31464). Members of the Stat, Src, ERK, and AKT signaling pathways have been shown to be downstream signal transducers of KIT signaling.

[0005] The fourth (D4) and fifth (D5) extracellular Ig-like domains of KIT are believed to mediate receptor dimerization (see, *e.g.*, International Patent Application Publication No. WO 2008/153926; Yuzawa *et al.*, Cell, 2007, 130:323-334).

[0006] Expression of KIT has been detected in various cell types, such as mast cells, stem cells, brain cells, melanoblasts, ovary cells, and cancer cells (*e.g.*, leukemia cells). Studies of loss-of-function KIT mutations indicate that KIT is important for the normal growth of hematopoietic progenitor cells, mast cells, melanocytes, primordial germ cells, and the interstitial cells of Cajal (see, *e.g.*, Besmer, P., Curr. Opin. Cell Biol., 1991, 3:939-946; Lyman *et al.*, Blood, 1998, 91:1101-1134; Ashman, L. K., Int. J. Biochem. Cell Biol., 1999, 31:1037-1051; Kitamura *et al.*, Mutat. Res., 2001, 477:165-171; Mol *et al.*, J. Biol. Chem., 2003, 278:31461-31464). Moreover, KIT plays an important role in hematopoiesis, melanogenesis, and gametogenesis (see Ueda *et al.*, Blood, 2002, 99:3342-3349).

[0007] Abnormal KIT activity has been implicated in connection with a number of cancers. For example, gain-of-function KIT mutations resulting in SCF-independent, constitutive activation of KIT are found in certain cancer cells and are associated with certain cancers such as leukemia (*e.g.*, chronic myelogenous leukemia) and gastrointestinal stromal tumors (*see, e.g.*, Mol *et al.*, J. Biol. Chem., 2003, 278:31461-31464).

3. SUMMARY

[0008] Provided herein, are antibodies, antigen-binding fragments thereof, and conjugates thereof, that immunospecifically bind to a domain 4 (D4) (or D4 region) of the extracellular domain of KIT (*e.g.*, human KIT) and inhibit a KIT activity, as well as related compositions, reagents and methods.

[0009] In one aspect, the present invention refers to an isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, wherein (i) the light chain variable region ("VL") comprises the amino acid sequence of SEQ ID NO: 8 and the heavy chain variable region ("VH") comprises the amino acid sequence of SEQ ID NO: 4; (ii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 3; (iii) the VL comprises the amino acid sequence of SEQ ID

NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 6; (iv) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 5; (v) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 2; (vi) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 3; (vii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 4; (viii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 6; (ix) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 2; (x) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 3; (xi) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 5; (xii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 2; (xiii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 3; (xiv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 4; (xv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 5; (xvi) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 6; (xvii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 2; (xviii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 4; (xix) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 5; or (xx) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 6, wherein the VL and VH are non-immunogenic in a human. In one aspect, the present invention refers to an isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, which comprises:(i) a light chain variable region ("VL") comprising the amino acid sequence: DIVMTQSPSX_{K1}LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPKX_{K2}LIYSASYRYSG VPDRFX_{K3}GSGSGTDFTLTISSLQX_{K4}EDFAX_{K5}YX_{K6}CQQYNSYPRTFGGGTKVEIK, wherein X_{K1} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K2} is an amino acid with

an aromatic or aliphatic hydroxyl side chain, X_{K3} is an amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and (ii) a heavy chain variable region ("VH") comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively, wherein the VL and VH are non-immunogenic in a human, wherein the antibody or antigen-binding fragment thereof inhibits tyrosine phosphorylation of KIT with an IC50 of about 600 pM or less as determined by ELISA, and wherein the antibody or antigen-binding fragment thereof induces KIT receptor internalization. In another aspect, the present invention refers to an isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, which comprises: (i) a VL comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and (ii) a VH comprising the amino acid sequence: QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINWVX_{H3}QAPGKGLEWIARIYPGS GNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H7}LSSLRSEDX_{H8}AVYFCARGVYYFDYW GQGTTVTVSS, wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid with an aliphatic side chain, X_{H6} is an amino acid with an acidic side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain, wherein the VL and VH are non-immunogenic in a human, wherein the antibody or antigen-binding fragment thereof inhibits tyrosine phosphorylation of KIT with an IC50 of about 600 pM or less as determined by ELISA, and wherein the antibody or antigen-binding fragment thereof induces KIT receptor internalization. In one aspect, the present invention refers to a conjugate comprising the antibody of the present invention or a antigen-binding fragment thereof linked to an agent. ~~In one aspect, provided~~Also disclosed herein is an antibody, or an antigen binding fragment thereof, which immunospecifically binds to a D4 of human KIT, comprising:

(i) a light chain variable region ("VL") comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and

(ii) a heavy chain variable region ("VH") comprising VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively.

