuticals

Johnson&Johnson

fast track for nosocomial pneumonia

penetration into Gram-negative;

zwitterion

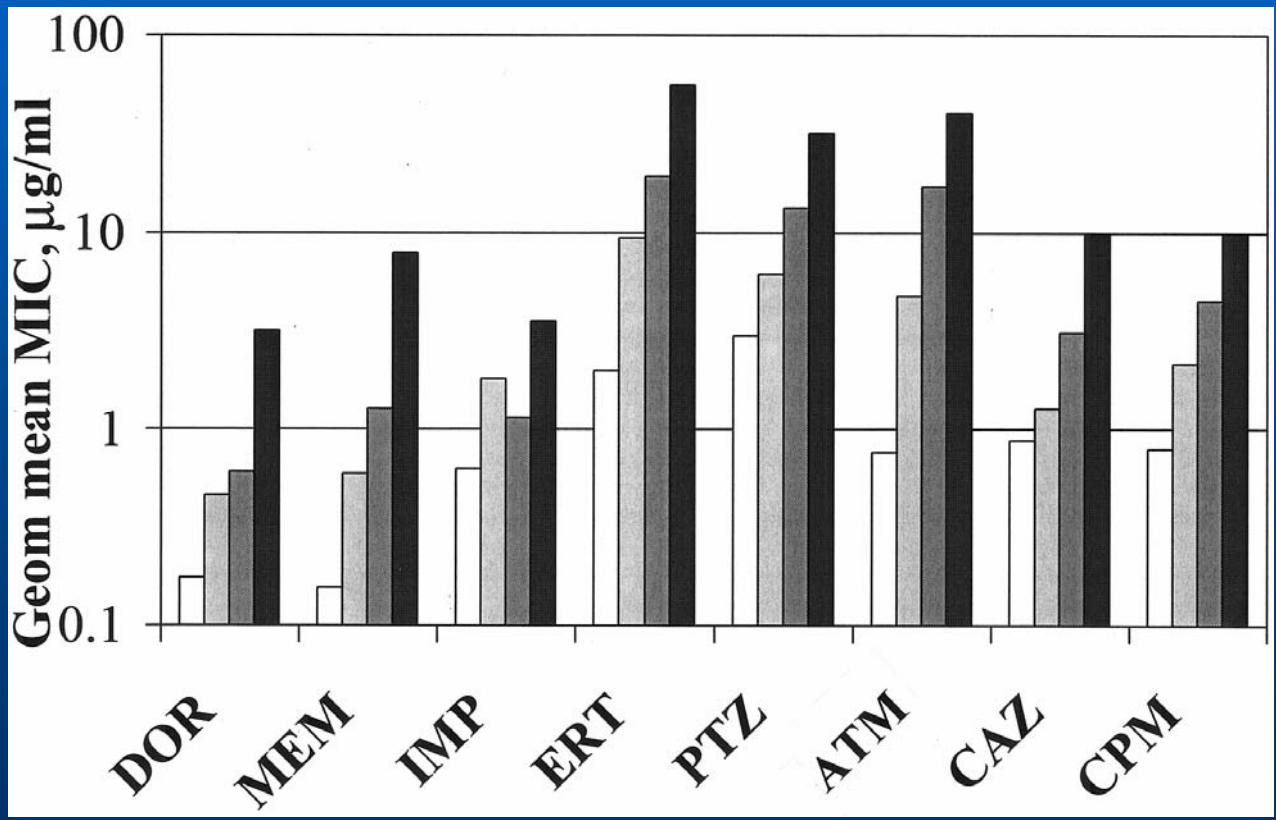
Pseudomonas

Doripenem

In vitro activity slightly higher than that of meropenem

MIC CAR

- ≤ 16
- 32-128
- 256
- ≥ 512



Mushtaq *et al.*, AAC (2004) 48:3086-92

Doripenem

Influence of resistance mechanisms

carbapenem	MexAB	MexEF	OprD	metallo β-lactamase
doripenem	R	nd	r	R
imipenem	S	r/R	R	R
meropenem	R	R	r	R

