

CLAIMS

1. An anti-FLT3 antibody or an antigen-binding portion thereof, wherein the antibody binds to the same epitope of human FLT3 as an antibody comprising:
- 5 a) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 3 and 75 and a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 4 and 76;
- 10 b) an HC comprising the amino acid sequences of SEQ ID NOs: 13 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 14 and 76;
- c) an HC comprising the amino acid sequences of SEQ ID NOs: 23 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 24 and 76;
- 15 d) an HC comprising the amino acid sequences of SEQ ID NOs: 33 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 34 and 76;
- e) an HC comprising the amino acid sequences of SEQ ID NOs: 43 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 44 and 76;
- 20 f) an HC comprising the amino acid sequences of SEQ ID NOs: 53 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 54 and 76;
- g) an HC comprising the amino acid sequences of SEQ ID NOs: 63 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 64 and 76; or
- 25 h) an HC comprising the amino acid sequences of SEQ ID NOs: 73 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 74 and 76.
- 30 2. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
- a) the heavy chain of said anti-FLT3 antibody comprises:
- i) heavy chain complementarity determining regions (H-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 5-7,

- respectively;
- 5 ii) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 3;
- iii) a VH comprising the amino acid sequence of SEQ ID NO: 3; or
- iv) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 3 and 75; and
- b) the light chain of said anti-FLT3 antibody comprises:
- 10 i) light chain complementarity determining regions (L-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 8-10, respectively;
- ii) a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 4;
- 15 iii) a VL comprising the amino acid sequence of SEQ ID NO: 4; or
- iv) a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 4 and 76.
3. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
- 20 a) the heavy chain of said anti-FLT3 antibody comprises:
- i) heavy chain complementarity determining regions (H-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 15-17, respectively;
- ii) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 13;
- 25 iii) a VH comprising the amino acid sequence of SEQ ID NO: 13; or
- iv) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 13 and 75; and
- 30 b) the light chain of said anti-FLT3 antibody comprises:
- i) light chain complementarity determining regions (L-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 18-20, respectively;
- ii) a light chain variable domain (VL) comprising an amino acid

- sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 14;
- iii) a VL comprising the amino acid sequence of SEQ ID NO: 14; or
- iv) a light chain (LC) comprising the amino acid sequences of SEQ
ID NOs: 14 and 76.
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4. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
- a) the heavy chain of said anti-FLT3 antibody comprises:
- i) heavy chain complementarity determining regions (H-CDR)-1-3
10 comprising the amino acid sequences of SEQ ID NOs: 25-27,
respectively;
- ii) a heavy chain variable domain (VH) comprising an amino acid
sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 23;
- 15 iii) a VH comprising the amino acid sequence of SEQ ID NO: 23; or
- iv) a heavy chain (HC) comprising the amino acid sequences of
SEQ ID NOs: 23 and 75; and
- b) the light chain of said anti-FLT3 antibody comprises:
- i) light chain complementarity determining regions (L-CDR)-1-3
20 comprising the amino acid sequences of SEQ ID NOs: 28-30,
respectively;
- ii) a light chain variable domain (VL) comprising an amino acid
sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 24;
- 25 iii) a VL comprising the amino acid sequence of SEQ ID NO: 24; or
- iv) a light chain (LC) comprising the amino acid sequences of SEQ
ID NOs: 24 and 76.
5. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
- 30 a) the heavy chain of said anti-FLT3 antibody comprises:
- i) heavy chain complementarity determining regions (H-CDR)-1-3
comprising the amino acid sequences of SEQ ID NOs: 35-37,
respectively;
- ii) a heavy chain variable domain (VH) comprising an amino acid

- sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 33;
- iii) a VH comprising the amino acid sequence of SEQ ID NO: 33; or
- iv) a heavy chain (HC) comprising the amino acid sequences of
SEQ ID NOs: 33 and 75; and
- 5 b) the light chain of said anti-FLT3 antibody comprises:
- i) light chain complementarity determining regions (L-CDR)-1-3
comprising the amino acid sequences of SEQ ID NOs: 38-40,
respectively;
- 10 ii) a light chain variable domain (VL) comprising an amino acid
sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 34;
- iii) a VL comprising the amino acid sequence of SEQ ID NO: 34; or
- iv) a light chain (LC) comprising the amino acid sequences of SEQ
ID NOs: 34 and 76.
- 15
6. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
- a) the heavy chain of said anti-FLT3 antibody comprises:
- i) heavy chain complementarity determining regions (H-CDR)-1-3
20 comprising the amino acid sequences of SEQ ID NOs: 45-47,
respectively;
- ii) a heavy chain variable domain (VH) comprising an amino acid
sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 43;
- 25 iii) a VH comprising the amino acid sequence of SEQ ID NO: 43; or
- iv) a heavy chain (HC) comprising the amino acid sequences of
SEQ ID NOs: 43 and 75; and
- b) the light chain of said anti-FLT3 antibody comprises:
- i) light chain complementarity determining regions (L-CDR)-1-3
30 comprising the amino acid sequences of SEQ ID NOs: 48-50,
respectively;
- ii) a light chain variable domain (VL) comprising an amino acid
sequence at least 90% identical to the amino acid sequence of
SEQ ID NO: 44;

- iii) a VL comprising the amino acid sequence of SEQ ID NO: 44; or
- iv) a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 44 and 76.

5 7. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein

a) the heavy chain of said anti-FLT3 antibody comprises:

i) heavy chain complementarity determining regions (H-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 55-57, respectively;

10 ii) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 53;

iii) a VH comprising the amino acid sequence of SEQ ID NO: 53; or

15 iv) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 53 and 75; and

b) the light chain of said anti-FLT3 antibody comprises:

i) light chain complementarity determining regions (L-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 58-60, respectively;

20 ii) a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 54;

iii) a VL comprising the amino acid sequence of SEQ ID NO: 54; or

25 iv) a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 54 and 76.

8. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein

a) the heavy chain of said anti-FLT3 antibody comprises:

i) heavy chain complementarity determining regions (H-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 65-67, respectively;

30 ii) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 63;

- iii) a VH comprising the amino acid sequence of SEQ ID NO: 63; or
- iv) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 63 and 75; and
- b) the light chain of said anti-FLT3 antibody comprises:
 - 5 i) light chain complementarity determining regions (L-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 68-70, respectively;
 - ii) a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 64;
 - 10 iii) a VL comprising the amino acid sequence of SEQ ID NO: 64; or
 - iv) a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 64 and 76.
- 15 9. The anti-FLT3 antibody or antigen-binding portion of claim 1, wherein
 - a) the heavy chain of said anti-FLT3 antibody comprises:
 - i) heavy chain complementarity determining regions (H-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 25-27, respectively;
 - 20 ii) a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 73;
 - iii) a VH comprising the amino acid sequence of SEQ ID NO: 73; or
 - iv) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 73 and 75; and
 - 25 b) the light chain of said anti-FLT3 antibody comprises:
 - i) light chain complementarity determining regions (L-CDR)-1-3 comprising the amino acid sequences of SEQ ID NOs: 28-30, respectively;
 - 30 ii) a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 74;
 - iii) a VL comprising the amino acid sequence of SEQ ID NO: 74; or
 - iv) a light chain (LC) comprising the amino acid sequences of SEQ

ID NOs: 74 and 76.

10. An anti-FLT3 antibody or an antigen-binding portion thereof, wherein said antibody comprises the H-CDR1-3 and L-CDR1-3 amino acid sequences of:
- 5 a) SEQ ID NOs: 5-10, respectively;
b) SEQ ID NOs: 15-20, respectively;
c) SEQ ID NOs: 25-30, respectively;
d) SEQ ID NOs: 35-40, respectively;
e) SEQ ID NOs: 45-50, respectively;
10 f) SEQ ID NOs: 55-60, respectively; or
g) SEQ ID NOs: 65-70, respectively.
11. The anti-FLT3 antibody or antigen-binding portion of claim 10, wherein said antibody comprises a heavy chain variable domain amino acid sequence and
15 a light chain variable domain amino acid sequence that are at least 90% identical to the amino acid sequences of:
- a) SEQ ID NOs: 3 and 4, respectively;
b) SEQ ID NOs: 13 and 14, respectively;
c) SEQ ID NOs: 23 and 24, respectively;
20 d) SEQ ID NOs: 33 and 34, respectively;
e) SEQ ID NOs: 43 and 44, respectively;
f) SEQ ID NOs: 53 and 54, respectively;
g) SEQ ID NOs: 63 and 64, respectively; or
h) SEQ ID NOs: 73 and 74, respectively.
- 25 12. The anti-FLT3 antibody or antigen-binding portion of claim 10, wherein said antibody comprises a heavy chain variable domain and a light chain variable domain comprising the amino acid sequences of:
- a) SEQ ID NOs: 3 and 4, respectively;
30 b) SEQ ID NOs: 13 and 14, respectively;
c) SEQ ID NOs: 23 and 24, respectively;
d) SEQ ID NOs: 33 and 34, respectively;
e) SEQ ID NOs: 43 and 44, respectively;
f) SEQ ID NOs: 53 and 54, respectively;

