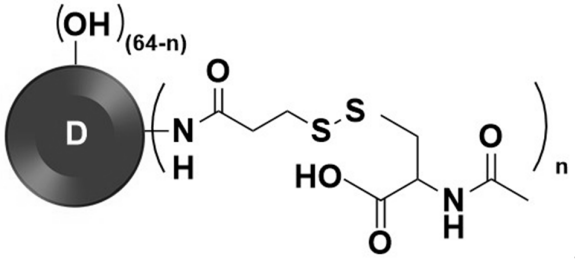
Claims

1. Use of a composition in the manufacture of a medicament for treating or preventing one or more symptoms of inflammation associated with acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) in a subject in need thereof; and wherein the composition comprises:

dendrimer-N-acetyl cysteine compounds of the formula:



,

wherein D comprises a PAMAM dendrimer, and n is 15-25;

histidine buffer; and

trehalose dihydrate.

2. The use of claim 1, wherein the inflammation is systemic inflammation involving multiple organs, tissues, and/or cell types of a body of the subject.

3. The use of claim 1 or 2, wherein the inflammation is associated with sepsis or septic shock.

4. The use of any one of claims 1-3, wherein the inflammation is caused by any mechanism of macrophage activation including macrophage activation syndrome.

5. The use of any one of claims 1-4, wherein the inflammation is associated with multi-organ dysfunction including neuroinflammation.

6. The use of any one of claims 1-5, wherein the inflammation is associated with over-reactive M1 macrophages and/or elevations in proinflammatory markers selected from the group consisting of IL-6, CRP, ferritin, and IL-1b.

7. The use of any one of claims 1-6, wherein the inflammation is characterized by cytokine storm.

8. The use of any one of claims 1-7, wherein the inflammation is associated with acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS) associated with or arising from ventilator use, viral infection, sepsis, or systemic bacterial infections in a subject in need thereof have been established.

9. The use of claim 8, wherein the therapeutic agent is covalently conjugated, or intra-molecularly dispersed or encapsulated with in an amount effective to treat, alleviate or prevent one or more symptoms of acute lung injury or acute respiratory distress syndrome.

10. The use of claim 8 or 9, wherein the acute lung injury is ventilator-induced lung injury.

11. The use of claim 8 or 9, wherein the acute respiratory distress syndrome is caused by infection with a virus.

12. The use of claim 11, wherein the virus is SARS-COVID-2.

13. The use of any one of claims 1-12, wherein the composition is to be administered in an amount effective to reduce inflammation in the lung.

14. The use of any one of claims 1-13, wherein the composition is to be administered in an amount effective to reduce vascular leakage or vascular permeability in the lung, increase alveolar cell integrity or endothelial cell integrity in the lung, increase the ratio of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), increase pulse oximetry-based peripheral blood oxygen saturation (SpO_2)/FiO2 (SpO_2/FiO_2) ratios, and/or reduce bronchoalveolar lavage (BAL) protein levels or bronchoalveolar lavage cell count.

15. The use of any one of claims 1-14, wherein the composition is to be administered in an amount effective to reduce one or more pro-inflammatory cells, chemokines, and/or cytokines in the lung.

16. The use of claim 15, wherein the composition is to be administered in an amount effective to reduce one or more pro-inflammatory chemokines selected from the group consisting of MCP-1, CXCL-8, CXCL-1, CXCL-5, and CCL-2.

17. The use of claim 15, wherein the composition is to be administered in an amount effective to reduce one or more pro-inflammatory cytokines selected from the group consisting of C-reactive protein (CRP), ferritin, IL-6, TNF-α, IL-12, IL-1β, and IL-18.

18. The use of claim 15, wherein the one or more pro-inflammatory cells are M1-like macrophages.

19. The use of any one of claims 1-18, wherein the composition is formulated for intravenous, subcutaneous, or intramuscular administration.

20. The use of any one of claims 1-18, wherein the composition is formulated for delivery enterally or to a mucosal surface such as the lungs.

21. The use of claim 20, wherein the composition is to be administered via intravenous, subcutaneous, or intramuscular route.

