Claims

1. An antagonist antibody or fragment thereof that binds to human OX40 comprising a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, and/or a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and/or a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and/or comprising a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, and/or a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5 and/or a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

2. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and/or comprises a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

3. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof is a murine antibody, chimeric antibody or a humanized antibody.

4. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof is a humanized antibody.

5. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 7.

6. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a non-CDR region of a heavy chain variable region sequence which is at least 80 % identical to the non-CDR region of the heavy chain variable region sequence of SEQ ID NO: 7.

7. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain sequence comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 35, 36, 37 and 38.

8. The antibody or fragment thereof of claim 7, wherein the heavy chain sequence comprises a non-CDR region which is at least 80 % identical to the non-CDR region of the heavy chain variable region sequence of the heavy chain sequence selected from the group consisting of SEQ ID NOS: 35, 36, 37 or 38.

9. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain variable region sequence comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 58, 59, 79 and 80.

10. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a non-CDR region of a heavy chain variable region sequence which is at least 80 % identical to the non-CDR region of the heavy chain variable region sequence selected from the group consisting of SEQ ID NOS: 58, 59, 79 and 80.

11. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain variable framework region that is the product of or derived from a human gene selected from the group consisting of IGHV2-70*10 (SEQ ID NO: 19), IGHV2-70*01 (SEQ ID NO: 20), IGHV2-70*13 (SEQ ID NO: 21), IGHV2-5*09 (SEQ ID NO: 22), and IGHV2-70*11 (SEQ ID NO: 23).

12. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain variable framework region that is the product of or derived from human gene IGHV2-70*10 (SEQ ID NO: 19) and wherein the heavy chain variable framework region comprises at least one amino acid modification from the corresponding heavy chain variable framework region of the corresponding murine antibody.

13. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 32 and wherein the heavy chain variable framework region comprises at least one amino acid modification from the corresponding heavy chain variable framework region of the

corresponding murine antibody.

14. The humanized antibody or fragment thereof of claim 12 or 13, wherein the amino acid modification comprises an amino acid substitution at amino acid position selected from the group consisting of 23, 35b, 48, 50, 60, and 62, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

15. The humanized antibody or fragment thereof of claim 12 or 13, wherein the amino acid modification comprises an amino acid substitution selected from the group consisting of 23S, 35bG, 48L, 50H, 60N, and 62A, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

16. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 8.

17. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a non-CDR region of a light chain variable region sequence which is at least 80 % identical to the non-CDR region of the light chain variable region sequence of SEQ ID NO: 8.

18. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain sequence comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 45, 46, 47 and 49.

19. The antibody or fragment thereof of claim 18, wherein the light chain sequence comprises a non-CDR region which is at least 80% identical to the non-CDR region of the light chain variable region sequence of the light chain sequence selected from the group consisting of SEQ ID NO: 45, 46, 47 or 49.

20. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain variable region sequence comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 60, 86, 87 and 89.

21. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a non-CDR region of a light chain variable region sequence which is at least 80% identical to the non-CDR region of the heavy chain variable region sequence selected from the group consisting of SEQ ID NOS: 60, 86, 87 and 89.

22. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain variable framework region that is the product of or derived from a human gene selected from the group consisting of IGKV3-11*01 (SEQ ID NO: 24), IGKV1-39*01 (SEQ ID NO: 25), IGKV1D-39*01 (SEQ ID NO: 26), IGKV3-11*02 (SEQ ID NO: 27) and IGKV3-20*01 (SEQ ID NO: 28).

23. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain variable framework region that is the product of or derived from human gene IGKV3-11*01 (SEQ ID NO: 24) and wherein the light chain variable framework region comprises at least one amino acid modification from the corresponding framework region of the light chain variable region of the corresponding murine antibody.

24. The antibody or fragment thereof of claims 1 or 2, wherein the antibody or fragment thereof comprises a light chain sequence comprising the amino acid sequence of SEQ ID NO: 39 and wherein the light chain variable framework region comprises at least one amino acid modification from the corresponding light chain variable framework region of the corresponding murine antibody.

