F-649

CF-301, a Phage Lysin, is Superior in Combination Therapy to Antistaphylococcal Antibiotics Alone in Murine *Staphylococcus aureus* Bacteremia

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INTRODUCTION

Bacteriophage lysins are enzymes that degrade bacterial peptidoglycans. Lysin CF-301 is being developed to treat *S. aureus* [methicillin-sensitive and resistant *S. aureus* (MSSA and MRSA)] because of its potent, specific, and rapid bacteriolytic effects. CF-301 also demonstrates activity on drug-resistant strains, has a low resistance profile, and eradicates biofilms. The various features of CF-301 makes it an attractive candidate for antimicrobial development.

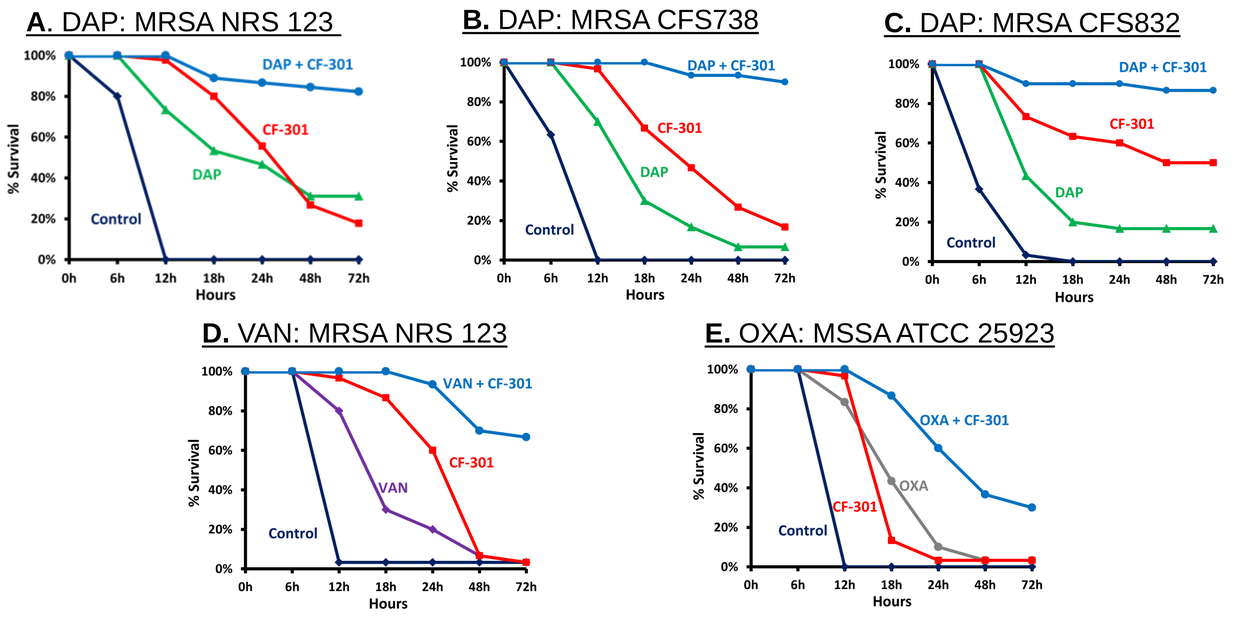
In this poster we show that CF-301 significantly enhances standard of care (SOC) antibiotic activities against staphylococcal-induced murine bacteremia under challenging conditions where high doses of single antibiotics fail, underscoring the effectiveness of the combination strategy for treating bacteremia.

METHODS

Murine bacteremia model: Healthy female BALB/c mice received a single intraperitoneal (IP) injection of 1 x 10^9 MRSA NRS 123, MRSA CFS738, MRSA CFS832 or MSSA ATCC 25923. The mice were treated with: i) vehicle; ii) CF-301 (5.25 mg/kg IP QD); iii) OXA (oxacillin) (200 mg/kg IM QID); iv) CF-301 plus OXA; v) VAN (vancomycin) (110 mg/kg SQ BID); vi) CF-301 plus VAN; vii) DAP (daptomycin) (50 mg/kg SQ QD); or viii) CF-301 plus DAP, each starting at 2 hours postinfection. The CF-301 minimum inhibitory concentration (MIC) for the strains are as follows: MRSA NRS 123 – 8µg/mL; MRSA CFS738 – 1µg/mL; MRSA CFS832 – 4µg/mL; ATCC 25923 – 16µg/mL. The DAP and VAN MIC for all the strains are 0.5µg/mL and 1µg/mL respectively.

