P2320

Enhancing colistin efficacy against multidrug-resistant *Klebsiella pneumoniae* using farnesol-loaded lipid nanoparticles

F.D. Imtiyaz[1], H. Grau[1], C. Faivre[2,3], S. Marchand[1,4], T. Henry[5], R. Bonnin[6], L. Dortet[6], N. Anton[3], M. Collot[2], J.M. Buyck[1], F. Tewes[1]

[1]Université de Poitiers, INSERM U1070, Poitiers, France
[2]Université de Strasbourg, CNRS U7021, Strasbourg, France
[3]Université de Strasbourg, INSERM U1260, Strasbourg, France
[4]CHU de Poitiers, Laboratoire de Toxicologie et de Pharmacocinétique, Poitiers, France
[5]Université Claude Bernard Lyon 1, INSERM U1111, CNRS U5308, Lyon, France
[6]Université Paris-Saclay, INSERM U1184, Le Kremlin Bicêtre, France

Introduction

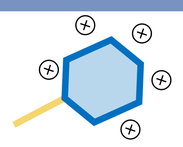
1

Farnesol

Can be used as CST adjuvant, but too hydrophobic for administration as a solution, then formulated as lipid nanoparticles (F-LNPs).

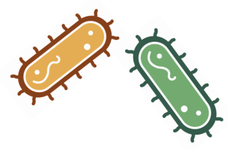
2

Farnesol-loaded LNPs (F-LNPs) + **Colistin (CST)**



↑ CST efficacy in *E. coli*[1] and *A. baumannii*[2]

3 Tested the combination against *K. pneumoniae* isolates



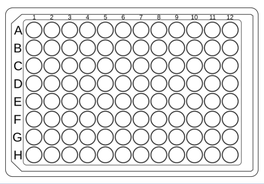
17 CST-resistant and 1 susceptible *K. pneumoniae* isolate(s)

This study evaluated F-LNPs as a CST adjuvant, their membrane effects, and their role in preventing CST resistance

Materials and Methods

1. Checkerboard MICs

18 isolates



2. Resistance acquisition

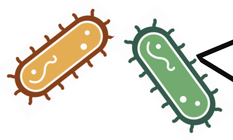
Against R2292 B (*mcr1*) strain

↓

Serial MICs

3. Outer (OM) and inner membrane (IM) permeabilities

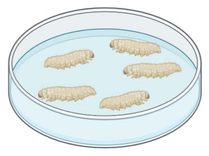
Against R2292 B (*mcr1*) strain



Nitrocefin for OM permeability

Propidium iodide (PI) for IM permeability

4. *In vivo* efficacy in *Galleria* larvae



Against R2292 B (*mcr1*) strain

Results

1. MICs

F-LNPs enhanced CST efficacy by 4- to 512-fold in *K. pneumoniae* (**Fig. 1**)

