Claims

1. An isolated antibody which binds to CXC chemokine receptor 4 (CXCR4) and which does not induce significant apoptosis of CXCR4 expressing cells.

2. The antibody of claim 1, wherein said antibody does not induce significant apoptosis of CXCR4 expressing cells if used at a concentration of $\geq$0.4 μg/ml.

3. The antibody of claim 1 or claim 2, wherein said antibody is capable of inhibiting the binding of a ligand to CXCR4, or is capable of inhibiting the ligand-induced migration of CXCR4 expressing cells, or is capable of inhibiting ligand-induced calcium flux in CXCR4 expressing cells.

4. The antibody of any one of claims 1 to 3, wherein said antibody comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,
wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of S/G Y X_3 M/I H/S (SEQ ID NO: 126), or X_1 Y X_3 M H (SEQ ID NO: 127) or S Y X_3 M H (SEQ ID NO: 128);

wherein X_1 can be S or G, preferably S;

X_3 can be any amino acid, preferably G or W or Y or A, more preferably W;

(ii) a VH CDR2 that has the amino acid sequence of X_1 I X_3 X_4 D G S X_8 X_9 X_{10} Y A D S V K G (SEQ ID NO:129);

wherein X_1, can be any amino acid, preferably V or R, more preferably R;

X_3 can be any amino acid, preferably S or N, more preferably N;

X_4 can be any amino acid, preferably Y or S, more preferably S;

X_8 can be any amino acid, preferably N or S, more preferably S;

X_9 can be any amino acid, preferably K or T, more preferably T; and

X_{10} can be any amino acid, preferably Y or S, more preferably S;

or a VH CDR2 that has the amino acid sequence of X_1 I X_3 P X_5 X_6 G X_8 X_9 N Y A Q K F Q G (SEQ ID NO: 131);

wherein X_1, can be any amino acid, preferably R or G, more preferably R;

X_3 can be any amino acid, preferably N or I, more preferably N;

X_5 can be any amino acid, preferably N or I, more preferably N;

X_6 can be any amino acid, preferably S or F, more preferably S;

X_8 can be any amino acid, preferably G or T, more preferably G; and

X_9 can be any amino acid, preferably T or A, more preferably T;

and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO:s 3, 9, 15 or 21 or a sequence substantially homologous thereto

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence.

5. An antibody according to any one of claims 1 to 4, wherein said antibody (a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 1 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 2 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 3 or a sequence substantially homologous thereto; and/or

wherein said light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 4 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 5 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 6 or a sequence substantially homologous thereto;

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

6. An antibody according to any one of claims 1 to 4, wherein said antibody (a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 7 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 8 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 9 or a sequence substantially homologous thereto; and/or

wherein said light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 10 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 11 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 12 or a sequence substantially homologous thereto;

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

7. An antibody according to any one of claims 1 to 4, wherein said antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,
wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 13 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 14 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 15 or a sequence substantially homologous thereto; and/or

wherein said light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 16 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 17 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 18 or a sequence substantially homologous thereto;

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

8. An antibody according to any one of claims 1 to 4, wherein said antibody
(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,
wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 19 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 20 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 21 or a sequence substantially homologous thereto; and/or

wherein said light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 22 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 23 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 24 or a sequence substantially homologous thereto;

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

9. An antibody according to any one of claims 1 to 4, wherein said antibody (a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

wherein said heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 1 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 2 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 3 or a sequence substantially homologous thereto; and/or

wherein said light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 88 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 89 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 90 or a sequence substantially homologous thereto;

wherein said substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or wherein

said substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

10. An antibody according to any one of claims 5 to 9, comprising one of each of the VH CDR domains (i), (ii) and (iii), and one of each of the VL CDR domains (iv), (v) and (vi).

