Claims

1. An aqueous solution composition of pH in the range 6.0 to 8.0 comprising:

- an engineered dimeric protein wherein each monomer of the dimeric protein comprises at least one human serpin polypeptide operably linked to a human immunoglobulin Fc polypeptide or a polypeptide that is derived from an immunoglobulin Fc polypeptide;

- optionally one or more buffers being substances having at least one ionisable group with a pK_a in the range 4.0 to 10.0 and which pK_a is within 2 pH units of the pH of the composition;

- a neutral amino acid; and

- an uncharged tonicity modifier;

wherein the buffers are present in the composition at a total concentration of 0-10 mM; and wherein the total ionic strength of the composition excluding the contribution of the engineered dimeric protein is less than 30 mM.

2. An aqueous solution composition according to claim 1, wherein the human serpin polypeptide is a human alpha- 1 antitrypsin (AAT) polypeptide or is derived from a human AAT polypeptide.

3. An aqueous solution composition according to claim 1 or claim 2, wherein each monomer of the dimeric protein comprises one human serpin polypeptide.

4. An aqueous solution composition according to claim 2 or 3, wherein the human serpin polypeptide has the sequence of SEQ ID NO: 1 or 2.

5. An aqueous solution composition according to any one of claims 1 to 4, wherein the human immunoglobulin Fc polypeptide or a polypeptide that is derived from an immunoglobulin Fc polypeptide is a modified human IgG4 Fc polypeptide.

6. An aqueous solution composition according to claim 5, wherein the human immunoglobulin Fc polypeptide or a polypeptide that is derived from an immunoglobulin Fc polypeptide is a modified human IgG4 Fc polypeptide and has the sequence of any one of SEQ ID NOs: 28-43.

7. An aqueous solution composition according to any one of claims 1 to 6, wherein each monomer of the dimeric protein has the sequence of SEQ ID No: 56.

8. An aqueous solution composition according to any one of claims 1 to 7, wherein the protein is present at a concentration of 1-400 mg/ml e.g. 10-200 mg/ml e.g. 20-100 mg/ml e.g. 30-60 mg/ml e.g. about 35 mg/ml or about 50 mg/ml.

9. An aqueous solution composition according to any one of claims 1 to 8, wherein buffers are present at a total concentration of 0.1-10 mM, such as 0.5-10 mM such as 1-10 mM, such as 1-8 mM, such as 1-6 mM, such as 2-6 mM, such as 2-5 mM e.g. 3-5 mM.

10. An aqueous solution composition according to any one of claims 1 to 8, which is substantially free of buffers.

11. An aqueous solution composition according to any one of claims 1 to 9, wherein the buffer comprises ionisable groups with pK_a within 1 unit of the pH of the composition.

12. An aqueous solution composition according to any one of claims 1 to 9 and 11, wherein the buffer or buffers is/are selected from the group consisting of citrate, histidine, maleate, sulphite, aspartame, aspartate, glutamate, tartrate, adenine, succinate, ascorbate, benzoate, phenylacetate, gallate, cytosine, *p*-aminobenzoic acid, sorbate, acetate, propionate, alginate, urate, 2-(*N*-morpholino)ethanesulphonic acid, bicarbonate, bis(2-hydroxyethyl) iminotris(hydroxymethyl)methane, *N*-(2-acetamido)-2-iminodiacetic acid, 2-[(2-amino-2-oxoethyl)amino]ethanesulphonic acid, piperazine, *N*,*N*'-bis(2-ethanesulphonic acid), phosphate, *N*,*N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid, 3-[*N*,*N*-bis(2-hydroxyethyl)amino]-2-hydroxypropanesulphonic acid, triethanolamine, piperazine-*N*,*N*'-bis(2-hydroxypropanesulphonic acid), tris(hydroxymethyl)aminomethane (TRIS), *N*-tris(hydroxymethyl)glycine and *N*-tris(hydroxymethyl)methyl-3-aminopropanesulphonic acid, and salts thereof, and combinations thereof.

13. An aqueous solution composition according to claim 12, wherein the buffer is selected from the group consisting of citrate, histidine, maleate, tartrate, benzoate, acetate, bicarbonate, phosphate and tris(hydroxymethyl)aminomethane (TRIS), for example, selected from phosphate and TRIS.

14. An aqueous solution composition according to any one of claims 1 to 13, wherein the uncharged tonicity modifier is selected from the group consisting of polyols, sugars (e.g. monosaccharides and disaccharides) and sugar alcohols.

