uncontrolled feedback loop which further escalates the inflammatory immune response causing prolonged and excessive systemic inflammation and life-threatening pathologies [5-8].

[0004] ARDS can be triggered by direct or indirect lung injury. Examples of ARDS resulting from direct lung injury include pneumonia due to bacterial, viral, fungal, or opportunistic infections, pulmonary contusions, traumatic injuries, inhalation injury from chemicals, particulates, or other irritants, aspirations of gastric contents, and near drowning. Examples of ARDS resulting from indirect lung injury include hemorrhagic shock, pancreatitis, major burn injury, drug overdose, transfusion of blood products, cardiopulmonary bypass, sepsis, and reperfusion injury. The initial insult triggering ARDS, whether due to direct or indirect lung injury, causes pulmonary damage that elicits a robust and heightened immune response. This immune response involves activation of resident immune cells (*e.g.*, bronchoalveolar macrophages) that produce pro-inflammatory cytokines and chemokines immediately followed by the rapid influx of inflammatory monocytes and neutrophils into the lungs within 24 to 48 hours of initial injury. Once at the lungs, peripherally derived inflammatory monocytes and neutrophils respond to the local inflammatory milieu and further promote inflammation via production of pro-inflammatory cytokines (*e.g.*, IL-6, IL-β, IFN-γ, IP-10, TNF-α, and MCP-1), chemokines (*e.g.,* CCL-2, CXCL- 1, CXCL-2, and CXCL-5), oxidants (*e.g.*, ROS), proteins (*e.g.*, c-reactive protein), neutrophil extracellular traps (NETs), and proteases (*e.g* MMP-9) While a certain degree of inflammation is important for the resolution of lung injury, excessive and prolonged inflammation, especially in the case of ARDS, results in significant respiratory damage and is associated with life-threatening pathologies[1,2,4].

[0005] Current approaches for the treatment of CSS and ARDS rely on broad immune suppressants (*e.g* anti-IL1β, anti-IL-6, anti-TNFα, and steroids) which cause toxic side effects leading to increased risk of infections and even death. There is an urgent need for targeted therapies for resolving pathological hyperinflammation during CSS and ARDS without causing broad immune suppression.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a use of negatively charged particles in the manufacture of a medicament for treating acute respiratory distress syndrome (ARDS) or cytokine storm syndrome (CSS) in a subject, wherein the negatively charged particles are free from other therapeutically active agents.

[0005b] In another aspect of the present disclosure, there is provided a use of negatively charged particles that are free from attached or encapsulated drug, in the manufacture of a medicament for treating acute inflammation in hospitalized adults with systemic inflammation, sepsis, or pneumonia associated with respiratory viral infections in a subject in need thereof, wherein the negatively charged particles comprise one or more biodegradable, pharmaceutically acceptable polymers; and particles are to be administered at a dose of between 1 mg/kg to 10 mg/kg.

[0006] The present disclosure relates to a method of treating cytokine storm syndrome (CSS) and/or acute respiratory distress syndrome (ARDS) in a subject, the method comprising administering to the subject negatively charged particles having a negative zeta potential, wherein the negatively charged particles are free from another therapeutic agent. In one example of the method disclosed herein, the subject suffers from CSS and/or ARDS

resulting from one or more conditions selected from: a viral infection, a bacterial infection, a fungal infection, an opportunistic infection, sepsis, cytokine release syndrome (CRS), severe inflammatory response syndrome (SIRS), hypercytokinemia, macrophage activation syndrome (MAS), reactive hemophagocytic syndrome, secondary hemophagocytic lymphohistiocytosis (sHLH), aspiration of gastric contents, a traumatic injury, burn injury, pancreatitis, pulmonary contusion, hemorrhagic shock, near drowning, blood transfusion, inhalation injury, or combinations thereof.

