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. The~~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. The~~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. The~~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.~~ The~~An~~ anti-IL-33 therapeutic agent for use according to any one of claims 1 to 4, wherein the kidney injury comprises inflammation~~.~~.

~~6.~~5. ~~An anti-IL-33 therapeutic agent for use according to claim 5,~~ wherein optionally the kidney injury is an inflammatory kidney injury.

~~7.~~ The~~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~~.~~.

6.

~~8.~~7. ~~An~~ The anti-IL-33 therapeutic agent for use according to any one of claims 1 to ~~7~~6, 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.~~ The~~An~~ anti-IL-33 therapeutic agent for use according to any preceding claim ~~9~~, wherein the therapeutic agent comprises an antibody or antigen-binding fragment thereof~~.~~

~~11.~~8. ~~An anti-IL-33 therapeutic agent for use according to claim 9 or 10~~, wherein optionally 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.~~9. The~~An~~ anti-IL-33 therapeutic agent for use according to claim ~~11 or 12~~8, 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.~~10. The~~An~~ anti-IL-33 therapeutic agent for use according to ~~any of~~ claims ~~11 to 13~~8 or claim 9, 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(on) greater than or equal to 10^5 M^{-1} sec^{-1}, 5 X 10^5 M^{-1} sec^{-1}, 10^6 M^{-1} sec^{-1}, or 5 X 10^6 $M^{-1}$$sec^{-1}$ or 10^7 $M^{-1}$$sec^{-1}$, in particular greater than or equal to 10^7 $M^{-1}$$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(off) less than or equal to 5 X 10^{-1} sec^{-1}, 10^{-1} sec^{-1}, 5 X 10^{-2} sec^{-1}, 10^{-2} sec^{-1}, 5 X $l0^{-3}$ 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.~~11. The~~An~~ anti-IL-33 therapeutic agent for use according to any one of claims ~~10~~ 8 to ~~18~~10, 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.~~12. The~~An~~ anti-IL-33 therapeutic agent for use according to any one of claims ~~10~~ 8 to ~~19~~11, 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% or 100% 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.

25.13. The~~An~~ anti-IL-33 therapeutic agent for use of any of claims 2 to ~~24~~12, wherein inhibition or attenuation of RAGE-EGFR signaling down-regulates or inhibits RAGE-EGFR mediated effects.

14. The~~An~~ anti-IL-33 therapeutic agent for use according to claim ~~25~~13, wherein the RAGE-EGFR mediated effect comprises:

26. abnormal epithelium physiology, such as abnormal epithelium remodelling; or.

a. An anti-IL-33 therapeutic agent for use according to claim 25, wherein the RAGE-EGFR mediated effect comprises

27. abnormal mesangial expansion, .

28.b. An anti-IL-33 therapeutic agent for use according to claim 27, wherein optionally abnormal mesangial expansion comprises abnormal mesangial cell proliferation.

29. The~~An~~ anti-IL-33 therapeutic agent for use according to any one of claims 1 to ~~28~~14, 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 optionally the ST2 mediated effect is abnormal inflammation in the kidney, optionally in .

31.15. An anti-IL-33 therapeutic agent for use of claim 30, wherein the abnormal inflammation is in the endothelium or the glomeruli.

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 (PCKD), 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(on) greater than or equal to 10^5 M^{-1} sec^{-1}, 5 X 10^5 M^{-1} sec^{-1}, 10^6 M^{-1} sec^{-1}, or 5 X 10^6 M^{-1} sec^{-1} or 10^7 M^{-1} sec^{-1}, in particular greater than or equal to 10^7 M^{-1} 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(off) less than or equal to 5 X 10^{-1} sec^{-1}, 10^{-1} sec^{-1}, 5 X 10^{-2} sec^{-1}, 10^{-2} sec^{-1}, 5 X $l0^{-3}$ 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.~~

~~An anti-IL-33 therapeutic agent for use according to claim 71, wherein the abnormal inflammation comprises increased IL-8 secretion or expression.~~

16. Use of an anti-IL-33 therapeutic agent in the manufacture of a medicament for 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.
17. The use of claim 16, wherein the IL-33-mediated RAGE signaling is IL-33-mediated RAGE-EGFR signaling.
18. The use of claim 16, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of reduced IL-33 protein (redIL-33) and thereby inhibits ST2 signalling.

19. The use of any of claims 16 to 18, wherein the anti-IL-33 therapeutic agent attenuates or inhibits activity of oxidised IL-33 protein (oxIL-33) and thereby inhibits RAGE signaling.
20. The use of any one of claims 16 to 19, wherein the kidney injury comprises inflammation, wherein optionally the kidney injury is an inflammatory kidney injury.
21. The use of claim 20, 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.
22. The use of any one of claims 16 to 21, wherein the kidney injury is diabetic kidney disease.
23. The use of any one of claims 16 to 22, wherein the therapeutic agent comprises an antibody or antigen-binding fragment thereof, wherein optionally the antibody or antigen-binding fragment thereof binds specifically to IL-33.
24. The use of claim 23, 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.
25. The use of claim 23 or claim 24, wherein the antibody or antigen-binding fragment thereof prevents binding of oxidised IL-33 to RAGE, thereby inhibiting RAGE-EGFR signalling.
26. The use of any one of claims 23 to 25, 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.
27. The use of any one of claims 23 to 26, wherein the VH and VL of said antibody or antigen-binding fragment thereof comprise amino acid sequences at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 1 and SEQ ID NO: 19, respectively.
28. The use of any of claims 17 to 27, wherein inhibition or attenuation of RAGE-EGFR signaling down-regulates or inhibits RAGE-EGFR mediated effects.
29. The use of claim 28, wherein the RAGE-EGFR mediated effect comprises:
    a. abnormal epithelium physiology, such as abnormal epithelium remodelling; or
    b. abnormal mesangial expansion, wherein optionally abnormal mesangial expansion comprises abnormal mesangial cell proliferation.

30. The use according to any one of claims 16 to 29, wherein inhibition or attenuation of ST2 signalling down-regulates or inhibits ST2 mediated effects, wherein optionally the ST2 mediated effect is abnormal inflammation in the kidney, optionally in the endothelium or the glomeruli.