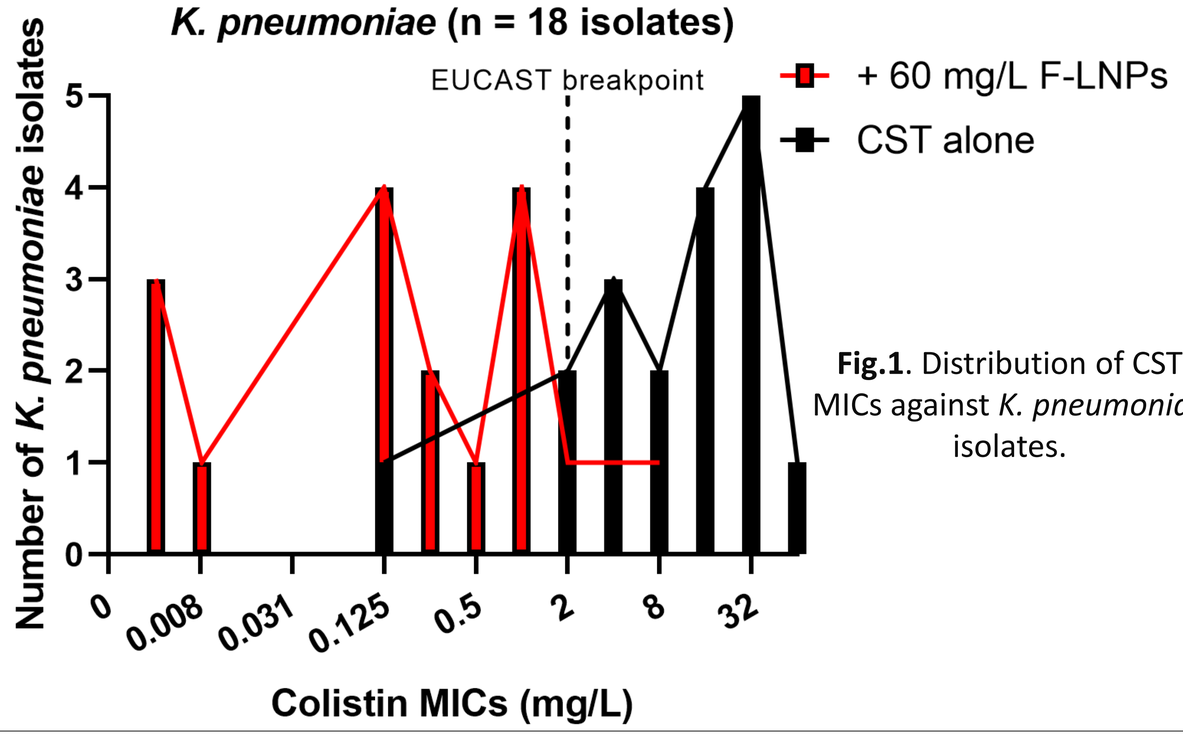


Fig.1. Distribution of CST MICs against *K. pneumoniae* isolates.

2. Resistance prevention study

After 12 serial MIC measurements, *F-LNPs* combined with CST minimized CST resistance (**Fig. 2**).

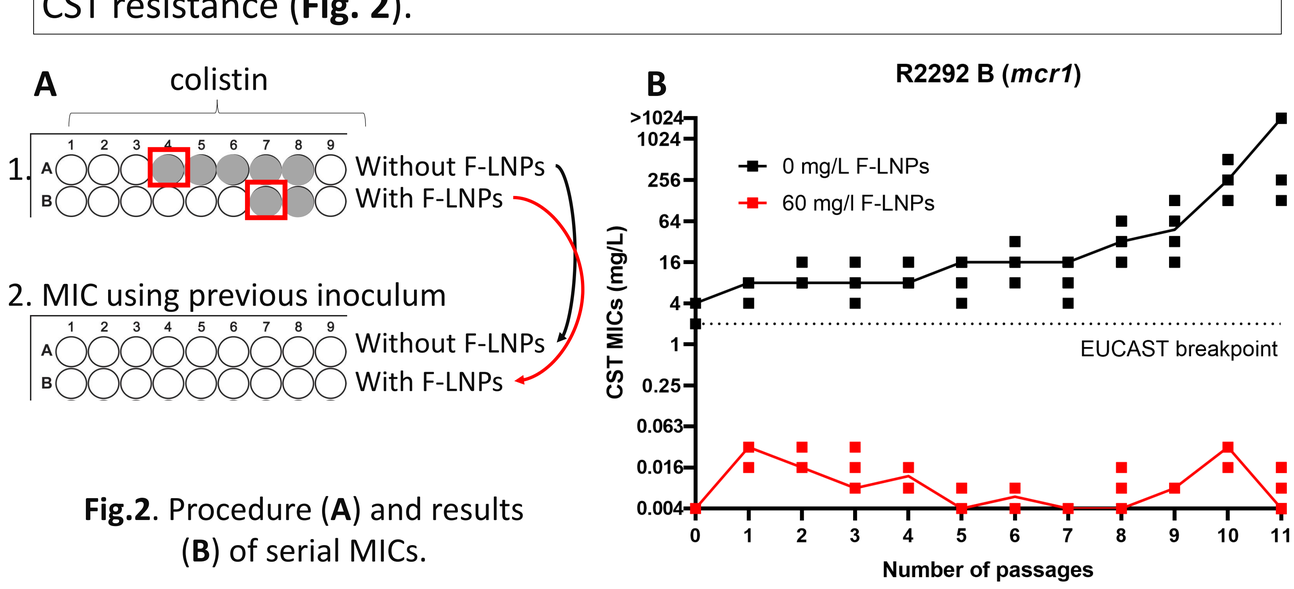


Fig.2. Procedure (**A**) and results (**B**) of serial MICs.

3. Outer and inner membrane study

F-LNPs permeabilised both membranes with CST at 1/8 MIC (**Fig. 3A-B**).

