Efficacy in Treating Bacterial Infection

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Technology description

A compound that inhibits the invasion of host cells and decreases intracellular persistence ofStaphylococcus aureus
The goal is to develop host-directed therapies that limit host cell invasion to break the cycle of recurrent infection. Researchers identified ML141 as a small molecule inhibitor that decreases host cell invasion in a dose-dependent, reversible manner [2]. Host cell viability and bactericidal assays indicated no detectable decrease in host or bacterial viability, indicating an underlying mechanism of inhibition through non-cytotoxic and non-bactericidal activities. Structural analogs were synthesized to improve bioavailability and are well positioned for examining efficacy in recurrent infection.

Background

Staphylococcus aureusis the most common agent in systemic infection and in the biofilm-mediated infection of implanted medical devices in the United States. Infections byStaphylococcus aureusdevelop repeatedly in individuals with chronic lung disease, including chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) [1]. Recently, treatment ofS. aureushas been complicated by the emergence of antibiotic resistance, an increase in elderly, immunocompromised populations of people, and prevalence in the use of surgically-implanted devices. Additionally, both resistant and susceptible strains ofS. aureusare capable of persisting asymptomatically for months to years after antimicrobial therapy is discontinued. Severe infection fromS. aureuscauses a number of chronic health problems including endocarditis, osteomyelitis, and recurrent lung infection. Severe infection also results in high mortality rates of 11-43%. The current cost-of-care of infection by methicillin resistantS. aureus, or MRSA, alone is estimated at $10 billion annually, a staggeringly high cost. Currently, options for improving treatment ofS. aureusinfections include the creation of new antibiotics and the development of adjunctive therapeutics.

Technology Description

A collaboration of researchers at the University of New Mexico and Ball State University have discovered a compound that inhibits the invasion of host cells and decreases intracellular persistence ofStaphylococcus aureus. It has also been discovered that using this particular compound at a certain host cell activation site decreases not only the chance of invasion by bacterial pathogens, but by viral

pathogens as well by inhibiting both uptake and replication. Such a discovery may prove to be a central target in developing aggressive new treatment strategies for invasive infection ofS. aureusand other pathogens.

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Underlying Pharmacology

ML141 is an allosteric inhibitor that dissociates GTP and GDP with specificity within the activation site of human CDC42 [3]. Our previous work had suggested a central regulatory role for hCDC42 in the endocytic pathway that is exploited byS. aureusto invade host cells [4]. We found ML141 decreases formation of the a5b1 integrin receptor complexes used byS. aureusto invade [2]. We also found that ML141 decreases host cell binding to fibronectin, the host ligand used byS. aureusto engage the integrin receptor. Thus, ML141 decreases invasion byS. aureusin part by impeding appropriate formation and function of the integrin complex needed byS. aureusto invade.

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Application area

May be used in the pharmaceutical industry to develop new, more effective antibiotics

Provides a novel strategy in the treatment of invasive infection ofS. aureusand other pathogens

Suggests new avenues for research regarding host immune responses and compound development for treatment of infection

Helps to limit populations of persisting bacteria, suggesting a new therapeutic approach for chronic, recurrent infections in: chronic obstructive pulmonary disease (COPD) and cystic fibrosis, prosthetic device implants, osteomyelitis, tonsillitis, infective endocarditis, rhinosinusitis

Institution

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