11. An antibody according to claim 1 or claim 5, wherein said antibody

(a) has a VH domain of SEQ ID NO: 69 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 70 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

12. An antibody according to claim 1 or claim 6 wherein said antibody

(a) has a VH domain of SEQ ID NO: 71 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 72 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

13. An antibody according to claim 1, or claim 7 wherein said antibody

(a) has a VH domain of SEQ ID NO: 73 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 74 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

14. An antibody according to claim 1, or claim 8 wherein said antibody

(a) has a VH domain of SEQ ID NO: 75 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 76 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

15. An antibody according to claim 1 or claim 9, wherein said antibody (a) has a VH domain of SEQ ID NO: 69 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 103 or a sequence having at least 80% sequence identity thereto; or (b) is an antibody which can compete with antibody (a) for binding to CXCR4.

16. An antibody according to any one of claims 5 to 15, wherein said antibody (b) can bind to substantially the same epitope as said antibody (a).

17. An antibody according to any one of claims 1 to 16, wherein said antibody is a human antibody, preferably a fully human antibody.

18. The antibody of any one of claims 1 to 17, wherein said antibody comprises all or a portion of an antibody heavy chain constant region and/or an antibody light chain constant region.

19. The antibody of claim 18, wherein said antibody is an IgG antibody, preferably an IgG1 antibody.

20. The antibody of claim 18 or claim 19, wherein said antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 108 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 109 or a sequence having at least 80% sequence identity thereto.

21. The antibody of claim 18 or claim 19, wherein said antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 112 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 113 or a sequence having at least 80% sequence identity thereto.

22. The antibody of claim 18 or claim 19, wherein said antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 116 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 117 or a sequence having at least 80% sequence identity thereto.

23. The antibody of claim 18 or claim 19, wherein said antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 120 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 121 or a sequence having at least 80% sequence identity thereto.

24. The antibody of claim 18 or claim 19, wherein said antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 125 or a sequence having at least 80% sequence identity thereto.

25. The antibody of any one of claims 1 to 24, wherein said antibody is an antigen binding fragment of an antibody.

26. The antibody of claim 25, wherein said antigen binding fragment of said antibody is a Fab', Fab, $F(ab')_2$, single domain antibody, TandAbs dimer, Fv, scFv, dsFv, ds-scFv, Fd, linear antibody, minibody, diabody, bispecific antibody fragment, bibody, tribody, sc-diabody, kappa(lamda) body, BiTE, DVD-Ig, SIP, SMIP, DART or a small antibody mimetic comprising one or more CDRs.

27. The antibody of any one of claims 1-26, wherein said antibody is attached to at least a second diagnostic or therapeutic agent.

28. The antibody of claim 27, wherein said antibody is attached to at least a radiotherapeutic agent, chemotherapeutic agent, anti-angiogenic agent, apoptosis-

inducing agent, anti-tubulin drug, anti-cellular or cytotoxic agent, steroid, cytokine antagonist, cytokine expression inhibitor, chemokine antagonist, chemokine expression inhibitor, ATPase inhibitor, anti-inflammatory agent, signalling pathway inhibitor, anti-cancer agent, other antibodies, coagulant or anti-viral agent, wherein said anti-viral agent is preferably selected from the group consisting of a nucleoside, a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor.

29. An immunoconjugate comprising the antibody of any one of claims 1-28 attached to at least a second therapeutic or diagnostic agent.

30. A composition comprising at least a first antibody according any one of claims 1-28 or an immunoconjugate thereof, wherein said composition is preferably a pharmaceutically acceptable composition.

31. The composition of claim 30, wherein said composition further comprises at least a second therapeutic agent.

32. A nucleic acid molecule comprising a nucleotide sequence region encoding the antibody of any one of claims 1-28.

33. The nucleic acid molecule of claim 32, wherein said nucleotide sequence region has the nucleotide sequence of SEQ ID NO: 34, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 67 or SEQ ID NO: 100, or a sequence having at least 80% sequence identity thereto.

