Artilysins are a novel class of enzyme-based antibacterials that quickly kill (multidrug-resistant) *Pseudomonas aeruginosa* and their persisters: from concept to application.

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Artilysins represent a novel, promising class of antibacterials, exploiting the lytic power of bacteriophage-encoded endolysins. These enzymes are produced by bacteriophages at the end of their lytic replication cycle. Once the endolysins have passed through the cytoplasmic membrane, they degrade the peptidoglycan layer rapidly, causing osmotic lysis of the infected cell and liberation of the progeny. Purified endolysins have successfully been exploited to kill Gram-positive pathogens. However, Gram-negative bacteria are not susceptible due to the presence of a protective outer membrane.

Artilysins tackle this barrier. Selected polycationic or amphipathic peptides that locally destabilize the LPS layer of the outer membrane have been covalently fused to endolysins. These peptides promote the transfer of the fused endolysin to the peptidoglycan layer through the outer membrane. Time-lapse microscopy has shown that cells are killed within seconds due to active peptidoglycan degradation and subsequent cell lysis.

LoGT-008, a first-generation Artilysin combining a polycationic nonapeptide and the PVP-SE1gp146 endolysin, kills *P. aeruginosa in vitro* with a 4 to 5 log reduction within 30 minutes and rescues infected nematodes (*Caenorhabditis elegans*) to the same extent as ciprofloxacin. Infected human keratinocytes were treated with LoGT-008, resulting in a full protection of the keratinocytes against an otherwise cytotoxic dose (10^5 CFU/ml) , associated with a corresponding reduction in bacterial load [1].

A second generation Artilysin, Art-175, comprises the 29 amino acid SMAP-29 peptide and the KZ144 endolysin, and kills *P. aeruginosa* in a rapid and highly efficient way. Art-175 is refractory to resistance development during serial passaging to subinhibitory doses, while resistance mechanisms against 21 therapeutically used antibiotics do not give cross-resistance. Art-175 has a superior killing effect against persisters (> 4 log reduction), presumably because Artilysins do not require an active bacterial metabolism to exert their bactericidal effect [2].

In summary, Artilysins have a completely novel mode-of-action, are highly bactericidal within a few minutes, irrespective the presence of drug resistance mechanisms, show a low probability of resistance development, and have unprecedented bactericidal activity against persisters.

Keywords: Artilysin; endolysin; bacteriophage; persister

References

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