CLAIMS

1. A composition comprising a lipocalin mutein or a fragment or variant thereof or a fusion protein or conjugate thereof that is capable of inhibiting IL-4 and/or IL-13 from binding to their respective receptors, for use in a method of treating, ameliorating or preventing a disorder.
2. A composition for the use according to claim 1, wherein the composition further comprises a pharmaceutically acceptable formulation.
3. A composition for the use according to claim 1, wherein said lipocalin mutein is capable of disrupting downstream signaling and/or cellular responses induced by IL-4 and/or IL-13.
4. A composition for the use according to claim 1, wherein said lipocalin mutein is capable of exhibiting an *in vivo* therapeutic activity in a subject in need thereof.
5. A composition for the use according to claim 4, where said lipocalin mutein is capable of inhibiting *in vivo* human IL-13 induced transcript Ccl11 (eotaxin).
6. A composition for the use according to claim 5, wherein said lipocalin mutein is more potent than an IL-4 mutant (R121D, Y124D) when inhibiting human IL-13 induced transcript Ccl11 (eotaxin) *in vivo*, as measured by a test essentially described in Example 5.-
7. A composition for the use according to claim 1, wherein said lipocalin mutein is capable of exhibiting a functional activity as good as an anti-IL-4RA monoclonal antibody having the variable light and heavy chain sequence as shown in SEQ ID NO: 14 and 15, respectively, as measured by a test essentially described in Example 8.
8. A composition for the use according to claim 7, wherein said lipocalin mutein is capable of inhibiting IL-13 induced goblet cell metaplasia as good as the anti-IL-4RA monoclonal antibody in said test.
9. A composition for the use according to any one of the preceding claims, wherein the subject is suffering from a disorder in which the IL-4 expression and/or IL-13 expression contributes or is related to disease pathogenesis or aggravation.
10. A composition for the use according to any one of the preceding claims, wherein the subject is suffering from a disorder that can be improved, ameliorated or inhibited by removal, inhibition or reduction of the IL-4 activity and/or IL-13 activity.
11. A composition for the use according to any one of the preceding claims, wherein said composition is locally administered to the lung.
12. A composition for the use according to any one of the preceding claims, wherein said composition is administered via aerosol inhalation.

13. A composition for the use according to any one of the preceding claims, wherein said composition is administered to a subject in need thereof at a frequency selected from the group consisting of: up to four times daily, up to three times daily, up to twice daily, up to once daily, up to once every other day, up to once every third day, up to once every week and up to once every other week.
14. A composition for the use according to of any one of the preceding claims, wherein said composition is administered to a subject in need thereof every time at a dosage level selected from the group consisting of: 0.06-600mg, 0.06-100mg, 0.3-10mg, and 1-3mg.
15. A composition for the use according to any one of the preceding claims, wherein said disorder is associated with an increase of the Th2 immune response.
16. A composition for the use according to any one of claims 1-14, wherein said disorder is associated with an allergic reaction or an allergic inflammation.
17. A composition for the use according to any one of claims 1-14, wherein said disorder is associated with a mucus production or a mucus secretion.
18. A composition for the use according to any one of claims 15-17, wherein the disorder is selected from the group consisting of allergic inflammation, allergic asthma, rhinitis, conjunctivitis, lung fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis or adult respiratory distress syndrome.
19. A composition for the use according to claim 18, wherein said allergic asthma is an airway inflammation in which the IL4/IL13 pathway contributes to disease pathogenesis.
20. A composition for the use according to claim 16, wherein said composition further comprises an anti-allergic medicament and/or an anti-allergic inflammation medicament.
21. A composition for the use according to any one of claims 1-14, wherein said disorder is a lung disorder.
22. A composition for the use according to claim 21, wherein the lung disorder is associated with pulmonary disorders, lung fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, adult respiratory distress syndrome, sarcoidosis and lung epithelium.
23. A composition for the use according to claim 17, wherein said composition further comprises an anti-mucus medicament.
24. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein is cross-reactive with marmoset IL-4RA.
25. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein is not cross-reactive with mouse IL-4RA and/or cynomolgus IL-4RA.

26. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein is essentially not cross-reactive with a related protein or non-related protein.

27. A composition for the use according to claim 26, wherein the related protein is an IL-23 receptor alpha chain and/or type I cytokine receptor with fibronectin type III domain.

28. A composition for the use according to claim 26, wherein said non-related protein is an IL-6 receptor and/or IL-18 receptor alpha chain.

29. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein has a mutated amino acid at any one or more amino acids positions corresponding to position 27, 28, 30, 31, 33, 53, 57, 61, 64, 66, 80, 83, 104-106 and 108 of the linear polypeptide sequence of the mature human tear lipocalin (SEQ ID NO: 1).

