aspects are provided methods inducing tumor regression in a subject who has a CXCR4 expressing tumor, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition, disclosed herein.

These and other aspects of the invention will be appreciated by a review of the application as a whole.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the h3G10 Heavy Chain variable region (VH) alignment.

Figure 2 shows the h3G10 Light Chain variable region (VL) alignment.

Figure 3A shows the cross reactivity of anti-human CXCR4 Ab h3G10.1.91.A58B to the cynomolgus CXCR4 by flow cytometry in a dilution series (0.007-267nM) on HPB-ALL (Human T cell leukemia) and Cyno-CXCR4 transfected CHO cells.

Figure 3B shows the cross reactivity of anti-human CXCR4 Ab h3G10.1.91.A58B to the cynomolgus CXCR4 by flow cytometry in a dilution series (0.007-267nM) on Raji (NHL; Human non-Hodgkin Lymphoma) and HSC-F (Cynomolgus T cell line).

Figure 4 shows the ADCC(A-C) and CDC(D-F) activities of anti-human CXCR4 antibodies on human cell lines expressing CXCR4.

Figure 4A shows the ADCC activities of 12A11, 6B6 and 3G10 anti-human CXCR4 antibodies on Ramos (NHL) cells.

Figure 4B shows ADCC activity comparison of m3G10-hIgG1 and m3G10-hIgG4 anti-human CXCR4 antibodies on MOLT-4 (T-acute lymphoblastic leukemia) cells.

Figure 4C shows ADCC activities of mouse (m3G10-) and humanized (h3G10-) anti-human CXCR4 antibodies on MOLT-4 (T-acute lymphoblastic leukemia) cells.

Figure 4D shows CDC activities of 12A11, 6B6 and 3G10 anti-human CXCR4 antibodies on Ramos (NHL) cells.

Figure 4E shows CDC activity comparison of m3G10-hIgG1 and m3G10-hIgG4 anti-human CXCR4 antibodies on Daudi (NHL) cells.

Claims

It is claimed:

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, 114, 108, 109, 115, 116, 117, 121 and 122; (ii) a VH CDR2 selected from the group consisting of SEQ ID NOs: 162, 128, 110, 111, 118, 119, 154, 123, 158, 124, 159, 125, 160, 126, 161, 127, 163, 164, 165, 166, 167, 168, 155, 129, 156, and 130, and, (iii) a VH CDR3 selected from the group consisting of SEQ ID NOs: 112, and 120; and/or;

b) a light chain variable region (VL) region comprising (i) a VL CDR1 selected from the group consisting of SEQ ID NOs: 144, 131, 135, 138, 141, 142, 143, 146, 147, 148, 149, 150, and 151; (ii) a VL CDR2 selected from the group consisting of 145, 132, 136, and 152; and (iii) a VL CDR3 selected from the group consisting of SEQ ID NO: 139, 133, 137, 140, and 153.

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, 114, 108, 109, 115, 116, 117, 121 or 122; (ii) a VH CDR2 comprising the sequence set forth as SEQ ID NOs: 162, 128, 110, 111, 118, 119, 154, 123, 158, 124, 159, 125, 160, 126, 161, 127, 163, 164, 165, 166, 167, 168, 155, 129, 156, or 130, and; (iii) a VH CDR3 comprising the sequence set forth as SEQ ID NOs: 112, or 120; and/or

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 NOs: 144, 131, 135, 138, 141, 142, 143, 146, 147, 148, 149, 150, or 151; (ii) a VL CDR2 comprising the sequence set forth as SEQ ID NOs 145, 132, 136, or 152; and (iii) a VL CDR3 comprising the sequence set forth as SEQ ID NOs: 139, 133, 137, 140, or 153.