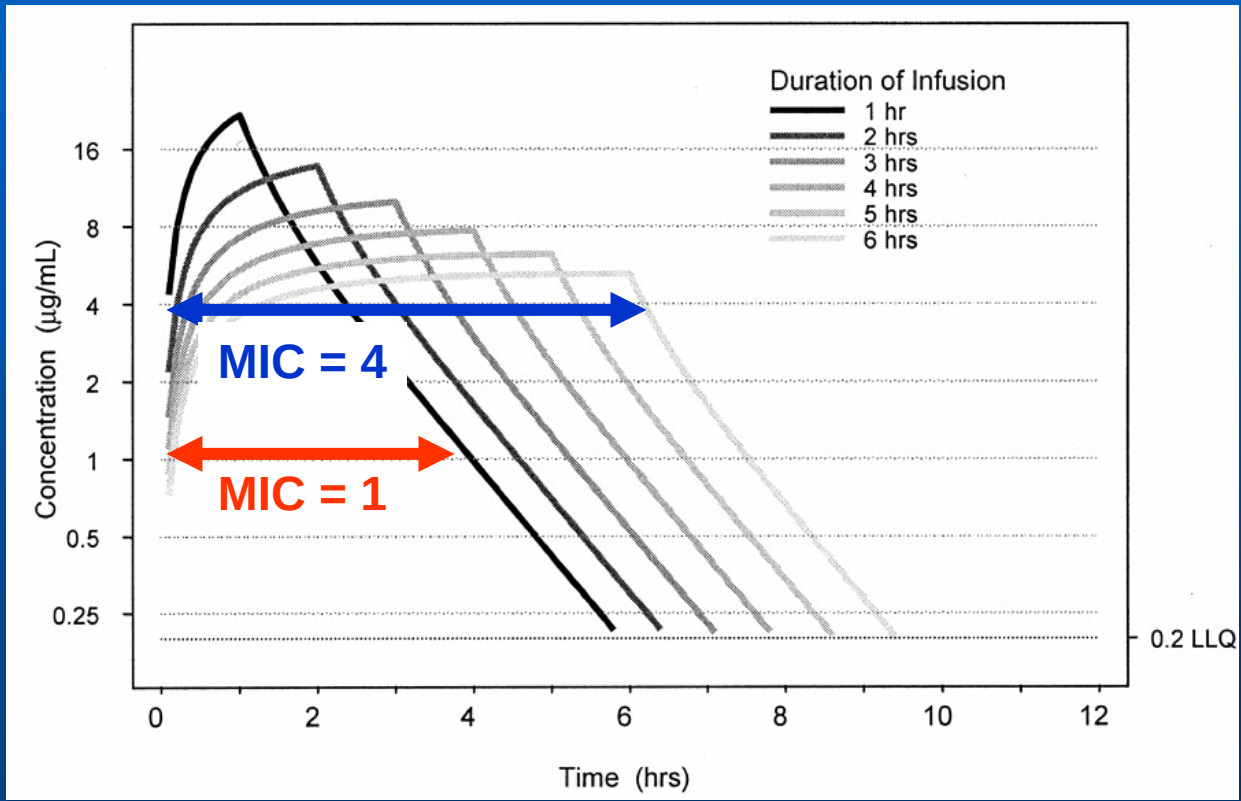
R : MIC > 8 mg/L
r : MIC < 8 mg/L

Dalhoff *et al.,* Biochem. Pharmacol. (2006) 71:1085-95

Doripenem

PK/PD in support to dosing : t > MIC ~ 20 %

500 mg
q 8 h

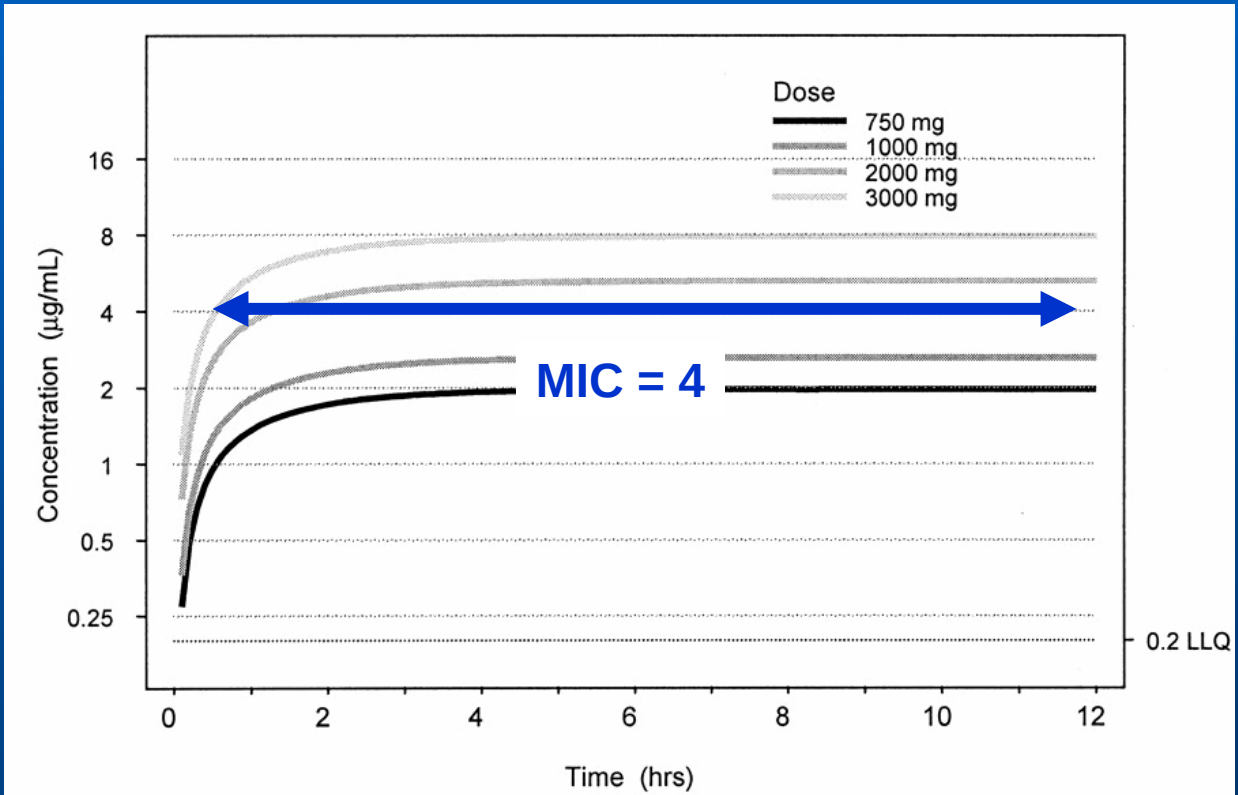


Bhavnani *et al.*, AAC (2005) 49:3944-47

Doripenem

Pk/PD in support to dosing : t > MIC ~ 20 %

continuous infusion



Bhavnani *et al.*, AAC (2005) 49:3944-47

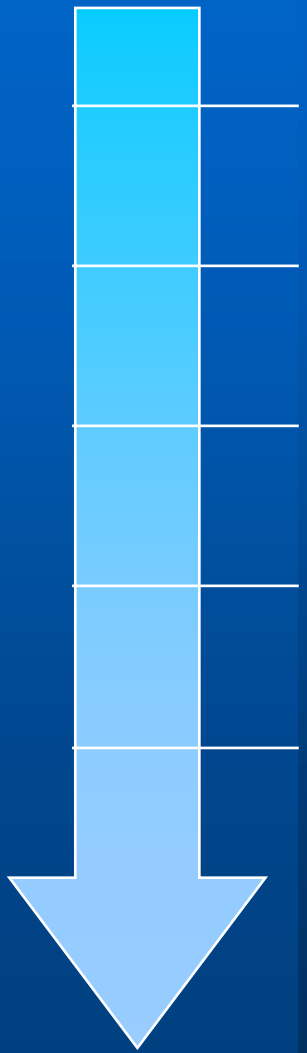
Doripenem

But what is the sensitivity of clinical isolates ?

Organism	Antimicrobial	MIC_{50}	MIC_{90}	Minimum	Maximum	Geometric mean	Mode
P. aeruginosa (CF isolates; $n = 82$)	Doripenem	0.25	2	0.25	256	0.52	0.25
	Imipenem	1	16	0.25	256	1.28	1
	Levofloxacin	1	16	0.25	128	1.75	0.5
	Piperacillin	8	256	0.25	>512	10.85	4
	Ceftazidime	2	32	0.25	256	3.47	2
	Aztreonam	8	64	0.25	>512	7.8	8
	Tobramycin	0.5	8	0.25	512	1.04	0.5
	Cefepime	2	16	0.25	64	3.52	2
P. aeruginosa (non-CF isolates; $n = 78$)	Doripenem	0.25	1	0.25	16	0.36	0.25
	Imipenem	1	2	0.25	32	0.95	1
	Levofloxacin	1	8	0.25	64	1.25	0.5
	Piperacillin	8	16	0.25	512	5.97	4
	Ceftazidime	2	8	0.25	64	2.61	2
	Aztreonam	8	16	0.25	64	4.07	8
	Tobramycin	1	2	0.25	>512	0.97	0.5
	Cefepime	2	16	0.25	32	3.47	2

Traczewski *et al.*, AAC (2006) 50:819-21

Anti - Pseudomonas carbapenems ?