In one ~~embodiment~~example, the VL and VH of an antibody provided herein or an antigen-binding fragment thereof are non-immunogenic in a human. In a particular ~~embodiment~~example, the antibody can be expressed in Chinese hamster ovary (CHO) cells at a titer of at least 0.45 μg/mL. In a particular example, the antibody can be expressed in Chinese hamster ovary (CHO) cells at a titer of at least 0.3 μg/mL, at least 0.6 μg/mL, at least 0.75 μg/mL, or at least 1 μg/mL.

[0010] In a certain example, provided herein is antibody, or an antigen-binding fragment thereof, or a conjugate thereof, which immunospecifically binds to a D4 of human KIT, comprising:

a light chain variable region ("VL") comprising the amino acid sequence: DIVMTQSPSX_{K1}LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPKX_{K2}LIYSASYRY SGVPDRFX_{K3}GSGSGTDFTLTISSLQX_{K4}EDFAX_{K5}YX_{K6}CQQYNSYPRTFGGGTKVEIK (SEQ ID NO: 11), wherein X_{K1} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K2} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K3} is an amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and

a heavy chain variable region ("VH") comprising a VH CDR1, VH CDR2, and VH CDR3 comprising the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively.

[0011] In a particular ~~aspect~~example, ~~provided~~ disclosed herein is antibody (or a fragment thereof or a conjugate thereof), which immunospecifically binds to a D4 of human KIT, comprising:

(i) a VL comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and

(ii) a VH comprising the amino acid sequence: QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINWVX_{H3}QAPGKGLEWIARIYP GSGNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H7}LSSLRSEDX_{H8}AVYFCARGVYYFD YWGQGTTVTVSS (SEQ ID NO: 12), wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid

with an aliphatic side chain, X_{H6} is an amino acid with an acidic side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain.

[0012] In a particular ~~embodiment~~example, X_{K1} is the amino acid F or S, X_{K2} is the amino acid A or S, X_{K3} is the amino acid T or S, X_{K4} is the amino acid S or P, X_{K5} is the amino acid D or T, and X_{K6} is the amino acid F or Y.

[0013] In a certain example, X_{K1} is the amino acid S, X_{K2} is the amino acid A, X_{K3} is the amino acid T, X_{K4} is the amino acid P, X_{K5} is the amino acid D, and X_{K6} is the amino acid F.

[0014] In a particular example, X_{K1} is the amino acid F, X_{K2} is the amino acid A, X_{K3} is the amino acid T, X_{K4} is the amino acid S, X_{K5} is the amino acid D, and X_{K6} is the amino acid F.

[0015] In a particular example, X_{K1} is the amino acid F or S, X_{K2} is the amino acid A, X_{K3} is the amino acid T, X_{K4} is the amino acid S or P, X_{K5} is the amino acid D, and X_{K6} is the amino acid F.

[0016] In a particular example, X_{K1} is the amino acid S, X_{K2} is the amino acid A, X_{K3} is the amino acid T, X_{K4} is the amino acid P, X_{K5} is the amino acid D, and X_{K6} is the amino acid F.

[0017] In a particular example, X_{K1} is the amino acid S, X_{K2} is the amino acid S, X_{K3} is the amino acid S, X_{K4} is the amino acid P, X_{K5} is the amino acid T, and X_{K6} is the amino acid Y.

[0018] In one embodiment, X_{H1} is the amino acid L or V, X_{H2} is the amino acid L or V, X_{H3} is the amino acid K or R, X_{H4} is the amino acid V or A, X_{H5} is the amino acid L or I, X_{H6} is the amino acid E or D, X_{H7} is the amino acid Q or E, and X_{H8} is the amino acid S or T.

[0019] In a specific example, X_{H1} is the amino acid V, X_{H2} is the amino acid L or V, X_{H3} is the amino acid R or Q, X_{H4} is the amino acid A, X_{H5} is the amino acid L or I, X_{H6} is the amino acid D, X_{H7} is the amino acid Q or E, and X_{H8} is the amino acid T.

[0020] In a specific example, X_{H1} is the amino acid V, X_{H2} is the amino acid L, X_{H3} is the amino acid R, X_{H4} is the amino acid A, X_{H5} is the amino acid L, X_{H6} is the amino acid D, X_{H7} is the amino acid Q, and X_{H8} is the amino acid T.

[0021] In a certain example, X_{H1} is the amino acid V, X_{H2} is the amino acid V, X_{H3} is the amino acid R, X_{H4} is the amino acid A, X_{H5} is the amino acid I, X_{H6} is the amino acid D, X_{H7} is the amino acid E, and X_{H8} is the amino acid T.

