CLAIMS

1. An isolated antibody, or an antigen binding fragment thereof, that binds to chemokine receptor 4 (CXCR4) and comprises:

a) a heavy chain variable (VH) region comprising (i) a VH CDR1 selected from the group consisting of SEQ ID NOs:107, 113, and 114; (ii) a VH CDR2 selected from the group consisting of SEQ ID NOs: 162, and 128, and, (iii) a VH CDR3 set forth as SEQ ID NO: 112; and

b) a light chain variable region (VL) region comprising (i) a VL CDR1 set forth as SEQ ID NO: 144; (ii) a VL CDR2 set forth as SEQ ID NO: 145; and (iii) a VL CDR3 set forth as SEQ ID NO: 139.

2. An isolated antibody, or an antigen binding fragment thereof, that binds to CXCR4 and comprises:

a) a heavy chain variable (VH) region comprising complementary determining regions selected from the group consisting of (i) a VH CDR1 comprising the sequence set forth as SEQ ID NOs: 107, 113, and 114; (ii) a VH CDR2 comprising the sequence set forth as SEQ ID NOs: 162 and 128, and; (iii) a VH CDR3 comprising the sequence set forth as SEQ ID NO: 112; and

b) a light chain variable region (VL) region comprising complementary determining regions selected from the group consisting of (i) a VL CDR1 comprising the sequence set forth as SEQ ID NO: 144; (ii) a VL CDR2 comprising the sequence set forth as SEQ ID NO 145; and (iii) a VL CDR3 comprising the sequence set forth as SEQ ID NOs: 139.

3. An isolated antibody, or an antigen binding fragment thereof, that binds to CXCR4 and comprises:

a) a light chain variable (VL) region comprising (i) VL CDR1 comprising the sequence X1SX2X3SLFNSX4X5RKNYLX6 wherein X1 is R or K; X2 is S or A; X3 is W, N or Q; X4 is H or R; X5 is T or F; and X6 is A, L, N, or M (SEQ ID NO: 151); (ii) a VL CDR2 comprising the sequence WASARX1S wherein X1 is G or E (SEQ ID NOs: 152), and (iii) VL CDR3 comprising the sequence KQSFX1LRT wherein X1 is N or R (SEQ ID NO: 153); and

b) a heavy chain variable (VH) region comprising (i) VH CDR1 comprising the sequence set forth as SEQ ID NOs: 107, 108, 109, 113, or 114; (ii) a VH CDR2 comprising the sequence set forth as SEQ ID NO: 157 and (iii) a VH CDR3 comprising the sequence set forth as SEQ ID NO: 112.

4. An isolated antibody, or an antigen binding fragment thereof, that binds to CXCR4 and comprises:

a heavy chain variable (VH) region sequence comprising: EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVX1FIRHKX2N X3X4TX5EYSTX6X7 X8GRFTISRDX9SKNX10LYLQMNSLX11X12EDTAVYYCAX13DLPGFAYWGQGTLVTV SS (SEQ ID NO: 106), wherein X1 is G or S; X2 is V or A; X3 is G , F, K, V, T, L, or I; X4 is E or Y; X5 is T or R; X6 is W or S; X7 is D or V; X8 is K, T, or R; X9 is D or N; X10 is T or S; X11 is R or K; X12 is A or T; and/or X13 is K or R; and

a light chain variable region (VL) region comprising (i) a VL CDR1 set forth as SEQ ID NO: 144; (ii) a VL CDR2 set forth as SEQ ID NO: 145; and (iii) a VL CDR3 set forth as SEQ ID NO: 139

5. The isolated antibody or antigen binding fragment thereof, that binds to chemokine receptor 4 (CXCR4) selected from the group consisting of:

a) a heavy chain variable (VH) region having a VH CDR1 of SEQ ID NO:107, 113 or 114; a VH CDR2 of SEQ ID NO:162 or 128 and a VH CDR3 of SEQ ID NO:112 and a light chain variable (VL) region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139;

b) a VH region having a VH CDR1 of SEQ ID NO:115, 116, 117, 121 or 122; a VH CDR2 of SEQ ID NO:118 or 119 and a VH CDR3 of SEQ ID NO:120 and a VL region having a VL CDR1 of SEQ ID NO:135; a VL CDR2 of SEQ ID NO:136 and a VL CDR3 of SEQ ID NO:137;

c) a VH region having a VH CDR1 of SEQ ID NO:107, 108, 109, 113 or 114; a VH CDR2 of SEQ ID NO:110 or 111 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:131; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:133;

d) a VH region having a VH CDR1 of SEQ ID NO:107, 108, 109, 113 or 114; a VH CDR2 of SEQ ID NO:154 or 123 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:139; and

e) a VH region having a VH CDR1 of SEQ ID NO:107, 108, 109, 113 or 114; a VH CDR2 of SEQ ID NO:157 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:151; a VL CDR2 of SEQ ID NO:152 and a VL CDR3 of SEQ ID NO:153.

