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Inhibition of Galectin 3 Binding to the Airway Epithelial Surface to Treat or Prevent Septic Shock Resulting from Influenza and Subsequent Pneumococcal Pneumonia Infection

Summary

The main cause of death during influenza pandemics is *Streptococcus pneumoniae* co-infection, which results in hyperinflammatory response leading to sepsis. While the exact mechanism behind this complication is not understood, influenza infection predisposes patients to pneumococcal pneumonia that often progresses to uncontrolled hypercytokinemia. The cellular response to influenza and streptococcal co-infection is varied, involving innate and adaptive immune mechanisms. Galectins, glycan-binding proteins, are involved in the innate immune response to pneumococcal infection, immune homeostasis, and in the recognition of glycans on viral and bacterial surfaces. UMB researchers have demonstrated that the activity of Galectin 3 (Gal3) at the airway epithelial surface modulates intracellular pathways that lead to the dysregulated expression and release of pro-inflammatory cytokines. As such, disruption of the binding of Gal3 to the airway epithelial surface can prevent and treat the ensuing pro-inflammatory response and the development of sepsis and septic shock. To this end, they have developed novel Thomsen-Friedenreich multivalent lactose-based and cyclodextrin-based synthetic inhibitors of Gal3.

Key Investigator
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Field
Therapeutics

Technology
Novel method and compounds for preventing sepsis in patients with influenza infection

Advantages
Novel inhibitors avoid immunogenicity

Increased galectin binding affinity

Status
Available for licensing
Available for sponsored research

UMB Docket Reference
GV-2015-133

External Reference
Wang H., et al. (2013) *Bioorg Med Chem.* 21(7):2037-2044.

Nita-Lazar M., et al. (2015) *Mol Immunol.* 68:194-202.

Nita-Lazar M., et al. (2015) *Mol Immunol.* 65 (1):1-16.

Market

During the 2015-2016 flu season, there were an estimated 310,000 people hospitalized for flu-related illness. Although the majority of deaths with typical seasonal influenza are estimated to occur in elderly subjects (80% are age 65 or older), most recent pandemic strains have had extensive morbidity in younger individuals. The 2009 H1N1 pandemic resulted in 64-96% of pediatric and adult patients admitted to ICUs requiring mechanical ventilation. Among hospitalized flu patients in the US, sepsis is associated with a 20-30% risk of death. Current treatments for influenza-associated sepsis are predominantly supportive- broad-spectrum antibiotics, fluids, oxygen, blood transfusion, and organ support as needed. There are no approved targeted therapies. The prevention and early identification (and therefore treatment) of sepsis in vulnerable patients, such as those with influenza and streptococcal infections, would greatly decrease these healthcare costs. It has been estimated that if the US achieved earlier sepsis identification and evidence-based treatment, there would be 92,000 fewer deaths annually, 1.25 million fewer hospital days annually, and reductions in hospital expenditures of over $1.5 billion.

Technology

Novel, Gal3 inhibitors include synthetic multivalent neoglycoproteins such as glycopeptides rich in Thomsen-Friedenreich disaccharide and multivalent lactose-based compounds. Several synthetic multivalent inhibitors have been designed, validated, and shown to block the binding of Gal3 to its carbohydrate ligands. A glycopeptide rich in Thomsen-Friedenreich disaccharide has also been designed and tested. This compound was found to effectively inhibit Gal3-mediated cell adhesion with picomolar affinity.

Technology Status

The inhibition of Gal3 binding by these novel inhibitors has been tested in immobilized adenocarcinomic human alveolar basal epithelial cells (A549) and a prostate cancer cell line (PC3).

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