34. An expression vector comprising the nucleic acid molecule of claim 32 or 33.

35. A host cell comprising the nucleic acid molecule of claim 32 or 33 or the expression vector of claim 34.

36. A virus comprising the nucleic acid molecule of claim 32 or 33 or the expression vector of claim 34.

37. A kit comprising, in at least a first container:

(a) the antibody of any one of claims 1 to 28;

(b) the immunoconjugate of claim 29;

(c) the composition of any one of claims 30-31;

(d) the nucleic acid molecule of claim 32 or 33;

(e) the expression vector of claim 34;

(f) the host cell of claim 35; or

(g) the virus of claim 36.

38. A method of producing an antibody, comprising:

(a) culturing a host cell that comprises the expression vector of claim 34 under conditions effective to express the encoded antibody; and

(b) obtaining the expressed antibody from said host cell.

39. A method of binding CXCR4, comprising contacting a composition comprising CXCR4 with the antibody of any one of claims 1-28, or an immunoconjugate thereof.

40. A method of detecting CXCR4, comprising contacting a composition suspected of containing CXCR4 with the antibody of any one of claims 1-28, or an immunoconjugate thereof, under conditions effective to allow the formation of complexes between said CXCR4 and said antibody and detecting said complexes so formed.

41. A method of diagnosing a disease associated with CXCR4 expression in an animal, comprising the step of:

(a) contacting a test sample taken from said animal with an antibody of any one of claims 1-28 or an immunoconjugate thereof; optionally

(b) measuring or detecting the presence and/or amount and/or location of antibody-antigen complex in the test sample; and, optionally

(c) comparing the presence and/or amount of antibody-antigen complex in the test sample to a control.

42. The method of claim 41, wherein said test sample is isolated from said animal and contacted with said antibody or immunoconjugate *in vitro*.

43. The method of claim 41, wherein said antibody or immunoconjugate is administered to said animal, thereby contacting said test sample *in vivo*.

44. The method of any one of claims 41-43, wherein said disease associated with CXCR4 expression is a disease mediated by CXCR4, or a disease characterised by aberrant proliferation of CXCR4+ cells, or a disease characterised by overexpression of CXCR4.

45. The method of any one of claims 41-43, wherein said disease is cancer, metastatic cancer, invasion of organs by cancer cells, diseases associated with angiogenesis, an inflammatory or immune disease, an auto-immune disorder such as rheumatoid athritis, a viral infection such as HIV infection, or a condition where it is desired to mobilize stem cells from the bone marrow in order to restore the immune system.

46. The method of any one of claims 41-45, wherein an increased amount of CXCR4 in said test sample is diagnostic of said disease.

47. A method for treating a disease associated with CXCR4 expression or activity in an animal, comprising administering to an animal with said disease a therapeutically effective amount of the antibody of any one of claims 1-28, or an immunoconjugate thereof.

48. The method of claim 47, wherein said disease associated with CXCR4 expression or activity is a disease mediated by CXCR4, or a disease characterised by aberrant proliferation of CXCR4+ cells, or a disease characterised by overexpression of CXCR4.

49. The method of any one of claims 47 to 48, wherein said disease is cancer, metastatic cancer, invasion of organs by cancer cells, diseases associated with angiogenesis, an inflammatory or immune disease, an auto-immune disorder such as rheumatoid athritis, a viral infection such as HIV infection, or a condition where it is desired to mobilize stem cells from the bone marrow in order to restore the immune system.

50. The method of any one of claims 47-49, wherein said antibody or immunoconjugate thereof causes one or more of the following:

(a) inhibition of the binding of CXCR4 to at least SDF-1;

(b) inhibition of CXCR4-mediated cellular responses to a CXCR4 ligand, preferably inhibition of the release of calcium ions in response to a CXCR4 ligand, or to inhibit ligand induced migration of CXCR4 expressing cells;

(c) induction of ADCC of CXCR4+ cells;

(d) induction of anti tumour effects *in vivo*;

(e) induction of CDC of CXCR4+ cells;

(f) inhibition of metastasis formation caused by an existing cancer;

(g) inhibition of cancer cells invading new organs;

(h) inhibiting the attraction of CXCR4+ cells to the tumor stroma, and/or activation of said cells to create a microenvironment favourable to the tumor;

(i) sensitizing tumor cells for treatment with other therapeutically effective compounds.

