Intra-osteoblastic synergy of daptomycin with beta-lactams for *S. aureus* BJI

Sophie Trouillet-Assant, Céline Dupieux, Caroline Camus, Sébastien Lustig, Christian Chidiac, Tristan Ferry, Frédéric Laurent and Florent Valour
on behalf of the **Lyon BJI study group**

Prof. Frédéric Laurent

frederic.laurent@univ-lyon1.fr

Daptomycin in BJI: success and pitfalls

Increasingly used in staphylococcal BJI

(i) Acceptable bone diffusion at high concentration

(ii) Good tolerance

(iii) Targetting pathophysiological pathways?

Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry

K. Mallios[1] · J. Sarma[2] · R. A. Seaton[3] · M. Militz[4] · F. Menichetti[5] · G. Riccio[6] · J. Gaudias[7] · U. Trostmann[8] · R. Pathan[9] · K. Hamed[10]

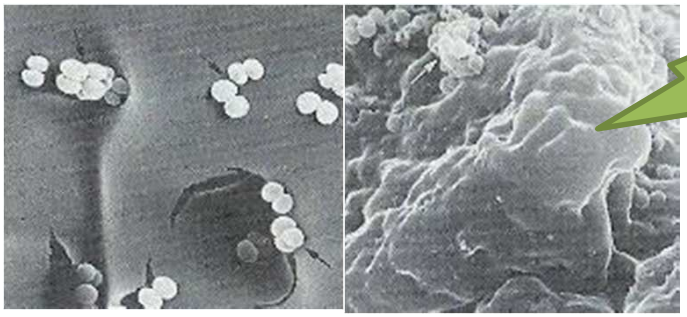
Eur J Clin Microbiol Infect Dis 2015

Daptomycin > 6 mg/kg/day as salvage therapy in patients with complex bone and joint infection: cohort study in a regional reference center

Sandrine Roux[1,2], Florent Valour[1,2,3], Judith Karsenty[1,2,4], Marie-Claude Gagnieu[5], Thomas Perpoint[1], Sébastien Lustig[2,6], Florence Ader[1,2,3], Benoit Martha[4], Frédéric Laurent[2,3,7], Christian Chidiac[1,2,3], Tristan Ferry[1,2,3]* and on behalf of the Lyon BJI Study group

BMC Infect Dis 2016

Good activity against bacteria embedded in biofilms



Daptomycin

Rasigade et al. Plos One 2012 – Valour et al. Plos One 2012

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BMC Infect Dis 2016

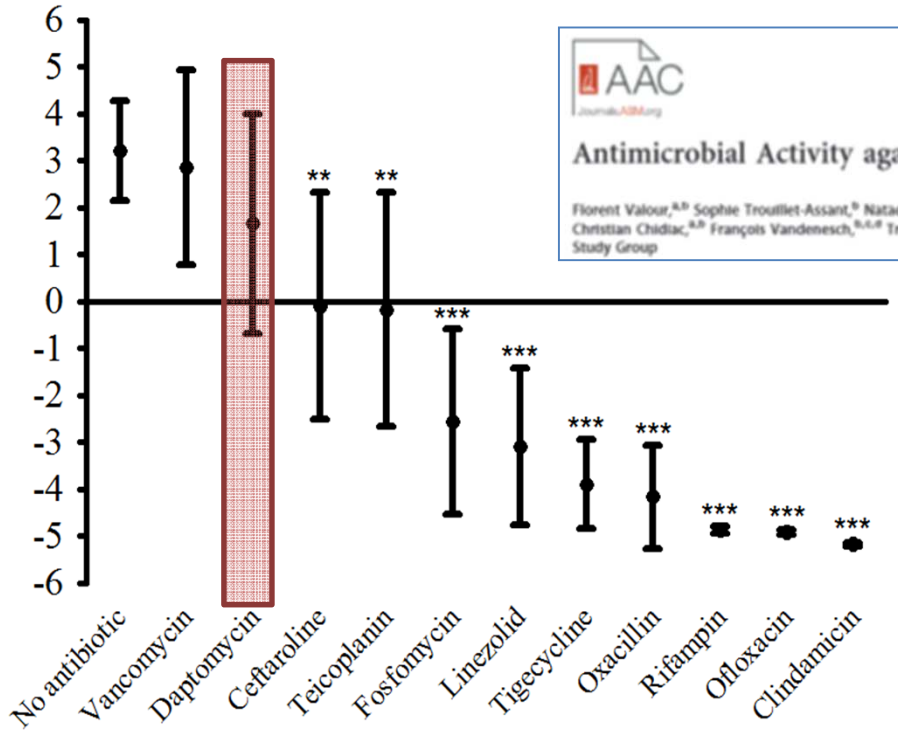
AAC

Antimicrobial Activity against Intraosteoblastic *Staphylococcus aureus*

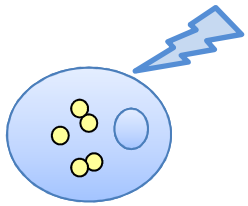
Florent Valour,[a,b] Sophie Trouillet-Assant,[b] Natacha Riffard,[b] Jason Tasse,[b] Sacha Flammier,[b] Jean-Philippe Rasigade,[b,c] Christian Chidiac,[a,b] François Vandenesch,[b,c,d] Tristan Ferry,[a,b] Frédéric Laurent,[b,c,d] on behalf of the Lyon Bone and Joint Infection Study Group