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 $X_1SX_2X_3SLFNSX_4X_5RKNYLX_6$ wherein X_1 is R or K; X_2 is S or A; X_3 is W, N or Q; X_4 is H or R; X_5 is T or F; and/or X_6 is A, L, N, or M (SEQ ID NO: 151); (ii) a VL CDR2 comprising the sequence $WASARX_1S$ Wherein X_1 is G or E (SEQ ID NOs: 152), and (iii) VL CDR3 comprising the sequence $KQSFX_1LRT$ Wherein X_1 is N or R (SEQ ID NO: 153); and/or

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:
$EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVX_1FIR$
$HKX_2NX_3X_4TX_5EYSTX_6$ X_7
$X_8GRFTISRDX_9SKNX_{10}LYLQMNSLX_{11}X_{12}EDTAVYYCAX_{13}DLPGFAYWGQGTLV$
$TVSS$ (SEQ ID NO: 106), wherein X_1 is G or S; X_2 is V or A; X_3 is G , F, K, V, T, L, or I; X_4 is E or Y; X_5 is T or R; X_6 is W or S; X_7 is D or V; X_8 is K, T, or R; X_9 is D or N; X_{10} is T or S; X_{11} is R or K; X_{12} is A or T; and/or X_{13} is K or R.

5. The isolated antibody or antigen binding fragment thereof of claim 1 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 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: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;

b) a VH region having a VH CDR1 of SEQ ID NO:115; a VH CDR2 of SEQ ID NO:118 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; a VH CDR2 of SEQ ID NO:110 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; a VH CDR2 of SEQ ID NO:154 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; 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.

7. An isolated antibody or antigen binding fragment thereof of claim 1 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 three CDRs set forth as SEQ ID NOs: 107, 162 and 112.

9. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody comprises: a light chain variable (VL) region comprising three CDRs set forth as SEQ ID NOs: 144, 145 and 139.

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

a) a heavy chain variable (VH) region comprising three CDRs set forth as SEQ ID NOs: 107, 162 and 112; and

b) a light chain variable (VL) region comprising three CDRs set forth as SEQ ID NOs: 144, 145 and 139.

11. The antibody or antigen binding fragment thereof of any one of claims 1-4, 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.

12. The antibody or antigen binding fragment thereof any one of claims 1-4, 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.

13. An isolated antibody, or an antigen binding fragment thereof any one of claims 1-4, 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.

14. The isolated antibody or antigen binding fragment thereof of claim 6 selected from the group consisting of:

a) 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;

b) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:13 and a VL region of SEQ ID NO:15;

c) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:5 and a VL region of SEQ ID NO:7;

d) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:21 and a VL region of SEQ ID NO:47; and

e) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:106 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.

15. The isolated antibody or antigen fragment thereof of claim 14, 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.

16. The antibody or antigen binding fragment thereof of claim 14, wherein the antibody comprises:

a) a heavy chain variable (VH) region of SEQ ID NO: 33; and/or

b) a light chain variable (VL) region of SEQ ID NO: 73.

17. The antibody or the antigen binding fragment of claim 8, wherein the antibody comprises a heavy chain variable (VH) region produced by the expression vector with ATCC Accession No. PTA-121353.

18. The antibody or the antigen binding fragment of claim 9, wherein the antibody comprises a light chain variable (VL) region produced by the expression vector with ATCC Accession No. PTA-121354.

19. An isolated antibody or antigen binding fragment thereof of claim 1 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.

20. An isolated antibody or antigen binding fragment thereof, that binds CXCR4, wherein the antibody or antigen binding fragment thereof competes for binding to CXCR4 with and/or binds to the same epitope of CXCR4 as an antibody or antigen binding fragment thereof of any one of claims 1 to 19.

21. The isolated antibody or antigen binding fragment thereof of claim 20, wherein said antibody comprises 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.

22. The antibody or antigen binding fragment thereof of any one of the preceding claims, wherein the antibody is a humanized, chimeric, CDR grafted, or recombinant human antibody.

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

24. The antibody or antigen binding fragment thereof any of the proceeding claims, wherein the antibody comprises an acyl donor glutamine-containing tag engineered at a specific site.