[0007] In any one of the methods disclosed herein, administering the negatively charged particles in the subject reduces one or more symptoms of CSS and/or ARDS. In examples, the symptom is selected from one or more of: multi-organ dysfunction, brain damage, lung damage, liver damage, kidney damage, heart damage, edema, cerebral edema, pulmonary edema, alveolar edema, respiratory distress, hypoxemia, respiratory acidosis, hypertriglyceridemia, leukopenia, cytopenia, or elevated levels of inflammatory markers. In any one of the methods disclosed herein, the present disclosure relates to improving one or more symptoms associated with CSS and/or ARDS, comprising administering the negatively charged particles as disclosed herein. In examples, the symptom associated with ARDS includes shortness of breath, rapid breathing (tachypnea), labored breathing, requiring mechanical ventilation, muscle fatigue, general fatigue, low blood pressure, low blood oxygen levels (hypoxemia), discoloration of the skin, discoloration of the nails, respiratory acidosis, hypercapnia, dry cough, fever, chest pain, headache, inflammation of the lungs, fluid buildup in the lungs, atelectasis, crackling or bubbling sound in the lungs, fast pulse rate, dizziness, mental confusion, edema, pulmonary edema, and/or alveolar edema. In examples, the symptom associated with CSS and/or ARDS includes one or more selected from: lung inflammation, atelectasis, distressed breathing, fatigue, low blood pressure, fever, headache, hypoxemia, respiratory acidosis, hypercapnia, edema, pulmonary edema, or alveolar edema. In examples, the inflammatory marker is IL-1β, IL-2, IL-6, IL-8, TNF-α, IFN-γ, MCP-1, c-reactive protein, or ferritin.

[0008] In any one of the methods disclosed herein, CSS and/or ARDS is the result of a viral infection. In examples, the viral infection is due to a DNA virus, an RNA virus, and/or a retrovirus. In examples, the DNA virus is a single-stranded DNA (ssDNA) virus, or a double-stranded (dsDNA) virus, and the RNA virus is a double-stranded RNA virus, a single-stranded RNA (ssRNA) (+) virus, ssRNA (-) virus, or a circular ssRNA virus. In examples, the virus is a respiratory virus. In examples, the virus is selected from the group consisting Adeno- associated virus, Aichi virus, Australian Bat Lyssavirus, BK polyomavirus, Banna

virus, Barmah forest virus, Bunyavirus snowshoe hare, Cercopithecine herpes virus, Chandipura virus, Chikungunya virus, Cosavirus A, Cowpox virus, Coxsackievirus, Crimean-Congo hemorrhagic fever virus, Coronavirus, Dengue virus, Dhori virus, Dugbe virus, Duvenhage virus, Eastern equine encephalitis virus, Echovirus, Encephalomyocarditis virus, Epstein-Barr virus, European Bat Lyssavirus, GB virus C/Hepatitis G virus, Hantaan virus, Hendra virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis delta virus, Human adenovirus, Human astrovirus, Human coronavirus, Human cytomegalovirus, Human enterovirus 68,70, Human herpesvirus 1, Human herpesvirus 2, Human herpesvirus 6, Human herpesvirus 7, Human Immunodeficiency Virus (HIV), Human papillomavirus 1, Human papillomavirus 2, Human papillomavirus 16,18, Human parainfluenza virus, Human parvovirus B19, Human respiratory syncytial virus, Human rhinovirus, Human SARS coronavirus, Human spumarterovirus, Human T-lymphotropic virus, Human torovirus, Influenza A virus, Influenza B virus, Influenza C virus, Isfahan virus, JC polyomavirus, Japanese encephalitis virus, Junin arenavirus, KI Polyomavirus, Kunjin virus, Lagos bat virus, Lake Victoria Marburgvirus, Langat virus, Lassa virus, Lordsdale virus, Louping ill virus, Lymphocytic choriomeningitis virus, Machupo virus, Mayaro visu, MERS coronavirus, Measles virus, Mengo encephalomyocarditis, Merkell cell polyomavirus, Mokola virus, Molluscum contagiosum virus, Monkeypox virus, Mumps virus, Murray valley encephalitis virus, New York virus, Nipah virus, Norwalk virus, O'Nyong-nyong virus, Orf virus, Oropouche virus, Pichinde virus, Poliovirus, Punta toro phlebovirus, Puumala virus, Rabies virus, Rift valley fever virus, Rosavirus A, Ross river virus, Rotavirus A, Rotavirus B, Rotavirus C, Rubella virus, Sagiyama, Salivirus A, Sandfly fever sicilian virus, Sapporo virus, SARS coronavirus-2, Semliki forest virus, Seoul virus, Simian foamy virus, Simian virus 5, Sindbis virus, Southampton virus, St. Louis encephalitis virus, Tick-borne Powassan virus, Torque teno virus, Toscana virus, Uukuniemi virus, Varicella-zoster virus, Variola virus, Venezuelan equine encephalitis virus, WU polyomavirus, Yaba Monkey tumor virus, Yaba-like disease virus, Yellow fever virus, or Zika virus.