15. An aqueous solution composition according to claim 14, wherein the uncharged tonicity modifier is selected from the group consisting of glycerol, 1,2-propanediol, mannitol, sorbitol, glucose, sucrose, trehalose, PEG300 and PEG400, and in particular is selected from glycerol, mannitol, sucrose and trehalose.

16. An aqueous solution composition according to claim 14 or claim 15, comprising a disaccharide as an uncharged tonicity modifier.

17. An aqueous solution composition according to claim 16, comprising sucrose and/or trehalose as the uncharged tonicity modifier, in particular trehalose.

18. An aqueous solution composition according to any one of claims 1 to 17, wherein the total concentration of the uncharged tonicity modifier, or combination of more than one tonicity modifier, is 50-1000 mM, such as 200-600 mM, 200-500 mM or wherein the total concentration of the uncharged tonicity modifier, or combination of more than one tonicity modifier, is 50-500 mM, such as 100-400 mM, 150-350 mM, 200-300 mM or about 250 mM.

19. An aqueous solution composition according to any one of claims 1 to 17, wherein the osmolarity of the composition is 200-500 mOsm/L e.g. about 300 mOsm/L or wherein the osmolarity of the composition is 300-500 mOsm/L e.g. about 400-460 mOsm/L.

20. An aqueous solution composition according to any one of claims 1 to 19, comprising a neutral amino acid selected from glycine, methionine, proline, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, asparagine and glutamine.

21. An aqueous solution composition according to claim 20, wherein the neutral amino acid is selected from glycine, methionine and proline.

22. An aqueous solution composition according to claim 20, comprising proline as a neutral amino acid.

23. An aqueous solution composition according to claim 20, comprising glycine as a neutral amino acid.

24. An aqueous solution composition according to claim 20, comprising proline and methionine as neutral amino acids.

25. An aqueous solution composition according to claim 20, comprising glycine and methionine as neutral amino acids.

26. An aqueous solution composition according to any one of claims 1 to 25, wherein the total concentration of the one or more neutral amino acids in the composition is 20 to 600 mM, such as 20 to 500 mM, such as 20 to 400 mM , such as 20 to 300 mM e.g. 50 to 300 mM.

27. An aqueous solution composition according to any one of claims 1 to 25, wherein the total concentration of the one or more neutral amino acids in the composition is 50 to 200 mM, 100 to 200 mM or 100 to 150 mM.

28. An aqueous solution composition according to any one of claims 1 to 27, wherein the total ionic strength of the composition excluding the contribution of the engineered dimeric protein is less than 20 mM.

29. An aqueous solution composition according to claim 28, wherein the total ionic strength of the composition excluding the contribution of the engineered dimeric protein is less than 10 mM.

30. An aqueous solution composition according to any one of claims 1 to 29, wherein the pH is between 6.8 and 7.8, for example between 7.0 and 7.8, between 7.1 and 7.6, between 7.1 and 7.5, between 7.2 and 7.5, between 7.1 and 7.4, between 7.2 and 7.3; or is about 7.2 or about 7.3.

31. An aqueous solution composition according to any one of claims 1 to 30, which comprises a non-ionic surfactant.

32. An aqueous solution composition according to claim 31, wherein the non-ionic surfactant is selected from the group consisting of an alkyl glycoside, a polysorbate, an alkyl ether of polyethylene glycol, a block copolymer of polyethylene glycol and polypropylene glycol (poloxamer), and an alkylphenyl ether of polyethylene glycol.

33. An aqueous solution composition according to claim 32, wherein the non-ionic surfactant is a polysorbate such as polysorbate 20 or polysorbate 80.

34. An aqueous solution composition according to claim 32, wherein the non-ionic surfactant is a block copolymer of polyethylene glycol and polypropylene glycol (poloxamer), such as poloxamer 188.

35. An aqueous solution composition according to any one of claims 31 to 34, wherein the non-ionic surfactant is present at a concentration of 10-2000 µg/ml, such as 50-1000 µg/ml, e.g. 100-500 µg/ml e.g. about 200 µg/ml or wherein the non-ionic surfactant is present at a concentration of 250-1500 µg/ml e.g. 750-1250 µg/ml e.g. about 1000 µg/ml.

36. An aqueous solution composition according to any one of claims 1 to 35, which comprises a preservative such as a phenolic or benzylic preservative.

