What is claimed:

1. An isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody binds to native human CXCR4 expressed on a cell surface.

2. The antibody of claim 1, wherein the antibody inhibits binding of SDF-1 to human CXCR4.

3. The antibody of claim 1, wherein the antibody does not inhibit binding of SDF-1 to human CXCR4.

4. The antibody of claim 1, which inhibits SDF-1-induced calcium flux in cells expressing human CXCR4.

5. The antibody of claim 1, which inhibits SDF-1-induced migration of cells expressing human CXCR4.

6. The antibody of claim 1, which inhibits capillary tube formation by human umbilical vein endothelial cells.

7. The antibody of claim 1, which induces apoptosis in cells expressing human CXCR4.

8. The antibody of claim 1, which inhibits growth or induces apoptosis of $CXCR4^+$ tumor cells *in vivo*.

9. The antibody of claim 1, wherein said antibody binds to human CXCR4 with a K_D of 1×10^{-7} M or less.

10. The antibody of claim 9, wherein said antibody binds to human CXCR4 with a K_D of 5×10^{-8} M or less.

11. An isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody:

(a) binds to native human CXCR4 expressed on a cell surface;

(b) inhibits binding of SDF-1 to human CXCR4;

(c) inhibits SDF-1-induced calcium flux in cells expressing human CXCR4;

(d) inhibits SDF-1-induced migration of cells expressing human CXCR4; and

(e) inhibits capillary tube formation by human umbilical vein endothelial cells.

12. The antibody of claim 11, which induces apoptosis in cells expressing human CXCR4.

13. The antibody of claim 11, which inhibits growth or induces apoptosis of $CXCR4^+$ tumor cells *in vivo*.

14. The antibody of claim 11, which inhibits binding of SDF-1 to human CXCR4 with an EC_{50} of 50 nM or less.

15. The antibody of claim 11, which inhibits SDF-1-induced calcium flux in cells expressing human CXCR4 with an EC_{50} of 3 nM or less.

16. The antibody of claim 11, which inhibits SDF-1-induced migration of cells expressing human CXCR4with an EC_{50} of 50 nM or less.

17. An isolated human monoclonal antibody, or antigen binding portion thereof, wherein the antibody cross-competes for binding to CXCR4 with a reference antibody, wherein the reference antibody comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 25 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29; or

(b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 26 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30; or

(c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 31; or

(d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32.

18. An isolated monoclonal antibody, or an antigen-binding portion thereof, comprising a heavy chain variable region that is the product of or derived from a human V_H 3-48 gene,

wherein the antibody specifically binds human CXCR4.

19. An isolated monoclonal antibody, or an antigen-binding portion thereof, comprising a light chain variable region that is the product of or derived from a human V_K L15 gene,

wherein the antibody specifically binds human CXCR4.

20. An isolated monoclonal antibody, or an antigen-binding portion thereof, comprising a heavy chain variable region that is the product of or derived from a human V_H 3-48 gene and a light chain variable region that is the product of or derived from a human V_K L15 gene, wherein the antibody specifically binds human CXCR4.

21. The antibody of claim 1, which comprises:

(a) a heavy chain variable region CDR1 comprising SEQ ID NO: 1;

(b) a heavy chain variable region CDR2 comprising SEQ ID NO: 5;

(c) a heavy chain variable region CDR3 comprising SEQ ID NO: 9;

(d) a light chain variable region CDR1 comprising SEQ ID NO: 13;

(e) a light chain variable region CDR2 comprising SEQ ID NO: 17; and

(f) a light chain variable region CDR3 comprising SEQ ID NO: 21.

22. The antibody of claim 1, which comprises:

(a) a heavy chain variable region CDR1 comprising SEQ ID NO: 2;

(b) a heavy chain variable region CDR2 comprising SEQ ID NO: 6;

(c) a heavy chain variable region CDR3 comprising SEQ ID NO: 10;

(d) a light chain variable region CDR1 comprising SEQ ID NO: 14;

(e) a light chain variable region CDR2 comprising SEQ ID NO: 18; and

(f) a light chain variable region CDR3 comprising SEQ ID NO: 22.

