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FibriLysins: playing the Reverse Uno card against Staphylococcus aureus

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In fracture-related infections (FRI), antibiotic-resistant *Staphylococcus aureus* frequently persists within fibrin-encapsulated biofilms and abscess communities that restrict immune clearance and antibiotic penetration. This trait is mediated by prophage-encoded accessory genes, which serve as major drivers of *Staphylococcus aureus* virulence.

We here present FibriLysins, a first-in-class antibacterial strategy that effectively plays a "Reverse Uno card" on the pathogen by repurposing staphylokinase, a prophage-encoded virulence factor used by *S. aureus* for dissemination, as a targeted fibrin-degrading module fused to a potent bacteriophage-derived endolysin. This dual-action strategy dismantles the protective fibrin barrier surrounding bacterial communities and subsequently eradicates the exposed bacteria.

From a library of screened FibriLysins, the lead candidate, FL-028, showed broad activity against diverse clinical *S. aureus* isolates. In vitro, FL-028 disrupted fibrin-encapsulated abscess communities and biofilms, reducing bacterial burdens by 3.4 and 2.3 log10, respectively, outperforming vancomycin. In a murine FRI model, FL-028 reduced bacterial burden approximately one log10 more effectively than vancomycin and eliminated abscess communities from infected tissues. Importantly, local administration showed no detectable adverse effects on bone healing.

These findings establish FibriLysins as a therapeutic platform that turns a key bacterial virulence mechanism against its host, illustrating how phage-derived antibacterials can exploit pathogen biology to overcome persistent, antibiotic-resistant staphylococcal FRI.

Reference #1

De Maesschalck, V. et al. FibriLysins disrupt Staphylococcus aureus biofilms and abscess communities. Natu

Reference #2

De Maesschalck, V., Gutiérrez, D., Paeshuyse, J., Lavigne, R. \textbackslash{}\& Briers, Y. Advanced engi

Reference #3

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