25. An antibody-drug conjugate of the formula:

Ab-(T-L-D),

wherein:

(a) Ab is an antibody or antigen-binding fragment thereof that binds to chemokine receptor 4 (CXC4);

(b) T is an acyl donor glutamine-containing tag that can be optionally included;

(c) L is a linker; and

(d) D is a drug.

26. The antibody-drug conjugate of claim 25, wherein Ab is selected from the group consisting of:

a) an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 107, 162 and 112 and a VL region comprising CDRs of SEQ ID NOs: 144, 145 and 139;

b) an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 115, 118 and 120 and a VL region comprising CDRs of SEQ ID NOs:135, 136 and 137;

c) an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 107, 110 and 112 and a VL region comprising CDRs of SEQ ID NOs:131, 132 and 133;

d) an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 107, 154 and 112 and a VL region comprising CDRs of SEQ ID NOs:138, 132 and 139;

e) an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 107, 157 and 112 and a VL region comprising CDRs of SEQ ID NOs:151, 152 and 153;

f) 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;

g) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:13 and a VL region of SEQ ID NO:15;

h) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:5 and a VL region of SEQ ID NO:7; and

i) an antibody or antigen-binding fragment thereof comprising a VH region of SEQ ID NO:21 and a VL region of SEQ ID NO:47.

27. The antibody-drug conjugate of claim 25, wherein Ab is a humanized, chimeric, CDR grafted, or recombinant human antibody or antigen binding fragment thereof.

28. The antibody-drug conjugate of claim 25, wherein T is selected from the group consisting of SEQ ID NOs: 171, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 172, 173, 102, 103 and LLQ.

29. The antibody-drug conjugate of claim 25, wherein T is selected from the group consisting of any of SEQ ID NOs: 91, 92 and 102.

30. The antibody-drug conjugate of claim 25, wherein L is selected from the group consisting of acetyl-lysine-valine-citrulline-p-aminobenzyloxycarbonyl (AcLys-VC-PABC), amino PEG6-propionyl, maleimidocapronic-valine-citruline-p-aminobenzyloxycarbonyl (vc) and maleimidocaproyl (mc).

31. The antibody-drug conjugate of claim 29, wherein L is acetyl-lysine-valine-citrulline-p-aminobenzyloxycarbonyl (AcLys-VC-PABC).

32. The antibody-drug conjugate of the antibody or the antigen binding fragment of claim 25, wherein the antibody or the antigen binding fragment is conjugated to a drug, wherein the D is selected from the group consisting of a cytotoxic agent, an immunomodulating agent, an imaging agent, a therapeutic protein, a biopolymer, and an oligonucleotide.

33. The antibody-drug conjugate of claim 32, wherein the D is a cytotoxic agent.

34. The antibody-drug conjugate of claim 33, wherein the cytotoxic agent is selected from the group consisting of an anthracycline, an auristatin, a camptothecin, a combretastain, a dolastatin, a duocarmycin, an enediyne, a geldanamycin, an indolino-benzodiazepine dimer, a maytansine, a puromycin, a pyrrolobenzodiazepine dimer, a taxane, a vinca alkaloid, a tubulysin, a hemiasterlin, a spliceostatin, a pladienolide, and calicheamicin.

35. The antibody-drug conjugate of claim 34, wherein the cytotoxic agent is an auristatin.

36. The antibody-drug conjugate of claim 35, wherein the auristatin is selected from the group consisting of 0101 (2-methylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-{[(1S)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide), MMAD (Monomethyl Auristatin D or monomethyl dolastatin 10 and 8261 (2-Methylalanyl-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide).

37. The antibody-drug conjugate of any of claims 25-36 wherein the conjugate is selected from the group consisting of:

a) Ab-LLQGA (SEQ ID NO: 91)-(acetyl-lysine-valine-citrulline-*p*-aminobenzyloxycarbonyl (AcLys-VC-PABC))-0101;

b) Ab-LLQGA (SEQ ID NO: 91)-(AcLys-VC-PABC)-MMAD;

c) Ab-LLQ$X_1X_2X_3X_4X_5$ (SEQ ID NO: 102)-(AcLys-VC-PABC)-0101;

d) Ab-LLQ$X_1X_2X_3X_4X_5$ (SEQ ID NO: 102)-(AcLys-VC-PABC)-MMAD;

e) Ab–GGLLQGA (SEQ ID NO: 92)- (AcLys-VC-PABC)-0101; and

f) Ab–GGLLQGA (SEQ ID NO: 92)-(AcLys-VC-PABC)-MMAD.

38. The antibody-drug conjugate of claim 37, wherein Ab is an antibody or antigen-binding fragment thereof comprising a VH region comprising CDRs of SEQ ID NOs: 107, 162 and 112 and a VL region comprising CDRs of SEQ ID NOs: 144, 145 and 139.

39. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 1-24 or the conjugate of any one of claims 25-38 and a pharmaceutically acceptable carrier.

40. An isolated polynucleotide comprising a nucleotide sequence encoding the antibody or antigen binding fragment thereof of any one of claims 1-24.

41. A vector comprising the polynucleotide of claim 40.

42. An isolated host cell that recombinantly produces the antibody or antigen binding fragment thereof of any one of claims 1-24.

43. A method of producing an antibody or antigen binding fragment thereof, comprising culturing the host cell of claim 42 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.

44. An effective amount of the pharmaceutical composition of claim 39 for use in the treatment of a disorder associated with CXCR4 function or expression.

45. The composition of claim 44, wherein the disorder is a cancer.

46. The composition of claim 45, wherein the cancer is a hematological cancer.

47. The composition of claim 45, wherein the cancer is a B cell or a T cell malignancy.

48. The composition of claim 44, wherein the cancer is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, mantle cell lymphoma (MCL), follicular lymphoma, Waldenstrom's macroglobulinemia (WM), B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

49. The composition of claim 45, wherein the cancer is selected from the group consisting of bladder, breast, cervical, choriocarcinoma, colon, esophageal, gastric, glioblastoma, head and neck, kidney, lung, oral, ovarian, pancreatic, prostate, and skin cancer.

50. An effective amount of the pharmaceutical composition of claim 39 for use in decreasing tumor growth or progression in a subject who has a CXCR4 expressing tumor.

51. An effective amount of the pharmaceutical composition of claim 39 for use in decreasing metastasis of CXCR4 expressing cancer cells in a subject.

52. An effective amount of the pharmaceutical composition of claim 39 for use in inducing tumor regression in a subject who has a CXCR4 expressing tumor.

53. Use of an effective amount of the pharmaceutical composition of claim 39 in the manufacture of a medicament for the treatment of a disorder associated with CXCR4 function or expression.

54. The use of claim 53, wherein the disorder is a cancer.

55. The use of claim 54, wherein the cancer is a hematological cancer.

56. The use of claim 54, wherein the cancer is a B cell or a T cell maligancy.

57. The use of claim 53, wherein the cancer is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple

myeloma (MM), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, mantle cell lymphoma (MCL), follicular lymphoma, Waldenstrom's macroglobulinemia (WM), B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

58. The use of claim 54, wherein the cancer is selected from the group consisting of bladder, breast, cervical, choriocarcinoma, colon, esophageal, gastric, glioblastoma, head and neck, kidney, lung, oral, ovarian, pancreatic, prostate, and skin cancer.

59. Use of an effective amount of the pharmaceutical composition of claim 39 in the manufacture of a medicament for decreasing tumor growth or progression in a subject who has a CXCR4 expressing tumor.

60. Use of an effective amount of the pharmaceutical composition of claim 39 in the manufacture of a medicament for decreasing metastasis of CXCR4 expressing cancer cells in a subject.

61. Use of an effective amount of the pharmaceutical composition of claim 39 in the manufacture of a medicament for inducing tumor regression in a subject who has a CXCR4 expressing tumor.

62. An isolated antibody or antigen binding fragment thereof of any one of claims 1-24 or the antibody-drug conjugate of any one of claims 25-38 for use in detecting, diagnosing and/or treating a disorder associated with expression of CXCR4.

63. Use of an isolated antibody of any one of claims 1-24 or the antibody-drug conjugate of any one of claims 25-38 in the manufacture of a medicament for treating a disorder associated with expression of CXCR4.

aspects are provided methods inducing tumor regression in a subject who has a CXCR4 expressing tumor, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition, disclosed herein.

These and other aspects of the invention will be appreciated by a review of the application as a whole.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the alignment of the amino acid of the variable region of the heavy chain (VH) of antibodies h3G10 (SEQ ID NO: 21), h3G10.A57 (SEQ ID NO: 23), h3G10.2.42 (SEQ ID NO: 41), h3G10.1.7 (SEQ ID NO: 27), h3G10.1.60 (SEQ ID NO: 29), h3G10.2.5 VH (SEQ ID NO: 31), h3G10.1.91 (SEQ ID NO: 33), h3G10.2.37 (SEQ ID NO: 35), h3G10.2.45 (SEQ ID NO: 37), h3G10.3.25 (SEQ ID NO: 45), h3G10.1.33 (SEQ ID NO: 43), h3G10.2.54 (SEQ ID NO: 39), h3G10.A59 (SEQ ID NO: 85), h3G10.A62 (SEQ ID NO: 87), and h3G10.B44 (SEQ ID NO: 25). The alignments also show the CDR regions of the VH from each antibody.

Figure 2 shows the alignment of the amino acid of the variable region of the light chain (VL) of antibodies h3G10 (SEQ ID NO: 47), h3G10.2.72 (SEQ ID NO: 49), h3G10.2.25 (SEQ ID NO: 83), h3G10.A11A (SEQ ID NO: 51), h3G10.A11B (SEQ ID NO: 67), h3G10.A18A (SEQ ID NO: 53), h3G10.A18B (SEQ ID NO: 69), h3G10.A19A (SEQ ID NO: 55), h3G10.A19B (SEQ ID NO: 71), h3G10.A58A (SEQ ID NO: 57), h3G10.A58B (SEQ ID NO: 73), h3G10.A65A (SEQ ID NO: 59), h3G10.A65B (SEQ ID NO: 75), h3G10.B12A (SEQ ID NO: 61), h3G10.B12B (SEQ ID NO: 77), h3G10.B13A (SEQ ID NO: 63), h3G10.B13B (SEQ ID NO: 79), h3G10.B18A (SEQ ID NO: 65), h3G10.B18B (SEQ ID NO: 81), and h3G10.L94D (SEQ ID NO: 169). The alignments also show the CDR regions of the VL from each antibody.

Figure 3A shows the cross reactivity of anti-human CXCR4 Ab h3G10.1.91.A58B to the cynomolgus CXCR4 by flow cytometry in a dilution series (0.007-267nM) on HPB-ALL (Human T cell leukemia) and Cyno-CXCR4 transfected CHO cells.

Figure 3B shows the cross reactivity of anti-human CXCR4 Ab h3G10.1.91.A58B to the cynomolgus CXCR4 by flow cytometry in a dilution series (0.007-267nM) on Raji (NHL; Human non-Hodgkin Lymphoma) and HSC-F (Cynomolgus T cell line).

Figure 4 shows the ADCC(A-C) and CDC(D-F) activities of anti-human CXCR4 antibodies on human cell lines expressing CXCR4.

Figure 4A shows the ADCC activities of 12A11, 6B6 and 3G10 anti-human CXCR4 antibodies on Ramos (NHL) cells.

Figure 4B shows ADCC activity comparison of m3G10-hIgG1 and m3G10-hIgG4 anti-human CXCR4 antibodies on MOLT-4 (T-acute lymphoblastic leukemia) cells.

Figure 4C shows ADCC activities of mouse (m3G10-) and humanized (h3G10-) anti-human CXCR4 antibodies on MOLT-4 (T-acute lymphoblastic leukemia) cells.

