

CLAIMS

54. An IL-33 antagonist for use in the prevention or treatment of abnormal epithelium physiology by modulating or inhibiting a RAGE-EGFR mediated effect.
62. An IL-33 antagonist for use according to claim 54, wherein the abnormal epithelium physiology is abnormal mucociliary physiology, preferably abnormal mucociliary physiology of respiratory epithelium.
- ~~3. An IL-33 antagonist for use according to claim 2, wherein optionally abnormal mucociliary physiology is selected from: abnormal mucus production; abnormal goblet cell differentiation, abnormal goblet cell proliferation; abnormal thickness of the epithelium; abnormal mucus clearance; and/or abnormal mucus composition.~~
- ~~4. An IL-33 antagonist for use according to claim 3, wherein abnormal mucus production comprises abnormal MUC5AC production; and/or wherein abnormal goblet cell differentiation comprises abnormal MUC5AC⁺ goblet cell differentiation; and/or wherein abnormal goblet cell proliferation comprises abnormal MUC5AC⁺ goblet cell proliferation; and/or wherein abnormal thickness of the epithelium comprises an abnormal amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.~~
75. An IL-33 antagonist for use according to claim 52, ~~3~~ or 64, 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.
86. An IL-33 antagonist for use according to claim 75, 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.
97. An IL-33 antagonist for use according to claim 63, 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.

108. An IL-33 antagonist for use according to claim 97, 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.

119. An IL-33 antagonist for use according to claim 54, wherein the abnormal epithelium physiology is abnormal epithelium remodeling.

1240. An IL-33 antagonist for use according to any preceding claim, wherein the abnormal epithelium physiology is of the respiratory tract, ~~preferably abnormal mucociliary physiology of the respiratory tract.~~

~~11. An IL-33 antagonist for use according to claim 10, wherein optionally the respiratory tract is the lower respiratory tract, preferably the bronchi.~~

~~12. An IL-33 antagonist for use in the prevention or treatment of an EGFR-mediated disease.~~

~~13. An IL-33 antagonist for use according to claim 12, wherein the EGFR-mediated disease is a RAGE-EGFR-mediated disease.~~

~~14. An IL-33 antagonist for use according to claim 12 or 13 wherein the EGFR-mediated disease is characterized by aberrant EGFR activity.~~

~~15. An IL-33 antagonist for use according to any of claims 12-14 wherein the EGFR-mediated disease is characterized by abnormal epithelium physiology.~~

~~16. An IL-33 antagonist for use in the prevention or treatment of a disease by improving epithelium physiology.~~

17. An IL-33 antagonist for use in the prevention or treatment of a respiratory disease by inhibiting an RAGE-EGFR-mediated-effect signaling, wherein the respiratory disease is characterized by abnormal epithelium physiology and/or aberrant EGFR activity.

~~18. An IL-33 antagonist for use according to claim 17, wherein the EGFR-mediated effect is EGFR signalling.~~

~~19. An IL-33 antagonist for use according to claim 17 or 18, wherein the EGFR-mediated effect is a RAGE-EGFR-mediated effect.~~

20. ~~An IL-33 antagonist for use according to any of claims 17-19, wherein the EGFR-mediated effect is RAGE-EGFR-mediated signalling.~~

21. ~~An IL-33 antagonist for use according to any of claims 16-20, wherein the disease is a respiratory disease.~~

22. ~~An IL-33 antagonist for use according to claim 21 wherein the respiratory disease is characterised by abnormal epithelium physiology and/or aberrant EGFR activity.~~

23. ~~An IL-33 antagonist for use according to claim 21 or 22, wherein the respiratory disease is a lower respiratory disease, preferably a respiratory disease of the bronchi.~~

24. ~~An IL-33 antagonist for use according to any of claims 1 or 21-23, 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);~~

25. ~~An IL-33 antagonist for use according to any of claims 21-24, wherein optionally the respiratory disease is COPD, preferably bronchitic COPD or;~~

26. ~~An IL-33 antagonist for use according to any of claims 21-24, wherein the respiratory disease is asthma, preferably bronchitic asthma.~~

27. ~~An IL-33 antagonist for use according to any of claims 1-26, wherein the prevention or treatment;~~

a. ~~improves mucus clearance;~~

28. ~~An IL-33 antagonist for use according to any of claims 16-27, wherein the prevention or treatment inhibits or reduces abnormal mucus production;~~

b.