[0009] In any of the methods disclosed here, CSS and/or ARDS is the result of a bacterial infection. In examples, the bacterial infection is due to Staphylococcus, Streptococcus, Mycobacterium, Bacillus, Salmonella, Vibrio, Spirochete, Neisseria, Diplococcus, Pseudomonas, Clostridium, Treponaema, Spirillum, or combinations thereof.

[0010] In any of the methods disclosed here, CSS and/or ARDS is due to one or more immune targeted therapies. In examples, the immune targeted therapy an antibody, a protein therapeutic, a peptide, a cytokine, an immune signaling modulator, an mRNA, an

oncolytic virus, or a cell-based therapy. In examples, the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a tri-specific antibody, or a bi-specific T-cell engager (BiTE) antibody. In examples, the antibody targets one or more of: CD2, CD3, CD20, CD27, CD28, CD30, CD40L, CD137, OX-40, GITR, LIGHT, DR3, SLAM, or ICOS. In examples, the cytokine is selected from IFN-α, IFN-γ, IL-2, IL-10, IL-12, IL-15, IL-15/IL-15Rα, IL-18, IL-21, GM-CSF, or variants thereof. In examples, the immune signaling modulator targets one or more of: IL-1R, IL-2Rα, IL-2Rβ, IL-2Rγ, IL-3Rα, CSF2RB, IL-4R, IL-5Rα, CSF2RB, IL-6Rα, gp130, IL-7Rα, IL-9R, IL-10Rα, IL-10Rβ, IL-12Rβ1, IL-12Rβ2, IL-13Rα1, IL-13Rα2, IL-15Rα, IL-21R, IL23R, IL-27Rα, IL-31Rα, OSMR, CSF-1R, GM-CSF-R, cell-surface IL-15, IL-10Rα, IL-10Rβ, IL-20Rα, IL-20Rβ, IL-22Rα1, IL-22Rα2, IL-22Rβ, IL-28RA, TLR, JAK, BTK, TYK, SYK, MAPK, PI3K, NFκB, NFAT, STAT, or a kinase. In examples, the cell-based therapy comprises allogenic, autologous, or iPSC-derived cells. In examples, the cell-based therapy comprises one or more of: T-cells, NK-cells, red blood cells, stem cells, antigen-presenting cells, macrophages, or dendritic cells.

[0011] In any one of the methods disclosed herein, the negatively charged particle comprises one or more of: polyglycolic acid (PGA), polylactic acid (PLA), polystyrene, poly (lactic-co- glycolic acid) (PLGA), chitosan, polysaccharide, a lipid, diamond, iron, zinc, cadmium, gold, or silver. In examples, the negatively charged particle is poly (lactic-co-glycolic acid) (PLGA) particle. In examples, the PLGA particle comprises a ratio of poly lactic acid : poly glycolic acid ranging from about 90:10 to about 10:90, from about 50:50 to about 90:10, from about 50:50 to about 80:20; from about 90:10 to about 50:50, or from about 80:20 to about 50:50. In examples, the negatively charged particle comprises 50:50 poly lactic acid : poly glycolic acid.