CFU of intracellular S. aureus after 24-h exposition

Δlog10 for 100,000 cells



antibiotic



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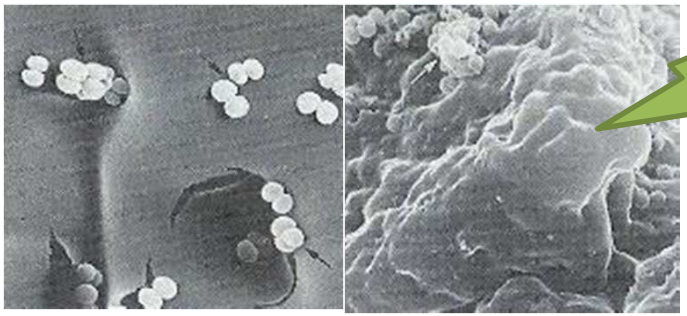
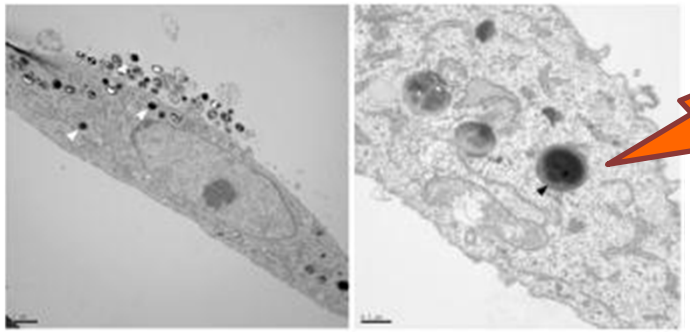
Good activity against bacteria embedded in biofilms



Daptomycin

BUT

Weak activity against staphylococcal intraosteoblastic reservoir



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Increasingly used in staphylococcal BJI

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- Good diffusion and activity within biofilms
- Weak intracellular activity

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BMC Infect Dis 2016

Use of daptomycin in *S. aureus* BJI without enhancing the risk of relapse due to the intracellular reservoir requires to improve its intra-ostoblastic activity

Daptomycin synergy with betalactam antibiotics

In vitro Synergy of daptomycin with betalactam antibiotics against MSSA and MRSA

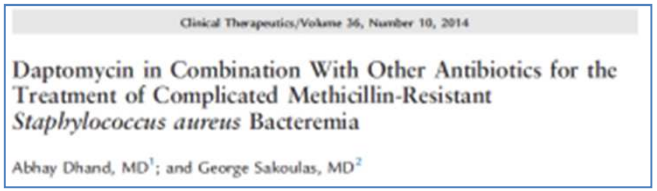
Mechanism: reduce the charge of the outer bacterial membrane which enhance daptomycin binding


AAC

β-Lactams Increase the Antibacterial Activity of Daptomycin against Clinical Methicillin-Resistant *Staphylococcus aureus* Strains and Prevent Selection of Daptomycin-Resistant Derivatives


Journal of Antimicrobial Chemotherapy

The combination of ceftaroline plus daptomycin allows for therapeutic de-escalation and daptomycin sparing against MRSA


Clinical Therapeutics/Volume 36, Number 10, 2014

Daptomycin in Combination With Other Antibiotics for the Treatment of Complicated Methicillin-Resistant *Staphylococcus aureus* Bacteremia