25. The humanized antibody or fragment thereof of claim 23 or 24, wherein the amino acid modification comprises an amino acid substitution at amino acid position selected from the group consisting of 1, 33, 34, 46, 47, 54, 56, and 71, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

26. The humanized antibody or fragment thereof of claim 23 or 24, wherein the amino acid modification comprises an amino acid substitution selected from the group consisting of 1Q, 33M, 34H, 46P, 47W, 54L, 56S, and 71Y, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

27. The humanized antibody or fragment thereof of claim 23 or 24, wherein the amino acid modification comprises an amino acid deletion at amino acid position 31, wherein the amino acid position is indicated according to the Kabat numbering.

28. The antibody or fragment thereof of claim 2, wherein the antibody or fragment thereof comprises:

(a) a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38; and

(b) a light chain sequence comprising the amino acid sequence of SEQ ID NO: 47.

29. The antibody or fragment thereof of claim 2, wherein the antibody or fragment thereof comprises:

(a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 58 or SEQ ID NO: 59; and

(b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 60.

30. The antibody or fragment thereof of any one of claims 1 to 29, wherein at least one of the heavy chain CDRs and/or at least one of the light chain CDRs comprises at least one amino acid modification.

31. The antibody or fragment thereof of any one of claims 1 to 30, further comprising heavy and/or light constant regions.

32. The antibody or fragment thereof of claim 31, wherein the human heavy constant region is selected from the group of human immunoglobulins consisting of IGHG1, non fucosylated IGHG1 and IGHG4.

33. The antibody or fragment thereof of any one of claims 1 to 31, wherein the antibody is a monovalent antibody.

34. The antibody or fragment thereof of any one of claims 1 to 31, wherein the antibody is a full length antibody.

35. The antibody or fragment thereof of any one of claims 1 to 31, wherein the antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fd, Fv, dAb, F(ab')2, scFv, bispecific single chain Fv dimers, diabodies, triabodies and scFv genetically fused to the same or a different antibody.

36. The antibody or fragment thereof of any one of claims 1 to 31, wherein the antibody comprises a variant Fc region which comprises at least one amino acid modification relative to the Fc region of the parent antibody, whereas the antibody comprising the variant Fc region exhibits altered effector function compared to the parent antibody.

37. The antibody or fragment thereof of any one of claims 1 to 36, wherein the antibody or fragment thereof binds to human OX40 with an affinity (KD) of 110 nM or less.

38. The antibody or fragment thereof of any one of claims 1 to 36, wherein the antibody or fragment thereof retains at least 75% of the OX40 binding affinity (K_D) of the corresponding chimeric antibody.

39. The antibody or fragment thereof of any one of claims 1 to 36, wherein the antibody or fragment thereof has equivalent or higher OX40 binding affinity (K_D) when compared to the corresponding chimeric antibody.

40. The antibody or fragment thereof of any one of claims 1 to 36, wherein the antibody has a FAB fragment thermostability temperature greater than 75°C.

41. An antibody or fragment thereof that binds to human OX40 and which binds to the same epitope as the antibody of any one of claims 1 to 36.

42. An epitope on the human OX40 extracellular domain which is bound by the antibody of any one of claims 1 to 36.

43. An epitope of claim 42, wherein the human OX40 extracellular domain is domain 2 (SEQ ID NO: 76).

44. An isolated nucleic acid encoding the antibody or fragment thereof of any one of claims 1 to 41.

45. The isolated nucleic acid of claim 44 comprising DNA encoding the heavy chain variable region comprising the nucleotide acid sequence of SEQ ID NO: 61 or 62; and/or DNA encoding the light chain variable region comprising the nucleotide acid sequence of SEQ ID NO: 63.

46. A vector comprising the isolated nucleic acid of claim 44 or 45.

47. A host cell comprising the isolated nucleic acid of claim 44 or 45 or the vector of claim 46.

48. A method of producing an antibody or fragment thereof that binds to human OX40 comprising culturing the host cell of claim 47 so that the nucleic acid is expressed and the antibody produced.

