Co-medications Improve Moxifloxacin (MXF) Activity in Models of Pneumococcal Naïve and Induced Biofilms (BF)

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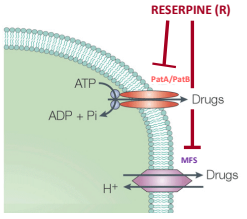
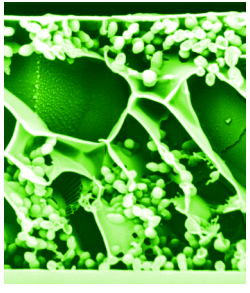




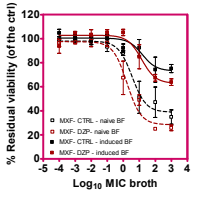
Results

Pharmacodynamic studies against naïve and induced 11 day-old biofilms of ATCC49619 (wide concentration range)

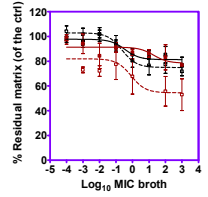
MOXIFLOXACIN (not substrate of efflux pumps) | **NORFLOXACIN** (substrate of efflux pumps)

DIAZEPAM

ACTIVITY ON SURVIVAL

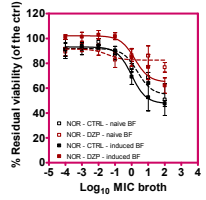


ACTIVITY ON BIOFILM MASS

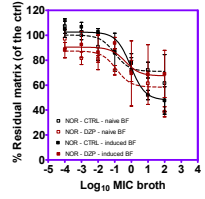


DZP : sligth increase of MXF efficacy on survival and biofilm mass

ACTIVITY ON SURVIVAL

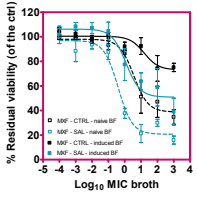


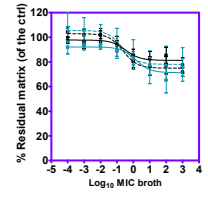
ACTIVITY ON BIOFILM MASS



DZP : decreased NOR efficacy on survival (not correlated with an effect on biofilm mass but potentially mediated by an induction of efflux pump PatA/B

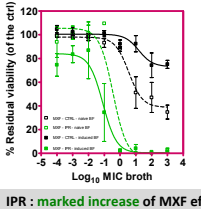
SALBUTAMOL

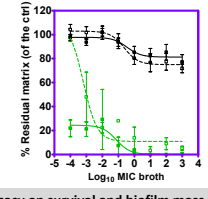




SAL : increase of MXF efficacy on survival, not correlated with an effect on biofilm mass

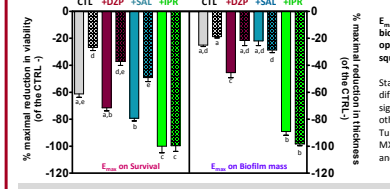
IPRATROPIUM





IPR : marked increase of MXF efficacy on survival and biofilm mass by drastic reduction of the matrix

Moxifloxacin maximal efficacies on bacterial survival within the biofilm and matrix thickness



Emax on survival (left) and biofilm thickness (right), open (naive biofilms) and squared bars (induced biofilms)

Statistical analysis: bars with different lowercase letters are significantly different from each other (One-way ANOVA with Tukey post test to compare MXF E_{max} between conditions and biofilm models)

All supplementations increase MXF maximal efficacy on survival against naive 11-days old biofilms, with IPR being most effective, improving MXF efficacy towards both survival and biofilm mass of naïve and induced biofilms

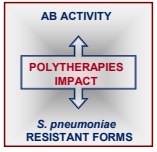
MINIMAL INHIBITORY CONCENTRATIONS (mg/L)

FLUOROQUINOLONES	Absence vs presence of Reserpine 10 mg/L in culture medium	CULTURE MEDIA			
		CONTROL	+ SALBUTAMOL 7,25 mg/L [a]	+ IPRATROPIUM 1,45 µg/L [a]	+ DIAZEPAM 1mg/L [b]
MOXIFLOXACIN	R -	0,125	0,125	0,125	0,063
	R +	0,063	ND	ND	0,063
NORFLOXACIN	R -	3	ND	ND	3
	R +	1,5	ND	ND	32

[a]SAL and IPR concentrations observed in respiratory tract after administration by inhalation ; MIC determined in the presence of these drugs to check for absence of interference
[b]DZP maximal concentration in human serum peak ; MIC determined after 8 days of culture in presence of this agent to induce efflux

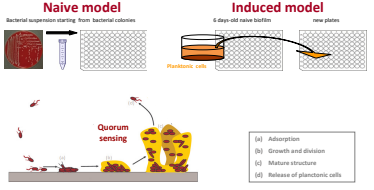
Background and aims

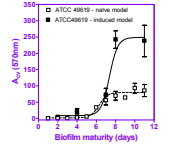
Biofilm plays a key role for chronic infections by *S. pneumoniae* in patients suffering from Chronic Obstructive Pulmonary Disease (COPD) [1]. We examined the influence on biofilm formation and fluoroquinolone activity of 2 bronchodilators (salbutamol [SAL] and ipratropium [IPR]) commonly used in the treatment of COPD, and of diazepam (DZP), a widely used benzodiazepine known to modulate antibiotic efflux. MXF was used as representative respiratory fluoroquinolnone (not subject to efflux) and NOR as preferential substrate for fluoroquinolone efflux [3].



Methods

Strain: ATCC49619 capsulated [19F] grown in 96-well plates for up to 11 days in caMHB supplemented with horse blood and 2 % glucose. Naïve model: freshly grown bacteria. Induced model: planktonic cells collected from the supernatant of 6-days old naïve biofilm. Fluoroquinolone activity (dose-effect) after 24 h incubation: (i) biomass [2] (crystal violet [CV] OD_{570nm}); (ii) bacterial viability [4] (reduction of resazurin to fluorescent resorufin [RF]), with fitting of a Hill equation to calculate E_{max}. Efflux induction: preculture with DZP during 8 days.

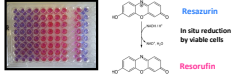




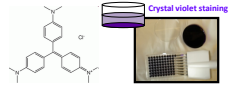
Biofilm mass ↑ overtime & with bacterial induction

EVALUATION OF THE ANTIBIOTIC ACTIVITY IN BIOFILMS

BACTERIAL VIABILITY WITHIN THE BIOFILM



TOTAL BIOFILM MASS : MATRIX + BACTERIA



Conclusions

Co-medications show synergistic effects with MXF on *S. pneumoniae* biofilms.
This effect is counteracted for DZP for NOR, possibly by induction of efflux. This model may be used to test for other antibiotic-drug combinations but will require validation in *in vivo* models.

References

[1]Moscoso et al, Int Microbiol. 2009 Jun;12(2):77-85;
[2]Roveta et al, Int J Antimicrob Agents. 2007 Nov;30(5):415-21;
[3]Tavio et al, J Med Microbiol 2004 53: 1119-22 ;
[4]Tote et al, Lett Appl Microbiol. 2008 Feb;46(2):249-54.

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