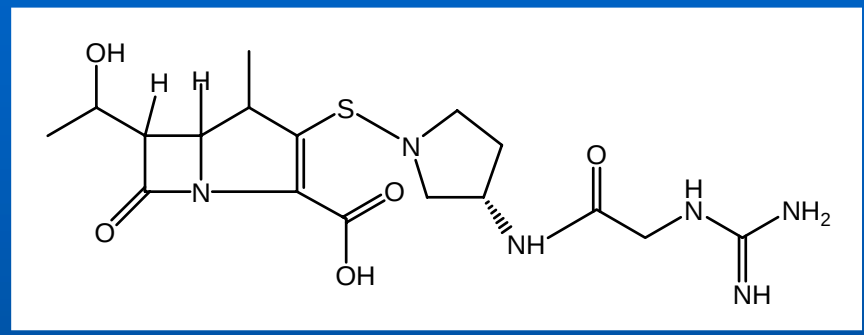
preclinical

Phase I

Phase II

Phase III

registration



RO 4908463

Roche

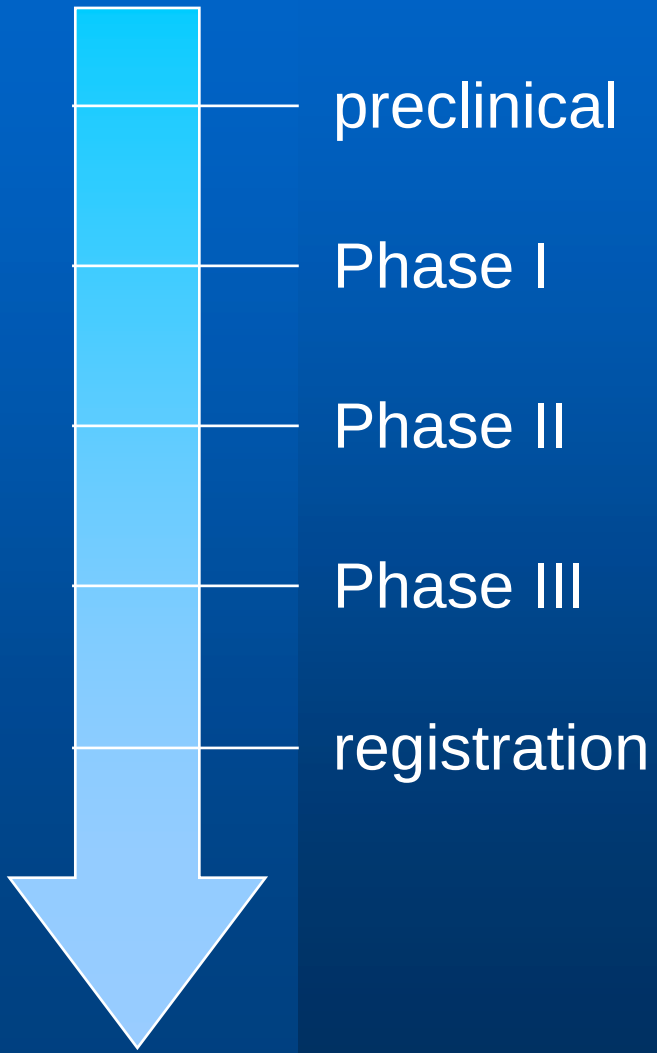
RO 4908463

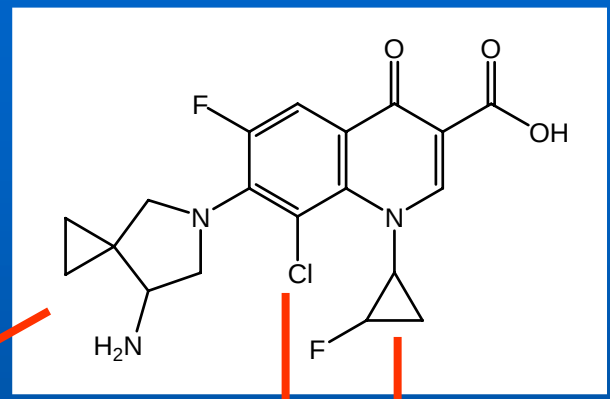
In vitro activity comparable to other carbapenems

carbapenem	MIC range (mg/L)	β-lactamase hydrolysis (class C & A)
RO 4908463	0.06 - 32	< 10 %
imipenem	0.25 - 32	< 10 %
meropenem	0.06 - 32	12 %

Koga *et al.*, AAC (2005) 49:3239-50

Anti-Pseudomonas fluoroquinolones ?