49. An antibody or fragment thereof that binds to human OX40 encoded by the isolated nucleic acid of claim 44 or 45.

50. A composition comprising the antibody or fragment thereof of any one of claims 1 to 41 and a pharmaceutically acceptable carrier.

51. An immunoconjugate comprising the antibody or fragment thereof of any one of claims 1 to 41 linked to a therapeutic agent.

52. A composition comprising the immunoconjugate of claim 51 and a pharmaceutically acceptable carrier.

53. The composition of claim 50 or 52 further comprising another pharmaceutically active agent.

54. A method for treating an OX40 mediated disorder in a subject, the method comprising administering to the subject a therapeutically effective amount of the antibody or fragment thereof of any one of claims 1 to 41.

55. The method of claim 54, wherein the OX40 mediated disorder is selected from the group consisting of infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, asthma, COPD, pelvic inflammatory disease, Alzheimer's Disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Peyronie's Disease, cochac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme disease, arthritis, meningoencephalitis, autoimmune uveitis, immune mediated inflammatory disorders of the central and peripheral nervous system such as multiple sclerosis, lupus (such as systemic lupus erythematosus) and Guillain-Barr syndrome, Atopic dermatitis, autoimmune hepatitis, fibrosing alveolitis, Grave's disease, IgA nephropathy, idiopathic thrombocytopenic purpura, Meniere's disease, pemphigus, primary biliary cirrhosis, sarcoidosis, scleroderma, Wegener's granulomatosis, other autoimmune disorders, pancreatitis, trauma (surgery), graft-versus-host disease (GVHD), transplant rejection, cardiovascular disease including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, osteoarthritis, periodontitis, hypochlorhydia and neuromyelitis optica.

56. The method of claim 54, wherein the OX40 mediated disorder is selected from the group consisting of infections (viral, bacterial, fungal and parasitic), endotoxic shock associated with infection, arthritis, rheumatoid arthritis, asthma, bronchitis, influenza, respiratory syncytial virus, pneumonia, COPD, idiopathic pulmonary fibrosis (IPF), cryptogenic fibrosing alveolitis (CFA), idiopathic fibrosing interstitial pneumonia, emphysema, pelvic inflammatory disease, Alzheimer's Disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Peyronie's Disease, coehac disease, gallbladder disease, Pilonidal disease, peritonitis, psoriasis, vasculitis, surgical adhesions, stroke, Type I Diabetes, lyme disease, arthritis, meningoencephalitis, autoimmune uveitis, immune mediated inflammatory disorders of the

central and peripheral nervous system such as multiple sclerosis, lupus (such as systemic lupus erythematosus) and Guillain-Barr syndrome, Atopic dermatitis, autoimmune hepatitis, fibrosing alveolitis, Grave's disease, IgA nephropathy, idiopathic thrombocytopenic purpura, Meniere's disease, pemphigus, primary biliary cirrhosis, sarcoidosis, scleroderma, Wegener's granulomatosis, other autoimmune disorders, pancreatitis, trauma (surgery), graft-versus-host disease (GVHD), transplant rejection, cardiovascular disease including ischaemic diseases such as myocardial infarction as well as atherosclerosis, intravascular coagulation, bone resorption, osteoporosis, osteoarthritis, periodontitis, hypochlorhydia and neuromyelitis optica.

57. The method of any one of claims 54 to 56, wherein the subject has a low expression level of OX40.

58. The method of any one of claims 54 to 56, wherein the antibody has enhanced cytotoxicity as compared to the antibody having human heavy chain constant region IGHG1.

59. Use of an antibody or fragment thereof of any one of claims 1 to 41 as a medicament.

60. Use of an antibody or fragment thereof of any one of claims 1 to 41 in the preparation of a medicament for the treatment of an OX40 mediated disorder.

61. Use of an antibody or fragment thereof according to claim 60, wherein the OX40 mediated disorder is GVHD and wherein the antibody or fragment thereof is more effective than Enbrel® at suppressing GVHD.

