bleeding. Sepsis can progress rapidly and the relatively slow mode of action of APC based sepsis therapeutics is a disadvantage relative to the rapid progression of acute sepsis. Xigris was withdrawn from sale on October 25, 2011.

Histones are small basic proteins that function in the cell nucleus to regulate gene expression and complex with DNA to form nucleosomes which assemble into chromatin structure. Xu *et al*, (Nat Med. 2009. **15**:1318-21) have reported a cytotoxic activity for histones released in response to inflammatory processes with the extracellular histones acting as mediators of endothelial cell dysfunction, organ failure and death in sepsis.

The present invention is predicated on the finding that polyanions can complex with extracellular histones in the circulation of a living animal and inhibit their cytotoxic activity. In addition the polyanions can complex with extracellular histones and prevent histone accumulation in organs. Further, these polyanions may have insignificant anticoagulant properties.

Summary

The present inventors have identified that the cytotoxic activity of extracellular histones and extracellular histone accumulation in an organ can be inhibited by the administration of an oligosaccharide polyanion. The administration of an oligosaccharide polyanion offers a means of ameliorating at least some of the deficiencies of currently available sepsis treatments. Further, the use of a nanoparticle labelled histone provides a means for screening for compounds capable of inhibiting histone accumulation in organs.

There is provided a method of inhibiting the cytotoxic activity of extracellular histones in a subject, said method comprising administering an effective amount of a polyanion to said subject.

There is provided a method of inhibiting extracellular histone accumulation in a subject, said method comprising administering an effective amount of a polyanion to said subject.

There is provided a method of treating sepsis by inhibiting the cytotoxic activity of extracellular histones in a subject, said method comprising administering an effective amount of a polyanion to said subject.

There is provided the use of an effective amount of a polyanion for the manufacture of a medicament for the treatment of sepsis by inhibiting the cytotoxic activity of extracellular histones.

There is provided an effective amount of a polyanion for use in the treatment of sepsis.

In an aspect, there is provided the use of an effective amount of a polyanion for the manufacture of a medicament for the treatment of sepsis by inhibiting the cytotoxic activity of extracellular histones in a subject having sepsis, wherein the polyanion does not have substantial anticoagulant activity such that the polyanion increases prothrombin time (PT), partial thromboplastin time (PTT), activated partial thromboplastin time (APTT), thrombin clotting time (TCT), or activated clotting time (ACT) by 0 to 10% of the normal range; and

wherein the polyanion is a polyanionic oligosaccharide having the general structure (I):

$$A—(B)_n—D \qquad (I)$$

wherein A and B are each independently a cyclic monosaccharide or a cyclic deoxy monosaccharide;

D is a cyclic monosaccharide, a cyclic deoxy monosaccharide, a ring-opened monosaccharide, or a sugar alcohol;

n is an integer selected from 0, 1, and 2; and

wherein each of the cyclic monosaccharide, the cyclic deoxy monosaccharide, the ring-opened monosaccharide, or the sugar alcohol is independently optionally substituted with OSO_3^-, COO^-, OPO_3^-, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted aryl, or an optionally substituted aralkyl; and

wherein the polyanionic oligosaccharide includes at least two anionic substituents selected from the group consisting of OSO_3^-, COO^- and OPO_3^-.