$\mathbf{X_{K4}}$ is an amino acid with an aliphatic hydroxyl side chain or is P, $\mathbf{X_{K5}}$ is an amino acid with a charged or acidic side chain, and $\mathbf{X_{K6}}$ is an amino acid with an aromatic side chain; and

ii) a VH comprising the amino acid sequence: QVQLVQSGAE$\mathbf{X_{H1}}$KKPGASVK$\mathbf{X_{H2}}$SCKASGYTFTDYYINWV$\mathbf{X_{H3}}$QAPGK GLEWIARIYPGSGNTYYNEKFKGR$\mathbf{X_{H4}}$T$\mathbf{X_{H5}}$TA$\mathbf{X_{H6}}$KSTSTAYM$\mathbf{X_{H7}}$LSSL RSED$\mathbf{X_{H8}}$AVYFCARGVYYFDYWGQGTTVTVSS, wherein $\mathbf{X_{H1}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H2}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H3}}$ is an amino acid with a polar or basic side chain, $\mathbf{X_{H4}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H5}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H6}}$ is an amino acid with an acidic side chain, $\mathbf{X_{H7}}$ is an amino acid with an acidic or amide derivative side chain, and $\mathbf{X_{H8}}$ is an amino acid with an aliphatic hydroxyl side chain.

[0028] In a particular example, X_{K1} to X_{K6} is an amino acid set forth in Table 6A, and/or X_{H1} to X_{H8} is an amino acid set forth in Table 6B.

[0029] In a particular ~~embodiment~~example, an antibody described herein specifically binds to CHO cells recombinantly expressing wild-type KIT with an EC_{50} of about 150 pM or less as determined by flow cytometry. In a particular example, an antibody described herein specifically binds to a recombinant D4/D5 region of human KIT with an EC_{50} of about 600 pM or less, or about 250 pM to about 600 pM, as determined by flow cytometry. In a certain ~~embodiment~~example, an antibody described herein inhibits tyrosine phosphorylation of KIT with an IC_{50} of about 600 pM or less as determined by ELISA.

[0030] In a specific example~~embodiment~~, an antibody described herein can be expressed in CHO cells with a titer of at least 1.0 μg/mL, or at least 1.1 μg/mL, or at least 1.2 μg/mL.

[0031] In a particular example~~embodiment~~, an antibody described herein further comprises a human light chain constant region and a human heavy chain constant region. In one example, the human light chain constant region of an antibody described herein is a human kappa light chain constant region. In a particular example, the human heavy chain constant region of an antibody described herein is a human gamma heavy chain constant region.

[0032] In a certain examplembodiment, an antibody described herein is a human IgG1 or IgG4 antibody. In a certain embodiment, an antibody described herein is an antigen-binding fragment or a Fab fragment. In a specific examplembodiment, an antibody described herein is an antigen-binding fragment or a Fab fragment. In a particular examplembodiment, an antibody described herein is a bispecific antibody. In a certain example, an antibody described herein is internalized by a cell.

[0033] In a particular examplaspect, provided disclosed herein is a conjugate comprising an antibody described herein, or a KIT-binding fragment thereof, linked to an agent. In a specific examplembodiment, the agent is a toxin. In a certain examplembodiment, the toxin is abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin. In one examplembodiment, the conjugate is internalized by a cell.

[0034] In a certain aspect, provided herein is a pharmaceutical composition comprising a conjugate described herein and a pharmaceutically acceptable carrier.

[0035] In another aspect, provided herein is a pharmaceutical composition comprising an antibody described herein and a pharmaceutically acceptable carrier.

[0036] In a particular aspect, provided herein is a polynucleotide comprising nucleotide sequences encoding a VH chain region, a VL chain region, or both a VL chain region and a VH chain region, of an antibody described herein.

[0037] In a specific embodimentexample, a polynucleotide (*e.g.*, isolated polynucleotide) provided herein comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH. In a scertain embodiment, a polynucleotide (*e.g.*, isolated polynucleotide) provided herein comprises SEQ ID NO: 27, 28, 29, or 30 encoding a VL. In a particular embodimentexample, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH, and SEQ ID NO: 27, 28, 29, or 30 encoding a VL.

[0038] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 22 encoding a VH, and SEQ ID NO: 27 encoding a VL.

[0039] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 22 encoding a VH, and SEQ ID NO: 28 encoding a VL.

[0050] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 25 encoding a VH, and SEQ ID NO: 27 encoding a VL.

[0051] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 25 encoding a VH, and SEQ ID NO: 28 encoding a VL.

[0052] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 25 encoding a VH, and SEQ ID NO: 29 encoding a VL.

[0053] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 25 encoding a VH, and SEQ ID NO: 30 encoding a VL.

[0054] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 26 encoding a VH, and SEQ ID NO: 27 encoding a VL.

[0055] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 26 encoding a VH, and SEQ ID NO: 28 encoding a VL.

[0056] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 26 encoding a VH, and SEQ ID NO: 29 encoding a VL.

[0057] In a particular example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 26 encoding a VH, and SEQ ID NO: 30 encoding a VL.

[0058] In one aspect, provided herein is a vector comprising a polynucleotide described herein for expressing an anti-KIT antibody or a fragment thereof. In a certain ~~embodiment~~example, a vector provided herein is a mammalian expression vector.

[0059] In a certain aspect, provided herein is a host cell comprising a vector provided herein or one or more polynucleotides provided herein for expressing an anti-KIT antibody or a fragment thereof.

[0060] In a particular ~~aspect~~example, ~~provided~~ disclosed herein is a cell producing an antibody described herein. In one ~~embodiment~~example, a cell provided herein comprises one or more polynucleotides described herein, wherein the cell can express an antibody which specifically binds to a D4 of human KIT. In a certain ~~embodiment~~example, the cell comprises a vector described herein.

[0061] In a specific ~~aspect~~example, ~~provided~~ disclosed herein is a kit comprising an antibody (or antigen-binding fragment thereof or conjugate thereof) described herein. In a particular embodiment, a kit comprises a conjugate described herein.

[0062] In a certain example, ~~provided~~ disclosed herein is a method for treating or managing a KIT-associated disorder (*e.g.*, cancer), comprising administering to a subject in need thereof a therapeutically effective amount of an antibody described herein or an antigen-binding fragment thereof or a conjugate thereof. In one further aspect, the present invention refers to the use of an antibody of the present invention from the manufacture of a medicament for treating or managing a KIT-associated disorderwherein the KIT-associated disorder is selected from the group consisting of cancer, an inflammatory condition, and fibrosis. In one further aspect, the present invention refers to the use of a conjugate of the present invention in the manufacture of a medicament for treating or managing a KIT-associated disorder, wherein the KIT-associated disorder is selected from the group consisting of cancer, inflammatory condition, and fibrosis.

[0063] In one example, ~~provided~~ disclosed herein is a method for treating or managing a KIT-associated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a conjugate described herein.

[0064] In a particular example, the KIT-associated disorder is cancer, an inflammatory condition, or fibrosis. In a specific ~~embodiment~~example, the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors. In one ~~embodiment~~example, the cancer is refractory to treatment by a tyrosine kinase inhibitor. In a further ~~embodiment embodiment~~example, the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

[0065] In a certain example, a method provided herein further comprises administering a second agent. In a specific ~~embodiment~~example, the second agent is a chemotherapeutic agent, tyrosine kinase inhibitor, a histone deacetylase inhibitor, an antibody, or a cytokine. In a particular ~~embodiment~~example, the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

[0066] In a specific example, provided herein is a method, such as an *in vitro* method, for diagnosing a subject with a KIT-associated disorder comprising contacting cells or a sample obtained from the subject with an antibody described herein (or an antigen-binding fragment thereof or a conjugate thereof) and detecting the expression level of KIT in the cells or the sample. For example, detection of the binding of an antibody described herein to a KIT antigen present in the cell or sample can be correlated to the expression level of KIT in the cell or sample. In a particular embodiment, the antibody is conjugated to a detectable molecule. In a certain embodiment, the detectable molecule is an enzyme, a fluorescent molecule, a luminescent molecule, or a radioactive molecule.

[0067] In a particular example, provided herein is a method, such as an *in vitro* method, for inhibiting KIT activity in a cell expressing KIT comprising contacting the cell with an effective amount of an antibody described herein (or an antigen-binding fragment thereof or a conjugate thereof).

[0068] In a particular example, provided herein is a method, such as an *in vitro* method, for inducing or enhancing apoptosis in a cell expressing KIT comprising contacting the cell with an effective amount an antibody described herein (or an antigen-binding fragment thereof or a conjugate thereof).

[0069] In a particular example, provided herein is a method, such as an *in vitro* method, for inducing cell differentiation comprising contacting a cell expressing KIT with an effective amount of an antibody described herein (or an antigen-binding fragment thereof or a conjugate thereof). In a particular embodiment, the cell is a stem cell.

[0070] In a certain aspect, provided herein is a method of making an antibody which immunospecifically binds to a D4 region of human KIT comprising culturing a cell or host cell described herein. In a certain example, provided herein is a method of making an antibody which immunospecifically binds to a D4 region of human KIT comprising expressing the antibody using a cell or host cell described herein. In a particular example, the cell is an isolated cell. In a particular example, the method further comprises the step of purifying the antibody obtained from the cell or host cell.

[0071] In one ~~aspect~~example, ~~provided~~ disclosed herein is an antibody or antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, wherein said antibody or antigen-binding fragment thereof comprises:

(i) a light chain variable region ("VL") comprising a VL CDR1, VL CDR2, and VL CDR3 selected from the group set forth in Tables 10-12; and

(ii) a heavy chain variable region ("VH") comprising VH CDR1, VH CDR2, and VH CDR3 selected from the group set forth in Tables 13-15.

[0072] In a certain example, described herein is an antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof comprises:

(i) VL comprising a VL FR1, VL FR2, VL FR3, AND VL FR4 selected from the group set forth in Tables 20-23; and

(ii) a VH comprising Vh FR1, VH FR2, VH FR3, and VH FR4 selected from the group set forth in Tables 16-19.