62. The antibody or fragment thereof of any one of claims 1 to 41 for use as a medicament.

63. The antibody or fragment thereof of any one of claims 1 to 41 for use in a method for treating an OX40 mediated disorder.

64. The antibody or fragment thereof of any one of claims 1 to 41 for use in a method for treating an OX40 mediated disorder, wherein the OX40 mediated disorder is GVHD and wherein the antibody or fragment thereof is more effective than Enbrel® at suppressing

GVIID.

65. An article of manufacture comprising the antibody or fragment thereof of any one of claims 1 to 41, the composition of claim 50, 52 or 53 or the immunoconjugate of claim 51 for the treatment of an OX40 mediated disorder.

66. A kit comprising the antibody or fragment thereof of any one of claims 1 to 30, the composition of claim 50, 52 or 53 or the immunoconjugate of claim 51 for the treatment of an OX40 mediated disorder.

67. An *in vitro* screening method to detect a patient having a low expression level of OX40, comprising the steps of:

(a) purifying peripheral blood mononuclear cells (PBMCs) from a patient blood sample;

(b) subjecting the PBMCs to flow cytometric analysis; and

(c) determining the number of OX40 positive cells in $CD4^+$ and/or $CD8^+$ T cells and comparing this number to control levels.

Claims

1. An antagonist antibody or fragment thereof that binds to human OX40 comprising a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and/or comprising a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5 and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6.

2. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof is a murine antibody, chimeric antibody or a humanized antibody.

3. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof is a humanized antibody.

4. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 7.

5. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a non-CDR region of a heavy chain variable region sequence which is at least 80% identical to the non-CDR region of the heavy chain variable region sequence of SEQ ID NO: 7.

6. The antibody or fragment thereof of claim 1, wherein the heavy chain sequence comprises a non-CDR region which is at least 80% identical to the non-CDR region of the heavy chain variable region sequence of the heavy chain sequence selected from the group consisting SEQ ID NOS: 35,36, 37 or 38.

7. The antibody or fragment thereof of claim 6, wherein the antibody or fragment thereof comprises a heavy chain sequence comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 35, 36, 37 and 38.

8. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain variable region sequence comprising the amino acid sequence

selected from the group consisting of SEQ ID NOS: 58, 59, 79 and 80.

9. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a non-CDR legion of a heavy chain variable region sequence which is at least 80% identical to the non-CDR region of the heavy chain variable region sequence selected from the group consisting of SEQ ID NOS: 58, 59, 79 and 80.

10. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain variable framework region that is the product of a human gene selected from the group consisting of IGHV2-70*10 (SEQ ID NO: 19), IGHV2-70*01 (SEQ ID NO: 20), IGHV2-70*13 (SEQ ID NO: 21), IGHV2-5*09 (SEQ ID NO: 22), and 1GHV2-70*11 (SEQ ID NO: 23).

11. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain variable framework region that is the product of human gene IGEIV2-70*10 (SEQ ID) NO: 19) and wherein the heavy chain variable framework region comprises at least one amino acid modification, wherein the amino acid modification comprises an amino acid substitution, from the corresponding heavy chain variable framework region of the corresponding murine antibody of SEQ ID NO: 7.

12. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 32 and wherein the heavy chain variable framework region comprises at least one amino acid modification, wherein the amino acid modification comprises an amino acid substitution, from the corresponding heavy chain variable framework region of the corresponding murine antibody of SEQ ID NO: 7.

13. The humanized antibody or fragment thereof of claim 11, wherein the amino acid substitution is at an amino acid position selected from the group consisting of 23, 35b, 48, 50, 60, and 62, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

14. The humanized antibody or fragment thereof of claim 12, wherein the amino acid substitution is at an amino acid position selected from the group consisting of 23, 35b, 48, 50, 60, and 62, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

15. The humanized antibody or fragment thereof of claim 11, wherein the amino acid substitution is selected front the group consisting of 23S, 35bG, 48L, 50H, 60N, and 62A, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

16. The humanized antibody or fragment thereof of claim 12, wherein the amino acid substitution is selected from the group consisting of 23S, 35bG, 48L, 50H, 60N, and 62A, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

17. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a light, chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 8.

18. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a non-CDR region of a light chain variable region sequence which is at least 80% identical to the non-CDR region of the light chain variable region sequence of SEQ ID NO: 8.

19. The antibody or fragment thereof of claim 1, wherein the light chain sequence comprises a non-CDR region which is at least 80% identical to the non-CDR region of the light chain variable region sequence of the light chain sequence selected from the group consisting of SEQ ID NO: 45, 46, 47 or 49.

20. The antibody or fragment thereof of claim 19, wherein the antibody or fragment thereof comprises a light chain sequence comprising the amino acid sequence selected from the group consisting of SEQ NO: 45, 46, 47 and 49.

21. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a light chain variable region sequence comprising the amino acid sequence selected from the group consisting, of SEQ ID NOS: 60, 86, 87 and 89.

22. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a non-CDR region of a light chain variable region sequence which is at least 80% indentical to the non-CDR region of the light chain variable region sequence selected from the group consisting of SEQ ID NOS: 60, 86, 87 and 89.

23. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a light chain variable framework region that is the product of a human gene selected from the group consisting of IGKV3-11*01 (SEQ ID NO: 24), IGKV1-39*01 (SEQ ID NO: 25), IGKV1D-39*01 (SEQ ID NO: 26), IGKV3-11*02 (SEQ ID NO: 27) and IGKV3-20*01 (SEQ ID NO: 28).

24. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a light chain variable framework region that is the product of human gene IGKV3-11*01 (SEQ ID NO: 24) and wherein the light chain variable framework region comprises at least one amino acid modification, wherein the amino acid modification is an amino acid substitution or deletion, from the corresponding framework region of the light chain variable region of the corresponding murine antibody of SEQ ID NO: 8.

25. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises a light chain sequence comprising the amino acid sequence of SEQ ID NO: 39 and wherein the light chain variable framework region comprises at least one amino acid modification, wherein the amino acid modification is an amino acid substitution or deletion, from the corresponding light chain variable framework region of the corresponding murine antibody of SEQ ID NO: 8.

26. The humanized antibody or fragment thereof of claim 24, wherein the amino acid substitution is at an amino acid position selected from the group consisting of 1, 33, 34, 46, 47, 54, 56, and 71, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

27. The humanized antibody or fragment thereof of claim 25, wherein the amino acid substitution is at an amino acid position selected from the group consisting of 1, 33, 34, 46, 47, 54, 56, and 71, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

28. The humanized antibody or fragment thereof of claim 24, wherein the amino acid substitution is selected from the group consisting of 1Q, 33M, 34H, 46P, 47W, 54L, 56S, and 71 Y, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

29. The humanized antibody or fragment thereof of claim 25, wherein the amino acid substitution is selected from the group consisting of 1Q, 33M, 34H, 46P, 47W, 54L 56S, and 71Y, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

30. The humanized antibody or fragment thereof of claim 24, wherein the amino acid deletion is at amino acid position 31, wherein the amino acid position is indicated according to the Kabat numbering.

31. The humanized antibody or fragment thereof of claim 25, wherein the amino acid deletion is at amino acid position 31, wherein the amino acid position is indicated according to the Kabat numbering.

32. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises: (a) a heavy chain sequence comprising the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 38; and (b) a light chain sequence comprising the amino acid sequence of SEQ ID NO: 47.

33. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof comprises: (a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 58 or SEQ ID NO: 59; and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 60.

34. An antagonist antibody or fragment thereof that binds to human OX40 comprising a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 3; and/or comprising a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 5 and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 6, wherein at least one of the heavy chain CDRs and/or at least one of the light chain CDRs comprises no more than three amino acid modifications, wherein the amino acid modification is an amino acid substitution, insertion and/or deletion.