- g) SEQ ID NOs: 63 and 64, respectively; or
 - h) SEQ ID NOs: 73 and 74, respectively.
13. The anti-FLT3 antibody of any one of claims 1-12, wherein the antibody is an IgG.
14. The anti-FLT3 antibody of claim 13, wherein the antibody is an IgG₁.
15. The anti-FLT3 antibody of any one of claims 1-14, wherein the antibody comprises at least one mutation in the F_C region.
16. The anti-FLT3 antibody of any one of claims 1-12, wherein the antibody is an IgG₁ and comprises a mutation in one or more of heavy chain amino acid positions 234 and 235, which are numbered according to the IMGT® numbering scheme.
17. The anti-FLT3 antibody of claim 16, wherein one or both of the amino acid residues at positions 234 and 235 are mutated from Leu to Ala.
18. An anti-FLT3 antibody that comprises:
- a) a heavy chain (HC) comprising the amino acid sequences of SEQ ID NOs: 3 and 75 and a light chain (LC) comprising the amino acid sequences of SEQ ID NOs: 4 and 76;
 - b) an HC comprising the amino acid sequences of SEQ ID NOs: 13 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 14 and 76;
 - c) an HC comprising the amino acid sequences of SEQ ID NOs: 23 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 24 and 76;
 - d) an HC comprising the amino acid sequences of SEQ ID NOs: 33 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 34 and 76;
 - e) an HC comprising the amino acid sequences of SEQ ID NOs: 43 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs:

- 44 and 76;
- f) an HC comprising the amino acid sequences of SEQ ID NOs: 53 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 54 and 76;
- 5 g) an HC comprising the amino acid sequences of SEQ ID NOs: 63 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs: 64 and 76; or
- h) an HC comprising the amino acid sequences of SEQ ID NOs: 73 and 75 and an LC comprising the amino acid sequences of SEQ ID NOs:
- 10 74 and 76.
19. The anti-FLT3 antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody or antigen-binding portion has at least one property selected from:
- 15 a) stimulates proliferation of EOL-1 cells *in vitro*;
- b) stimulates proliferation of OCI-AML5 cells *in vitro*;
- c) binds to human FLT3 with a K_D of 20 nM or less;
- d) specifically binds to cynomolgus FLT3;
- e) specifically binds to mouse FLT3;
- 20 f) does not block FLT3 ligand binding to human FLT3 *in vitro*;
- g) does not block binding of FLT3L-Fc to cell-displayed human, cynomolgus, or mouse FLT3 protein *in vitro*;
- h) stimulates proliferation of primary human CD34⁺ stem cells;
- i) stimulates differentiation of primary human CD34⁺ stem cells;
- 25 j) induces dendritic cell mobilization *in vivo* in Balb/c mice; and
- k) induces dendritic cell mobilization *in vivo* in immunocompromised mice reconstituted with human CD34⁺ stem cells.
20. The anti-FLT3 antibody or antigen-binding portion of claim 19, wherein the
- 30 antibody or antigen-binding portion has at least two, three, four, five, six, seven, eight, nine, ten, or all of said properties.
21. A pharmaceutical composition comprising the anti-FLT3 antibody or antigen-binding portion of any one of claims 1-20 and a pharmaceutically acceptable

excipient.