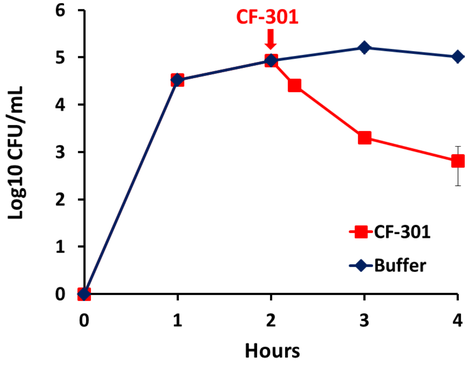
CFU in blood: To measure CFU in blood, mice received a single IP injection of 1 x 10^9 MRSA NSR 123 and were bled retro-orbitally at each time point. CF-301 (5.25mg/kg IP QD) was administered at 2-hours post-infection. CFU were measured in the blood of infected mice before and after treatment with CF-301 (*n*=3 per time-point).

FIGURE 1. Combination therapy is superior to monotherapy in murine models of *S. aureus* bacteremia



[A-C] Survival rates of CF-301 + DAP combination compared to monotherapy in a 72-hour murine model of MRSA bacteremia, *n*=30-45. **[D]** Survival rates of CF-301 + VAN combination compared to monotherapy in a 72-hour murine model of MRSA bacteremia, *n*=30. **[E]** Survival rates of CF-301 + OXA combination compared to monotherapy in a 72-hour murine model of MSSA bacteremia, *n*=30.

FIGURE 2. CF-301 has rapid bactericidal activity in vivo



Rapid bactericidal activity of CF-301 was demonstrated in the bloodstream. Treatment with CF-301 at 2-hours post-infection produced a decrease of 0.5-$\log_{10}$ CFU within 15 minutes and a 2.0-$\log_{10}$ decrease in 60 minutes.

Lysin Killing Bacteria	Lysin Mechanism of Action

RESULTS

Combination therapy is superior to monotherapy in murine models of *S. aureus* bacteremia:

- DAP + CF-301 combination treatment is superior to single-drug regimens. 72-hour survival rates were: i) CF-301 (17-50%); ii) DAP (7-31%); iii) CF-301 plus DAP combination (82-90%; P<.0001) (**Figure 1A-C**).
- VAN + CF-301 combination treatment is superior to single-drug regimens. 72-hour survival rates were: CF-301 (3%); ii) VAN (3%); iii) CF-301 plus VAN combination (67%; P<.0001) (**Figure 1D**).
- OXA + CF-301 combination treatment is superior to single-drug regimens. 72-hour survival rates were: i) CF-301 (3%); ii) OXA (3%); iii) CF-301 plus OXA combination (30%; P<.0001) (**Figure 1E**).

CF-301 has rapid bactericidal activity in vivo

- 0.5-$\log_{10}$ CFU within 15 minutes of CF-301 treatment.
- 2.0-$\log_{10}$ decrease within 60 minutes of CF-301 treatment (**Figure 2**).

CONCLUSIONS

Overall, the in vivo results demonstrate that CF-301 has rapid bactericidal activity and when combined with SOC antibiotics is superior to single-drug regimens for treating bacteremia. Compared to currently available single-drug options with SOC antibiotics, therapies using lysins in combination with antibiotics should provide unique and superior alternatives for treating bacteremia caused by *S. aureus*.

ACKNOWLEDGEMENTS

We acknowledge Berice Ruisi for help in poster preparation and Robert Durso and Adam Vigil for technical assistance.

Disclosures: VAF is a consultant to ContraFect Corporation.