WHAT IS CLAIMED:

1. An isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, wherein

(i) the light chain variable region ("VL") comprises the amino acid sequence of SEQ ID NO: 8 and the heavy chain variable region ("VH") comprises the amino acid sequence of SEQ ID NO: 4;

(ii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(iii) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(iv) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(v) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(vi) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(vii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(viii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(ix) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(x) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(xi) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(xii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(xiii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(xiv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(xv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(xvi) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(xvii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(xviii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(xix) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 5; or

(xx) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 6,

wherein the VL and VH are non-immunogenic in a human.

2. An isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, which comprises:

(i) a light chain variable region ("VL") comprising the amino acid sequence: DIVMTQSPS$\mathbf{X_{K1}}$LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPK$\mathbf{X_{K2}}$LIYSASYR YSGVPDRF$\mathbf{X_{K3}}$GSGSGTDFTLTISSLQ$\mathbf{X_{K4}}$EDFA$\mathbf{X_{K5}}$Y$\mathbf{X_{K6}}$CQQYNSYPRTFGGGTKVEI K, wherein $\mathbf{X_{K1}}$ is an amino acid with an aromatic or aliphatic hydroxyl side chain, $\mathbf{X_{K2}}$ is an amino acid with an aromatic or aliphatic hydroxyl side chain, $\mathbf{X_{K3}}$ is an amino acid with an aliphatic hydroxyl side chain, $\mathbf{X_{K4}}$ is an amino acid with an aliphatic hydroxyl side chain or is P, $\mathbf{X_{K5}}$ is an amino acid with a charged or acidic side chain, and $\mathbf{X_{K6}}$ is an amino acid with an aromatic side chain; and

(ii) a heavy chain variable region ("VH") comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively,

wherein the VL and VH are non-immunogenic in a human,

wherein the antibody or antigen-binding fragment thereof inhibits tyrosine phosphorylation of KIT with an IC50 of about 600 pM or less as determined by ELISA, and

wherein the antibody or antigen-binding fragment thereof induces KIT receptor internalization.

3. An isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, which comprises:

(i) a VL comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and

(ii) a VH comprising the amino acid sequence: QVQLVQSGAE$\mathbf{X_{H1}}$KKPGASVK$\mathbf{X_{H2}}$SCKASGYTFTDYYINWV$\mathbf{X_{H3}}$QAPGKGLEWIARIYPGSGNTYYNEKFKGR$\mathbf{X_{H4}}$T$\mathbf{X_{H5}}$TA$\mathbf{X_{H6}}$KSTSTAYM$\mathbf{X_{H7}}$LSSLRSED$\mathbf{X_{H8}}$AVYFCARGVYYFDYWGQGTTVTVSS, wherein $\mathbf{X_{H1}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H2}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H3}}$ is an amino acid with a polar or basic side chain, $\mathbf{X_{H4}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H5}}$ is an amino acid with an aliphatic side chain, $\mathbf{X_{H6}}$ is an amino acid with an acidic side chain, $\mathbf{X_{H7}}$ is an amino acid with an acidic or amide derivative side chain, and $\mathbf{X_{H8}}$ is an amino acid with an aliphatic hydroxyl side chain,

wherein the VL and VH are non-immunogenic in a human,

wherein the antibody or antigen-binding fragment thereof inhibits tyrosine phosphorylation of KIT with an IC50 of about 600 pM or less as determined by ELISA, and

wherein the antibody or antigen-binding fragment thereof induces KIT receptor internalization.

4. The antibody of claim 2 or 3, which comprises:

(i) a light chain variable region ("VL") comprising the amino acid sequence:

DIVMTQSPS$\mathbf{X_{K1}}$LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPK$\mathbf{X_{K2}}$LIYSASYRYSGVPDRF$\mathbf{X_{K3}}$GSGSGTDFTLTISSLQ$\mathbf{X_{K4}}$EDFA$\mathbf{X_{K5}}$Y$\mathbf{X_{K6}}$CQQYNSYPRTFGGGTKVEIK, wherein $\mathbf{X_{K1}}$ is an amino acid with an aromatic or aliphatic hydroxyl side chain, $\mathbf{X_{K2}}$ is an amino acid with an aromatic or aliphatic hydroxyl side chain, $\mathbf{X_{K3}}$ is an

amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and

(ii) a VH comprising the amino acid sequence: QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINWVX_{H3}QAPGKGLEWIARIYPGSGNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H7}LSSLRSEDX_{H8}AVYFCARGVYYFDYWGQGTTVTVSS, wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid with an aliphatic side chain, X_{H6} is an amino acid with an acidic side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain.

5. The antibody of claim 4, wherein X_{K1} is the amino acid F or S, X_{K2} is the amino acid A or S, X_{K3} is the amino acid T or S, X_{K4} is the amino acid S or P, X_{K5} is the amino acid D or T, and X_{K6} is the amino acid F or Y.

6. The antibody of claim 4, wherein X_{H1} is the amino acid L or V, X_{H2} is the amino acid L or V, X_{H3} is the amino acid K or R, X_{H4} is the amino acid V or A, X_{H5} is the amino acid L or I, X_{H6} is the amino acid E or D, X_{H7} is the amino acid Q or E, and X_{H8} is the amino acid S or T.