29. ~~An IL-33 antagonist for use according to claim 28, wherein the prevention or treatment inhibits or reduces MUC5AC production; and/or~~

c.

30. ~~An IL-33 antagonist for use according to any of claims 16-29, wherein the prevention or treatment inhibits an abnormal mucus composition;~~

31. ~~An IL-33 antagonist for use according to claim 30, wherein the prevention or treatment such as inhibits or reduces the ratio of MUC5AC:MUC5B; and/or wherein the prevention or treatment inhibits or reduces MUC5AC in mucus; and/or wherein the prevention or treatment reduces the thickness of mucus;~~

~~32. An IL-33 antagonist for use according to any of claims 16-31, wherein the prevention or treatment inhibits abnormal epithelium remodelling;~~

d.

~~33. An IL-33 antagonist for use according to any of claims 16-32, wherein the prevention or treatment inhibits abnormal goblet cell differentiation or proliferation;~~

~~34. An IL-33 antagonist for use according to claim 33, wherein optionally the abnormal goblet cell differentiation or proliferation is abnormal MUC5AC⁺ goblet cell differentiation or proliferation; and/or~~

e.

~~35. An IL-33 antagonist for use according to any of claims 16-34, wherein the prevention or treatment reduces the thickness of the respiratory epithelium;~~

~~36. An IL-33 antagonist for use according to claim 35, wherein optionally the prevention or treatment reduces the amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.~~

1337. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist inhibits the activity of oxidised IL-33.

1438. 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 ~~signalling~~signaling.

~~39. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist down-regulates or inhibits RAGE-EGFR dependent signalling and/or RAGE-EGFR mediated effects.~~

~~40. An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist is a binding molecule or fragment thereof which binds to IL-33, preferably which binds to reduced IL-33 or oxidised IL-33, preferably which binds to reduced IL-33.~~

1541. 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.

42. ~~An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist is a binding molecule which comprises complementarity determining regions (CDRs) of a variable heavy domain (VH) and a variable light domain (VL) pair selected from Table 1.~~

43. ~~An IL-33 antagonist for use according to any preceding claim, wherein the IL-33 antagonist is a binding molecule which comprises a variable heavy domain (VH) and variable light domain (VL) pair selected from Table 1.~~

1644. An IL-33 antagonist for use according to ~~any preceding claim~~ 15, wherein the antibody or antigen-binding fragment thereof ~~IL-33 antagonist is a binding molecule which 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.

~~45. A method for the prevention or treatment of abnormal epithelium physiology in a subject, by administering a therapeutically effective amount of an IL-33 antagonist to modulate or inhibit a RAGE-EGFR mediated effect.~~

~~46. The method of claim 45, wherein the abnormal epithelium physiology is abnormal mucociliary physiology, preferably abnormal mucociliary physiology of respiratory epithelium.~~

~~47. The method of claim 46, wherein abnormal mucociliary physiology is selected from: abnormal mucus production; abnormal goblet cell differentiation; abnormal goblet cell proliferation; abnormal thickness of the epithelium;; abnormal mucus clearance; and/or abnormal mucus composition.~~

~~48. The method of claim 47, wherein abnormal mucus production comprises abnormal MUC5AC production; and/or wherein abnormal goblet cell differentiation comprises abnormal MUC5AC⁺ goblet cell differentiation; and/or wherein abnormal goblet cell proliferation comprises abnormal MUC5AC⁺ goblet cell proliferation; and/or wherein abnormal thickness of the epithelium comprises an abnormal amount of MUC5AC⁺ goblet cells in the total tissue area of the epithelium.~~

~~49. The method of claim 47 or 48, 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.~~

50. The method of claim 49, 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.
51. The method of claim 47, 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.
52. The method of claim 51, 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.
53. The method of claim 45, wherein the abnormal epithelium physiology is abnormal epithelium remodelling.
54. The method of any of claims 45-53, wherein the abnormal epithelium physiology is of the respiratory tract, preferably abnormal mucociliary physiology of the respiratory tract.
55. The method of claim 54, wherein the respiratory tract is the lower respiratory tract, preferably the bronchi.
56. The method for the prevention or treatment of an EGFR mediated disease, by administering a therapeutically effective amount of an IL-33 antagonist.
57. The method of claim 56, wherein the EGFR mediated disease is a RAGE-EGFR mediated disease.
58. The method of claim 56 or 57, wherein the EGFR mediated disease is characterised by aberrant EGFR activity.
59. The method of any of claims 56-58 wherein the EGFR mediated disease is characterised by abnormal epithelium physiology.