22. The use of any one of claims 1-21, wherein the composition is to be administered prior to, in conjunction, subsequent to, or in alternation with treatment with one or more additional therapies or procedures.

23. The use of claim 22, wherein the one or more additional therapies are selected from the group consisting of antimicrobials, surfactant, and corticosteroids.

24. The use of claim 23, wherein the one or more additional procedures are selected from the group consisting of prone positioning, recruitment maneuver, inhalation of NO, extracorporeal membrane oxygenation (ECMO), intubation, and/or inhalation of PGI_2.

25. The use any one of claims 1-24, wherein the composition is in an amount between 0.1 mg/kg body weight of the subject, and 40 mg/kg body weight of the subject.

26. The use of claim 25, wherein the composition is in an amount between 2 mg/kg body weight of the subject, and 8 mg/kg body weight of the subject, and

wherein the composition is to be administered by subcutaneous injection.

27. The use of claim 25, wherein the dendrimer conjugated to N-acetyl cysteine is in an amount between 20 mg/kg body weight of the subject, and 40 mg/kg body weight of the subject, and

wherein the composition is to be administered by intravenous infusion.

28. The use of any one of claims 1-27, wherein the composition comprises:

200 mg/mL of the dendrimer-N-acetyl cysteine compound;

10 mM histidine, pH 5.5; and

4.4% trehalose dihydrate.

29. The use of any one of claims 1-27, wherein the composition comprises:

400 mg/mL of the dendrimer-N-acetyl cysteine compound;

20 mM histidine, pH 5.5; and

80 mg/mL trehalose dihydrate.

30. The use of any one of claims 1-27, wherein the composition comprises:

200 mg/mL of the dendrimer-N-acetyl cysteine compound;

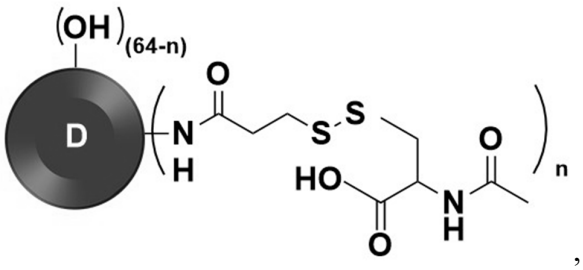
histidine buffer;

trehalose dihydrate; and

saline.

31. A pharmaceutical composition comprising:

dendrimer-N-acetyl cysteine compounds of the formula:



,

wherein D comprises a PAMAM dendrimer, and n is 15-25;

histidine pH 5.5; and

trehalose dihydrate.

32. The pharmaceutical composition of claim 31, wherein the composition is in the form of a solution.

33. The pharmaceutical composition of claim 32, wherein the solution is an aqueous solution.

34. The pharmaceutical composition of claim 32 or 33, wherein the solution comprises:

200 mg/mL of the dendrimer-N-acetyl cysteine compound;

10 mM histidine, pH 5.5; and

4.4% trehalose dihydrate.

35. The pharmaceutical composition of any one of claims 32-34, wherein the solution is in a volume between 0.1 mL and 10 mL, preferably 2.5 mL.

36. The pharmaceutical composition of claim 31, wherein the composition is a lyophilized powder.

37. The pharmaceutical composition of claim 31, wherein the composition comprises:

400 mg/mL of the dendrimer-N-acetyl cysteine compound;

20 mM histidine, pH 5.5; and

80 mg/mL trehalose dihydrate.

38. The pharmaceutical composition of claim 31, wherein the composition further comprises saline.

39. The pharmaceutical composition of claim 38, wherein the saline is an aqueous solution of 0.9% sodium chloride.

40. The pharmaceutical composition of claim 31, wherein the composition comprises:
200 mg/mL of the dendrimer-N-acetyl cysteine compound;
histidine buffer;
trehalose dihydrate; and
saline.

41. The use of any one of claims 1-30 or pharmaceutical composition of any one of claims 31-40, wherein the dendrimer-N-acetyl cysteine compounds are of the formula:

