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, ~~in one aspect,~~ 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, provided 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, 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, the antibody can be expressed in Chinese hamster ovary (CHO) cells at a titer of at least 0.45 μg/mL. In a particular ~~embodiment~~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 ~~aspect~~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$_{K2}$LIYS ASYRYSGVPDRFX$_{K3}$GSGSGTDFTLTISSLQX$_{K4}$EDFAX$_{K5}$YX$_{K6}$CQQYNSYPRTFG GGTKVEIK (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, provided 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$_{H3}$QAPGKGLEWI ARIYPGSGNTYYNEKFKGRX$_{H4}$TX$_{H5}$TAX$_{H6}$KSTSTAYMX$_{H7}$LSSLRSEDX$_{H8}$AVY FCARGVYYFDYWGQGTTVTVSS (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, 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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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.

[0022] In a certain ~~embodiment~~example, X_{H1} is the amino acid L, X_{H2} is the amino acid L, X_{H3} is the amino acid K, X_{H4} is the amino acid A, X_{H5} is the amino acid L, X_{H6} is the amino acid E, X_{H7} is the amino acid Q, and X_{H8} is the amino acid S.

[0023] In a certain ~~embodiment~~example, X_{H1} is the amino acid V, X_{H2} is the amino acid L, X_{H3} is the amino acid K, X_{H4} is the amino acid A, X_{H5} is the amino acid L, X_{H6} is the amino acid E, X_{H7} is the amino acid Q, and X_{H8} is the amino acid T.

[0024] In a certain ~~embodiment~~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 V, 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.

[0025] In a particular ~~embodiment~~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.

[0026] In a particular ~~aspect~~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:

i) 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

ii) 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.

[0027] In a certain ~~aspect~~example, provided herein is antibody, or an antigen-binding fragment thereof, or a conjugate thereof, which immunospecifically binds to a D4 region of human KIT, comprising:

i) a light chain variable region ("VL") comprising the amino acid sequence: DIVMTQSPS$\mathbf{X_{K1}}$LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPK$\mathbf{X_{K}}$ $_{2}$LIYSASYRYSGVPDRF$\mathbf{X_{K3}}$GSGSGTDFTLTISSLQ$\mathbf{X_{K4}}$EDFA$\mathbf{X_{K5}}$Y$\mathbf{X_{K6}}$CQQ YNSYPRTFGGGTKVEIK, 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 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 ~~embodiment~~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, 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 ~~embodiment~~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, 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 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 embodiment, an antibody described herein further comprises a human light chain constant region and a human heavy chain constant region. In one ~~embodiment~~example, the human light chain constant region of an antibody described herein is a human kappa light chain constant region. In a particular ~~embodiment~~example, the human heavy chain constant region of an antibody described herein is a human gamma heavy chain constant region.

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

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

[0040] In a particular ~~embodiment~~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: 29 encoding a VL.

[0041] In a particular ~~embodiment~~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: 30 encoding a VL.

[0042] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 23 encoding a VH, and SEQ ID NO: 27 encoding a VL.

[0043] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 23 encoding a VH, and SEQ ID NO: 28 encoding a VL.

[0044] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 23 encoding a VH, and SEQ ID NO: 29 encoding a VL.

[0045] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 23 encoding a VH, and SEQ ID NO: 30 encoding a VL.

[0046] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 24 encoding a VH, and SEQ ID NO: 27 encoding a VL.

[0047] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 24 encoding a VH, and SEQ ID NO: 28 encoding a VL.

[0048] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 24 encoding a VH, and SEQ ID NO: 29 encoding a VL.

[0049] In a particular ~~embodiment~~example, a polynucleotide (*e.g.*, isolated polynucleotide) or a population of polynucleotides (*e.g.*, population of isolated polynucleotides) provided herein comprises SEQ ID NO: 24 encoding a VH, and SEQ ID NO: 30 encoding a VL.

[0050] In a particular ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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, 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, provided herein is a cell producing an antibody described herein. In one embodiment, 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, the cell comprises a vector described herein.

[0061] In a specific aspect, provided 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 ~~aspect~~example, provided 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 ~~aspect~~example, provided 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 ~~embodiment~~example, the KIT-associated disorder is cancer, an inflammatory condition, or fibrosis. In a specific embodiment, the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors. In one embodiment, the cancer is refractory to treatment by a tyrosine kinase inhibitor. In a further embodiment embodiment, the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

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

[0066] In a specific ~~aspect~~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 ~~aspect~~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 ~~aspect~~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 ~~aspect~~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 ~~aspect~~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 ~~embodiment~~example, the cell is an isolated cell. In a particular ~~embodiment~~example, the method further comprises the step of purifying the antibody obtained from the cell or host cell.

[0071] In one aspect, provided 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 ~~aspect~~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.

[0073] In a particular ~~aspect~~example, the antibody or antigen-binding fragment described herein comprises an Fc region with an amino acid modification. In a certain ~~aspect~~example, the antibody or antigen-binding fragment described herein comprises an Fc region which is an IgG1 isotype or an IgG4 isotype. In one ~~aspect~~example, the antibody or antigen-binding fragment described herein is a humanized antibody. In a particular ~~aspect~~example, the antibody or antigen-binding fragment thereof described herein is a bispecific antibody.

[0074] In a certain ~~aspect~~example, described herein is an antibody or antigen-binding fragment thereof which is conjugated to another agent.

[0075] In one ~~aspect~~example, provided herein is a composition comprising an antibody or antigen-binding fragment thereof described herein.

[0076] In a particular ~~aspect~~example, 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 or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15). Also provided is a vector comprising the polynucleotide described herein. In one ~~aspect~~example, the vector is a mammalian expression vector.

[0077] In a certain ~~aspect~~example, provided herein is a host cell comprising a vector of or one or more polynucleotides described herein. In one ~~aspect~~example, provided herein is a cell producing an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15).

[0078] In a particular ~~aspect~~example, provided herein is a kit comprising an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15).

[0079] In a certain ~~aspect~~example, provided 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 an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15). In one ~~embodiment~~example, the KIT-associated disorder is cancer, an inflammatory condition, or fibrosis. In a particular ~~embodidment~~example, the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors.

[0080] In a particular ~~aspect~~example, the method for treating or managing a KIT-associated disorder described herein further comprises administering a second agent. In a particular ~~embodiment~~example, the second agent is a chemotherapeutic agent, tyrosine kinase inhibitor, a histone deacetylase inhibitor, an antibody, a cytokine, an HSP90 inhibitor, a PGP inhibitor, or a proteosome inhibitor.

[0081] In one ~~aspect~~example, provided herein is a method for diagnosing a subject with a KIT-associated disorder comprising contacting cells or a sample obtained from the subject with an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15) and detecting the expression level of KIT in the cells or the sample. In a certain ~~embodiment~~example, the antibody is conjugated to a detectable molecule.

[0082] In a certain ~~aspect~~example, provided herein is a method for inhibiting KIT activity in a cell expressing KIT comprising contacting the cell with an effective amount of an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15).

[0083] A method for inducing or enhancing apoptosis in a cell expressing KIT comprising contacting the cell with an effective amount of an antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen binding fragment thereof comprising sequences set forth in Tables 10-15).

[0084] A method of making an antibody which immunospecifically binds to a D4 region of human KIT comprising culturing, and/or expressing the antibody using, a cell described herein.

4. BRIEF DESCRIPTION OF THE FIGURES

[0085] **Fig. 1** depicts the amino acid sequence of full length human KIT (SEQ ID NO: 1), GenBank™ accession number AAC50969. The first through fifth extracellular Ig-like domains (*i.e.*, D1, D2, D3, D4, and D5) are indicated; "{" depicts the amino-terminal residue of each domain and "}" depicts the carboxyl-terminal residue of each domain. The D1 domain is depicted at P34 to R112, the D2 domain is depicted at D113 to P206, the D3 domain is depicted at A207 to D309, the D4 domain is depicted at K310 to N410 (SEQ ID NO: 15), the hinge region between D4 and D5 is located at V409 to N410, and the D5 domain is depicted at T411 to K509. Also, the D1/D2 hinge region is located at D113 to L117; the D2/D3 hinge region is located at P206 to

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 ~~A method~~ for treating or managing a KIT-associated disorder~~, comprising administering to a subject in need thereof a therapeutically effective amount of the antibody of any one of claims 1 to 10~~wherein 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 ~~A method~~ 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~~comprising administering to a subject in need thereof a therapeutically effective amount of the conjugate of claim 20~~.

~~40. The method of claim 38, wherein the KIT-associated disorder is cancer, an inflammatory condition, or fibrosis.~~

~~41.~~40. The ~~method~~ use of claim ~~40~~38 or 39, wherein the cancer is leukemia, chronic myelogenous leukemia, lung cancer, small cell lung cancer, or gastrointestinal stromal tumors.

~~42.~~41. The use~~method~~ of claim ~~41~~40, wherein the cancer is refractory to treatment by a tyrosine kinase inhibitor.

~~43.~~42. The use~~method~~ of claim ~~42~~41, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

~~44.~~43. The use~~method~~ of claim 38 or 39, wherein the use~~method~~ further comprises ~~administering~~ administration of a second therapeutic agent.

~~45.~~44. The use~~method~~ of claim ~~44~~43, wherein the second therapeutic agent is a chemotherapeutic agent, tyrosine kinase inhibitor, a histone deacetylase inhibitor, an antibody, or a cytokine.

~~46.~~45. The use~~method~~ of claim ~~45~~44, wherein the tyrosine kinase inhibitor is imatinib mesylate or SU11248.

~~47.~~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.

~~48.~~47. The method of claim ~~47~~46, wherein the antibody is conjugated to a detectable molecule.

~~49.~~48. The method of claim ~~48~~47, wherein the detectable molecule is an enzyme, a fluorescent molecule, a luminescent molecule, or a radioactive molecule.

~~50.~~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.

~~51.~~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.

~~52.~~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.

~~53.~~52. The method of claim ~~52~~51, wherein the cell is a stem cell.

~~54.~~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.

~~55.~~54. The method claim ~~54~~53 further comprising purifying the antibody obtained from said cell.

~~56.~~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.

~~57.~~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.