7. The antibody of any one of claims 1 to 6, wherein the antibody specifically binds to CHO cells recombinantly expressing wild-type KIT with an EC50 of about 150 pM or less as determined by flow cytometry.

8. The antibody of any one of claims 1 to 6, which can be expressed in CHO cells at a titer of at least 1.0 μg/mL, or at least 1.1 μg/mL, or at least 1.2 μg/mL.

9. The antibody of any one of claims 1 to 6, wherein the antibody further comprises a human kappa light chain constant region and a human gamma heavy chain constant region.

10. The antibody of any one of claims 1 to 6, wherein the antibody is a human IgG1 or IgG4 antibody.

11. The antibody of any one of claims 1 to 6, which is a monoclonal antibody.

12. The antibody of any one of claims 1 to 6, which is an antigen-binding fragment or a Fab fragment.

13. The antibody of any one of claims 1 to 6, which is a bispecific antibody.

14. The antibody of any one of claims 1 to 6, which is fused to a heterologous polypeptide.

15. A conjugate comprising the antibody of any one of claims 1 to 6 or a antigen-binding fragment thereof linked to an agent.

16. The conjugate of claim 15, wherein the agent is a toxin.

17. The conjugate of claim 16, wherein the toxin is abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.

18. The conjugate of claim 15, wherein the conjugate is internalized by a cell.

19. A pharmaceutical composition comprising the conjugate of claim 15 and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising the antibody of any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

21. A polynucleotide comprising nucleotide sequences encoding a VH chain region, a VL chain region, or both a VL chain region and a VH chain region, of an antibody of any one of claims 1 to 6.

22. The polynucleotide of claim 21, which comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH.

23. The polynucleotide of claim 21, which comprises SEQ ID NO: 27, 28, 29, or 30 encoding a VL.

24. The polynucleotide of claim 21, which comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH, and SEQ ID NO: 27, 28, 29, or 30 encoding a VL.

25. A vector comprising the polynucleotide of claim 21.

26. The vector of claim 25, which is a mammalian expression vector.

27. A host cell comprising the vector of claim 25 or one or more polynucleotides of claim 21.

28. An isolated cell producing an antibody according to any one of claims 1 to 6.

29. An isolated cell comprising one or more polynucleotides of claim 21, wherein the cell can express an antibody which specifically binds to a D4 of human KIT.

30. A cell comprising the vector of claim 25.

31. A kit comprising the antibody of any one of claims 1 to 6.

32. A kit comprising the conjugate of claim 15.

33. Use of an antibody of any one of claims 1 to 6 in the manufacture of a medicament for treating or managing a KIT-associated disorderwherein the KIT-associated disorder is selected from the group consisting of cancer, an inflammatory condition, and fibrosis.

34. Use of a conjugate of claim 15 in the manufacture of a medicament for treating or managing a KIT-associated disorder, wherein the KIT-associated disorder is selected from the group consisting of cancer, an inflammatory condition, and fibrosis.

35. The use of claim 33 or 34, wherein the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors.

36. The use of claim 35, wherein the cancer is refractory to treatment by a tyrosine kinase inhibitor.

37. The use of claim 36, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

38. The use of claim 33 or 34, wherein the use further comprises administration of a second therapeutic agent.

39. The use of claim 38, wherein the second therapeutic agent is a chemotherapeutic agent, tyrosine kinase inhibitor, a histone deacetylase inhibitor, an antibody, or a cytokine.

40. The use of claim 39, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

41. An *in vitro* method for diagnosing a subject with a KIT-associated disorder comprising contacting cells or a sample obtained from the subject with the antibody of any one of claims 1 to 6 and detecting the expression level of KIT in the cells or the sample.

42. The method of claim 41, wherein the antibody is conjugated to a detectable molecule.

43. The method of claim 42, wherein the detectable molecule is an enzyme, a fluorescent molecule, a luminescent molecule, or a radioactive molecule.

44. An *in vitro* method for inhibiting KIT activity in a cell expressing KIT comprising contacting the cell with an effective amount of the antibody of any one of claims 1 to 6.

45. An *in vitro* method for inducing or enhancing apoptosis in a cell expressing KIT comprising contacting the cell with an effective amount of the antibody of any one of claims 1 to 6.

46. An *in vitro* method for inducing cell differentiation comprising contacting a cell expressing KIT with an effective amount of the antibody of any one of claims 1 to 6.

47. The method of claim 46, wherein the cell is a stem cell.

48. A method of making an antibody which immunospecifically binds to a D4 region of human comprising culturing, and/or expressing the antibody using, the cell of claim 27.

49. The method claim 48 further comprising purifying the antibody obtained from said cell.

WHAT IS CLAIMED:

1. An isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, comprising:

(i) a light chain variable region ("VL") comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and

(ii) a heavy chain variable region ("VH") comprising VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively;

wherein the VL and VH are non-immunogenic in a human.

2. The antibody of claim 1, wherein the antibody can be expressed in Chinese hamster ovary (CHO) cells at a titer of at least 0.45 μg/mL.