30. A composition for the use according to claim 29, wherein said lipocalin mutein further has mutated amino acids at any two or more amino acids positions corresponding to position 26, 32, 34, 55, 56, 58 and 63 of the linear polypeptide sequence of the mature human tear lipocalin (SEQ ID NO: 1).

31. A composition for the use according to claim 29 or 30, wherein said lipocalin mutein has at least 75% identity to the sequence of mature human tear lipocalin (SEQ ID NO: 1).

32. The lipocalin mutein, a fragment or variant thereof or a fusion protein or conjugate thereof used in a method as defined in any one of the preceding claims.

33. A pharmaceutical composition comprising at least an IL-4RA antagonist, or a fragment or variant thereof or a fusion protein or conjugate thereof, for use in a method of treating a subject in need thereof comprising administering to the said subject via nebulization a pharmaceutical composition at a concentration ranging from 0.01 mg/ml to 100mg/ml in a solution, wherein the said solution comprises:
    (a) a pH level between about 5.5 and 8.0,
    (b) an osmolality value between about 150 and 550 mOsm/L, and
    (c) an ion concentration between about 31 and 300 mM of chloride as a permeant anion, and wherein the resulted aerosol having a mass median aerodynamic diameter (MMAD) ranging from 1 μm to 10 μm.

34. A pharmaceutical composition for the use according to claim 33, wherein said solution further has a viscosity value less than about 1.5 cp.

35. A pharmaceutical composition for the use according to claim 33, wherein said pharmaceutical composition has a concentration level of one or more antagonists of IL-4 and/or IL-13 or a fusion protein or conjugate thereof selected from the group

consisting of: 0.05 mg/ml to 50 mg/ml, 0.1 mg/ml to 50 mg/ml, 0.05 mg/ml to 25 mg/ml, 0.1 mg/ml to 25 mg/ml, 0.05 mg/ml to 15 mg/ml, 0.1 mg/ml to 15 mg/ml, 0.05 mg/ml to 10 mg/ml and 0.1 mg/ml to 10 mg/ml.

36. A pharmaceutical composition for the use according to claim 33, wherein said solution has an adjusted pH selected from the group consisting of between 5.5 and 8.0, between 6.0 and 8.0, between 6.0 and 7.5, between 5.5 and 7.5, between 6.0 and 7.0 and between 6.5 and 7.5.

37. A pharmaceutical composition for the use according to claim 33, wherein said solution has an osmolality value selected from the group consisting of: between about 150 and 550 mOsm/kg, between about 150 and 500 mOsm/kg, between about 200 and 550 mOsm/kg, between about 200 and 500 mOsm/kg, between about 200 and 450 mOsm/kg and between about 150 and 450 mOsm/kg.

38. A pharmaceutical composition for the use according to claim 33, wherein said solution has an ion concentration of chloride as a permeant anion from the group consisting of between 31 and 300 mM, between 50 and 200 mM, between 50 and 300 mM, between 50 and 150 mM, 100 and 200 mM, between 100 and 300 mM, between 100 and 250 mM, between 150 and 250 mM, between 150 and 300 mM and between 200 and 300 mM.

39. A pharmaceutical composition for the use according to claim 33, wherein said solution has a viscosity selected from the group consisting of between 0 and 1.5 cp, between 0 and 1.0 cp, 0 and 0.5 cp, between 0.5 and 1.0 cp, between 0.5 and 1.5 cp and between 1.0 and 1.5 cp.

40. A pharmaceutical composition for the use according to any one of claims 31-37, wherein the resulted aerosol has a mass median aerodynamic diameter (MMAD) selected from the group consisting of between 1 μm to 10 μm, between 2 μm to 8 μm, between 2 μm to 5 μm, between 1.5 μm to 4 μm, between 3 μm to 4.5 μm and between 2.5 μm to 3.5 μm.

41. A pharmaceutical composition for the use according to any one of claims 33-40, wherein an electronic nebulizer, jet, ultrasonic, or with a vibrating perforated membrane or a vibrating mesh nebulizer is used.

42. A pharmaceutical composition for the use according to any one of claims 33-41, wherein said antagonist maintains its functional and structural integrity upon and after nebulization.

43. A pharmaceutical composition for the use according to claim 42, wherein said antagonist remains monomeric upon and after nebulization.

44. A pharmaceutical composition for the use according to any one of claims 33-43, wherein said antagonist is a lipocalin mutein according to claim 32.

45. The solution used in a method as defined in any one of claims 33 to 44.

46. An efficacious amount of a pharmaceutical composition according to claim 33 comprising the solution of claim 45 for use in a method of delivery by inhalation within 1-3 minutes.

47. An efficacious amount of a pharmaceutical composition for the use according to claim 46, wherein the delivery by inhalation is locally to the lung.