[0012] In any one of the methods disclosed herein, the negatively charged particle is surface- functionalized by the addition of one or more carboxyl groups on the particle's surface.

[0013] In any one of the methods disclosed herein, the negatively charged particle has a zeta potential between about -100 mV and about -1 mV. In examples, the negatively charged particle has a zeta potential between about -80 mV and about -30 mV.

[0014] In any one of the methods disclosed herein, the negatively charged particle has a mean diameter in the range of about 0.1 μm to about 10 μm. In examples, the negatively charged particle has a mean diameter in the range of about 300 nm to about 800 nm.

[0015] In any one of the methods disclosed herein, the negatively charged particles are administered intravenously.

What is claimed is:

1. Use of negatively charged particles in the manufacture of a medicament for treating acute respiratory distress syndrome (ARDS) or cytokine storm syndrome (CSS) in a subject, wherein the negatively charged particles are free from other therapeutically active agents.

2. The use of claim 1, wherein the ARDS or the CSS are the result of direct lung-injury or indirect lung- injury.

3. The use of claim 1, wherein the ARDS or the CSS are the result of pneumonia, lung inflammation, bacterial infection, viral infection, fungal infection, opportunistic infection, sepsis, aspiration of gastric contents, traumatic injury, burn injury, pancreatitis, pulmonary contusion, hemorrhagic shock, near drowning, blood transfusion, inhalation injury, cytokine release syndrome (CRS), severe inflammatory response syndrome (SIRS), hypercytokinemia, macrophage activation syndrome (MAS), reactive hemophagocytic syndrome, secondary hemophagocytic lymphohistiocytosis (sHLH), a traumatic injury, or combinations thereof.

4. The use of claim 3, wherein the ARDS or the CSS are the result of the viral infection, and wherein the viral infection is due to a DNA virus, an RNA virus, or a retrovirus.

5. The use of claim 4, wherein the DNA virus is a single-stranded DNA (ssDNA) virus, or a double-stranded (dsDNA) virus, and wherein the RNA virus is a double-stranded RNA virus, a single-stranded RNA (ssRNA) (+) virus, ssRNA (-) virus, or a circular ssRNA virus.

6. The use of claims 4 or 5, wherein the DNA virus, the RNA virus, or the retrovirus is a respiratory virus.

7. The use of any one of claims 4-6, wherein the DNA virus, the RNA virus, or the retrovirus is selected from the group consisting of: Adeno- associated virus, Aichi virus, Australian Bat Lyssavirus, BK polyomavirus, Banna virus, Barmah forest virus, Bunyavirus snowshoe hare, Cercopithecine herpes virus, Chandipura virus, Chikungunya virus, Cosavirus A, Cowpox virus, Coxsackievirus, Crimean-Congo hemorrhagic fever virus, Coronavirus, Dengue virus, Dhori virus, Dugbe virus, Duvenhage virus, Eastern equine encephalitis virus, Echovirus, Encephalomyocarditis virus, Epstein- Barr virus, European Bat Lyssavirus, GB