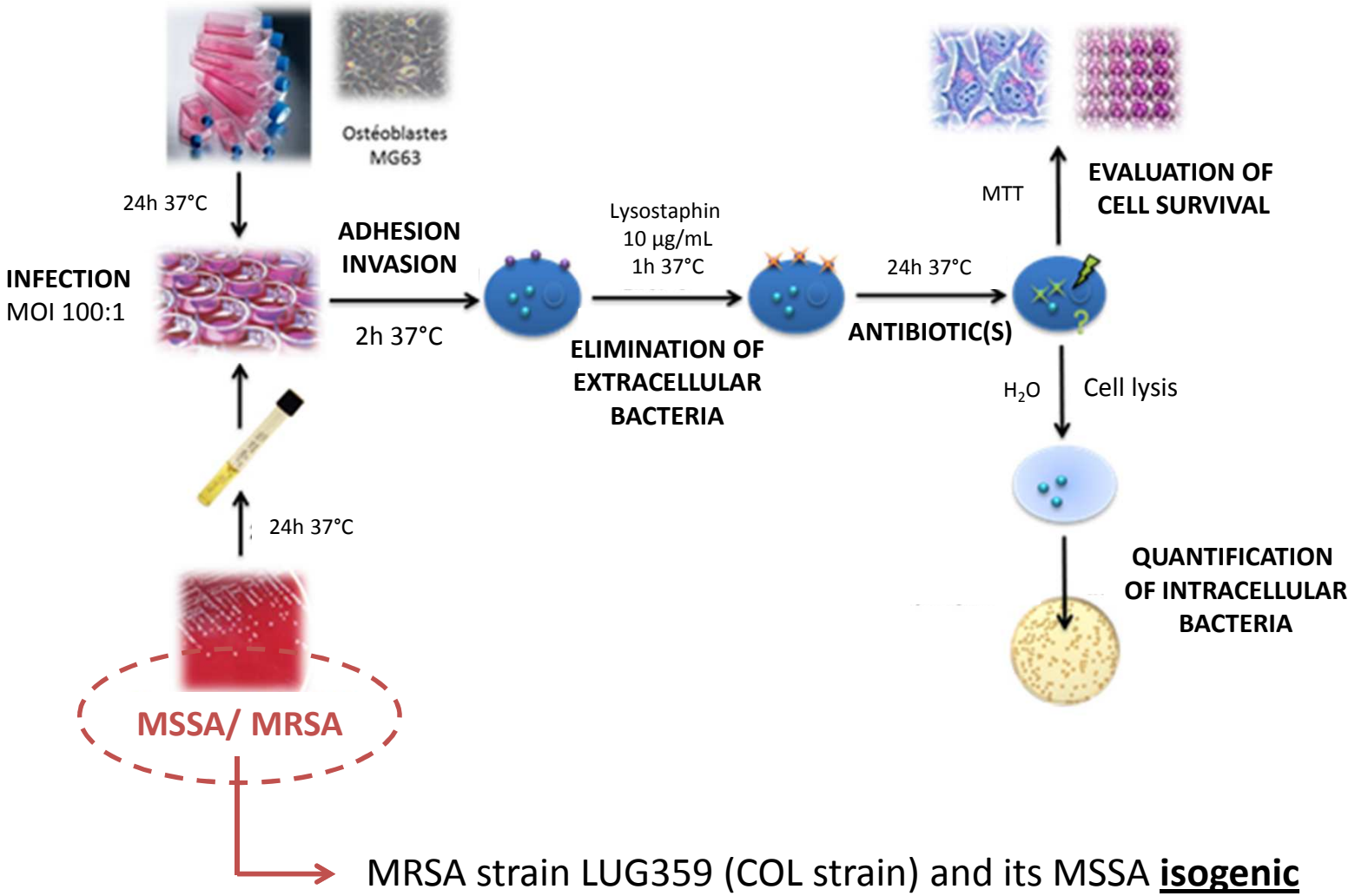
Abhay Dhand, MD[1]; and George Sakoulas, MD[2]

In vivo Daptomycin-oxacillin synergy in experimental models (IE, foreing body infection)

Clinical studies: case reports of MRSA bacteremia +/- BJI (“rescue therapy”)