Figure 4D shows CDC activities of 12A11, 6B6 and 3G10 anti-human CXCR4 antibodies on Ramos (NHL) cells.

Figure 4E shows CDC activity comparison of m3G10-hIgG1 and m3G10-hIgG4 anti-human CXCR4 antibodies on Daudi (NHL) cells.

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/or 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/or

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 X3X4TX5EYSTX6 X7 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.

5. The isolated antibody or antigen binding fragment thereof of claim 1 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 of claim 1 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 three CDRs set forth as SEQ ID NOs: 107, 162 and 112.

9. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody comprises: a light chain variable (VL) region comprising three CDRs set forth as SEQ ID NOs: 144, 145 and 139.

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

a) a heavy chain variable (VH) region comprising three CDRs set forth as SEQ ID NOs: 107, 162 and 112; and

b) a light chain variable (VL) region comprising three CDRs set forth as SEQ ID NOs: 144, 145 and 139.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. An antibody or antigen binding fragment thereof, wherein the antibody comprises:

a) a heavy chain variable (VH) region of SEQ ID NO: 33; and

b) a light chain variable (VL) region of SEQ ID NO: 73.

17. 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.

18. 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.

19. An isolated antibody or antigen binding fragment thereof of claim 1 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.

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

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

22. 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.

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

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

25. A vector comprising the polynucleotide of claim 24.

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

27. A method of producing an antibody or antigen binding fragment thereof, comprising culturing the host cell of claim 26 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.

28. A method of treating a disorder associated with CXCR4 function or expression in a subject comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 23.

29. The method of claim 28, wherein the disorder is a cancer.

30. The method of claim 29, wherein the cancer is a hematological cancer.

31. The method of claim 29, wherein the cancer is a B cell or a T cell malignancy.

32. The method of claim 28, wherein the cancer is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, mantle cell lymphoma (MCL), follicular lymphoma, Waldenstrom's macroglobulinemia (WM), B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

33. The method of claim 29, wherein the cancer is selected from the group consisting of bladder, breast, cervical, choriocarcinoma, colon, esophageal, gastric, glioblastoma, head and neck, kidney, lung, oral, ovarian, pancreatic, prostate, and skin cancer.

34. A method of decreasing tumor growth or progression in a subject who has a CXCR4 expressing tumor, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 23. .

35. A method of decreasing metastasis of CXCR4 expressing cancer cells in a subject, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 23.

36. A method of inducing tumor regression in a subject who has a CXCR4 expressing tumor, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 23.

37. An isolated antibody or antigen binding fragment thereof of claim 1 for use in detecting, diagnosing and/or treating a disorder associated with expression of CXCR4.

38. Use of an isolated antibody of claim 1 in the manufacture of a medicament for treating a disorder associated with expression of CXCR4.

39. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the disorder is a cancer.

40. The isolated antibody or antigen binding fragment thereof of claim 1 wherein the cancer is a hematological cancer.

41. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the cancer is a B cell or a T cell malignancy.

42. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the cancer is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, mantle cell lymphoma (MCL), follicular lymphoma, Waldenstrom's macroglobulinemia (WM), B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

43. The isolated antibody or antigen binding fragment thereof of claim 1 wherein the cancer is selected from the group consisting of bladder, breast, cervical, choriocarcinoma, colon, esophageal, gastric, glioblastoma, head and neck, kidney, lung, oral, ovarian, pancreatic, prostate, and skin cancer.

44. Use of an effective amount of the pharmaceutical composition of claim 23 in the manufacture of a medicament for decreasing metastasis of CXCR4 expressing cancer cells in a subject.

45. Use of an effective amount of the pharmaceutical composition of claim 23 in the manufacture of a medicament for inducing tumor regression in a subject who has a CXCR4 expressing tumor.

46. An isolated antibody or antigen binding fragment thereof of any one of claims 1-22 for use in detecting, diagnosing and/or treating a disorder associated with expression of CXCR4.

47. Use of an isolated antibody of any one of claims 1-22 in the manufacture of a medicament for treating a disorder associated with expression of CXCR4.