51. The method of any one of claims 47-50, further comprising administering a second therapeutic agent to said animal.

52. The method of any one of claims 41-51, wherein said antibody is a bivalent or polyvalent antibody comprising at least two antigen binding fragments of said antibody.

53. The method of any one of claims 41-52, wherein said animal is a human subject.

54. The antibody of any one of claims 1 to 28, or an immunoconjugate thereof, for use in therapy, imaging or diagnosis.

55. The antibody or immunoconjugate of claim 54 for use in therapy, imaging or diagnosis of a condition associated with CXCR4 expression or activity.

56. The antibody or immunoconjugate of claim 55, wherein said disease is as defined in any one of claims 48 or 49.

CLAIMS

1. An isolated antibody which binds to CXC chemokine receptor 4 (CXCR4) and which does not induce significant apoptosis of CXCR4 expressing cells, in which levels of apoptosis induced in the presence of the antibody are comparable to or not significantly different from levels of apoptosis induced in the absence of the antibody, and in which the antibody comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs, in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of S/G Y X_3 M/I H/S (SEQ ID NO: 126), or X_1 Y X_3 M H (SEQ ID NO: 127) or S Y X_3 M H (SEQ ID NO: 128);

in which X_1 can be S or G, preferably S;

X_3 can be any amino acid, preferably G or W or Y or A, more preferably W;

(ii) a VH CDR2 that has the amino acid sequence of X_1 I X_3 X_4 D G S X_8 X_9 X_{10} Y A D S V K G (SEQ ID NO:129);

in which X_1, can be any amino acid, preferably V or R, more preferably R;

X_3 can be any amino acid, preferably S or N, more preferably N;

X_4 can be any amino acid, preferably Y or S, more preferably S;

X_8 can be any amino acid, preferably N or S, more preferably S;

X_9 can be any amino acid, preferably K or T, more preferably T; and

X_{10} can be any amino acid, preferably Y or S, more preferably S;

or a VH CDR2 that has the amino acid sequence of X_1 I X_3 P X_5 X_6 G X_8 X_9 N Y A Q K F Q G (SEQ ID NO: 131);

in which X_1, can be any amino acid, preferably R or G, more preferably R;

X_3 can be any amino acid, preferably N or I, more preferably N;

X_5 can be any amino acid, preferably N or I, more preferably N;

X_6 can be any amino acid, preferably S or F, more preferably S;

X_8 can be any amino acid, preferably G or T, more preferably G; and

X_9 can be any amino acid, preferably T or A, more preferably T;

and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NOs 3, 9, 15 or 21 or a sequence substantially homologous thereto

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence.

2. An antibody according to Claim 1, in which the antibody does not induce significant apoptosis of CXCR4 expressing cells if used at a concentration of ≥0.4 µg/ml.

3. An antibody according to Claim 1 or Claim 2, in which the antibody is capable of inhibiting the binding of a ligand to CXCR4, or is capable of inhibiting the ligand-induced migration of CXCR4 expressing cells, or is capable of inhibiting ligand-induced calcium flux in CXCR4 expressing cells.

