# Methods for preventing or treating certain disorders

## FIELD OF THE INVENTION

**[0001]** The present disclosure relates to a composition for use in a method of treating, ameliorating or preventing a disorder in a subject. In some embodiments, the disorder is preferably associated with an increase of the Th2 immune response. In some embodiments, administration is preferably locally to the lung in order to treat, ameliorate or prevent allergic asthma, rhinitis, conjunctivitis, lung fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis or adult respiratory distress syndrome.

## BACKGROUND

**[0002]** Proteins that selectively bind to selected targets by way of non-covalent interaction play a crucial role as reagents in biotechnology, medicine, bioanalytics as well as in the biological and life sciences in general. Antibodies, i.e. immunoglobulins, are a prominent example of this class of proteins. Despite the manifold needs for such proteins in conjunction with recognition, binding and/or separation of ligands/targets, almost exclusively immunoglobulins are currently used.

**[0003]** Additional proteinaceous binding molecules that have antibody-like functions are the members of the lipocalin family, which have naturally evolved to bind ligands. Lipocalins occur in many organisms, including vertebrates, insects, plants and bacteria. The members of the lipocalin protein family (Pervaiz, S., & Brew, K. (1987) FASEB J. 1, 209-214) are typically small, secreted proteins and have a single polypeptide chain. They are characterized by a range of different molecular-recognition properties: their ability to bind various, principally hydrophobic molecules (such as retinoids, fatty acids, cholesterols, prostaglandins, biliverdins, pheromones, tastants, and odorants), their binding to specific cell-surface receptors and their formation of macromolecular complexes. Although they have, in the past, been classified primarily as transport proteins, it is now clear that the lipocalins fulfill a variety of physiological functions. These include roles in retinol transport, olfaction, pheromone signaling, and the synthesis of prostaglandins. The lipocalins have also been implicated in the regulation of the immune response and the mediation of cell homoeostasis (reviewed, for example, in Flower, D.R. (1996) *Biochem. J.* **318**, 1-14 and Flower, D.R. et al.

15858-63; Prescott G. Woodruff) (T-helper Type 2-driven inflammation defines major subphenotypes of Asthma, Am.J. Respir.Crti.Care Med., 2009, 180:388-395).

**[0007]** Therefore, it would be desirable to have improved therapeutic methods involving therapeutically effective amount of a composition comprising muteins of human tear lipocalin, binding to IL-4RA with high binding affinity and therefore inhibiting IL-4 and/or IL-13 from binding to their respective receptors, that exhibit *in vivo* therapeutic activities in a subject in need thereof. When used in the present application, a subject in need thereof may be a mammal, such as a human, a dog, a mouse, a rat, a pig, an ape such as cynomolgus to name only a few illustrative examples, which is in need of a treatment or prevention of a disorder.

## SUMMARY

**[0007a]** An aspect of the invention is defined in the independent claim. Some optional features of the invention are defined in the dependent claims.

**[0008]** The present disclosure relates to a method of treating, ameliorating or preventing a disorder comprising administering a therapeutically effective amount of a composition to a subject in need of such composition, wherein said composition comprises a lipocalin mutein of the disclosure that is capable of inhibiting IL-4 and/or IL-13 from binding to their respective receptors. In some further embodiment, the lipocalin mutein is capable of disrupting downstream signaling and/or cellular responses induced by IL-4 and/or IL-13. In various embodiments, the disorder is a disorder in which the IL4/IL13 pathway contributes to disease pathogenesis. In various further embodiments, the composition may be locally administered to the lung. In various preferred embodiments, the composition may be administered via aerosol inhalation. In some still preferred embodiments, the 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.

**[0009]** In some embodiments, when used in the present application, a subject in need of such composition 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. In some embodiments, the subject, in need of such composition, 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. In some further embodiments, a subject in need of such composition may be suffering from one or more disorders including, for example, allergic inflammation, allergic asthma, rhinitis, conjunctivitis, lung fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis or adult respiratory distress syndrome. It

**Claims**

1. A composition comprising a human tear lipocalin mutein or a fragment 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 in a subject, wherein said lipocalin mutein or fragment is capable of exhibiting an *in vivo* therapeutic activity in the subject and is capable of inhibiting *in vivo* human IL-13 induced transcript Ccl11 (eotaxin), wherein said lipocalin mutein or fragment has at least 75% sequence identity to the amino acid sequence of the mature human tear lipocalin (SEQ ID NO: 1), wherein said lipocalin mutein or fragment has the same amino acids as set forth in SEQ ID NO: 6 at amino acid positions corresponding to position 26, 27, 28, 30, 31, 32, 33, 34, 53, 55, 56, 57, 58, 61, 63, 64, 66, 80, 83, 104-106, and 108 of the linear polypeptide sequence of the mature human tear lipocalin (SEQ ID NO: 1), and wherein the fragment of the lipocalin mutein lacks at least one of the N-terminal and/or C-terminal amino acids compared to said lipocalin mutein.

2. A composition for the use according to claim 1, wherein said lipocalin mutein or fragment is capable of disrupting downstream signaling and/or cellular responses induced by IL-4 and/or IL-13.

3. A composition for the use according to claim 1, wherein said lipocalin mutein or fragment is more potent than an IL-4 mutant (R121D, Y124D) when inhibiting human IL-13 induced transcript Ccl11 (eotaxin) in vivo.

4. A composition for the use according to claim 1, wherein said lipocalin mutein or fragment is capable of exhibiting a functional activity as good as the anti-IL-4RA monoclonal antibody AMG 317 (SEQ ID NOs: 14 and 15).

5. A composition for the use according to claim 4, wherein said lipocalin mutein or fragment is capable of inhibiting IL-13-induced goblet cell metaplasia as effectively as the anti-IL-4RA monoclonal antibody AMG 317 (SEQ ID NOs: 14 and 15).

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

7. A composition for the use according to any one of the preceding claims, wherein said composition is to be locally administered to the lung.

8. A composition for the use according to any one of the preceding claims, wherein said composition is to be administered via aerosol inhalation.

9. A composition for the use according to any one of the preceding claims, wherein said composition is to be 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.

10. A composition for the use according to any one of the preceding claims, wherein said composition is to be 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.

11. 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.

12. A composition for the use according to any one of claims 1-10, wherein said disorder is associated with an allergic reaction or an allergic inflammation.

13. A composition for the use according to any one of claims 1-12, wherein said disorder is allergic inflammation, allergic asthma, rhinitis, conjunctivitis, lung fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis or adult respiratory distress syndrome.

14. A composition for the use according to any one of claims 1-12, wherein said disorder is allergic asthma, rhinitis, conjunctivitis or dermatitis.

15. A composition for the use according to claim 12, wherein said composition further comprises an anti-allergic medicament and/or an anti-allergic inflammation medicament.

16. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein or fragment is essentially not cross-reactive with IL-23 receptor alpha chain, type I cytokine receptor with fibronectin type III domain, IL-6 receptor, or IL-18 receptor alpha chain.

17. A composition for the use according to any one of claims 1-10 wherein said disorder is a lung disorder.

18. A composition for the use according to any one of the preceding claims, wherein said lipocalin mutein or fragment binds to IL-4 receptor alpha chain.