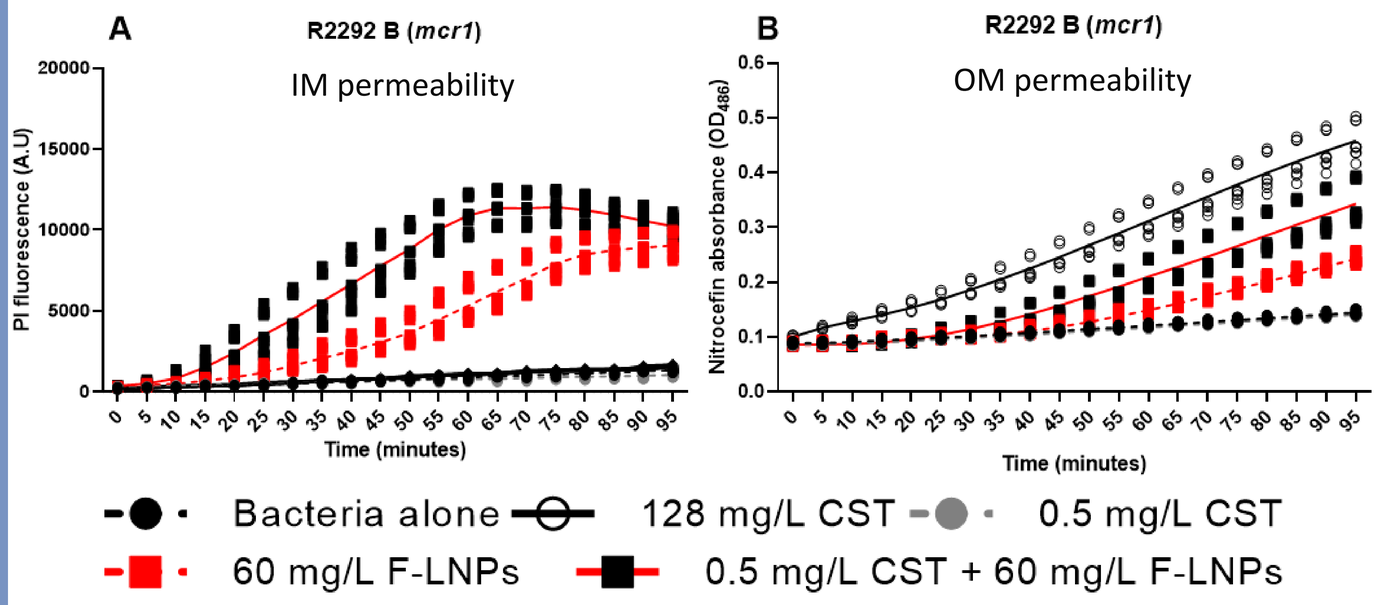


Fig.3. Inner (**A**) and outer (**B**) membrane permeability studies on a *K. pneumoniae* isolate.

4. *In vivo* efficacy assay

The CST-*F-LNP* combination improved infected larvae survival to 43%.

30 larvae/group infected at 10^6 CFU/larva with *K. pneumoniae* R2292 B (*mcr1*) 30 min before treatment

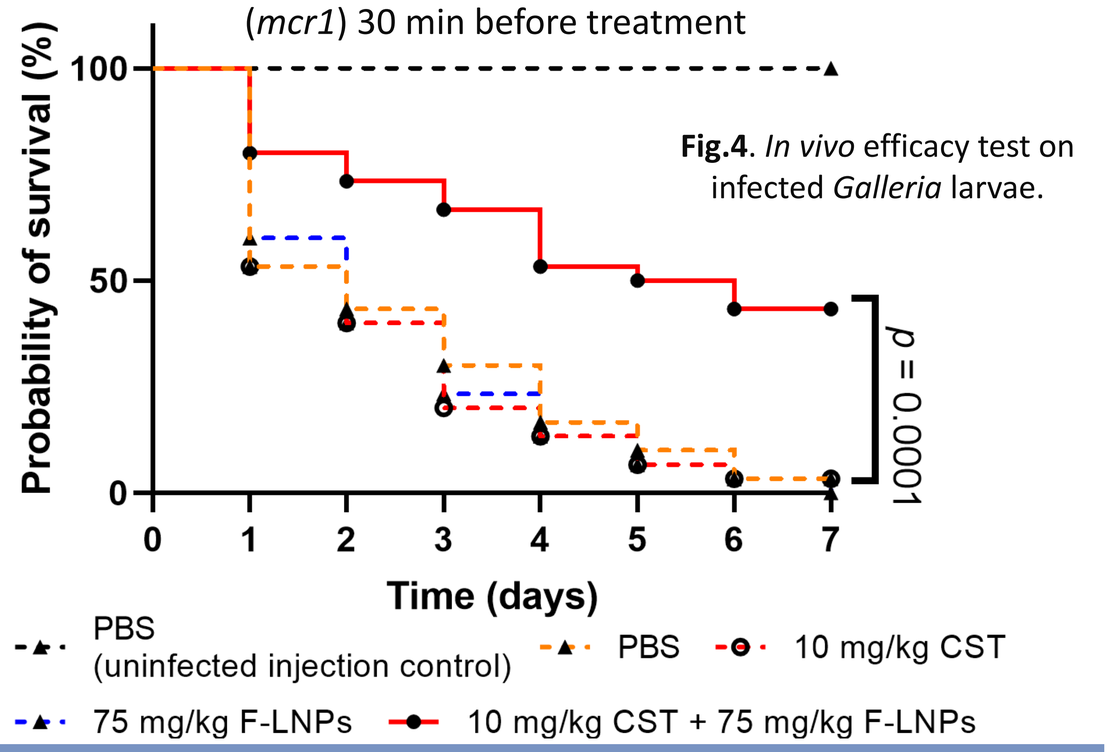


Fig.4. *In vivo* efficacy test on infected *Galleria* larvae.

Conclusion

Our results highlight the potential of the CST-*F-LNP* combination to overcome *K. pneumoniae* CST resistance in 18 clinical isolates by enhancing membrane permeabilisation and minimising resistance development.

Acknowledgement

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References

1) 10.1016/j.ijpharm.2024.124907
2) 10.3390/pharmaceutics13111849