4. An antibody according to any of Claims 1 to 3, in which the antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 1 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 2 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 3 or a sequence substantially homologous thereto; and/or

in which the light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 4 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 5 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 6 or a sequence substantially homologous thereto;

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

5. An antibody according to any of Claims 1 to 3, in which the antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 7 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 8 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 9 or a sequence substantially homologous thereto; and/or

in which the light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 10 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 11 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 12 or a sequence substantially homologous thereto;

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

6. An antibody according to any of Claims 1 to 3, in which the antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 13 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 14 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 15 or a sequence substantially homologous thereto; and/or

in which the light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 16 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 17 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 18 or a sequence substantially homologous thereto;

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

7. An antibody according to any of Claims 1 to 3, in which the antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 19 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 20 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 21 or a sequence substantially homologous thereto; and/or

in which the light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 22 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 23 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 24 or a sequence substantially homologous thereto;

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

8. An antibody according to any of Claims 1 to 3, in which the antibody

(a) comprises at least one heavy chain variable region that comprises three CDRs and at least one light chain variable region that comprises three CDRs,

in which the heavy chain variable region comprises:

(i) a variable heavy (VH) CDR1 that has the amino acid sequence of SEQ ID NO: 1 or a sequence substantially homologous thereto;

(ii) a VH CDR2 that has the amino acid sequence of SEQ ID NO: 2 or a sequence substantially homologous thereto; and

(iii) a VH CDR3 that has the amino acid sequence of SEQ ID NO: 3 or a sequence substantially homologous thereto; and/or

in which the light chain variable region comprises:

(iv) a variable light (VL) CDR1 that has the amino acid sequence of SEQ ID NO: 88 or a sequence substantially homologous thereto;

(v) a VL CDR2 that has the amino acid sequence of SEQ ID NO: 89 or a sequence substantially homologous thereto; and

(vi) a VL CDR3 that has the amino acid sequence of SEQ ID NO: 90 or a sequence substantially homologous thereto;

in which the substantially homologous sequence is a sequence containing 1, 2 or 3 amino acid substitutions compared to the given CDR sequence, or in which the substantially homologous sequence is a sequence containing conservative amino acid substitutions of the given CDR sequence; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

9. An antibody according to any of Claims 4 to 8, comprising one of each of the VH CDR domains (i), (ii) and (iii), and one of each of the VL CDR domains (iv), (v) and (vi).

10. An antibody according to any of Claims 1 to 3, in which the antibody comprises

a variable heavy (VH) CDR1 having the amino acid sequence of SEQ ID NO:1, a VH CDR2 having the amino acid sequence of SEQ ID NO:2, a VH CDR3 having the amino acid sequence of SEQ ID NO:3, a variable light (VL) CDR1 having the amino acid sequence of SEQ ID NO:4, a VL CDR2 having the amino acid sequence of SEQ ID NO:5, and a VL CDR3 having the amino acid sequence of SEQ ID NO:6 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a variable heavy (VH) CDR1 having the amino acid sequence of SEQ ID NO:7, a VH CDR2 having the amino acid sequence of SEQ ID NO:8, a VH CDR3 having the amino acid sequence of SEQ ID NO:9, a variable light (VL) CDR1 having the amino acid sequence of SEQ ID NO:10, a VL CDR2 having the amino acid sequence of SEQ ID NO:11, and a VL CDR3 having the amino acid sequence of SEQ ID NO:12 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a variable heavy (VH) CDR1 having the amino acid sequence of SEQ ID NO:13, a VH CDR2 having the amino acid sequence of SEQ ID NO:14, a VH CDR3 having the amino acid sequence of SEQ ID NO:15, a variable light (VL) CDR1 having the amino acid sequence of SEQ ID NO:16, a VL CDR2 having the amino acid sequence of SEQ ID NO:17, and a VL CDR3 having the amino