CLAIMS

1. Use of a lipocalin mutein or a fragment or variant thereof or a fusion protein or conjugate thereof that is capable of inhibiting IL-4 and/or IL-13 from binding to their respective receptors for the manufacture of a medicament for treating, ameliorating or preventing a disorder in a subject, wherein said lipocalin mutein is capable of exhibiting an *in vivo* therapeutic activity in the subject.

2. The use according to claim 1, wherein the composition further comprises a pharmaceutically acceptable formulation.

3. The use according to claim 1, wherein said lipocalin mutein is capable of disrupting downstream signaling and/or cellular responses induced by IL-4 and/or IL-13.

4. The use according to claim 1, wherein said lipocalin mutein has an amino acid sequence as set forth in any one of SEQ ID NO: 2-11.

5. The use according to claim 1, where said lipocalin mutein is capable of inhibiting *in vivo* human IL-13 induced transcript Ccl11 (eotaxin).

6. The use according to claim 5, wherein said lipocalin mutein is more potent than an IL-4 mutant (R121D, Y124D) when inhibiting human IL-13 induced transcript Ccl11 (eotaxin) in vivo, as measured by a test essentially described in Example 5.

7. The use according to claim 1, wherein said lipocalin mutein is capable of exhibiting a functional activity as good as an anti-IL-4RA monoclonal antibody having the variable light and heavy chain sequence as shown in SEQ ID NO: 14 and 15, respectively, as measured by a test essentially described in Example 8.

8. The use according to claim 7, wherein said lipocalin mutein is capable of inhibiting IL-13 induced goblet cell metaplasia as good as the anti-IL-4RA monoclonal antibody in said test.

9. The use according to any one of the preceding claims, wherein the subject is suffering from a disorder in which the IL-4 expression and/or IL-13 expression contributes or is related to disease pathogenesis or aggravation.

10. The use according to any one of the preceding claims, wherein the subject is suffering from a disorder that can be improved, ameliorated or inhibited by removal, inhibition or reduction of the IL-4 activity and/or IL-13 activity.

11. The use according to any one of the preceding claims, wherein said composition is locally administered to the lung.

12. The use according to any one of the preceding claims, wherein said composition is administered via aerosol inhalation.

13. The use according to any one of the preceding claims, wherein said composition is administered to a subject in need thereof at a frequency selected from the group consisting of: up to four times daily, up to three times daily, up to twice daily, up to once daily, up to once every other day, up to once every third day, up to once every week and up to once every other week.

14. The use according to of any one of the preceding claims, wherein said composition is administered to a subject in need thereof every time at a dosage level selected from the group consisting of: 0.06-600mg, 0.06-100mg, 0.3-10mg, and 1-3mg.

15. The use according to any one of the preceding claims, wherein said disorder is associated with an increase of the Th2 immune response.

16. The use according to any one of claims 1-14, wherein said disorder is associated with an allergic reaction or an allergic inflammation.

17. The use according to any one of claims 1-14, wherein said disorder is associated with a mucus production or a mucus secretion.

18. The use according to any one of claims 15-17, wherein the disorder is selected from the group consisting of allergic inflammation, allergic asthma, rhinitis, conjunctivitis, lung fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis or adult respiratory distress syndrome.

19. The use according to claim 18, wherein said allergic asthma is an airway inflammation in which the IL4/IL13 pathway contributes to disease pathogenesis.

20. The use according to claim 16, wherein said composition further comprises an anti-allergic medicament and/or an anti-allergic inflammation medicament.

21. The use according to any one of claims 1-14, wherein saiddisorder is a lung disorder.

22. The use according to claim 21, wherein the lung disorder is associated with pulmonary disorders, lung fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, adult respiratory distress syndrome, sarcoidosis and lung epithelium.

23. The use according to claim 17, wherein said composition further comprises an anti-mucus medicament.

24. The use according to any one of the preceding claims, wherein said lipocalin mutein is cross-reactive with marmoset IL-4RA.

25. The use according to any one of the preceding claims, wherein said lipocalin mutein is not cross-reactive with mouse IL-4RA and/or cynomolgus IL-4RA.

26. The use according to any one of the preceding claims, wherein said lipocalin mutein is essentially not cross-reactive with a related protein or non-related protein.

27. The use according to claim 26, wherein the related protein is an IL-23 receptor alpha chain and/or type I cytokine receptor with fibronectin type III domain.

28. The use according to claim 26, wherein said non-related protein is an IL-6 receptor and/or IL-18 receptor alpha chain.

29. The use according to any one of the preceding claims, wherein said lipocalin mutein has a mutated amino acid at any one or more amino acids positions corresponding to position 27, 28, 30, 31, 33, 53, 57, 61, 64, 66, 80, 83, 104-106 and 108 of the linear polypeptide sequence of the mature human tear lipocalin (SEQ ID NO: 1).