virus C/Hepatitis G virus, Hantaan virus, Hendra virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis delta virus, Human adenovirus, Human astrovirus, Human coronavirus, Human cytomegalovirus, Human enterovirus 68,70, Human herpesvirus 1, Human herpesvirus 2, Human herpesvirus 6, Human herpesvirus 7, Human Immunodeficiency Virus (HIV), Human papillomavirus 1, Human papillomavirus 2, Human papillomavirus 16,18, Human parainfluenza virus, Human parvovirus B19, Human respiratory syncytial virus, Human rhinovirus, Human SARS coronavirus, Human spumarterovirus, Human T-lymphotropic virus, Human torovirus, Influenza A virus, Influenza B virus, Influenza C virus, Isfahan virus, JC polyomavirus, Japanese encephalitis virus, Junin arenavirus, KI Polyomavirus, Kunjin virus, Lagos bat virus, Lake Victoria Marburgvirus, Langat virus, Lassa virus, Lordsdale virus, Louping ill virus, Lymphocytic choriomeningitis virus, Machupo virus, Mayaro visu, MERS coronavirus, Measles virus, Mengo encephalomyocarditis, Merkell cell polyomavirus, Mokola virus, Molluscum contagiosum virus, Monkeypox virus, Mumps virus, Murray valley encephalitis virus, New York virus, Nipah virus, Norwalk virus, O'Nyong-nyong virus, Orf virus, Oropouche virus, Pichinde virus, Poliovirus, Punta toro phlebovirus, Puumala virus, Rabies virus, Rift valley fever virus, Rosavirus A, Ross river virus, Rotavirus A, Rotavirus B, Rotavirus C, Rubella virus, Sagiyama, Salivirus A, Sandfly fever sicilian virus, Sapporo virus, SARS coronavirus-2, Semliki forest virus, Seoul virus, Simian foamy virus, Simian virus 5, Sindbis virus, Southampton virus, St. Louis encephalitis virus, Tick- borne Powassan virus, Torque teno virus, Toscana virus, Uukuniemi virus, Varicella-zoster virus, Variola virus, Venezuelan equine encephalitis virus, WU polyomavirus, Yaba Monkey tumor virus, Yaba-like disease virus, Yellow fever virus, and Zika virus.

8. The use of claim 3, wherein the ARDS or the CSS are the result of the bacterial infection, and wherein the bacterial infection is due to Staphylococcus, Streptococcus, Mycobacterium, Bacillus, Salmonella, Vibrio, Spirochete, Neisseria, Diplococcus, Pseudomonas, Clostridium, Treponaema, Spirillum, or combinations thereof.

9. The use of claim 1, wherein the ARDS or the CSS are due to one or more immune-targeted therapies.

10. The use of claim 9, wherein the one or more immune-targeted therapies is an antibody, a protein therapeutic, a peptide, a cytokine, an immune signaling modulator, an mRNA, an oncolytic virus, or a cell-based therapy.

11. The use of claim 10, wherein the one or more immune-targeted therapies comprise the antibody, and wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a tri-specific antibody, or a bi-specific T-cell engager (BiTE) antibody.

12. The use of claim 11, wherein the antibody targets CD2, CD3, CD20, CD27, CD28, CD30, CD40L, CD137, OX-40, GITR, LIGHT, DR3, SLAM, ICOS, LILRB2, LILRB3, LILRB4, PD-1, PD-L1, CTLA-4, IL-12, or IL-15,RTK, EGFR, VEGF, VEGFR, PDGF, PDGFR, HER2/Neu, ER, PR, TGF-β1, TGF-β2, TGF-β3, SIRP-α, PD-1, PD-L1, CTLA-4, CD3, CD25, CD19, CD20, CD39, CD47, CD73, FAP, IL-1β, IL-2R, IL-12, IL-15, IL-15R, IL-23, IL-33, IL-2R, IL-4Rα T-cells, B-cells, NK cells, macrophages, monocytes, or neutrophils.

13. The use of claim 10, wherein the one or more immune-targeted therapies comprise the cytokine, and wherein the cytokine is selected from IFN-a, IFN-y, IL-2, IL-10, IL-12, IL-15, IL-15/IL-15Ra, IL-18, IL-21, GM-CSF, or variants thereof.

