Abstract
Sepsis, the tenth leading cause of death in the United States, is a whole-body inflammatory response to infection. Sepsis leads to septic shock, a condition with a 30-40% mortality rate caused by multiple organ failure and development of hypotension. Lack of understanding of the pathophysiology of sepsis limits successful treatment options. Gram-negative bacteria are a major cause of sepsis. The outer membrane of Gram-negative bacteria contains lipopolysaccharide (LPS). LPS is recognized by a receptor complex expressed by certain immune cells that includes the transmembrane glycoprotein, Toll-like receptor 4 (TLR4), and myeloid differentiation factor-2 (MD-2). Over-stimulation of immune cells by LPS through TLR4-MD-2 results in sepsis. TLR4-mediated activation of immune cells is also responsible for allergic contact dermatitis due to nickel, a common and less fatal condition than sepsis. The crystal structure of TLR4-MD-2-LPS has elucidated residues involved in LPS binding to TLR4/MD-2 and in TLR4 dimerization, which are essential events involved in immune cell activation and induction of sepsis. A better understanding of interactions between TLR4, LPS and MD-2 will help create better drugs to disrupt the interactions. The Laconia SMART (Students Modeling A Research Topic) Team used 3-D printing technology to model the TLR4 dimer in collaboration with MSOE.

Introduction
Sepsis is an overwhelming, whole body inflammatory response to an infection, which if left unresolved progresses to severe sepsis, a state of inflammation and organ failure.

The Clinical Burden of Sepsis
Common: There are 500,000 - 750,000 cases per year in US1,2
Expensive: The estimated annual cost of treatment in the US is estimated at $17 billion2
Fatal: 30-40% of patients with severe sepsis will die1
Severe sepsis is among the leading causes of death in non-coronary intensive care units.1
Sepsis is the 10th leading cause of death in United States3
About 50% of sepsis cases are caused by Gram-negative bacteria1

Recognition of Foreign Pathogens by the Innate Immune System
- Lipopolysaccharide (LPS), which is a component of Gram-negative bacteria is an example of a PAMP
- Constitutive - always expressed
- Evolutionarily conserved - present on all pathogens of that type
- Foreign - expressed on microbes but are absent from the host

LPS-Induced TLR4-Mediated Cellular Activation
1. Gram negative bacteria such as E. coli are lysed by cells of the innate immune system resulting in the release of LPS from the outer membrane.
2. Free LPS attaches to LPS binding protein (LBP).
3. The LBP-LPS complex binds to a CD14 molecule on the plasma membrane of an innate immune cell and transfers LPS to a TLR-4/MD-2 molecule.
4. The binding of LPS to TLR4/MD2 facilitates the dimerization of TLR4 molecules leading to intracellular signal transduction resulting in the transcription and translation of cytokines. Cytokines recruit and activate other immune cells. Over-production of cytokines results in sepsis.

Nickel Allergy
- Nickel contact dermatitis is initiated by the binding of inorganic nickel to His 456 and 458 (green in B, left) on adjacent TLR4 molecules resulting in their dimerization and signaling.
- According to UW Health nickel allergy affects 10% of the U.S. population.

Conclusion
- Currently, the number of cases of sepsis in the United States is on the rise, and there are no effective treatments due to a lack of understanding of the pathophysiology of the disease.
- Without a cure for sepsis, it will continue to take an increasing toll on the human population, both financially and in terms of human lives.
- Understanding the structures and interactions between TLR4/MD-2 complex and LPS could lead to therapeutic advances.

Sources
4. Rothberg, M., Nature Immunology, 2010; 11:781-782

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