23. The antibody of claim 1, which comprises:

(a) a heavy chain variable region CDR1 comprising SEQ ID NO: 3;

(b) a heavy chain variable region CDR2 comprising SEQ ID NO: 7;

(c) a heavy chain variable region CDR3 comprising SEQ ID NO: 11;

(d) a light chain variable region CDR1 comprising SEQ ID NO: 15;

(e) a light chain variable region CDR2 comprising SEQ ID NO: 19; and

(f) a light chain variable region CDR3 comprising SEQ ID NO: 23.

24. The antibody of claim 1, which comprises:

(a) a heavy chain variable region CDR1 comprising SEQ ID NO: 4;

(b) a heavy chain variable region CDR2 comprising SEQ ID NO: 8;

(c) a heavy chain variable region CDR3 comprising SEQ ID NO: 12;

(d) a light chain variable region CDR1 comprising SEQ ID NO: 16;

(e) a light chain variable region CDR2 comprising SEQ ID NO: 20; and

(f) a light chain variable region CDR3 comprising SEQ ID NO: 24.

25. An isolated monoclonal antibody, or antigen binding portion thereof, comprising:

(a) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 25-28 and 41-44; and

(b) a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 29-32 and 45-48;

wherein the antibody specifically binds human CXCR4.

26. The antibody of claim 25, which comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 25 or 41; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 29 or 45.

27. The antibody of claim 25, which comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 26 or 42; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 30 or 46.

28. The antibody of claim 25, which comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 27 or 43; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 31 or 47.

29. The antibody of claim 25, which comprises:

(a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 28 or 44; and

(b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 32 or 48.

30. A composition comprising the antibody, or antigen-binding portion thereof, of claim 1, and a pharmaceutically acceptable carrier.

31. An immunoconjugate comprising the antibody, or antigen-binding portion thereof, of claim 1, linked to a therapeutic agent.

32. A composition comprising the immunoconjugate of claim 31 and a pharmaceutically acceptable carrier.

33. The immunoconjugate of claim 31, wherein the therapeutic agent is a cytotoxin.

34. A composition comprising the immunoconjugate of claim 33 and a pharmaceutically acceptable carrier.

35. The immunoconjugate of claim 31, wherein the therapeutic agent is a radioactive isotope.

36. A composition comprising the immunoconjugate of claim 35 and a pharmaceutically acceptable carrier.

37. An isolated nucleic acid molecule encoding the antibody, or antigen-binding portion thereof, of claim 1.

38. An expression vector comprising the nucleic acid molecule of claim 37.

39. A host cell comprising the expression vector of claim 38.

40. A method for preparing an anti-CXCR4 antibody which comprises expressing the antibody in the host cell of claim 39 and isolating the antibody from the host cell.

41. A method of modulating CXCR4 activity in a cell comprising contacting the cell with the antibody, or antigen-binding portion thereof, of claim 1 such that CXCR4 activity in the cell is modulated.

42. The method of claim 41, wherein CXCR4 activity is modulated *in vitro* by culturing the cell with the antibody, or antigen-binding portion thereof.

43. The method of claim 41, wherein CXCR4 activity is modulated *in vivo* in a subject by administering to the subject the antibody, or antigen-binding portion thereof.

44. The method of claim 41, wherein the cell is a tumor cell expressing CXCR4 and the method results in inhibition of growth of the tumor cell or inhibition of metastasis of the tumor cell.

45. The method of claim 41, wherein the cell is a T cell expressing CXCR4 and the method results in inhibition of entry of HIV into the cell.

46. The method of claim 41, wherein the cell is a lymphocyte in an inflammatory disorder and the method results in inhibition of inflammation.

47. The method of claim 41, wherein the cell is involved in vascularization and the method results in modulation of angiogenesis.

48. A method of stimulating mobilization of $CD34^+$ stem cells from bone marrow to peripheral blood in a subject, the method comprising administering to the subject the antibody, or antigen-binding portion thereof, of claim 1 such that mobilization of $CD34^+$ stem cells from bone marrow to peripheral blood is stimulated.

