A Novel Method of Treating or Preventing Sepsis

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Background

Sepsis is a major challenge in the intensive care unit, where it is one of the leading causes of death. It arises unpredictability and can progress rapidly. *Staphylococcus aureus* and *Escherichia coli* are among the most common microorganisms isolated from sepsis patients. There is an estimated 20 million new cases of sepsis worldwide per year with a mortality rate of up to 50%. Those who survive sepsis recover normally however often require life-long follow-on treatment. Currently there are no approved specific treatments for the underlying pathophysiology of sepsis and therefore the management plan focuses on reducing the infection through use of aggressive intravenous antibiotic therapy often delivered in high concentrations for long periods of time. The use of antibiotics in the treatment of sepsis is not a reliable long term solution due to the rapid global emergence of antibiotic resistant strains of bacteria.

The vascular endothelium is a major target of sepsis-induced events and endothelial damage accounts for much of the pathology of septic shock. During sepsis the vascular endothelial barrier breaks down leaking fluid into the extravascular space leading to life threatening oedema in the lungs, kidney and brain of septic patients which results in multi-organ failure. The inflammatory response also plays a key role in the sepsis phenotype and an excessive or sustained inflammatory response contributes to the tissue damage and death.

The Technology

The Cardiovascular Infection Research Group in RCSI has demonstrated that cilengitide prevents both *S. aureus* and *E. coli* from binding to the endothelium thus inhibiting early signal generation that results in endothelial cell dysfunction in sepsis.

S. aureus clumping factor A uses plasma fibrinogen to crosslink to αVβ3, a fibrinogen receptor highly expressed on vascular endothelial cells. In contrast, *E. coli* binds directly to αVβ3 expressed on vascular endothelial cells (in the absence of plasma proteins). Once these interactions occur it generates an intracellular signal in the endothelial cell (via αVβ3) that leads to dysregulation [inhibition of proliferation, apoptosis and loss of barrier function (increased vascular permeability)]. These functional responses are consistent with the sepsis phenotype observed clinically. Cilengitide prevents the interaction between the bacteria (*S. aureus* or *E. coli*) and endothelial cells.

In vitro characterisation of cilengitide

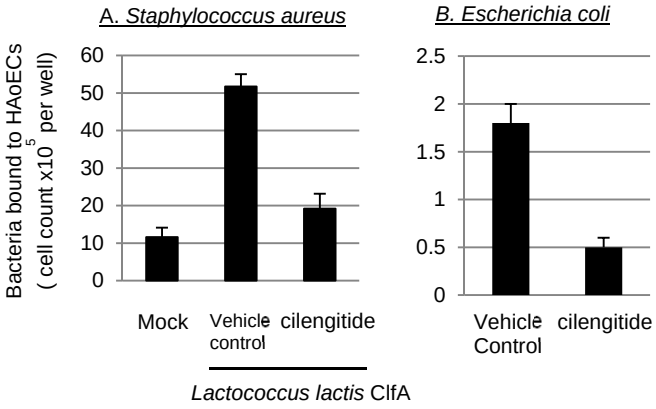

Figure 1. Cilengitide inhibits *S. aureus* ClfA and *E. coli* from binding to human vascular endothelial cells, P<0.01.

In vivo characterisation of cilengitide

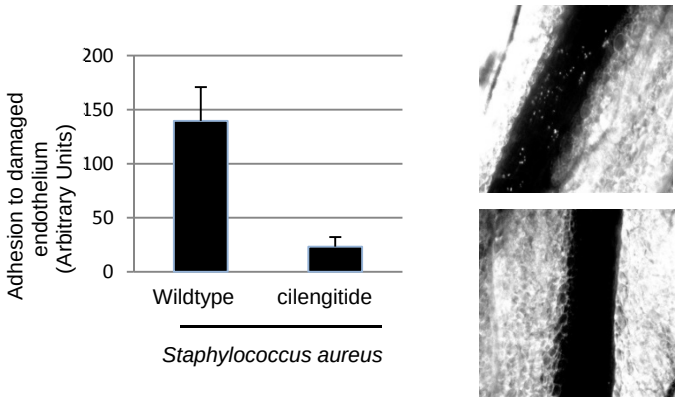

Figure 2. Cilengitide inhibits *S. aureus* binding to endothelial cells *in vivo* using a mesenteric perfusion mouse model P<0.001.

Advantages

- Cilengitide offers a novel therapeutic option for sepsis that acts early to prevent bacteria binding to the host vascular endothelial cell in the first place and preventing endothelium break down.
- This novel approach avoids selective pressure on bacteria which has led to multi drug resistance
- Cilengitide blocks bacteria binding to the endothelium thus preventing the infection from progressing to septic shock and a life threatening situation as a result of multi-organ failure.

Patent

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