broad spectrum

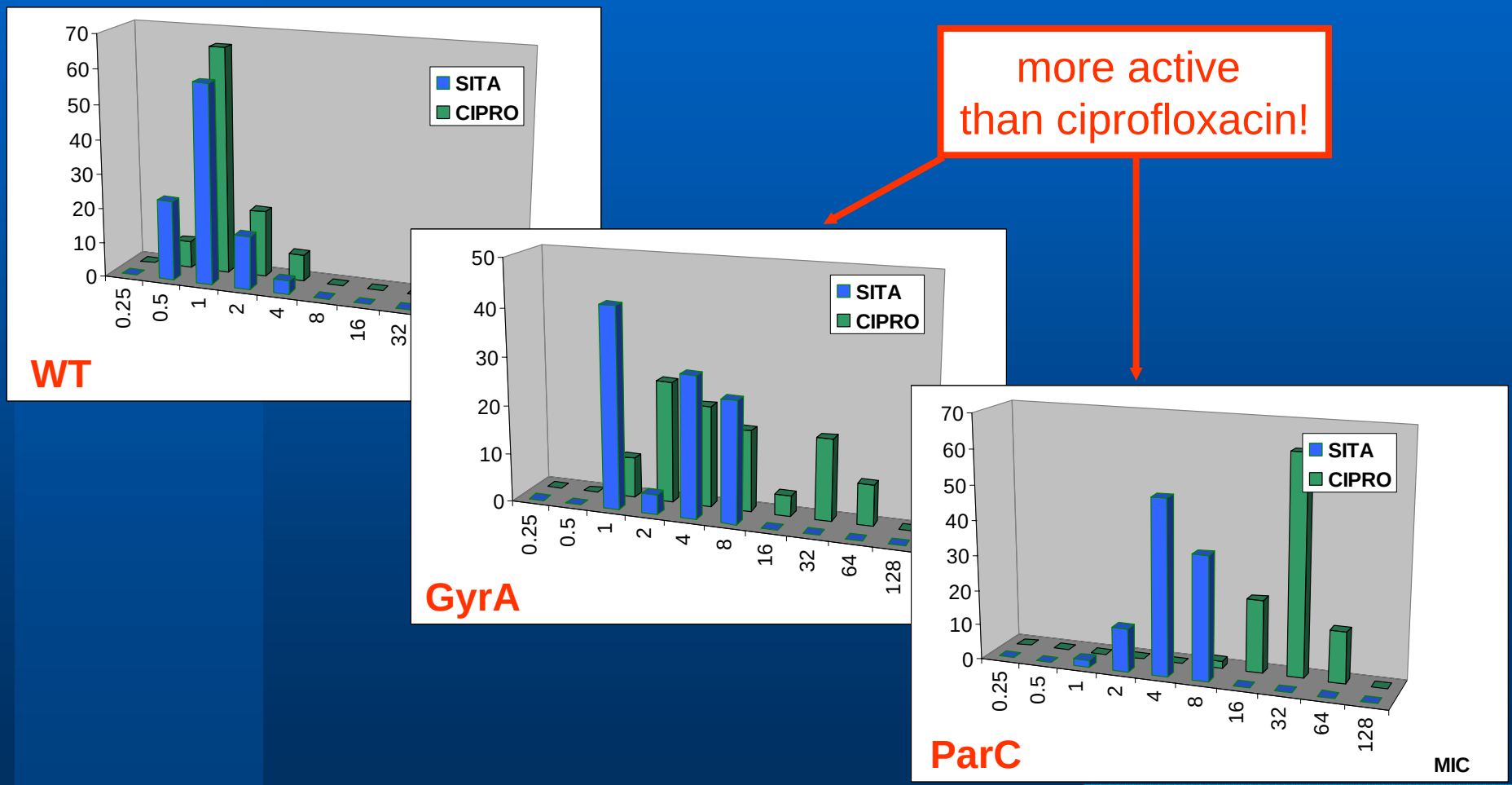
increased activity

sitafloxacin (Japan)

DAIICHI PHARMACEUTICAL CO.LTD.

Sitafloxacin

MIC distributions in WT and resistant strains



Kitamura *et al.*, AAC (1995) 39:1467-71

Sitafloxacin

Higher affinity than ciprofloxacin for mutated targets

fluoroquinolone	IC 50 (mg/L)			
	DNA Gyrase		Topo IV	
	WT	T831I	WT	S871I
sitafloxacin	0.42	1.85	2.12	8.62
ciprofloxacin	0.55	8.29	4.06	33.0

Kitamura *et al.*, AAC (1995) 39:1467-71

Anti-Pseudomonas fluoroquinolones ?

preclinical

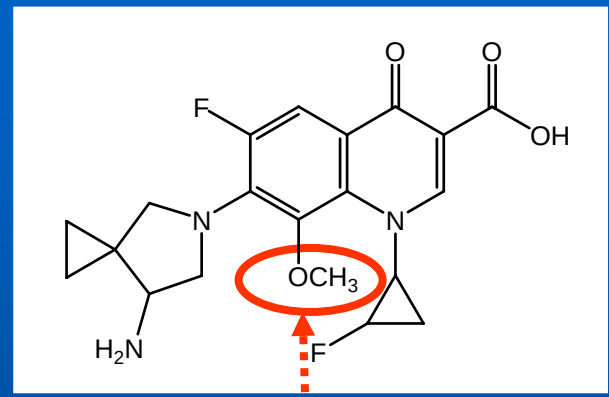
Phase I

Phase II

Phase III

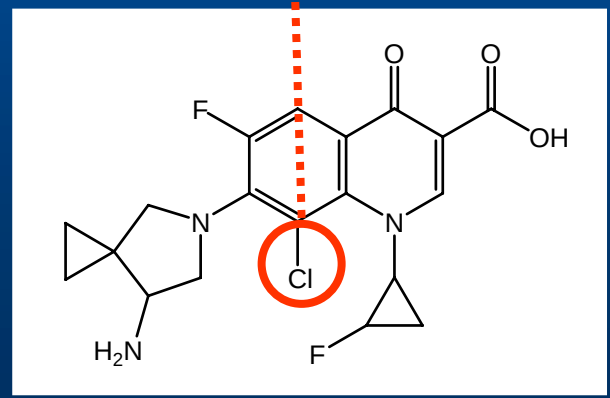
registration

DK 507k



reduced risk of phototoxicity

sitafloxacin (Japan)



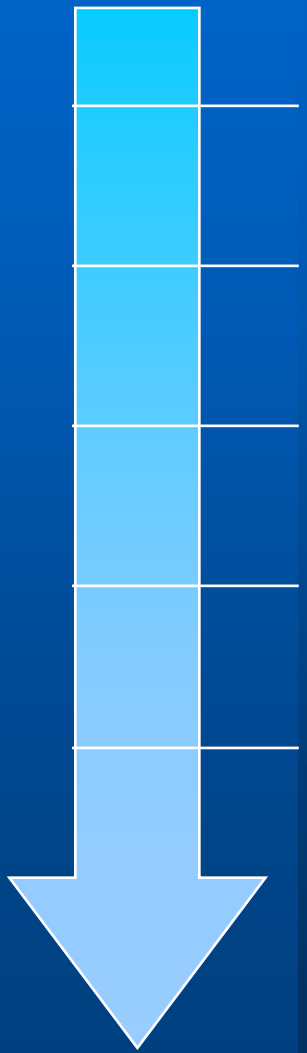
DK 507k

Less active than sitafloxacin against Pseudomonas

fluoroquinolone	MIC range (mg/L)	MIC 50	MIC 90
DK 507k	0.03 - 4	0.06	0.5
sitafloxacin	0.015 – 0.5	0.03	0.25
ciprofloxacin	0.015 - 16	0.03	0.5

Otani *et al.*, AAC (2003) 47:3750-9

Inhibitors of Pseudomonas efflux pumps ?



preclinical

Phase I

Phase II

Phase III

registration

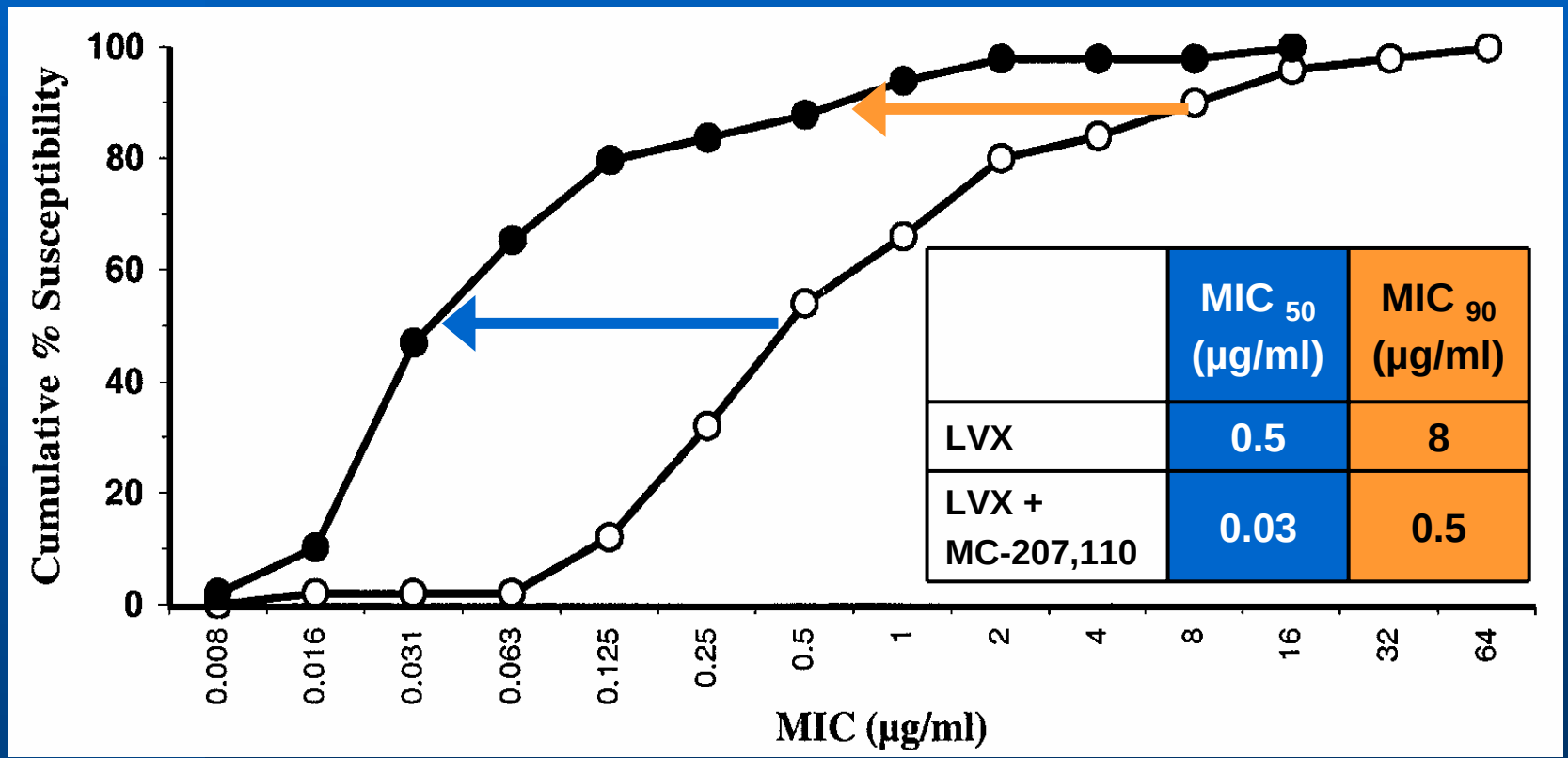
MP 601,205

Mpex Pharmaceuticals, Inc.

