

CLAIMS

1. Use of an IL-33 antagonist in the manufacture of a medicament for the 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 wherein the IL-33 antagonist is an antibody or antigen-binding fragment thereof, and 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).
2. The use according to claim 1, wherein the respiratory disease is COPD, preferably bronchitic COPD.
- 10 3. The use according to claim 1 wherein the respiratory disease is asthma, preferably bronchitic asthma.
4. The use according to any of claims 1-3, wherein the treatment:
 - a. improves mucus clearance, inhibits or reduces abnormal mucus production;
 - b. inhibits or reduces MUC5AC production; and/or
 - 15 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 abnormal goblet cell differentiation or proliferation is abnormal MUC5AC⁺ goblet
20 cell differentiation or proliferation; and/or
 - e. reduces the thickness of the respiratory epithelium, wherein optionally the treatment reduces the amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.
5. The use according to any preceding claim, wherein the abnormal epithelium physiology is of
25 the respiratory tract, wherein optionally the respiratory tract is the lower respiratory tract, preferably the bronchi.
6. The use according to any preceding claim, wherein the IL-33 antagonist inhibits the activity of oxidised IL-33.
7. The use according to any preceding claim, wherein the IL-33 antagonist prevents binding of
30 oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signaling.

8. The use according to any preceding claim, wherein the IL-33 antagonist is an anti-IL-33 antibody or antigen-binding fragment thereof, preferably an anti-reduced-IL-33 antibody or antigen-binding fragment thereof.
- 5 9. The use according to claim 8, 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 10. The use according to claim 9, 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.