

CLAIMS

1. An anti-IL-33 therapeutic agent for use in a method of treating kidney injury in a subject, wherein the anti-IL-33 therapeutic agent is to be administered to the subject to attenuate or inhibit IL-33-mediated ST2 signalling and IL-33-mediated RAGE signaling.
2. An anti-IL-33 therapeutic agent for use according to claim 1, wherein the IL-33-mediated RAGE signaling is IL-33-mediated RAGE-EGFR signaling.
3. An anti-IL-33 therapeutic agent for use according to claim 1, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of reduced IL-33 protein (redIL-33) and thereby inhibits ST2 signalling.
4. An anti-IL-33 therapeutic agent for use according to any of claims 1 to 3, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of oxidised IL-33 protein (oxIL-33) and thereby inhibits RAGE signaling.
5. An anti-IL-33 therapeutic agent for use according to any one of claims 1 to 4, wherein the kidney injury comprises inflammation.
6. An anti-IL-33 therapeutic agent for use according to claim 5, wherein the kidney injury is an inflammatory kidney injury.
7. An anti-IL-33 therapeutic agent for use according to claim 5 or 6, wherein the kidney injury is selected from diabetic kidney disease, fibrosis, glomerulonephritis (for example non-proliferative (such as minimal change glomerulonephritis, membrane glomerulonephritis, focal segmental glomerulosclerosis) or prolative (such as IgA nephropathy, membranoproliferative glomerulonephritis, post infectious glomerulonephritis, and rapidly progressive glomerulonephritis [such as Goodpastures syndrome and vasculitic disorders {which includes Wegners granulomatosis and microscopic polyangiitis}]), systemic lupus erythematosus, albuminuria, unilateral ureteral obstruction, Alport syndrome, polycystic kidney disease (PCKD), hypertensive glomerulosclerosis, chronic glomerulosclerosis, chronic obstructive uropathy, chronic tubulo-interstitial nephritis and ischemic nephropathy.
8. An anti-IL-33 therapeutic agent for use according to any one of claims 1 to 7, wherein the kidney injury is diabetic kidney disease.
9. An anti-IL-33 therapeutic agent for use according to any one of claims 1 to 8, wherein the anti-IL-33 therapeutic agent is selected from a chemical inhibitor and an antibody or antigen-binding fragment thereof.
10. An anti-IL-33 therapeutic agent for use according to claim 9, wherein the therapeutic agent comprises an antibody or antigen-binding fragment thereof.
11. An anti-IL-33 therapeutic agent for use according to claim 9 or 10, wherein the antibody or antigen-binding fragment thereof binds specifically to IL-33.

12. An anti-IL-33 therapeutic agent for use according to claim 11, wherein the antibody or antigen-binding fragment has the complementarity determining regions (CDRs) of a variable heavy domain (VH) and a variable light domain (VL) pair selected from Table 1.
13. An anti-IL-33 therapeutic agent for use according to claim 11 or 12, wherein the antibody or antigen-binding fragment thereof specifically binds to redIL-33 and attenuates or inhibits activity of redIL-33, thereby inhibiting ST2 signalling.
14. An anti-IL-33 therapeutic agent for use according to any of claims 11 to 13, wherein the antibody or antigen-binding fragment thereof prevents binding of oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signalling.
15. An anti-IL-33 therapeutic agent for use according to any one of claims 11 to 14, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a binding affinity of less than or equal to 100 pM, or less than or equal to 10 pM, for example less than or equal to 1 pM, such as 0.5pM, in particular 0.05pM (for example when measured using KinExA).
16. An anti-IL-33 therapeutic agent for use according to any one of claims 11 to 15, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a $k(\text{on})$ greater than or equal to $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$, in particular greater than or equal to $10^7 \text{ M}^{-1} \text{ sec}^{-1}$.
17. An anti-IL-33 therapeutic agent for use according to any one of claims 11 to 16, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a $k(\text{off})$ less than or equal to $5 \times 10^{-1} \text{ sec}^{-1}$, 10^{-1} sec^{-1} , $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$ or 10^{-3} sec^{-1} , in particular less than or equal to 10^{-3} sec^{-1} .
18. An anti-IL-33 therapeutic agent for use according to any one of claims 11 to 17, wherein the antibody or an antigen-binding fragment attenuates or inhibits the activity of oxIL-33 and thereby inhibits RAGE signaling.
19. An anti-IL-33 therapeutic agent for use according to any one of claims 10 to 18, wherein the antibody or antigen-binding fragment 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.
20. An anti-IL-33 therapeutic agent for use according to any one of claims 10 to 19, wherein the antibody or antigen-binding VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 1 and SEQ ID NO: 19, respectively.
21. An anti-IL-33 therapeutic agent for use according to claim 20, wherein the antibody or antigen-binding fragment comprises a VH having the sequence of SEQ ID NO: 1 and a VL having the sequence of SEQ ID NO: 19.