14. The use of claim 10, wherein the one or more immune-targeted therapies comprise the immune signaling modulator, and wherein the immune signaling modulator targets one or more of: IL- 1R, IL-2Ra, IL-2Rα, IL-2Ry, IL-3Ra, CSF2RB, IL-4R, IL-5Ra, CSF2RB, IL-6Ra, gp130, IL-7Ra, IL-9R, IL-10Rα, IL-10Rα, IL-12Rα1, IL-12Rα2, IL-13Rα1, IL-13Rα2, IL-15Rα, IL- 21R, IL23R, IL-27Rα, IL-31Ra, OSMR, CSF-1R, GM-CSF-R, cell-surface IL-15, IL-10Ra, IL-10Rα, IL-20Rα, IL-20Rα, IL-22Rα1, IL-22Rα2, IL-22Rα, IL-28RA, TLR, JAK, BTK, TYK, SYK, MAPK, PI3K, NFKB, NFAT, STAT, or a kinase.

15. The use of claim 10, wherein the one or more immune-targeted therapies comprise the cell-based therapy, and wherein the cell-based therapy comprises allogenic, autologous, or iPSC-derived cells.

16. The use of claim 10, wherein the one or more immune-targeted therapies comprise the cell-based therapy, and wherein the cell-based therapy comprises one or more of: T- cells, NK-cells, red blood cells, stem cells, antigen-presenting cells, macrophages, or dendritic cells.

17. The use of any one of the preceding claims, wherein the negatively charged particles comprise one or more biodegradable polymers.

18. The use of any one of claims 1-17, wherein the negatively charged particles comprise one or more of: polyglycolic acid (PGA), polylactic acid (PLA), polystyrene, poly (lactic-co-glycolic acid) (PLGA), chitosan, polysaccharide, a lipid, diamond, iron, zinc, cadmium, gold, or silver.

19. The use of claim 18, wherein the negatively charged particles comprise the PLGA.

20. The use of claim 18, wherein the negatively charged particles that comprise PLGA comprise a ratio of poly lactic acid:poly glycolic acid ranging from about 90:10 to about 10:90, from about 50:50 to about 90:10, about 50:50 to about 80:20; from about 90:10 to about 50:50, or from about 80:20 to about 50:50.

21. The use of claim 20, wherein the negatively charged particles that comprise the PLGA comprise the ratio of poly lactic acid: poly glycolic acid ranging from about 50:50.

22. The use of any one of claims 1-21, wherein the negatively charged particles further comprise carboxyl groups on a surface.

23. The use of any one of claims 1-22, wherein the negative zeta potential ranges from about -100 mV and about -1 mV.

24. The use of claim 23, wherein the negative zeta potential ranges from about -80 mV and about -30 mV.

25. The use of any one of claims 1-24, wherein the negatively charged particles have a mean diameter ranging from about 0.1 μm to about 10 μm.

26. The use of claim 25, wherein the mean diameter of the negatively charged particle ranges from about 300 nm to about 800 nm.

27. The use of any one of claims 1-26, wherein the negatively charged particles are to be administered to the subject, and wherein the negatively charged particles improves one or more symptoms associated with the ARDS or CSS.

28. The use of claim 27, wherein the one or more symptoms associated with the ARDS or the CSS are selected from the group consisting of lung inflammation, atelectasis, distressed breathing, fatigue, low blood pressure, fever, headache, hypoxemia, respiratory acidosis, hypercapnia, edema, pulmonary edema, alveolar edema, multi-organ dysfunction, brain damage, lung damage, liver damage, kidney damage, heart damage, edema, cerebral edema, pulmonary edema, alveolar edema, respiratory distress, hypoxemia, respiratory acidosis, hypertriglyceridemia, leukopenia, cytopenia, and elevated levels of inflammatory markers.

29. The use of claim 28, wherein the inflammatory markers consist of IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, TNF-α, IFN-γ, IP-10, MIP-1β, MCP-1, GM-CSF, c-reactive protein, d-dimer, ferritin, neutrophil extracellular traps (NETs), and combinations thereof.