Making Proven Antibiotics Better

Inhibitors of Pseudomonas efflux pumps

Shift of MIC distributions with pumps inhibitors !



	MIC $_{50}$ (µg/ml)	MIC $_{90}$ (µg/ml)
LVX	0.5	8
LVX + MC-207,110	0.03	0.5

Lomovskaya *et al*. JMMB (2001) 3: 225-36

Inhibitors of Pseudomonas efflux pumps

Mpex Pharmaceuticals, Inc.

Making Proven Antibiotics Better

Home : Research & Development : Team : News : Employment : Contact

News:

Mpex Pharmaceuticals Announces Initiation of Second Phase Ib Clinical Trial for an Aerosol Candidate to Treat Respiratory Infections Associated with Cystic Fibrosis

Company is developing efflux pump inhibitors to improve antibiotic effectiveness to prevent or reverse antibiotic resistance

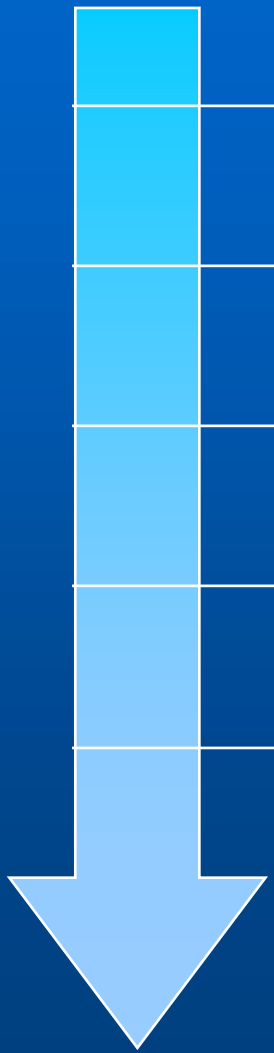
San Diego, CA - Aug 1, 2005 - Mpex Pharmaceuticals, Inc., a biopharmaceutical company focused on the discovery and development of antibacterials for the treatment of life-threatening infections, today announced that it has initiated a second Phase Ib clinical trial to study an aerosol drug candidate in cystic fibrosis (CF) patients. Candidate MP-601,205 is a bacterial efflux pump inhibitor that may significantly increase the effectiveness of antibiotics in the treatment of chronic and acute bacterial respiratory infections in cystic fibrosis, hospital acquired pneumonias, and certain chronic obstructive pulmonary diseases. The Cystic Fibrosis Foundation is providing financial and administrative support for the clinical trial that is being conducted at the Nemours Childrens Clinic in Orlando, Florida.

The clinical endpoint for the study is the demonstration that a dose projected to be efficacious is likely to be tolerated and safe in the broader CF population. This study is a follow-on to an initial Phase Ib study completed earlier this year in order to evaluate different doses in a different device.

"The successful completion of the earlier Phase I study has enabled Mpex to initiate a second trial in patients to test the tolerability, safety and PK of the drug at higher doses and with a different delivery technology", states Keith Bostian, CSO. Completion of this study and finalization of the drug product/delivery system will permit the initiation of a Phase II program.

Efflux pumps are proteins located in bacterial membranes that pump-out antibiotics and other substances toxic to bacteria. The resulting diminished antibiotic concentration in the bacteria cell reduces the potency of otherwise effective drugs and enables the selection of resistant mutants. An efflux pump inhibitor when combined with an antibiotic significantly improves the potency of the antibiotic and should suppress the emergence of resistant bacterial strains.

Do wide spectrum glycylcyclines act upon Pseudomonas ?



