NANOGLOBULAR AND LINEAR ANTIMICROBIALS AGAINST BIOFILMS FORMED BY *BURKHOLDERIA CEPACIA* ISOLATED FROM CYSTIC FIBROSIS PATIENTS

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Abstract

Most patients with cystic fibrosis are chronically infected with *Burkholderia cepacia* that, once established, is impossible to eradicate and is associated with major morbidity[1]. Novel broad-spectrum antimicrobial **Mul-1867** can be effective in treatment of chronic lung Infections in cystic fibrosis.

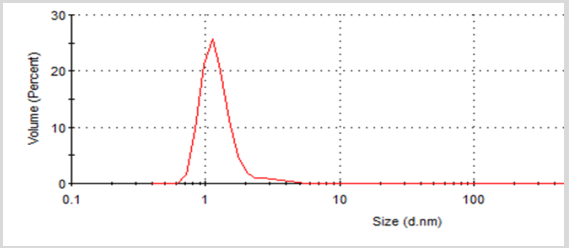
Methods

The MICs, for antimicrobials were determined by using the broth macrodilution method.
Antibiofilm activity was evaluated against clinical isolates of *B.cepacia* from cystic fibrosis patients.

Nanoglobular antimicrobial	Linear antimicrobial[2]
Mul-1867 100 times MIC	**Chlorhexidine** 100 times MIC
Time-kill test pre-formed, 24-h-old biofilm *B. cepacia* treated 60 sec	**Time-kill test** pre-formed, 24-h-old biofilm *B. cepacia* treated 60 sec

Background

Mul-1867 is hydrazine derivative, nanosized molecule 1.5-2.0-nm



Results

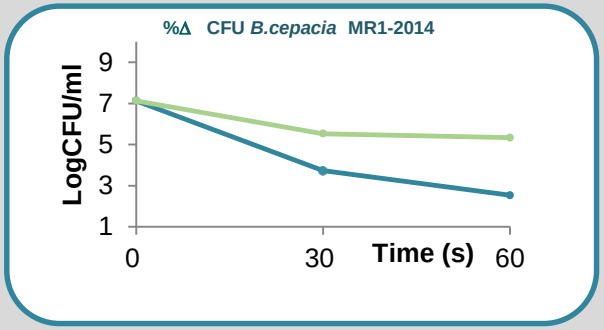
In vitro antibacterial activity of antimicrobials against multiresistant *B.cepacia* strains (mg/L)

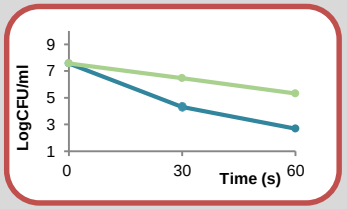
Organism	Mul-1867	CHG	Aztreonam	Amoxycillin
B.cepacia MR1-2014	**0.25**	16.0	32.0	32.0
B.cepacia VT28	**0.125**	8.0	64.0	128.0
B.cepacia SEV145	**0.5**	4.0	32.0	32.0

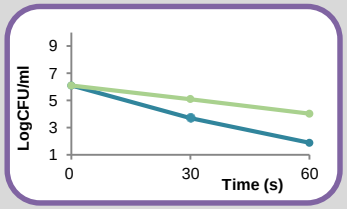
Mul-1867 inhibited the growth of all clinical isolates strains of *B.cepacia*, with MIC values ranging from 0.125 to 0.5 mg/L.

Reduction in median log10 cfu/ml for established **24-h-old *B. cepacia* biofilms**:

Mul-1867 100 MIC - 4.6 ± 0.5 log10/mL
Chlorhexidine 100 MIC - 1.8 ± 0.4 log10/mL







Mul-1867 was up to 1000 times more efficient than Chlorhexidine at all time points assessed.

Conclusion

Our study demonstrated that a nanoglobular antimicrobial Mul-1867 possesses greater antibiofilm activity against 24-h-old *B.cepacia* biofilm than a linear Chlorhexidine.
Both Chlorhexidine and Mul-1867 compromises bacterial membrane integrity but Mul-1867 additionally disrupt the peptidoglycan cell-wall layer. Thus, the greater antibacterial effect of the nanoglobular Mul-1867 may be because it penetrated the surface of the biofilm more effectively than the linear antimicrobial.
In this study, Mul-1867 was shown to exhibit fast-acting microbicidal activity against all tested strains, including, which were previously shown to respond poorly to treatment with existing medicines. Importantly, Mul-1867 broth macrodilution MICs were consistently lower (up to 64 times) than Chlorhexidine MICs against all the isolates.
Time-kill studies demonstrated that nanoglobular Mul-1867 was up to 1000 times more efficient than linear one at all time points assessed.
This work provides insight into the potential to develop nanotechnology products that can affect *B.cepacia* biofilms, a major cause of morbidity in chronic infections like cystic fibrosis. Further studies will be directed towards development of Mul-1867 as a locally acting antimicrobial.

References

1. Delhaes, Laurence, et al. "The airway microbiota in cystic fibrosis: a complex fungal and bacterial community—implications for therapeutic management." *PloS one* 7.4 (2012): e36313.
2. Zeng, Pengyun, et al. "Concentration dependent aggregation properties of chlorhexidine salts." International journal of pharmaceutics 367.1 (2009): 73-78.

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