acid sequence of SEQ ID NO:18 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a variable heavy (VH) CDR1 having the amino acid sequence of SEQ ID NO:19, a VH CDR2 having the amino acid sequence of SEQ ID NO:20, a VH CDR3 having the amino acid sequence of SEQ ID NO:21, a variable light (VL) CDR1 having the amino acid sequence of SEQ ID NO:22, a VL CDR2 having the amino acid sequence of SEQ ID NO:23, and a VL CDR3 having the amino acid sequence of SEQ ID NO:24 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a variable heavy (VH) CDR1 having the amino acid sequence of SEQ ID NO:1, a VH CDR2 having the amino acid sequence of SEQ ID NO:2, a VH CDR3 having the amino acid sequence of SEQ ID NO:3, a variable light (VL) CDR1 having the amino acid sequence of SEQ ID NO:88, a VL CDR2 having the amino acid sequence of SEQ ID NO:89, and a VL CDR3 having the amino acid sequence of SEQ ID NO:90 or is an antibody which can compete with the antibody for binding to CXCR4.

11. An antibody according to Claim 1 or Claim 4, in which the antibody

(a) has a VH domain of SEQ ID NO: 69 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 70 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

12. An antibody according to Claim 1 or Claim 5, in which the antibody

(a) has a VH domain of SEQ ID NO: 71 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 72 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

13. An antibody according to Claim 1 or Claim 6, in which the antibody

(a) has a VH domain of SEQ ID NO: 73 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 74 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

14. An antibody according to Claim 1 or Claim 7, in which the antibody

(a) has a VH domain of SEQ ID NO: 75 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 76 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

15. An antibody according to Claim 1 or Claim 8, in which the antibody

(a) has a VH domain of SEQ ID NO: 69 or a sequence having at least 80% sequence identity thereto, and/or a VL domain of SEQ ID NO: 103 or a sequence having at least 80% sequence identity thereto; or

(b) is an antibody which can compete with antibody (a) for binding to CXCR4.

16. An antibody according to any of Claims 1 to 3, in which the antibody comprises

a heavy chain variable region (VH) that has the amino acid sequence of SEQ ID NO:69 and a light chain variable region (VL) that has the amino acid sequence of SEQ ID NO:70 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a heavy chain variable region (VH) that has the amino acid sequence of SEQ ID NO:71 and a light chain variable region (VL) that has the amino acid sequence of SEQ ID NO:72 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a heavy chain variable region (VH) that has the amino acid sequence of SEQ ID NO:73 and a light chain variable region (VL) that has the amino acid sequence of SEQ ID NO:74 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a heavy chain variable region (VH) that has the amino acid sequence of SEQ ID NO:75 and a light chain variable region (VL) that has the amino acid sequence of SEQ ID NO:76 or is an antibody which can compete with the antibody for binding to CXCR4; or

in which the antibody comprises a heavy chain variable region (VH) that has the amino acid sequence of SEQ ID NO:69 and a light chain variable region (VL) that has the amino acid sequence of SEQ ID NO:103 or is an antibody which can compete with the antibody for binding to CXCR4.

17. An antibody according to any of Claims 4 to 9 or 11 to 15, in which the antibody (b) can bind to substantially the same epitope as the antibody (a).

18. An antibody according to any of Claims 1 to 17, in which the antibody is a human antibody, preferably a fully human antibody.

19. An antibody according to any of Claims 1 to 18, in which the antibody comprises all or a portion of an antibody heavy chain constant region and/or an antibody light chain constant region.

20. An antibody according to Claim 19, in which the antibody is an IgG antibody, preferably an IgG1 antibody.

21. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 108 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 109 or a sequence having at least 80% sequence identity thereto.

22. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 112 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 113 or a sequence having at least 80% sequence identity thereto.

23. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 116 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 117 or a sequence having at least 80% sequence identity thereto.

24. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 120 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 121 or a sequence having at least 80% sequence identity thereto.

25. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124 or a sequence having at least 80% sequence identity thereto, and/or a light chain that comprises the amino acid sequence of SEQ ID NO: 125 or a sequence having at least 80% sequence identity thereto.

