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Highly potent small molecules prevent tissue damage following *S. aureus* infection by inhibiting α-hemolysin

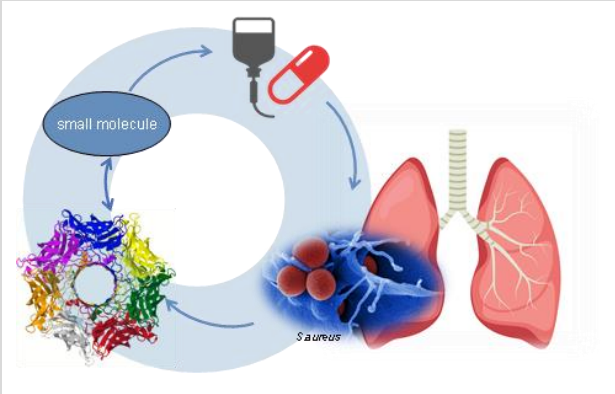
Keywords: Staphylococcus aureus, MRSA, HAP, VAP, alpha-hemolysin, small molecule, inhibitor

INVENTION NOVELTY

Provided are novel inhibitors of α-hemolysin and the use thereof for the prophylaxis and treatment of infections caused by *Staphylococcus aureus*, especially *S. aureus* lung infections.

VALUE PROPOSITION

Hospital-acquired bacterial pneumonia is the most frequent nosocomial infection, classified as HAP (developed in hospitalized patients), and VAP (occurs in patients who have received mechanical ventilation). Both diseases have a high mortality rate (>20%) despite of adequate antibiotic therapy and require substantial health resources. *S. aureus* is among the most common pathogens associated with hospital acquired pneumonia worldwide. Due to the global emergence of resistance to commonly used antibiotics, such MRSA strains are a major problem in hospitals, resulting in mortality as high as 56%. To meet the limited effectiveness of available standard-of-care treatments, an improvement of current treatment regimens is critically needed for patients with HAP/VAP caused by *S. aureus*. However, an improvement cannot be achieved by killing the pathogen with antibiotics alone but require therapies preventing or ameliorating the disease pathology on the host side. A highly promising and clinically validated approach is to block the key virulence factor α-hemolysin (Hla), leading to a decreased capacity of *S. aureus* to colonize the lungs, which stops pathogenesis until the host immune response or antibiotics eradicate the bacteria.



TECHNOLOGY DESCRIPTION

The invention relates to novel inhibitors of virulence factor α-hemolysin (Hla) which is an exotoxin of *S. aureus*. Hla initially exists as a monomer. On contact with host cells, it forms pores in their cell membrane by heptamerization. Through these pores, the cell loses low-molecular metabolites; in addition, ionic homeostasis is disturbed. In infections, these processes lead to cell and tissue damage and to strong inflammatory reactions. These are often considered the actual cause of the relatively high lethality of, for example, pneumonia caused by *S. aureus*. The inventive small molecule inhibitors interact with Hla and block the detrimental effects of the toxin on all relevant human cell types.

COMMERCIAL OPPORTUNITY

The small molecule inhibitors are developed for pre-emptive and/or adjunctive treatment of infections caused by *Staphylococcus aureus*, especially *S. aureus* lung infections. The technology is offered for co-development and/or licensing.

DEVELOPMENT STATUS

In context of ongoing SAR studies more than 400 derivatives have been generated and thoroughly characterized. Very promising molecules with high cellular activity in the low nanomolar range and neglectable cytotoxicity have been identified. The compounds are well-tolerated *in vivo*. PK studies and positive *in vivo* proof-of-concept studies in lung infection models demonstrating efficacy in combination and as a standalone agent are available.

PATENT SITUATION

A European priority application was filed on July 8, 2021 (EP21184557.3)

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