30. The use of any one of claims 1-29, wherein the negatively charged particles are to be administered to the subject, and wherein the negatively charged particles reduces accumulation of inflammatory mediators in circulation or at sites of inflammation.

31. The use of any of the preceding claims, wherein the negatively charged particles are to be administered to the subject intravenously.

32. Use of negatively charged particles that are free from attached or encapsulated drug, in the manufacture of a medicament for treating acute inflammation in hospitalized adults with systemic inflammation, sepsis, or pneumonia associated with respiratory viral infections in a subject in need thereof, wherein the negatively charged particles comprise one or more biodegradable, pharmaceutically acceptable polymers; and particles are to be administered at a dose of between 1 mg/kg to 10 mg/kg.

33. The use of claim 32, wherein respiratory viral infection is associated with influenza and SARS-CoV-2.

34. The use of any one of claims 32-33, wherein the negatively charged particles are to be administered at a dose level of between 1 mg/kg to 6 mg/kg.

35. The use of any one of claims 32-34, wherein the negatively charged particles are to be administered at a dose level of 5 mg/kg.

36. The use of any one of claims 32-35, wherein the negatively charged particles are to be administered at a dose level of between 50 mg to 400 mg.

37. The use of any one of claims 32-36, wherein the negatively charged particles comprise one or more biodegradable polymers.

38. The use of any one of claims 32-37, wherein the negatively charged particles comprise Poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA), poly (glycolic acid) (PGA), or polystyrene.

39. The use of any one of claims 32-38, wherein the negatively charged particles comprise PLGA.

40. The use of any one of claims 32-39, wherein the negatively charged particles have a zeta potential is between about -30 mV and -80 mV.

41. The use of any one of claims 32-40, wherein the negatively charged particles have an average diameter between 0.3μm and 3μm, or between 0.3μm and 1μm.

42. The use of any one of claims 32-41, wherein the negatively charged particles leads to a reduction from baseline in the levels of serum c-reactive protein.

43. The use of claim 42, wherein the levels of serum c-reactive protein are reduced by 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold compared to baseline.

44. The use of any one of claims 32-43, wherein the negatively charged particles leads to a reduction from baseline in the levels of serum ferritin.

45. The use of claim 44, wherein the levels of the serum ferritin are reduced by 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold compared to baseline.

46. The use of any one of claims 32-45, wherein the negatively charged particles leads to a reduction from baseline in the levels of serum d-dimer.

47. The use of claim 46, wherein the levels of the serum d-dimer protein are reduced by 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold compared to baseline.

48. The use of any one of claims 32-47, wherein the negatively charged particles leads to a reduction from baseline in the number of neutrophils in blood.

49. The use of claim 48, wherein the number of neutrophils in the blood are reduced by 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold compared to baseline.

50. The use of any one of claims 32-49, wherein the negatively charged particles leads to an increase from baseline in the number of lymphocytes in blood.

51. The use of claim 50, wherein the number of lymphocytes in the blood are increased by 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold compared to baseline.

52. The use of any one of claims 32-51, wherein the negatively charged particles leads to a decrease from baseline in the neutrophil to lymphocyte ratio (NLR).

53. The use of claim 52, wherein the negatively charged particles leads to an NLR of ≤ 4.

54. The use of any one of claims 32-53, wherein the negatively charged particles leads to an increase from baseline in a SpO_2/FiO_2 ratio.

55. The use of claim 54, wherein the SpO_2/FiO_2 ratio is ≥ 300 mmHg.

56. The use of any one of claims 32-55, wherein the negatively charged particles leads to a reduction in the number of hospitalization days.

57. The use of any one of claims 32-56, wherein the negatively charged particles leads to an increase in the number of ventilator-free days.

58. The use of any one of claims 32-57, wherein the negatively charged particles leads to a reduced risk of mortality.

59. The use of any one of claims 32-58, wherein the negatively charged particles leads to improved lung function compared to baseline.