preclinical

Phase I

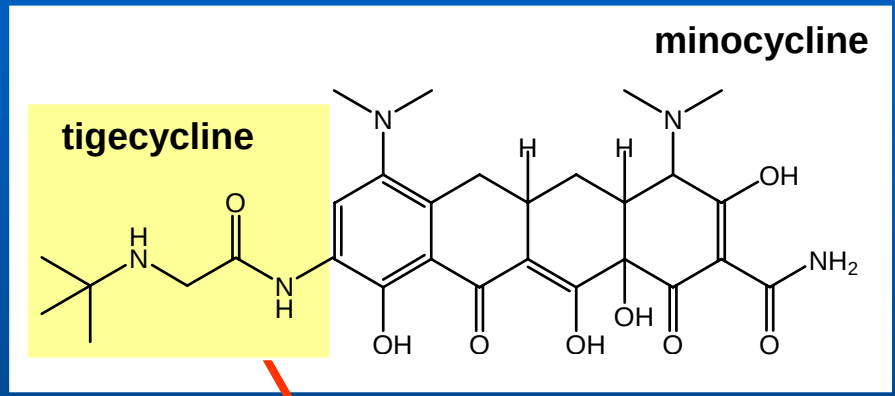
Phase II

Phase III

registration

tigecycline

Wyeth



evades resistance by
- **efflux by Tet pumps**
- **ribosomal protection**

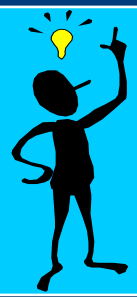
Tigecycline

XXL spectrum ….what about Pseudomonas ?

phenotype	MIC (mg/L)
WT	8
Δ mexXY	0.5

deceiving …

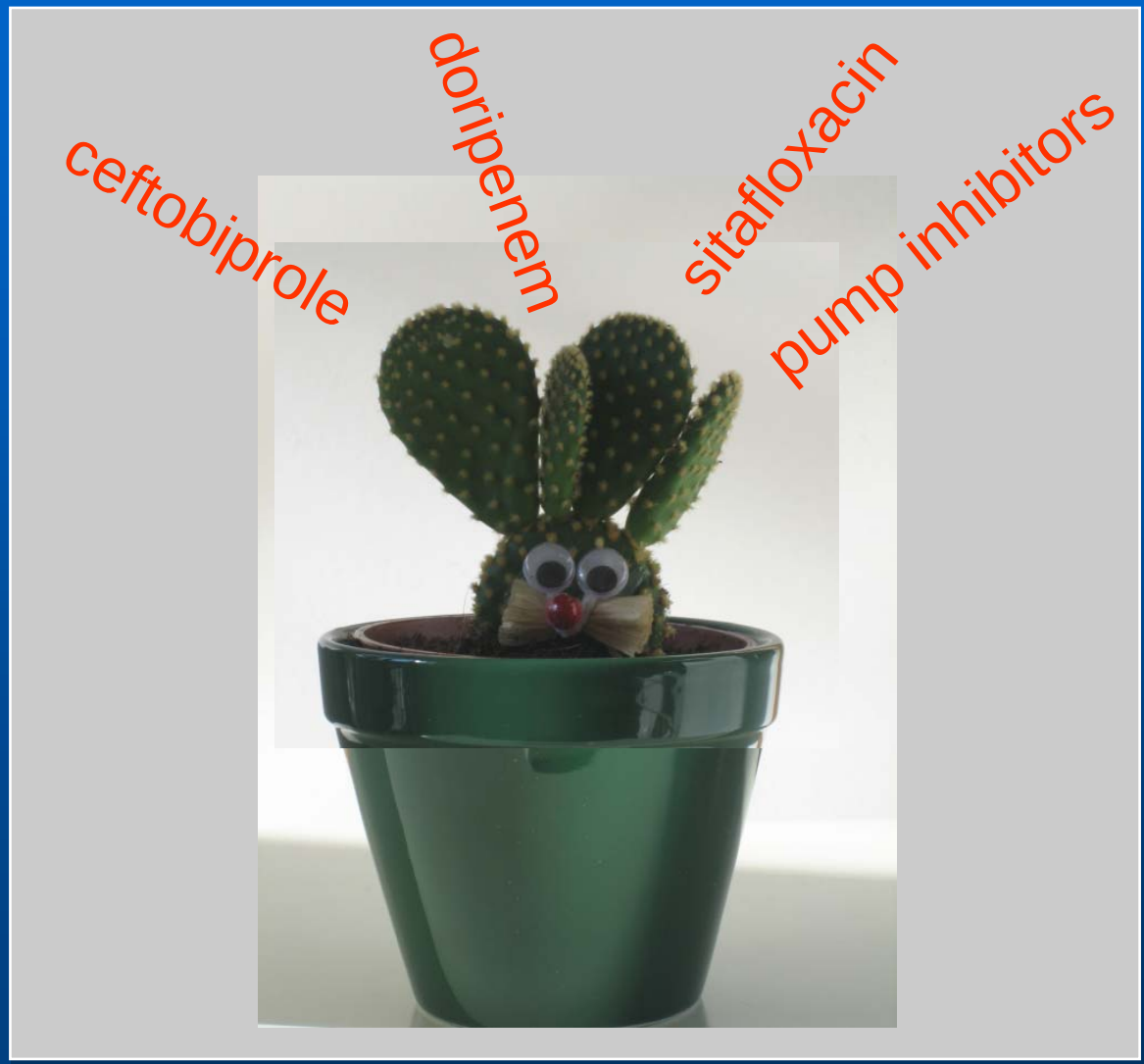
interesting !



combine with efflux pump inhibitors ?

Dean *et al.*, AAC (2003) 47:972-8

Which of these weapons will win the battle ?



Joyeuses fêtes de Pâques !