POLSKY Center for Entrepreneurship and Innovation
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Small Molecule Treatment for *Staphylococcus aureus* Infections

SUMMARY

Dr. Juliane Bubeck Wardenburg has developed a novel anti-infective for the treatment of *Staphylococcus aureus* (*S. aureus*) lung or skin and soft tissue infections (SSTIs) such as abscesses and cellulitis. The inhaled or topical delivery of small molecule ADAM10 inhibitors blocks bacterial infection, reduces disease severity, and promotes the healing process while avoiding common antibiotic resistance mechanisms.

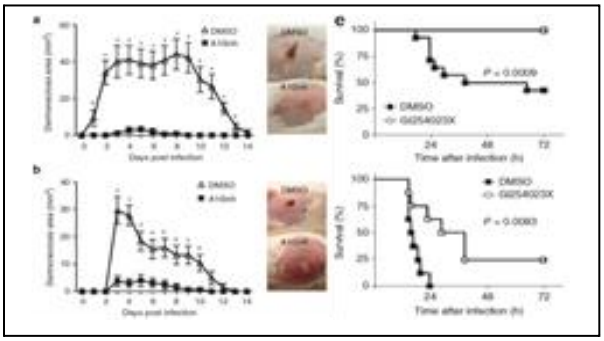
KEY RESULTS

The host metalloprotease, ADAM10, was identified as a critical target of α-hemolysin, a cytoxic agent released by S. aureus to perforate host cell membranes. Inhibition of ADAM10 using small molecule ADAM10 inhibitors was shown in murine models to reduce infection severity, promote healing, and reduce the severity of recurrent S. aureus skin infections. Pre-treatment of mice with an ADAM10 inhibitor 3-5 days prior to lung infection protected mice in a lethal challenge model.

ADVANTAGES

- Reduces severity of recurrent SSTI infections.
- Anti-infective (but not antibiotic) host-directed strategy avoids the development of resistant S. aureus strains.
- Inhaled or topical treatment delivers the therapeutic directly to the local site of infection to provide a high therapeutic index.

ADAM10 inhibitor protects against Hla-induced skin and soft tissue infection



*Left: Skin Infection Model (a) Systemic Delivery: Dermonecrosis area recorded from wild-type mice receiving either the vehicle (DMSO) or ADAM10 inhibitor (GI254023X) treatment intraperitoneally; (b) Topical Delivery: Dermonecrosis area recorded from wild-type mice receiving either the vehicle (DMSO) or GI254023X treatment topically. *P<0.001*

Right: Lung Infection (c) Mortality curves in mice treated with intraperitoneal injection of DMSO vehicle or GI254023X prior to infection.

APPLICATIONS

- Inhaled formulation for pneumonia prevention and treatment, for example, in the ICU.
- Topical formulation for prevention and treatment of SSTIs.

TECHNICAL DESCRIPTION

Staphylococcus aureus infection is a major public health challenge. 500,000 individuals contract *S. aureus* infections and approximately 20,000 die of their infections per year in the United States alone. The pathogen secretes α-hemolysin, a pore-forming cytotoxin that contributes to the pathogenesis of pneumonia and skin and soft tissue infections (SSTI) by facilitating bacterial invasion through epithelial barriers, such as those present in the lung or skin. Dr. Bubeck-Wardenburg and her team have identified new therapeutic molecules to block the interaction between the pathogenically secreted α-hemolysin and the host ADAM10, thereby inhibiting the ability of α-hemolysin to perforate and destroy host cells.

REFERENCE
UCHI 1971

DEVELOPMENT STAGE
In vivo animal models

THERAPEUTIC AREAS
Lung, soft tissue infections

PUBLICATION
Inoshima et al. Nat. Med. 17(10) 2011

Powers ME et al. J Infect Dis. 2012

INTELLECTUAL PROPERTY
US Patent Application No. 13/884,502
EP Patent Application No. 11839643.1

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