49. The method of claim 48, which further comprises collecting the $CD34^+$ stem cells from the peripheral blood.

Claims

1. A human monoclonal antibody, or an antigen-binding portion thereof, which binds specifically to native human CXCR4 expressed on a cell surface and comprises:
a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 1;
a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 5;
a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 9;
a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 13;
a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 17; and
a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 21.

2. The monoclonal antibody, or antigen-binding portion thereof, of claim 1, which comprises:
a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 25 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 29.

3. The monoclonal antibody of claim 1 or claim 2, wherein said monoclonal antibody is a full-length antibody.

4. The monoclonal antibody of claim 3, wherein said monoclonal antibody is of the IgG1 or IgG4 isotype.

5. The monoclonal antibody antigen-binding portion of claim 1 or claim 2, wherein said antigen-binding portion is a Fab fragment, a $F(ab')_2$ fragment, a Fab' fragment, a Fd fragment, a Fv fragment, or a scFv.

6. The monoclonal antibody antigen-binding portion of claim 5, wherein said antigen-binding portion is a $F(ab')_2$ fragment.

7. An immunoconjugate comprising the monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6, linked to a therapeutic agent; optionally wherein the therapeutic agent is a cytotoxin or a radioactive isotype.

8. A bispecific molecule comprising the monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6 linked to a second functional moiety having a different binding specificity than the monoclonal antibody or antigen-binding portion thereof.

9. A composition comprising a pharmaceutically acceptable carrier and either:
   (a) the monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6;
   (b) the immunoconjugate of claim 7; or
   (c) the bispecific molecule of claim 8.

10. An isolated nucleic acid encoding the monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6.

11. An expression vector comprising the nucleic acid of claim 10.

12. A host cell comprising the expression vector of claim 11.

13. A method for preparing an anti-CXCR4 antibody, or an antigen-binding portion thereof, which comprises expressing the antibody or antigen-binding portion thereof in the host cell of claim 12 and isolating the antibody or antigen-binding portion thereof from the host cell.

14. An *in-vitro* method of modulating CXCR4 activity in a cell comprising contacting the cell with the monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6 such that CXCR4 activity in the cell is modulated;
optionally wherein:
   (a) the cell is a tumor cell expressing CXCR4 and the method results in inhibition of growth of the tumor cell or inhibition of metastasis of the tumor cell;
   (b) the cell is a T cell expressing CXCR4 and the method results in inhibition of entry of HIV into the cell;
   (c) the cell is a lymphocyte in an inflammatory disorder and the method results in inhibition of inflammation; or

(d) the cell is involved in vascularization and the method results in modulation of angiogenesis.

15. The monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6 for use in a method of modulating CXCR4 activity in a cell of a subject, wherein:

(a) the cell is a tumor cell expressing CXCR4 and the method results in inhibition of growth of the tumor cell or inhibition of metastasis of the tumor cell in the subject;

(b) the cell is a T cell expressing CXCR4 and the method results in inhibition of entry of HIV into the cell of the subject;

(c) the cell is a lymphocyte in an inflammatory disorder and the method results in inhibition of inflammation in the subject; or

(d) the cell is involved in vascularization and the method results in modulation of angiogenesis in the subject.

16. The monoclonal antibody, or antigen-binding portion thereof, for use according to claim 15, wherein the tumor cell is chosen from a cell of a breast cancer, an ovarian cancer, a prostate cancer, a non-small cell lung cancer, a pancreatic cancer, a thyroid cancer, a nasopharyngeal carcinoma, a melanoma, a renal cell carcinoma, a lymphoma, a neuroblastoma, a glioblastoma, a rhabdomyosarcoma, a colorectal cancer, a kidney cancer, an osteosarcoma, an acute lymphoblastic leukemia, an acute myeloid leukemia, a small-cell lung carcinoma, and a metastatic lung cancer.

17. The monoclonal antibody, or antigen-binding portion thereof, of any one of claims 1 to 6 for use in a method of transplantation comprising stimulating mobilization of CD34+ stem cells from bone marrow to peripheral blood; optionally wherein the method further comprises collecting the CD34+ stem cells from the peripheral blood.