22. An anti-IL-33 therapeutic agent for use according to any one of claims 10 to 21, wherein the antibody or an antigen-binding fragment thereof is a human antibody, a chimeric antibody, and a humanized antibody.
23. An anti-IL-33 therapeutic agent for use according to any one of claims 10 to 22, wherein the antibody or the antibody or an antigen-binding fragment thereof is a naturally-occurring antibody, an scFv fragment, an Fab fragment, an F(ab')₂ fragment, a minibody, a diabody, a triabody, a tetrabody, or a single chain antibody.
24. An anti-IL-33 therapeutic agent for use according to any one of claims 10 to 23, wherein the antibody or an antigen-binding fragment thereof is a monoclonal antibody.
25. An anti-IL-33 therapeutic agent for use of any of claims 2 to 24, wherein inhibition or attenuation of RAGE-EGFR signaling down-regulates or inhibits RAGE-EGFR mediated effects.
26. An anti-IL-33 therapeutic agent for use according to claim 25, wherein the RAGE-EGFR mediated effect comprises abnormal epithelium physiology, such as abnormal epithelium remodelling.
27. An anti-IL-33 therapeutic agent for use according to claim 25, wherein the RAGE-EGFR mediated effect comprises abnormal mesangial expansion.
28. An anti-IL-33 therapeutic agent for use according to claim 27, wherein abnormal mesangial expansion comprises abnormal mesangial cell proliferation.
29. An anti-IL-33 therapeutic agent for use according to any of claims 1 to 28, wherein inhibition or attenuation of ST2 signalling down-regulates or inhibits ST2 mediated effects.
30. An anti-IL-33 therapeutic agent for use according to claim 29, wherein the ST2 mediated effect is abnormal inflammation in the kidney.
31. An anti-IL-33 therapeutic agent for use of claim 30, wherein the abnormal inflammation is in the endothelium.
32. An anti-IL-33 therapeutic agent for use according to claim 31, wherein the abnormal inflammation comprises increased IL-4, IL-6, IL-8, IL-12, TNFa and/or IL1b secretion or expression, optionally increased IL-4, IL-6, IL-8 and/or IL-12 secretion or expression.
33. An anti-IL-33 therapeutic agent for use according to either claim 31 or 32, wherein the abnormal inflammation comprises MAP kinase activation.
34. An anti-IL-33 therapeutic agent for use according to claim 33, wherein MAP kinase activation comprises p38 or JNK kinase activation.
35. An anti-IL-33 therapeutic agent for use according to claim 30, wherein the abnormal inflammation is in the glomeruli.
36. An anti-IL-33 therapeutic agent for use according to claim 35, wherein the abnormal inflammation comprises increased IL-8 secretion or expression.

37. A method of treating kidney injury in a subject in need thereof, the method comprising administering to the subject an anti-IL-33 therapeutic agent to attenuate or inhibit IL-33-mediated ST2 signalling and IL-33-mediated RAGE signaling.
38. A method according to claim 37, wherein the IL-33-mediated RAGE signaling is IL-33-mediated RAGE-EGFR signaling.
39. A method according to claim 37 or 38, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of reduced IL-33 protein (redIL-33) and thereby inhibits ST2 signalling.
40. A method according to claims 37 to 39, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of oxidised IL-33 protein (oxIL-33) and thereby inhibits RAGE signaling.
41. A method according to any one of claims 37 to 40, wherein the kidney injury comprises inflammation.
42. A method according to claim 41, wherein the kidney injury is an inflammatory kidney injury.
43. A method according to claim 41 or 42, wherein the kidney injury is selected from diabetic kidney disease, fibrosis, glomerulonephritis (for example non-proliferative (such as minimal change glomerulonephritis, membrane glomerulonephritis, focal segmental glomerulosclerosis) or prolative (such as IgA nephropathy, membranoproliferative glomerulonephritis, post infectious glomerulonephritis, and rapidly progressive glomerulonephritis [such as Goodpastures syndrome and vasculitic disorders {which includes Wegners granulomatosis and microscopic polyangiitis}]), systemic lupus erythematosus, albuminuria, unilateral ureteral obstruction, Alport syndrome, polycystic kidney disease (PKD), hypertensive glomerulosclerosis, chronic glomerulosclerosis, chronic obstructive uropathy, chronic tubulo-interstitial nephritis and ischemic nephropathy.
44. A method according to any one of claims 37 to 43, wherein the kidney injury is diabetic kidney disease.
45. A method according to any one of claims 37 to 44, wherein the anti-IL-33 therapeutic agent is selected from a chemical inhibitor and an antibody or antigen-binding fragment thereof.
46. A method according to claim 45, wherein the therapeutic agent comprises an antibody or antigen-binding fragment thereof.
47. A method according to claim 45 or 46, wherein the antibody or antigen-binding fragment thereof binds specifically to IL-33.
48. A method according to claim 47, wherein the antibody or antigen-binding fragment has the complementarity determining regions (CDRs) of a variable heavy domain (VH) and a variable light domain (VL) pair selected from Table 1.
49. A method according to claim 47 or 48, wherein the antibody or antigen-binding fragment thereof specifically binds to redIL-33 and attenuates or inhibits activity of redIL-33, thereby inhibiting ST2 signalling.