22. The pharmaceutical composition of claim 21, further comprising an immunostimulatory agent, a vaccine, a chemotherapeutic agent, an anti-neoplastic agent, an anti-angiogenic agent, or a tyrosine kinase inhibitor.
23. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof, or a nucleotide sequence that encodes the light chain or an antigen-binding portion thereof, or both, of the anti-FLT3 antibody of any one of claims 1-20.
24. The isolated nucleic acid molecule of claim 23, wherein said nucleic acid molecule comprises the nucleotide sequence of any one of SEQ ID NOs: 1, 2, 11, 12, 21, 22, 31, 32, 41, 42, 51, 52, 61, 62, 71, and 72.
25. A vector comprising the isolated nucleic acid molecule of claim 23 or 24, wherein said vector further comprises an expression control sequence.
26. A host cell comprising a nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof, and a nucleotide sequence that encodes the light chain or an antigen-binding portion thereof, of the anti-FLT3 antibody of any one of claims 1-20.
27. A method for producing an anti-FLT3 antibody or an antigen-binding portion thereof, comprising providing a host cell of claim 26, culturing said host cell under conditions suitable for expression of the antibody or portion, and isolating the resulting antibody or portion.
28. A bi-specific binding molecule comprising the antigen-binding domain of one or two distinct anti-FLT3 antibodies of any one of claims 1-20.
29. A method of using the anti-FLT3 antibody or antigen-binding portion of any one of claims 1-20, the pharmaceutical composition of claim 21 or 22, or the bi-specific binding molecule of claim 28 in a diagnostic process.

30. A method for enhancing immune activity in a patient in need thereof,
comprising administering to said patient a therapeutically effective amount of
the anti-FLT3 antibody or antigen-binding portion of any one of claims 1-20,
5 the pharmaceutical composition of claim 21 or 22, or the bi-specific binding
molecule of claim 28.
31. A method for treating cancer in a patient, comprising administering to said
patient a therapeutically effective amount of the anti-FLT3 antibody or
10 antigen-binding portion of any one of claims 1-20, the pharmaceutical
composition of claim 21 or 22, or the bi-specific binding molecule of claim 28.
32. The method of claim 31, wherein the cancer is in a tissue selected from the
group consisting of skin, lung, intestine, colon, ovary, brain, prostate, kidney,
15 soft tissues, the hematopoietic system, head and neck, liver, bone, bladder,
breast, stomach, uterus, cervix, and pancreas.
33. The method of any one of claims 30-32, wherein the patient has melanoma,
glioma, glioblastoma multiforme, head and neck squamous cell cancer, breast
20 cancer, non-small cell lung cancer, colorectal cancer, renal cell cancer, kidney
cancer, lymphoma, leukemia, multiple myeloma, plasma cell neoplasm,
myelodysplastic disease, or myeloproliferative disease.
34. The method of any one of claims 30-33, further comprising administering to
25 the patient an immunostimulatory agent, a vaccine, a chemotherapeutic
agent, an anti-neoplastic agent, an anti-angiogenic agent, a tyrosine kinase
inhibitor, or radiation therapy.
35. A method for treating an immune disorder in a patient in need thereof,
30 comprising administering to said patient a therapeutically effective amount of
the anti-FLT3 antibody or antigen-binding portion of any one of claims 1-20,
the pharmaceutical composition of claim 21 or 22, or the bi-specific binding
molecule of claim 28.

36. Use of the anti-FLT3 antibody or antigen-binding portion of any one of claims 1-20, the pharmaceutical composition of claim 21 or 22, or the bi-specific binding molecule of claim 28 for the manufacture of a medicament for:
- a) enhancing immune activity in a patient;
 - 5 b) treating cancer in a patient; or
 - c) treating an immune disorder in a patient,
- according to the method of any one of claims 30-35.
37. The antibody or antigen-binding portion of any one of claims 1-20, the
- 10 pharmaceutical composition of claim 21 or 22, or the bi-specific binding molecule of claim 28, for use in:
- a) enhancing immune activity in a patient;
 - b) treating cancer in a patient; or
 - c) treating an immune disorder in a patient,
- 15 according to the method of any one of claims 30-35.
38. The method of any one of claims 30-35, the use of claim 36, or the antibody or antigen-binding portion for use, pharmaceutical composition for use, or bi-specific binding molecule for use of claim 37, wherein the patient is human.
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