37. An aqueous solution composition according to claim 36, wherein the phenolic or benzylic preservative is selected from the group consisting of phenol, m-cresol, chlorocresol, benzyl alcohol, propyl paraben and methyl paraben.

38. An aqueous solution composition according to claim 36 or claim 37, wherein the preservative is present at a concentration of 10-100 mM, such as 20-80 mM e.g. 25-50 mM.

39. An aqueous solution composition according to any one of claims 1 to 38, which is a composition for use in therapy.

40. An aqueous solution composition according to any one of claims 1 to 38, which is a pharmaceutical composition.

~~41. A method of treating or alleviating a symptom of a disease or disorder associated with aberrant serine protease expression or activity in a subject in need thereof, the method comprising administering an aqueous solution composition according to any one of claims 1 to 40.~~

~~42. A method of treating or alleviating inflammation or a symptom of an inflammatory disease or disorder while reducing the risk of infection, in a subject in need thereof, the method comprising administering to said subject an aqueous solution composition according to any one of claims 1 to 40.~~

~~43. A method of reducing the risk of infection in a subject in need thereof, the method comprising administering to said subject an aqueous solution composition according to any one of claims 1 to 40.~~

~~44. A method of treating or alleviating a symptom of AAT deficiency in a subject in need thereof, the method comprising administering to said subject an aqueous solution composition according to any one of claims 1 to 40, wherein the human serpin polypeptide is a human alpha- 1 antitrypsin (AAT) polypeptide or is derived from a human AAT polypeptide.~~

~~45. An aqueous solution composition according to any one of claims 1 to 40, for use in a method of treating or alleviating a symptom of a disease or disorder associated with aberrant serine protease expression or activity in a subject in need thereof.~~

~~46. An aqueous solution composition according to any one of claims 1 to 40, for use in a method of treating or alleviating inflammation or a symptom of an inflammatory disease or disorder while reducing the risk of infection, in a subject in need thereof.~~

~~47. An aqueous solution composition according to any one of claims 1 to 40, for use in a method of reducing the risk of infection in a subject in need thereof.~~

~~48. An aqueous solution composition according to any one of claims 1 to 40, for use in a method of treating or alleviating a symptom of AAT deficiency in a subject in need thereof, wherein the human serpin polypeptide is a human alpha- 1 antitrypsin (AAT) polypeptide or is derived from a human AAT polypeptide.~~

~~49~~41. Use of an aqueous solution composition according to any one of claims 1 to 40, for the manufacture of a medicament for treating or alleviating a symptom of a disease or disorder associated with aberrant serine protease expression or activity in a subject in need thereof.

~~50~~42. Use of an aqueous solution composition according to any one of claims 1 to 40, for the manufacture of a medicament for treating or alleviating inflammation or a symptom of an inflammatory disease or disorder while reducing the risk of infection, in a subject in need thereof.

~~51~~43. Use of an aqueous solution composition according to any one of claims 1 to 40, for the manufacture of a medicament for reducing the risk of infection in a subject in need thereof.

~~52~~44. Use of an aqueous solution composition according to any one of claims 1 to 40, for the manufacture of a medicament for treating or alleviating a symptom of AAT deficiency in a subject in need thereof, wherein the human serpin polypeptide is a human alpha- 1 antitrypsin (AAT) polypeptide or is derived from a human AAT polypeptide.

~~53~~45. The ~~method, aqueous solution composition for use, or~~ use~~,~~ according to any one of claims ~~42, 46 and 50~~41 to 44, wherein the inflammatory disease or disorder is selected from the following: alpha- 1 antitrypsin (AAT) deficiency, emphysema, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), allergic asthma, cystic fibrosis, cancers of the lung, ischemia-reperfusion injury, ischemia/reperfusion injury following cardiac transplantation, myocardial infarction, rheumatoid arthritis, septic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, type I and/or type II diabetes, pneumonia, sepsis, graft versus host disease (GVHD), wound healing, systemic lupus erythematosus, and multiple sclerosis.

~~54~~46. The ~~method, aqueous solution composition for use, or~~ use~~,~~ according ~~to any one of~~ claim~~s~~ 42~~,~~ or 43~~, 46, 47, 50 and 51~~, wherein the infection is selected from bacterial infections, fungal infections and viral infections.

~~55~~47. The ~~method, aqueous solution composition for use, or~~ use~~,~~ according to any one of claims 41 to ~~54~~46, wherein the subject is a human.