

CLAIMS

1. An IL-33 antagonist for use in the prevention or treatment of a respiratory disease by inhibiting RAGE-EGFR-mediated signaling, wherein the respiratory disease is characterized by abnormal epithelium physiology and/or aberrant EGFR activity.
- 5 2. An IL-33 antagonist for use according to claim 1, wherein the respiratory disease is a lower respiratory disease, preferably a respiratory disease of the bronchi.
3. An IL-33 antagonist for use according to claim 1 or 2, wherein the respiratory disease is selected from: COPD, bronchitis, emphysema, bronchiectasis, such as CF-bronchiectasis or non-CF-bronchiectasis, asthma or asthma and COPD overlap (ACO), wherein optionally the
10 respiratory disease is COPD, preferably bronchitic COPD or asthma, preferably bronchitic asthma.
4. An IL-33 antagonist for use according to any of claims 1-3, wherein the prevention or treatment:
 - a. improves mucus clearance, inhibits or reduces abnormal mucus production;
 - 15 b. inhibits or reduces MUC5AC production; and/or
 - c. inhibits abnormal mucus composition, such as inhibits or reduces the ratio of MUC5AC:MUC5B; inhibits or reduces MUC5AC in mucus; and/or reduces the thickness of mucus; inhibits abnormal epithelium remodelling;
 - d. inhibits abnormal goblet cell differentiation or proliferation, wherein optionally the
20 abnormal goblet cell differentiation or proliferation is abnormal MUC5AC⁺ goblet cell differentiation or proliferation; and/or
 - e. reduces the thickness of the respiratory epithelium, wherein optionally the prevention or treatment reduces the amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.
- 25 5. An IL-33 antagonist for use in the prevention or treatment of abnormal epithelium physiology by modulating or inhibiting a RAGE-EGFR mediated effect.
6. An IL-33 antagonist for use according to claim 5, wherein the abnormal epithelium physiology is abnormal mucociliary physiology, preferably abnormal mucociliary physiology of respiratory epithelium, wherein optionally abnormal mucociliary physiology is selected from:
30 abnormal mucus production; abnormal goblet cell differentiation, abnormal goblet cell proliferation; abnormal thickness of the epithelium; abnormal mucus clearance; and/or abnormal mucus composition.

7. An IL-33 antagonist for use according to claim 5 or 6, wherein abnormal mucociliary physiology comprises: increased mucus production; increased goblet cell differentiation; increased goblet cell proliferation; increased thickness of the epithelium; and/or decreased mucus clearance.
- 5 8. An IL-33 antagonist for use according to claim 7, wherein increased mucus production comprises increased MUC5AC production; and/or wherein increased goblet cell differentiation comprises increased MUC5AC⁺ goblet cell differentiation; and/or wherein increased goblet cell proliferation comprises increased MUC5AC⁺ goblet cell proliferation; and/or wherein increased thickness of the epithelium comprises an increased amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.
- 10 9. An IL-33 antagonist for use according to claim 6, wherein abnormal mucus composition comprises an increase or a decrease in the ratio of the different mucus compounds contained in mucus; an increase or decrease in one or more mucus compounds; and/or an increase or decrease in the concentration or thickness of mucus.
- 15 10. An IL-33 antagonist for use according to claim 9, wherein abnormal mucus composition comprises an increase in the ratio of MUC5AC:MUC5B; and/or wherein abnormal mucus composition comprises an increase in MUC5AC contained in mucus; and/or wherein abnormal mucus composition comprises an increase in thickness of mucus.
- 20 11. An IL-33 antagonist for use according to claim 5, wherein the abnormal epithelium physiology is abnormal epithelium remodeling.
12. An IL-33 antagonist for use according to any preceding claim, wherein the abnormal epithelium physiology is of the respiratory tract, wherein optionally the respiratory tract is the lower respiratory tract, preferably the bronchi.
- 25 13. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist inhibits the activity of oxidised IL-33.
14. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist prevents binding of oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signaling.
15. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist is an antibody or antigen-binding fragment thereof, preferably an anti-IL-33 antibody or antigen-

binding fragment thereof, preferably an anti-reduced-IL-33 antibody or antigen-binding fragment thereof.

5 16. An IL-33 antagonist for use according to claim 15, wherein the antibody or antigen-binding fragment thereof comprises a VHCDR1 having the sequence of SEQ ID NO: 37, a VHCDR2 having the sequence of SEQ ID NO: 38, a VHCDR3 having the sequence of SEQ ID NO: 39, a VLCDR1 having the sequence of SEQ ID NO: 40, a VLCDR2 having the sequence of SEQ ID NO: 41, and a VLCDR3 having the sequence of SEQ ID NO: 42.

10 17. An IL-33 antagonist for use according to claim 16, wherein the antibody or antigen binding fragment thereof comprises a VH and VL, wherein the VH has an amino acid sequence consisting of SEQ ID NO: 1, and the VL has an amino acid sequence consisting of SEQ ID NO: 19.