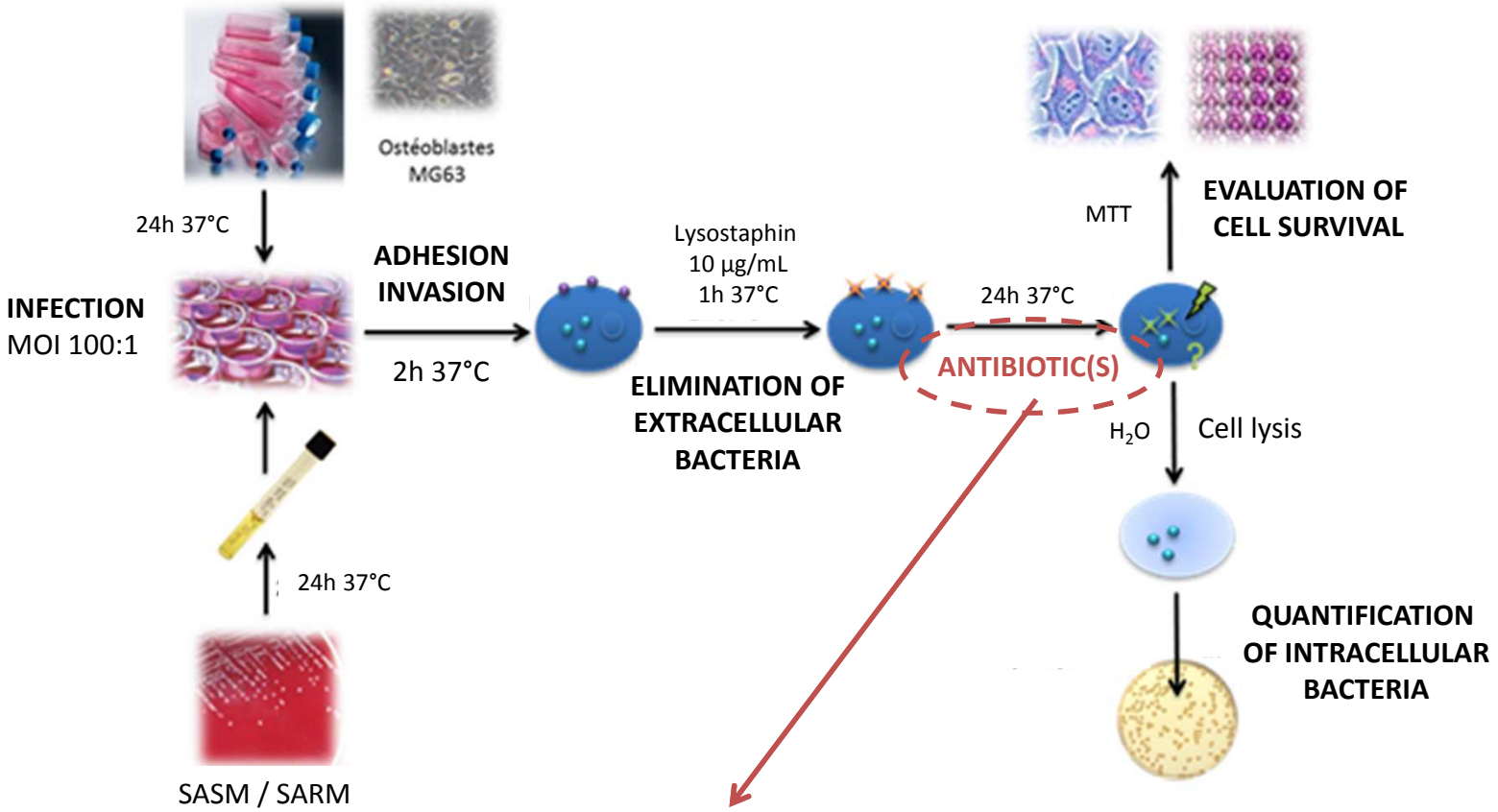
Objective: Assessing the efficacy of daptomycin in combination with oxacillin and daptomycin against intracellular MSSA and MRSA in an *ex vivo* model of human osteoblastic cell infection

Methods



MRSA strain LUG359 (COL strain) and its MSSA **isogenic** counterpart obtained by inactivation of the *mec*A gene by allelic replacement