26. An antibody according to Claim 19 or Claim 20, in which the antibody comprises a heavy chain that has the amino acid sequence of SEQ ID NO:108 and a light chain that has the amino acid sequence of SEQ ID NO:109; or

in which the antibody comprises a heavy chain that has the amino acid sequence of SEQ ID NO:112 and a light chain that has the amino acid sequence of SEQ ID NO:113; or

in which the antibody comprises a heavy chain that has the amino acid sequence of SEQ ID NO:116 and a light chain that has the amino acid sequence of SEQ ID NO:117; or

in which the antibody comprises a heavy chain that has the amino acid sequence of SEQ ID NO:120 and a light chain that has the amino acid sequence of SEQ ID NO:121; or

in which the antibody comprises a heavy chain that has the amino acid sequence of SEQ ID NO:124 and a light chain that has the amino acid sequence of SEQ ID NO:125.

27. An antibody according to any of Claims 1 to 26, in which the antibody is an antigen binding fragment of an antibody.

28. An antibody according to Claim 27, in which the antigen binding fragment of the antibody is a Fab', Fab, $F(ab')_2$, single domain antibody, TandAbs dimer, Fv, scFv, dsFv, ds-scFv, Fd, linear antibody, minibody, diabody, bispecific antibody fragment, bibody, tribody, sc-diabody, kappa(lamda) body, BiTE, DVD-Ig, SIP, SMIP, DART or a small antibody mimetic comprising one or more CDRs.

29. An antibody according to any of Claims 1 to 28, in which the antibody is attached to at least a second diagnostic or therapeutic agent.

30. An antibody according to Claim 29, in which the antibody is attached to at least a radiotherapeutic agent, chemotherapeutic agent, anti-angiogenic agent, apoptosis-inducing

agent, anti-tubulin drug, anti-cellular or cytotoxic agent, steroid, cytokine antagonist, cytokine expression inhibitor, chemokine antagonist, chemokine expression inhibitor, ATPase inhibitor, anti-inflammatory agent, signalling pathway inhibitor, anti-cancer agent, other antibodies, coagulant or anti-viral agent, in which the anti-viral agent is preferably selected from the group consisting of a nucleoside, a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor.

31. An immunoconjugate comprising an antibody according to any of Claims 1 to 30 attached to at least a second therapeutic or diagnostic agent.

32. A composition comprising at least a first antibody according any of Claims 1 to 30 or an immunoconjugate thereof, in which the composition is preferably a pharmaceutically acceptable composition.

33. A composition according to Claim 32, in which the composition further comprises at least a second therapeutic agent, preferably the second therapeutic agent is as defined in Claim 30.

34. A nucleic acid molecule comprising a nucleotide sequence region encoding an antibody according to any of Claims 1 to 30.

35. A nucleic acid molecule according to Claim 34, in which the nucleotide sequence region has the nucleotide sequence of SEQ ID NO: 34, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 67 or SEQ ID NO: 100, or a sequence having at least 80% sequence identity thereto.

36. An expression vector comprising the nucleic acid molecule of Claim 34 or 35.

37. A host cell comprising the nucleic acid molecule of Claim 34 or 35 or the expression vector of Claim 36.

38. A virus comprising the nucleic acid molecule of Claim 34 or 35 or the expression vector of Claim 36.

39. A kit comprising, in at least a first container:

(a) an antibody according to any of Claims 1 to 30;

(b) an immunoconjugate according to Claim 31;

(c) a composition according to any of Claims 32 to 33;

(d) a nucleic acid molecule according to Claim 34 or 35;

(e) a expression vector according to Claim 36;

(f) a host cell according to Claim 37; or

(g) a virus according to Claim 38.

40. A method of producing an antibody, comprising:

(a) culturing a host cell that comprises the nucleic acid molecule of Claim 34 or 35 or the expression vector of Claim 36 under conditions effective to express the encoded antibody; and

(b) obtaining the expressed antibody from the host cell.

41. A method of binding CXCR4, comprising contacting a composition comprising CXCR4 with an antibody according to any of Claims 1 to 30, or an immunoconjugate thereof.