50. A method according to any of claims 47 to 49, wherein the antibody or antigen-binding fragment thereof prevents binding of oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signalling.
51. A method according to any one of claims 47 to 50, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a binding affinity of less than or equal to 100 pM, or less than or equal to 10 pM, for example less than or equal to 1 pM, such as 0.5pM, in particular 0.05pM (for example when measured using KinExA).
52. A method according to any one of claims 47 to 51, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a $k(\text{on})$ greater than or equal to $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$, in particular greater than or equal to $10^7 \text{ M}^{-1} \text{ sec}^{-1}$.
53. A method according to any one of claims 47 to 52, wherein the antibody or an antigen-binding fragment thereof binds to redIL-33 with a $k(\text{off})$ less than or equal to $5 \times 10^{-1} \text{ sec}^{-1}$, 10^{-1} sec^{-1} , $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$ or 10^{-3} sec^{-1} , in particular less than or equal to 10^{-3} sec^{-1} .
54. A method according to any one of claims 47 to 53, wherein the antibody or an antigen-binding fragment attenuates or inhibits the activity of oxIL-33 and thereby inhibits RAGE signaling.
55. A method according to any one of claims 47 to 54, wherein the antibody or antigen-binding fragment 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.
56. A method according to any one of claims 47 to 55, wherein the antibody or antigen-binding VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences at least 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 1 and SEQ ID NO: 19, respectively.
57. A method according to claim 56, wherein the antibody or antigen-binding fragment comprises a VH having the sequence of SEQ ID NO: 1 and a VL having the sequence of SEQ ID NO: 19.
58. A method of any one of claims 47 to 57, wherein the antibody or an antigen-binding fragment thereof is a human antibody, a chimeric antibody, and a humanized antibody.
59. A method of any one of claims 47 to 57, wherein the antibody or the antibody or an antigen-binding fragment thereof is a naturally-occurring antibody, an scFv fragment, an Fab fragment, an F(ab')₂ fragment, a minibody, a diabody, a triabody, a tetrabody, or a single chain antibody.
60. A method of any one of claims 47 to 59, wherein the antibody or an antigen-binding fragment thereof is a monoclonal antibody.
61. The method of claim 48 to 60, wherein inhibition or attenuation of RAGE-EGFR signaling down-regulates or inhibits RAGE-EGFR mediated effects.

62. A method of claim 61, wherein the RAGE-EGFR mediated effect comprises abnormal epithelium physiology, such as abnormal epithelium remodelling.
63. A method according to claim 61, wherein the RAGE-EGFR mediated effect comprises abnormal mesangial expansion.
64. A method according to claim 63, wherein abnormal mesangial expansion comprises abnormal mesangial cell proliferation.
65. A method according to any of claims 47 to 64, wherein inhibition or attenuation or ST2 signalling down-regulates or inhibits ST2 mediated effects.
66. A method according to claim 65, wherein the ST2 mediated effect is abnormal inflammation in the kidney.
67. A method of claim 66, wherein the abnormal inflammation is in the endothelium.
68. A method according to claim 67, wherein the abnormal inflammation comprises increased IL-4, IL-6, IL-8, IL-12, TNFa and/or IL1b secretion or expression, optionally increased IL-4, IL-6, IL-8 and/or IL-12 secretion or expression.
69. A method according to claim 67, wherein the abnormal inflammation comprises MAP kinase activation.
70. A method according to claim 69, wherein MAP kinase activation comprises p38 or JNK kinase activation.
71. A method according to claim 66, wherein the abnormal inflammation is in the glomeruli.
72. An anti-IL-33 therapeutic agent for use according to claim 71, wherein the abnormal inflammation comprises increased IL-8 secretion or expression.