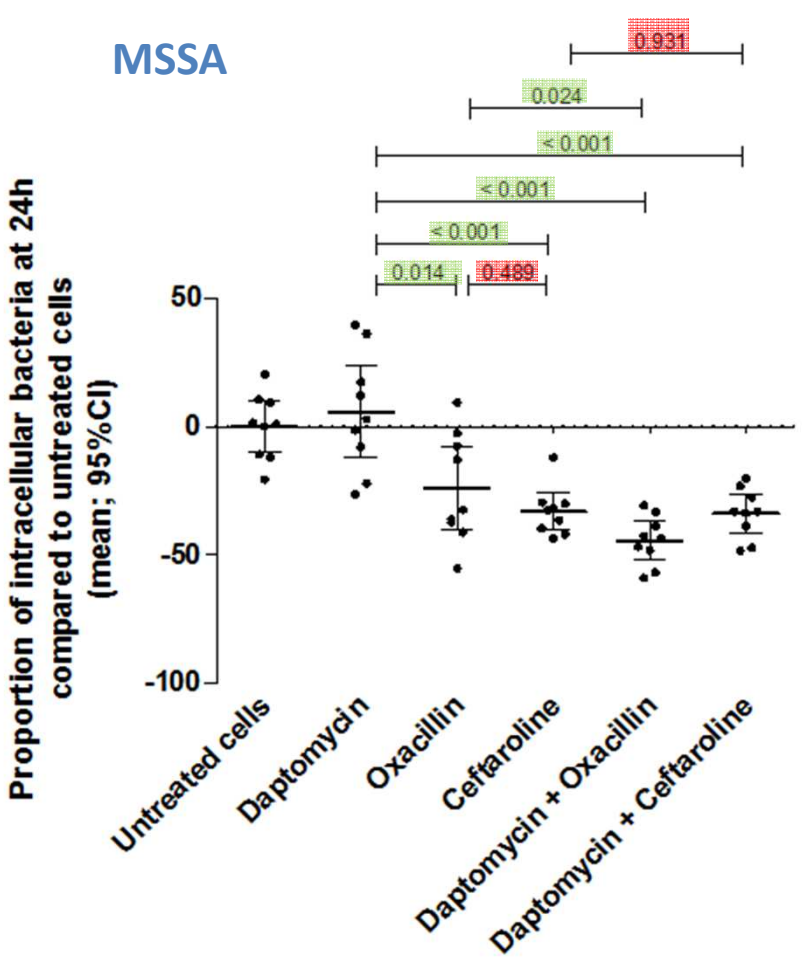
Methods

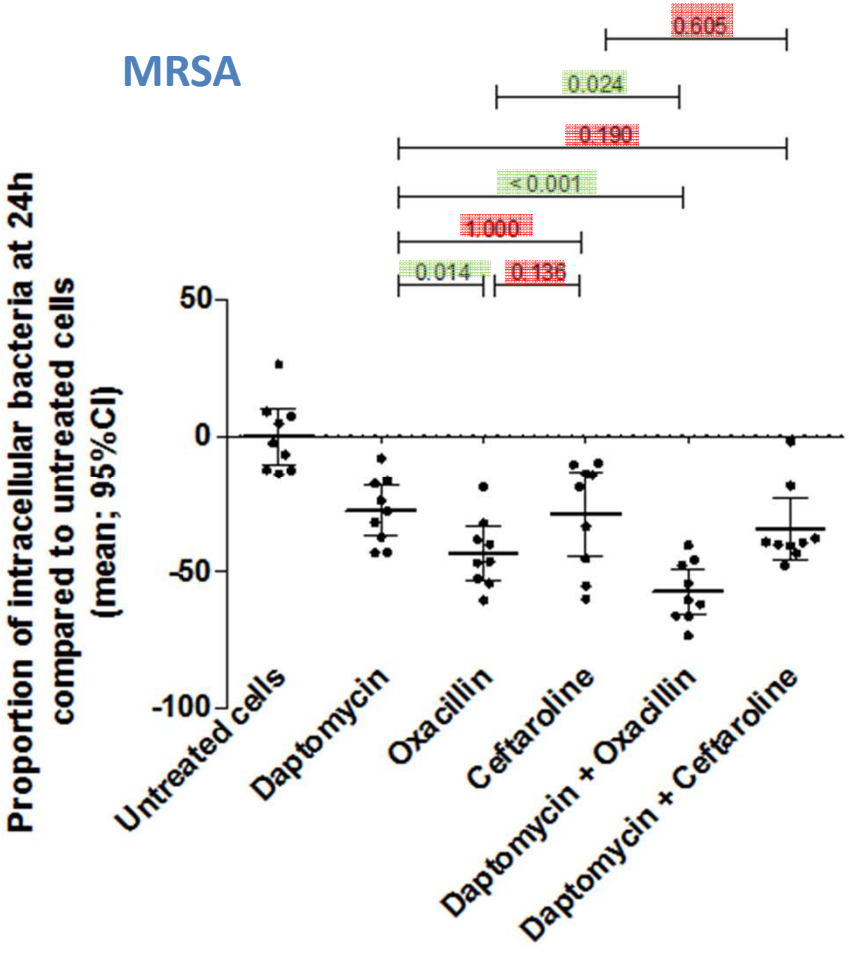


Daptomycin
Oxacillin
Ceftarolin

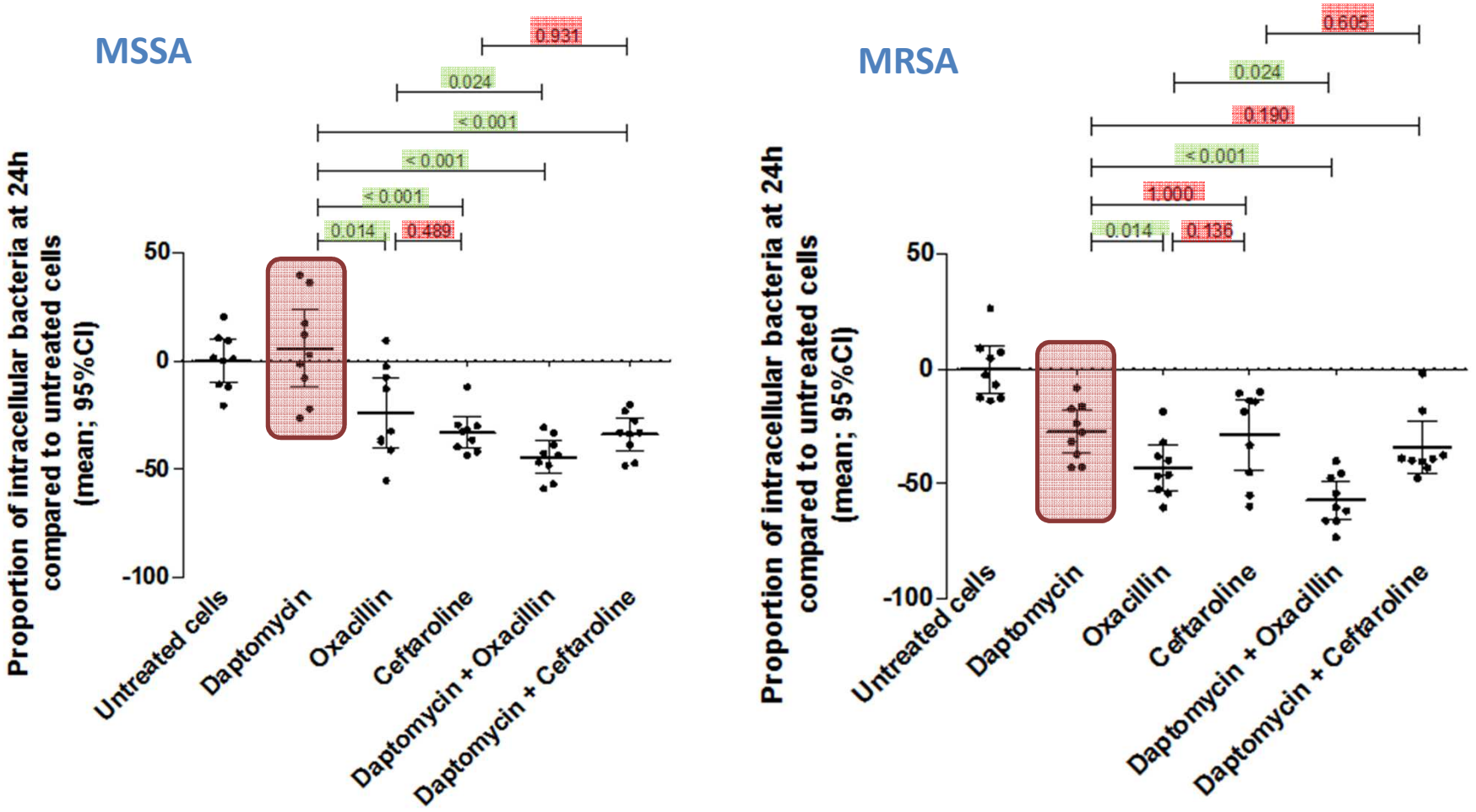
→ Alone or in combination
At human bone concentration

Results


MSSA
Proportion of intracellular bacteria at 24h compared to untreated cells (mean; 95%CI)
0.931
0.024
< 0.001
< 0.001
< 0.001
0.014
0.489
50
0
-50
-100
Untreated cells
Daptomycin
Oxacillin
Ceftaroline
Daptomycin + Oxacillin
Daptomycin + Ceftaroline