42. A method of detecting CXCR4, comprising contacting a composition suspected of containing CXCR4 with an antibody according to any of Claims 1 to 30, or an immunoconjugate thereof, under conditions effective to allow the formation of complexes between the CXCR4 and the antibody and detecting the complexes so formed.

43. An *in vitro* method of diagnosing a disease associated with CXCR4 expression in an animal, comprising the step of:

(a) contacting a test sample taken from the animal with an antibody according to any of Claims 1 to 30 or an immunoconjugate thereof; optionally

(b) measuring or detecting the presence and/or amount and/or location of antibody-antigen complex in the test sample; and, optionally

(c) comparing the presence and/or amount of antibody-antigen complex in the test sample to a control.

44. A method according to Claim 43, in which the disease associated with CXCR4 expression is a disease mediated by CXCR4, or a disease characterised by aberrant proliferation of CXCR4+ cells, or a disease characterised by overexpression of CXCR4.

45. A method according to Claim 43 or Claim 44, in which the disease is cancer, metastatic cancer, invasion of organs by cancer cells, diseases associated with angiogenesis,

an inflammatory or immune disease, an auto-immune disorder such as rheumatoid athritis, a viral infection such as HIV infection, or a condition where it is desired to mobilize stem cells from the bone marrow in order to restore the immune system.

46. A method according to any of Claims 43 to 45, in which an increased amount of CXCR4 in the test sample is diagnostic of the disease.

47. A method according to any of Claims 43 to 46, in which the animal is a human subject.

48. An antibody according to any of Claims 1 to 30, or an immunoconjugate thereof, for use in therapy, imaging or diagnosis.

49. An antibody or immunoconjugate according to Claim 48 for use in therapy, imaging or diagnosis of a condition associated with CXCR4 expression or activity.

50. An antibody or immunoconjugate according to Claim 49, in which the condition associated with CXCR4 expression or activity is a disease mediated by CXCR4, or a disease characterised by aberrant proliferation of CXCR4+ cells, or a disease characterised by overexpression of CXCR4.

51. An antibody or immunoconjugate according to Claim 49 or Claim 50, in which the condition or disease is cancer, metastatic cancer, invasion of organs by cancer cells, diseases associated with angiogenesis, an inflammatory or immune disease, an auto-immune disorder such as rheumatoid arthritis, a viral infection such as HIV infection, or a condition where it is desired to mobilize stem cells from the bone marrow in order to restore the immune system.

52. An antibody or immunoconjugate according to any of Claims 49 to 51, in which the antibody or immunoconjugate thereof causes one or more of the following:

(a) inhibition of the binding of CXCR4 to at least SDF-1;

(b) inhibition of CXCR4-mediated cellular responses to a CXCR4 ligand, preferably inhibition of the release of calcium ions in response to a CXCR4 ligand, or to inhibit ligand induced migration of CXCR4 expressing cells;

(c) induction of ADCC of CXCR4+ cells;

(d) induction of anti tumour effects *in vivo*;

(e) induction of CDC of CXCR4+ cells;

(f) inhibition of metastasis formation caused by an existing cancer;

(g) inhibition of cancer cells invading new organs;

(h) inhibiting the attraction of CXCR4+ cells to the tumor stroma, and/or activation of the cells to create a microenvironment favourable to the tumor;

(i) sensitizing tumor cells for treatment with other therapeutically effective compounds.

53. An antibody or immunoconjugate according to any of Claims 48 to 52, in which the therapy, imaging or diagnosis is carried out on a human subject.

54. An antibody or immunoconjugate according to any of Claims 48 to 53, further comprising the use of a second therapeutic agent, preferably the second therapeutic agent is as defined in Claim 30.

55. A method according to any of Claims 43 to 47, or an antibody or immunoconjugate for use according to any of Claims 48 to 54, in which the antibody is a bivalent or polyvalent antibody comprising at least two antigen binding fragments of the antibody.