3. The antibody of claim 1, wherein the VL comprises the amino acid sequence of SEQ ID NO: 8, 10, 7, or 9, and the VH comprises the amino acid sequence of SEQ ID NO: 4, 3, 6, 5, or 2.

4. The antibody of claim 1, wherein

(i) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(ii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(iii) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(iv) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(v) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(vi) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(vii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(viii) the VL comprises the amino acid sequence of SEQ ID NO: 7 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(ix) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(x) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(xi) the VL comprises the amino acid sequence of SEQ ID NO: 8 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(xii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(xiii) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 3;

(xiv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(xv) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 5;

(xvi) the VL comprises the amino acid sequence of SEQ ID NO: 9 and the VH comprises the amino acid sequence of SEQ ID NO: 6;

(xvii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 2;

(xviii) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 4;

(xix) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 5; or

(xx) the VL comprises the amino acid sequence of SEQ ID NO: 10 and the VH comprises the amino acid sequence of SEQ ID NO: 6.

5. The antibody of claim 1, which comprises:

(i) a light chain variable region ("VL") comprising the amino acid sequence:

DIVMTQSPSX_{K1}LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPKX_{K2}LIYSASYRYSG

VPDRFX_{K3}GSGSGTDFTLTISSLQX_{K4}EDFAX_{K5}YX_{K6}CQQYNSYPRTFGGGTKVEIK, wherein X_{K1} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K2} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K3} is an amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and

(ii) a heavy chain variable region ("VH") comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO: 16, SEQ ID NO: 17, and SEQ ID NO: 18, respectively.

6. The antibody of claim 1, which comprises:

(i) (i) a VL comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO: 19, SEQ ID NO: 20, and SEQ ID NO: 21, respectively; and

(ii) (ii) a VH comprising the amino acid sequence: QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINWVX_{H3}QAPGKGLEWIARIYPGSGNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H7}LSSLRSEDX_{H8}AVYFCARGVYYFDYWGQGTTVTVSS, wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid with an aliphatic side chain, X_{H6} is an amino acid with an acidid side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain.

7. The antibody of claim 1, which comprises:

(iii) a VL comprising an amino acid sequence that is: at least 90% identical to SEQ ID NO: 7, at least 88% identical to SEQ ID NO: 8, at least 87% identical to SEQ ID NO: 9, or at least 84% identical to SEQ ID NO: 10; and

(iv) a VH comprising an amino acid sequence that is: at least 93% identical to SEQ ID NO: 2, at least 92% identical to SEQ ID NO: 3, at least 90% identical to SEQ ID NO: 4, at least 87% identical to SEQ ID NO: 5, or at least 86% identical to SEQ ID NO: 6.

8. An isolated antibody, or an antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, comprising:

(i) a light chain variable region ("VL") comprising the amino acid sequence: DIVMTQSPSX_{K1}LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAP KX_{K2}LIYSASYRYSGVPDRFX_{K3}GSGSGTDFTLTISSLQX_{K4}EDFAX_{K5}Y X_{K6}CQQYNSYPRTFGGGTKVEIK, wherein X_{K1} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K2} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K3} is an amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and

(ii) a VH comprising the amino acid sequence: QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINWVX_{H3}QAP GKGLEWIARIYPGSGNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H} $_{7}$LSSLRSEDX_{H8}AVYFCARGVYYFDYWGQGTTVTVSS, wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid with an aliphatic side chain, X_{H6} is an amino acid with an acidid side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain.

9. The antibody of claim 8, wherein X_{K1} is the amino acid F or S, X_{K2} is the amino acid A or S, X_{K3} is the amino acid T or S, X_{K4} is the amino acid S or P, X_{K5} is the amino acid D or T, and X_{K6} is the amino acid F or Y.

10. The antibody of claim 8, wherein X_{H1} is the amino acid L or V, X_{H2} is the amino acid L or V, X_{H3} is the amino acid K or R, X_{H4} is the amino acid V or A, X_{H5} is the amino acid L or I, X_{H6} is the amino acid E or D, X_{H7} is the amino acid Q or E, and X_{H8} is the amino acid S or T.

11. The antibody of any one of claims 1 to 10, wherein the antibody specifically binds to CHO cells recombinantly expressing wild-type KIT with an EC50 of about 150 pM or less as determined by flow cytometry.

12. The antibody of any one of claims 1 to 10, wherein the antibody inhibits tyrosine phosphorylation of KIT with an IC50 of about 600 pM or less as determined by ELISA.

13. The antibody of any one of claims 1 to 10, which can be expressed in CHO cells at a titer of at least 1.0 μg/mL, or at least 1.1 μg/mL, or at least 1.2 μg/mL.

14. The antibody of any one of claims 1 to 10, wherein the antibody further comprises a human kappa light chain constant region and a human gamma heavy chain constant region.