30. The use according to claim 29, wherein said lipocalin mutein further has mutated amino acids at any two or more amino acids positions corresponding to position 26, 32, 34, 55, 56, 58 and 63 of the linear polypeptide sequence of the mature human tear lipocalin (SEQ ID NO: 1).

31. The use according to claim 29 or 30, wherein said lipocalin mutein has at least 75% identity to the sequence of mature human tear lipocalin (SEQ ID NO: 1).

32. The lipocalin mutein, a fragment or variant thereof or a fusion protein or conjugate thereof used in a method as defined in any one of the preceding claims.

33. A pharmaceutical composition comprising at least an IL-4RA antagonist, or a fragment or variant thereof or a fusion protein or conjugate thereof, for use in a method of treating a subject in need thereof comprising administering to the said subject via nebulization a pharmaceutical composition at a concentration ranging from 0.01 mg/ml to 100mg/ml in a solution, wherein the said solution comprises:

(a) a pH level between about 5.5 and 8.0,

(b) an osmolality value between about 150 and 550 mOsm/L, and

(c) an ion concentration between about 31 and 300 mM of chloride as a permeant anion, and wherein the resulted aerosol having a mass median aerodynamic diameter (MMAD) ranging from 1 μm to 10 μm.

34. A pharmaceutical composition for the use according to claim 33, wherein said solution further has a viscosity value less than about 1.5 cp.

35. A pharmaceutical composition for the use according to claim 33, wherein said pharmaceutical composition has a concentration level of one or more antagonists of IL-4 and/or IL-13 or a fusion protein or conjugate thereof selected from the group consisting of:

0.05 mg/ml to 50 mg/ml, 0.1 mg/ml to 50 mg/ml, 0.05 mg/ml to 25 mg/ml, 0.1 mg/ml to 25 mg/ml, 0.05 mg/ml to 15 mg/ml, 0.1 mg/ml to 15 mg/ml, 0.05 mg/ml to 10 mg/ml and 0.1 mg/ml to 10 mg/ml.

36. A pharmaceutical composition for the use according to claim 33, wherein said solution has an adjusted pH selected from the group consisting of between 5.5 and 8.0, between 6.0 and 8.0, between 6.0 and 7.5, between 5.5 and 7.5, between 6.0 and 7.0 and between 6.5 and 7.5.

37. A pharmaceutical composition for the use according to claim 33, wherein said solution has an osmolality value selected from the group consisting of: between about 150 and 550 mOsm/kg, between about 150 and 500 mOsm/kg, between about 200 and 550 mOsm/kg, between about 200 and 500 mOsm/kg, between about 200 and 450 mOsm/kg and between about 150 and 450 mOsm/kg.

38. A pharmaceutical composition for the use according to claim 33, wherein said solution has an ion concentration of chloride as a permeant anion from the group consisting of between 31 and 300 mM, between 50 and 200 mM, between 50 and 300 mM, between 50 and 150 mM, 100 and 200 mM, between 100 and 300 mM, between 100 and 250 mM, between 150 and 250 mM, between 150 and 300 mM and between 200 and 300 mM.

39. A pharmaceutical composition for the use according to claim 33, wherein said solution has a viscosity selected from the group consisting of between 0 and 1.5 cp, between 0 and 1.0 cp, 0 and 0.5 cp, between 0.5 and 1.0 cp, between 0.5 and 1.5 cp and between 1.0 and 1.5 cp.

40. A pharmaceutical composition for the use according to any one of claims 31-37, wherein the resulted aerosol has a mass median aerodynamic diameter (MMAD) selected from the group consisting of between 1 μm to 10 μm, between 2 μm to 8 μm, between 2 μm to 5 μm, between 1.5 μm to 4 μm, between 3 μm to 4.5 μm and between 2.5 μm to 3.5 μm.

41. A pharmaceutical composition for the use according to any one of claims 33-40, wherein an electronic nebulizer, jet, ultrasonic, or with a vibrating perforated membrane or a vibrating mesh nebulizer is used.

42. A pharmaceutical composition for the use according to any one of claims 33-41, wherein said antagonist maintains its functional and structural integrity upon and after nebulization.

43. A pharmaceutical composition for the use according to claim 42, wherein said antagonist remains monomeric upon and after nebulization.

44. A pharmaceutical composition for the use according to any one of claims 33-43, wherein said antagonist is a lipocalin mutein according to claim 32.

45. The solution used in a method as defined in any one of claims 33 to 44.

46. An efficacious amount of a pharmaceutical composition according to claim 33 comprising the solution of claim 45 for use in a method of delivery by inhalation within 1-3 minutes.

47. An efficacious amount of a pharmaceutical composition for the use according to claim 46, wherein the delivery by inhalation is locally to the lung.