Claims

1. ~~A method of inhibiting the cytotoxic activity of extracellular histones in a subject, said method comprising administering an effective amount of~~ Use of an effective amount of a polyanion in the manufacture of a medicament for inhibiting the cytotoxic activity of extracellular histones in a subject~~to said subject~~, wherein the polyanion does not have substantial anticoagulant activity; 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, 2, 3, 4, 5, 6, 7 and 8; 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^-.

2. ~~A method of inhibiting extracellular histone accumulation in a subject, said method comprising administering an effective amount of~~ Use of an effective amount of a polyanion for the manufacture of a medicament for inhibiting extracellular histone accumulation in a subject~~ to said subject~~, wherein the polyanion does not have substantial anticoagulant activity; 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, 2, 3, 4, 5, 6, 7 and 8; 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^-.

3. Use ~~A method of treating sepsis by inhibiting the cytotoxic activity of extracellular histones in a subject, said method comprising administering an effective amount~~ 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~~to said subject~~, wherein the polyanion does not have substantial anticoagulant activity; 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, 2, 3, 4, 5, 6, 7 and 8; 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^-.

4. ~~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, wherein the polyanion does not have substantial anticoagulant activity; and~~

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

~~$A-(B)_n-D$ (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, 2, 3, 4, 5, 6, 7 and 8; 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^-.~~

~~5.~~ The ~~method~~ use of any one of claims 1 to 3 ~~or the use of claim 4~~ wherein the polyanion is substantially non-immunogenic.

~~5~~6. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the cyclic monosaccharide is selected from the group consisting of glucose, galactose, fructose, ribose, arabinose, xylose, lyxose, allose, altrose, mannose, gulose, idose, talose, ribulose, xylulose, psicose, sorbose, tagatose and sedoheptulose.

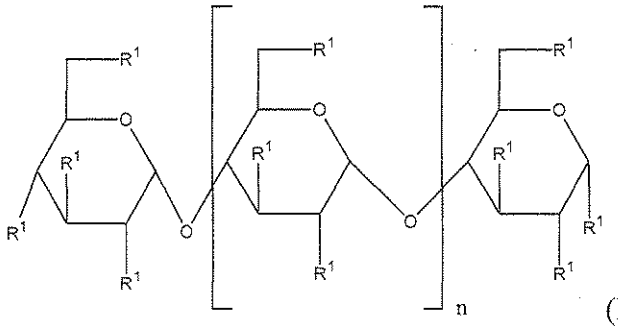
~~6~~7. The ~~method or~~ use of any one of claims 1 to ~~5~~6 wherein the cyclic monosaccharide is selected from the group consisting of glucose, galactose and fructose.

~~8~~7. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the cyclic deoxy monosaccharide is selected from the group consisting of fucose, deoxyribose and rhamnose.

98. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the sugar alcohol is selected from the group consisting of glycol, glycerol, erythritol, threitol, ribitol, arabitol, xylitol, sorbitol (glucitol), mannitol, dulcitol (galactitol), iditol and fucitol.

~~109~~. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the ring-opened monosaccharide is selected from the group consisting of glucose, galactose, fructose, erythrose, threose, erythrulose, ribose, arabinose, xylose, lyxose, allose, altrose, mannose, gulose, idose, talose, ribulose, xylulose, psicose, sorbose, tagatose and sedoheptulose.

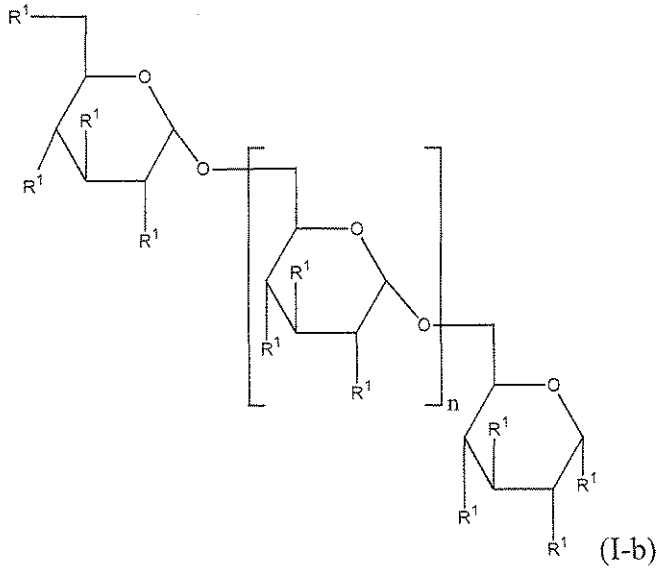
~~1110~~. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the polyanionic oligosaccharide has the general structure (I-a):