15. The antibody of any one of claims 1 to 10, wherein the antibody is a human IgG1 or IgG4 antibody.

16. The antibody of any one of claims 1 to 10, which is a monoclonal antibody.

17. The antibody of any one of claims 1 to 10, which is an antigen-binding fragment or a Fab fragment.

18. The antibody of any one of claims 1 to 10, which is a bispecific antibody.

19. The antibody of any one of claims 1 to 10, which is fused to a heterologous polypeptide.

20. A conjugate comprising the antibody of any one of claims 1 to 10 or a antigen-binding fragment thereof linked to an agent.

21. The conjugate of claim 20, wherein the agent is a toxin.

22. The conjugate of claim 21, wherein the toxin is abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin.

23. The conjugate of claim 20, wherein the conjugate is internalized by a cell.

24. A pharmaceutical composition comprising the conjugate of claim 20 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising the antibody of any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

26. A polynucleotide comprising nucleotide sequences encoding a VH chain region, a VL chain region, or both a VL chain region and a VH chain region, of an antibody of any one of claims 1 to 10.

27. The polynucleotide of claim 26, which comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH.

28. The polynucleotide of claim 26, which comprises SEQ ID NO: 27, 28, 29, or 30 encoding a VL.

29. The polynucleotide of claim 26, which comprises SEQ ID NO: 22, 23, 24, 25, or 26 encoding a VH, and SEQ ID NO: 27, 28, 29, or 30 encoding a VL.

30. A vector comprising the polynucleotide of claim 26.

31. The vector of claim 30, which is a mammalian expression vector.

32. A host cell comprising the vector of claim 30 or one or more polynucleotides of claim 26.

33. An isolated cell producing an antibody according to any one of claims 1 to 10.

34. An isolated cell comprising one or more polynucleotides of claim 26, wherein the cell can express an antibody which specifically binds to a D4 of human KIT.

35. A cell comprising the vector of claim 30.

36. A kit comprising the antibody of any one of claims 1 to 10.

37. A kit comprising the conjugate of claim 20.

38. Use of an antibody of any one of claims 1 to 10 in the manufacture of a medicament for treating or managing a KIT-associated disorderwherein the KIT-associated disorder is selected from the group consisting of cancer, an inflammatory condition, and fibrosis.

39. Use of a conjugate of claim 20 in the manufacture of a medicament for treating or managing a KIT-associated disorder, wherein the KIT-associated disorder is selected from the group consisting of cancer, an inflammatory condition, and fibrosis.

40. The use of claim 38 or 39, wherein the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors.

41. The use of claim 40, wherein the cancer is refractory to treatment by a tyrosine kinase inhibitor.

42. The use of claim 41, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

43. The use of claim 38 or 39, wherein the use further comprises administration of a second therapeutic agent.

44. The use of claim 43, wherein the second therapeutic agent is a chemotherapeutic agent, tyrosine kinase inhibitor, a histone deacetylase inhibitor, an antibody, or a cytokine.

45. The use of claim 44, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

46. An *in vitro* method for diagnosing a subject with a KIT-associated disorder comprising contacting cells or a sample obtained from the subject with the antibody of any one of claims 1 to 10 and detecting the expression level of KIT in the cells or the sample.

47. The method of claim 46, wherein the antibody is conjugated to a detectable molecule.

48. The method of claim 47, wherein the detectable molecule is an enzyme, a fluorescent molecule, a luminescent molecule, or a radioactive molecule.

49. An *in vitro* method for inhibiting KIT activity in a cell expressing KIT comprising contacting the cell with an effective amount of the antibody of any one of claims 1 to 10.

50. An *in vitro* method for inducing or enhancing apoptosis in a cell expressing KIT comprising contacting the cell with an effective amount of the antibody of any one of claims 1 to 10.

51. An *in vitro* method for inducing cell differentiation comprising contacting a cell expressing KIT with an effective amount of the antibody of any one of claims 1 to 10.

52. The method of claim 51, wherein the cell is a stem cell.

53. A method of making an antibody which immunospecifically binds to a D4 region of human comprising culturing, and/or expressing the antibody using, the cell of claim 32.

54. The method claim 53 further comprising purifying the antibody obtained from said cell.

55. An isolated antibody or antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, wherein said antibody or antigen-binding fragment thereof comprises:

(i) a light chain variable region ("VL") comprising a VL CDR1, VL CDR2, and VL CDR3 selected from the group set forth in Tables 10-12; and

(ii) a heavy chain variable region ("VH") comprising VH CDR1, VH CDR2, and VH CDR3 selected from the group set forth in Tables 13-15.

56. An isolated antibody or antigen-binding fragment thereof, which immunospecifically binds to a D4 region of human KIT, wherein said antibody or antigen-binding fragment thereof comprises:

(i) a light chain variable region ("VL") comprising a VL CDR1, VL CDR2, and VL CDR3 selected from the group set forth in Tables 2 and 3; and

(ii) a heavy chain variable region ("VH") comprising VH CDR1, VH CDR2, and VH CDR3 selected from the group set forth in Tables 2 and 3.