6. The isolated antibody or antigen binding fragment thereof of claim 1 wherein the antibody comprises a heavy chain variable (VH) region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a light chain variable (VL) region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139.

7. An isolated antibody or antigen binding fragment thereof, that binds to chemokine receptor 4 (CXCR4) selected from the group consisting of:

a) a heavy chain variable (VH) region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a light chain variable (VL) region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:139;

b) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

c) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:150; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

d) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:141; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

e) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140;

f) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:147; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

g) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:159 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

h) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:160 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

i) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:161 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

j) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

k) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

l) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:164 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

m) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:165 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

o) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:166 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

p) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:167 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

q) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:168 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

r) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:168 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

s) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140;

t) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139;

u) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139;

v) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139; and

w) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140.

8. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody comprises: a heavy chain variable (VH) region comprising VH CDR1, VH CDR2 and VH CDR3 from a VH region of SEQ ID NO: 33.

9. The antibody or antigen binding fragment thereof any one of claim 1, wherein the antibody comprises: a light chain variable (VL) region comprising VL CDR1, VL CDR2 and VL CDR3 from a VL region of SEQ ID NO: 73.

10. An isolated antibody, or an antigen binding fragment thereof of claim 1, wherein the antibody comprises:

a) a heavy chain variable (VH) region comprising VH CDR1, VH CDR2 and VH CDR3 from a VH region of SEQ ID NO: 33; and

b) a light chain variable (VL) region comprising VL CDR1, VL CDR2 and VL CDR3 from a VL region of SEQ ID NO: 73.

11. The isolated antibody or antigen binding fragment thereof of claim 6 that comprises an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:33 and a VL region of SEQ ID NO:73.

12. The isolated antibody or antigen fragment thereof of claim 6, wherein the antibody or antigen fragment thereof comprises a heavy chain variable region having an amino acid sequence that is at least 95% identical to SEQ ID NO: 33 and a light chain variable having an amino acid sequence that is at least 95% identical to SEQ ID NO: 73.

13. The antibody or the antigen binding fragment of claim 1, wherein the antibody comprises a heavy chain variable (VH) region produced by the expression vector with ATCC Accession No. PTA-121353.

14. The antibody or the antigen binding fragment of claim 1, wherein the antibody comprises a light chain variable (VL) region produced by the expression vector with ATCC Accession No. PTA-121354.

15. An isolated antibody or antigen binding fragment thereof of, that binds to chemokine receptor 4 (CXCR4) selected from the group consisting of:

a) a heavy chain variable (VH) region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a light chain variable (VL) region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:139;

b) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

c) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:150; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

d) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:141; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

e) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140;

f) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:147; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

g) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:159 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

h) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:160 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

i) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:161 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

j) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

k) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

l) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:164 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

m) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:165 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

n) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:166 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

o) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:167 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

p) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:168 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

q) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:168 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:138; a VL CDR2 of SEQ ID NO:132 and a VL CDR3 of SEQ ID NO:140;

r) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140;

s) a VH region having a VH CDR1 of SEQ ID NO: 107; a VH CDR2 of SEQ ID NO:158 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139;

t) a VH region having a VH CDR1 of SEQ ID NO: 107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139;

u) a VH region having a VH CDR1 of SEQ ID NO: 107; a VH CDR2 of SEQ ID NO:163 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:139; and

v) a VH region having a VH CDR1 of SEQ ID NO:107; a VH CDR2 of SEQ ID NO:162 and a VH CDR3 of SEQ ID NO:112 and a VL region having a VL CDR1 of SEQ ID NO:144; a VL CDR2 of SEQ ID NO:145 and a VL CDR3 of SEQ ID NO:140.

16. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody is a humanized, chimeric, CDR grafted, or recombinant human antibody.

17. The antibody or antigen binding fragment thereof of claim 1 any one of the preceding claims, wherein the antibody is not caninized or felinized.

18. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody comprises an acyl donor glutamine-containing tag engineered at a specific site.

19. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen binding fragment thereof of claim 1 and a pharmaceutically acceptable carrier.

20. An isolated polynucleotide comprising a nucleotide sequence encoding the antibody or antigen binding fragment thereof of claim 1.

21. A vector comprising the polynucleotide of claim 20.

22. An isolated host cell that recombinantly produces the antibody or antigen binding fragment thereof of claim 1.

23. A method of producing an antibody or antigen binding fragment thereof, comprising culturing the host cell of claim 22 under conditions that result in production of the antibody or antigen binding fragment thereof, and isolating the antibody or antigen binding fragment thereof from the host cell or culture medium.

24. Use of an effective amount of the pharmaceutical composition of claim 19 in the manufacture of a medicament for decreasing tumor growth or progression in a subject who has a CXCR4 expressing tumor.

25. Use of an effective mount of the pharmaceutical composition of claim 19 in the manufacture of a medicament for decreasing metastasis of CXCR4 expressing cancer cells in a subject.

26. Use of an effective amount of the pharmaceutical composition of claim 19 in the manufacture of a medicament for inducing tumor regression in a subject who has a CXCR4 expressing tumor.