60. A method for the prevention or treatment of a disease, by administering a therapeutically effective amount of an IL-33 antagonist to improve epithelium physiology.

61. A method for the prevention or treatment of a disease, by administering a therapeutically effective amount of an IL-33 antagonist to inhibit an EGFR-mediated effect.

5 62. The method of claim 61, wherein the EGFR-mediated effect is EGFR signalling.

63. The method of claim 61 or 62, wherein the EGFR-mediated effect is a RAGE-EGFR-mediated effect.

64. The method of any of claims 61-63, wherein the EGFR-mediated effect is RAGE-EGFR-mediated signalling.

10 65. The method of any of claims 60-64, wherein the disease is a respiratory disease.

66. The method of claim 65, wherein the respiratory disease is characterised by abnormal epithelium physiology and/or aberrant EGFR activity.

67. The method of claim 65 or 66, wherein the respiratory disease is a lower respiratory disease, preferably a respiratory disease of the bronchi.

15 68. The method of any of claims 65-67, wherein the respiratory disease is selected from: COPD, bronchitis, emphysema, bronchiectasis, such as CF bronchiectasis or CF bronchiectasis, asthma or asthma and COPD overlap (ACO).

69. The method of any of claims 65-68, wherein the respiratory disease is COPD, preferably bronchitic COPD.

20 70. The method of any of claims 65-69, wherein the respiratory disease is asthma, preferably bronchitic asthma.

71. The method of any of claims 45-70, wherein the method improves mucus clearance.

72. The method of any of claims 45-71, wherein the method inhibits or reduces abnormal mucus production.

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73. The method of claim 72, wherein the abnormal mucus production is an increase in MUC5AC production.

74. The method of any of claims 45-73, wherein the method inhibits an abnormal mucus composition.

5 75. The method of claim 74, wherein the method inhibits or reduces the ratio of MUC5AC:MUC5B; and/or wherein the method inhibits or reduces MUC5AC in mucus; and/or wherein the method reduces the thickness of mucus.

76. The method of any of claims 45-75, wherein the method inhibits abnormal epithelium remodeling.

10 77. The method of any of claims 45-76, wherein the method inhibits or reduces abnormal goblet cell differentiation or proliferation.

78. The method of claim 77, wherein the method inhibits or reduces abnormal MUC5AC⁺ goblet cell differentiation or proliferation.

15 79. The method of any of claims 45-78, wherein the method reduces the thickness of the respiratory epithelium.

80. The method of claim 79, wherein the method reduces the amount of MUC5AC⁺ goblet cells in the total tissue area of the respiratory epithelium.

81. The method of any of claims 45-80, wherein the IL-33 antagonist inhibits the activity of oxidised IL-33.

20 82. The method of any of claims 45-81, wherein the IL-33 antagonist prevents binding of oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signalling.

83. The method of any of claims 45-82, wherein the IL-33 antagonist down-regulates or inhibits RAGE-EGFR dependent signalling and/or RAGE-EGFR mediated effects.

25 84. The method of any of claims 45-83, wherein the IL-33 antagonist is a binding molecule or fragment thereof which binds to IL-33, preferably reduced IL-33 or oxidised IL-33, preferably reduced IL-33.

85. ~~The method of any of claims 45-84, 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.~~

86. ~~The method of any of claims 45-85, wherein the IL-33 antagonist is a binding molecule which comprises complementarity determining regions (CDRs) of a variable heavy domain (VH) and a variable light domain (VL) pair selected from Table 1.~~

87. ~~The method of any of claims 45-86, wherein the IL-33 antagonist is a binding molecule which comprises a variable heavy domain (VH) and variable light domain (VL) pair selected from Table 1.~~

88. ~~The method of any of claims 45-87, wherein the IL-33 antagonist is a binding molecule which 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.~~

1789. An ~~The method of any of claims 45-88, or the IL-33 antagonist for use according to any of claims 16-44, wherein the IL-33 antagonist is an anti-IL33 antibody or antigen binding fragment thereof comprising a VH and VL, wherein the VH domain of the~~ has an amino acid sequence consisting of SEQ ID NO: 1, and a the VL domain of the has an amino acid sequence consisting of SEQ ID NO: 19.