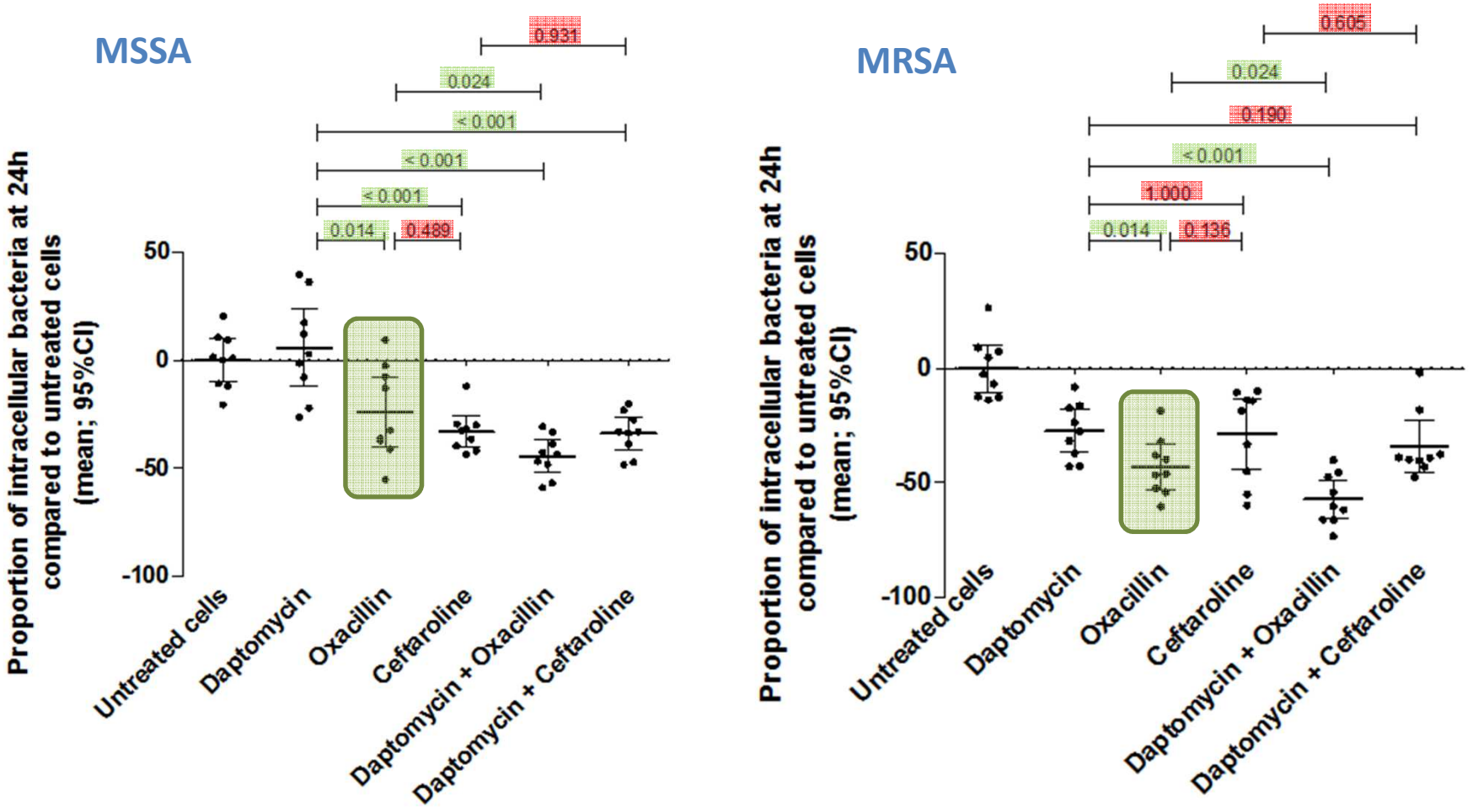

MRSA
Proportion of intracellular bacteria at 24h compared to untreated cells (mean; 95%CI)
0.605
0.024
0.190
< 0.001
1.000
0.014
0.136
50
0
-50
-100
Untreated cells
Daptomycin
Oxacillin
Ceftaroline
Daptomycin + Oxacillin
Daptomycin + Ceftaroline

Results



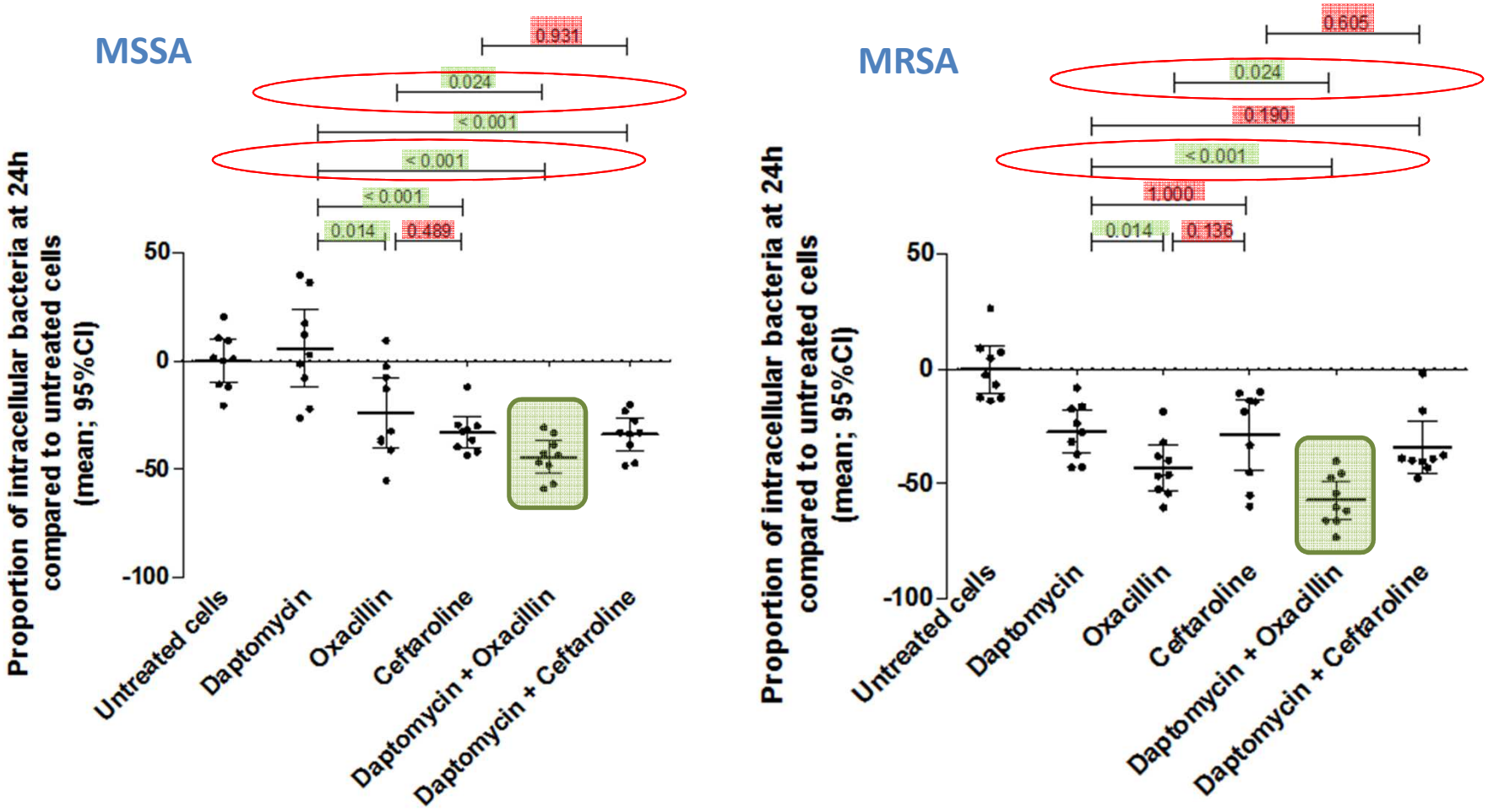
→ **Confirmation of the weak activity of daptomycin against intracellular MSSA/MRSA**

