LYSG101: A Highly Potent Chimeric Bacteriophage Lysin Against *Staphylococcus aureus*

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We report the in vitro and in vivo efficacy of LYSG101, a chimeric bacteriophage lysin (cell wall hydrolase) being developed for *Staphylococcus aureus* infections, including methicillin-resistant *S. aureus* (MRSA). LYSG101 exhibits potent activity against a range of clinical isolates, including MRSA and coagulase-negative staphylococci (CoNS). In standard Cation Adjusted Mueller Hinton Broth (CAMHB) MIC50 was 1 µg/ml and MIC90 was 2 µg/ml for both *S. aureus* (n=142) and coagulase-negative staphylococci (CoNS, n=40); similar values were observed for methicillin-sensitive *S. aureus* (MSSA, n=77) and MRSA (n=69). LYSG101 is highly bactericidal, in CAMHB MBC50 was 2 µg/ml and MBC90 was 4 µg/ml for both *S. aureus* and CoNS; similar values were observed for MSSA and MRSA. In CAMHB supplemented with 25% horse serum (a CLSI-approved method for staphylococcal lysins) MIC50 was 0.0625 µg/ml for MSSA (n=158) and 0.03125 µg/ml for MRSA (n=114), and MIC90 was 0.125 µg/ml for both MSSA and MRSA; evaluation of a subset of the isolates in human serum showed equal or better results to CAMHB 25% horse serum. No resistant isolates were encountered during these studies. The rapid killing activity of LYSG101 was visualized by time-lapse microscopy, showing cell lysis within 20 seconds. These results were in agreement with time-kill assays, showing a rapid reduction in colony-forming units (CFU). Moreover, LYSG101 displayed potent anti-biofilm activity, disassembling biofilms within one hour at physiologically relevant concentrations. Additionally, LYSG101 was highly protective in murine lethal models of infection. These results demonstrate a highly favorable activity profile for LYSG101 compared to other staphylococcal lysins in clinical development.