35. The antibody of fragment thereof of claimed 1, further comprising heavy and/or light constant regions.

36. The antibody or fragment thereof of claim 35, wherein the human heavy constant region is selected from the group of human immunoglobulins consisting of IGHG1, non fucosylated IGHG1 and IGHG4.

37. The antibody or fragment thereof of claim 1, wherein the antibody is a monovalent antibody.

38. The antibody or fragment thereof of claim 1, wherein the antibody is a full length antibody.

39. The antibody or fragment thereof of claim 1, wherein the antibody is an antibody fragment selected from the group consisting of Fab, Fab', Fab'-SH, Fd, Fv, dAb, F(ab')2, scFv, bispecific single chain Fv dimers, diabodies, triabodies and scFv genetically fused to the same or a different antibody.

40. The antibody or fragment thereof of claim 1, wherein the antibody comprises a variant Fe region which comprises at least one amino acid modification relative to the Fc region of the parent antibody, whereas the antibody comprising the variant Fe region exhibits altered effector function compared to the parent antibody.

41. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof binds to human OX40 with an affinity (KD) of 110 nM or less.

42. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof retains at least 75% of the OX40 binding affinity (K.sub.D) of the corresponding chimeric antibody.

43. The antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof has equivalent or higher OX40 binding affinity (K.sub.D) when compared to the corresponding chimeric antibody.

44. The antibody or fragment thereof of claim 1, wherein the antibody has a FAB fragment thermostability temperature greater than 75.degree. C.

45. An antibody or fragment thereof that binds to human OX40 and which binds to the same epitope as the antibody of claim 1.

46. An epitope on the human OX40 extracellular domain which is bound by the antibody of claim 1.

47. An epitope of claim 46, wherein the epitope is on domain 2 (SEQ ID NO: 76) of the human OX40 extracellular domain.

48. An isolated nucleic acid encoding the antibody or fragment thereof of claim 1.

49. The isolated nucleic acid of claim 48 comprising DNA encoding the heavy chain variable region comprising the nucleotide acid sequence of SEQ ID NO: 61 or 62; and/or DNA encoding the light chain variable region comprising the nucleotide acid sequence of SEQ ID NO: 63.

50. A vector comprising the isolated nucleic acid of claim 48.

51. A host cell comprising the isolated nucleic acid of claim 48.

52. A host cell comprising the vector of claim 50.

53. A method of producing an antibody or fragment thereof that binds to human OX40 comprising culturing the host cell of claim 51 so that the nucleic acid is expressed and the antibody produced.

54. An antibody or fragment thereof that binds to human OX40 encoded by the isolated nucleic acid of claim 48.

55. A composition comprising the antibody or fragment thereof of claim 1 and a pharmaceutically acceptable carrier.

56. An immunoconjugate comprising the antibody or fragment thereof of claim 1 linked to a therapeutic agent.

57. A composition comprising the immunoconjugate of claim 56 and a pharmaceutically acceptable carrier.

58. The composition of claim 55 further comprising another pharmaceutically active agent.

59. The composition of claim 56 further comprising a pharmaceutically acceptable carrier and another pharmaceutically active agent.

60. An article of manufacture comprising the antibody or fragment thereof of claim 1 for the Treatment of an OX40 mediated disorder, wherein the OX40 mediated disorder is selected from the group consisting of: allergy, asthma, graft-versus-host disease (GVHD) and transplant rejection.

61. A kit comprising the antibody or fragment thereof of claim 1 for the treatment of an OX40 mediated disorder, wherein the OX40 mediated disorder is selected from the group consisting of: allergy, asthma, graft-versus-host disease (GVHD) and transplant rejection.

62. A vector comprising the isolated nucleic acid of claim 49.

63. A host cell comprising the isolated nucleic ack of claim 49.

64. A method of producing an antibody or fragment thereof that binds to human OX40 comprising culturing the host cell of claim 52 so that the nucleic acid is expressed and the antibody produced.

65. An antibody or fragment thereof that binds to human OX40 encoded by the isolated nucleic acid of claim 49.