Results



→ **Acceptable efficacy of oxacillin against intracellular *S. aureus* INCLUDING MRSA**

Results



→ **Superiority of the daptomycin-oxacillin combination compared to each molecule alone not observed for the daptomycin-ceftarolin combination**

Complementary investigations

Intraosteoblastic *S. aureus* : partly intralysosomal = acidic pH

→ **Evaluation of the impact of pH on antibiotic activity**

Methods: - MICs evaluations at pH 7 and pH 5
- Synergy evaluations at pH 7 and pH 5 (E-test, checkerboard)

MIC mg/L	SASM			SARM		
	pH 7	**pH 5**	*p*-value	**pH 7**	**pH 5**	*p*-value
Daptomycin	0,25	1,83	0,002	0,29	2,00	0,002
Oxacillin	0,50	0,06	0,047	106,70	0,35	0,001

→ **Weak intracellular activity of daptomycin might be partly due to its decreased activity at acidic pH**

→ **Intracellular restauration of oxacillin activity against MRSA is (at least partly) due to a major decrease in MICs at the intralysosomal acidic pH**

→ No *in vitro* synergy was observed using these methods (partial results, not shown)

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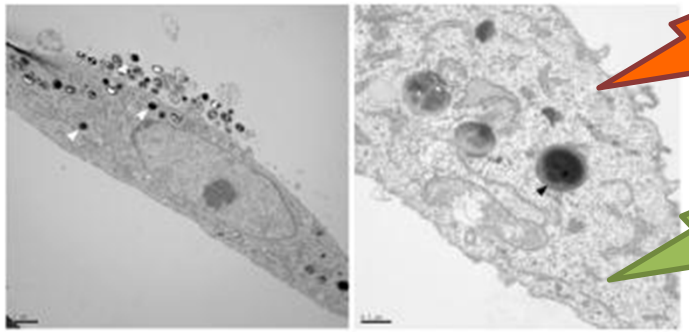
Conclusions and perspectives

Intracellular *S. aureus*



Daptomycin alone

. Oxacillin, including against MRSA

. **Daptomycin-oxacillin combination** including MRSA

Local chemical conditions importantly impact the intracellular activity of antistaphylococcal molecules

Perspective: Evaluation of adjuvants modulating intracellular pH conditions for enhancing the ability of antimicrobials to eradicate the *S. aureus* intraosteoblastic reservoir leading to BJI chronicity and relapse

Aknowledgements: Lyon BJI study group

ID department – *Florence Ader, André Boibieux, François Biron, Evelyne Braun, Christian Chidiac, Fatiha Daoud, Tristan Ferry, Johanna Lippman, Patrick Miailhes, Thomas Perpoint, Dominique Peyramond, Julien Saison, Marie-Paule Vallat, and Florent Valour*

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Hospices Civils de Lyon

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