(I-a)

wherein each R^1 is independently selected from OSO_3^-, COO^-, OPO_3^-, OH or H; and n is an integer between 0, 1, 2, 3, 4, 5, 6, 7, and 8; and wherein at least two of R^1 are selected from the group consisting of OSO_3^-, COO^-, and OPO_3^-.

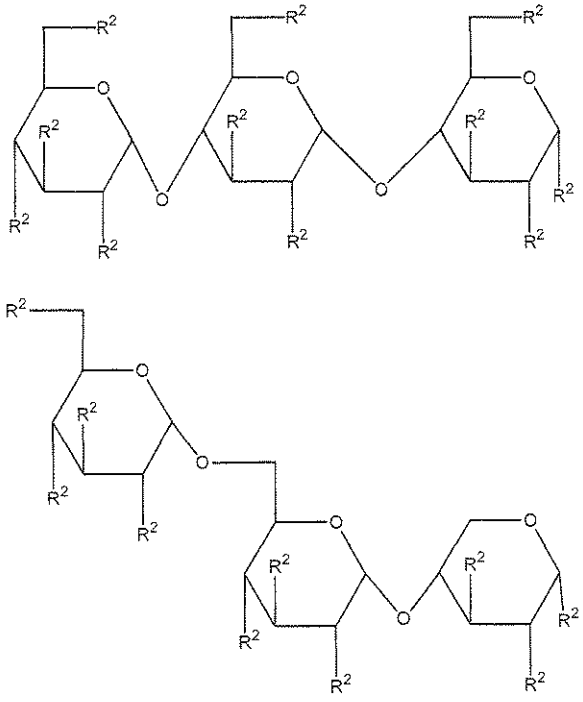
1112. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the polyanionic oligosaccharide has the general structure (I-b):

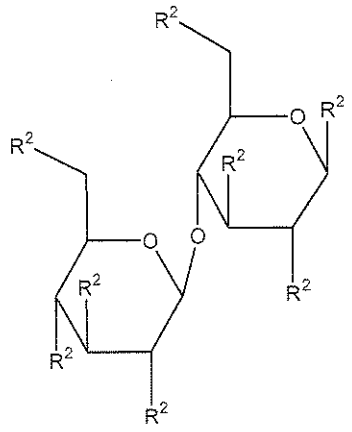


(I-b)

where each R^1 is independently selected from OSO_3^-, COO^-, OPO_3^-, OH or H; and n is an integer between 0, 1, 2, 3, 4, 5, 6, 7, and 8; and wherein at least two of R^1 are selected from the group consisting of OSO_3^-, COO^-, and OPO_3^-.

1312. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the polyanionic oligosaccharide is selected from the group consisting of:





wherein each R^2 is independently selected from OSO_3^-, COO^-, OPO_3^-, OH or H; and wherein at least two of R^2 are selected from the group consisting of OSO_3^-, COO^-, and OPO_3^-.

~~14~~13. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the polyanionic oligosaccharide is selected from the group consisting of maltose sulfate, maltotriose sulfate, maltotetraose sulfate, maltopentaose sulfate, maltohexaose sulfate, maltoheptaose sulfate, maltooctaose sulfate, maltononaose sulfate and maltodecaose sulfate, panose sulfate, isomaltotriose sulfate, erlose sulfate, cellobiose sulfate and raffinose sulfate.

~~15~~14. The ~~method~~ use of any one of claims 1 to 3 ~~or use of claim 4~~ wherein the polyanionic oligosaccharide is cellobiose sulfate.