

[00152] In certain embodiments, the LILRB4 antibody has a light chain variable region comprising a light chain complementarity determining region (LC-CDR) 1 having an amino acid sequence of SEQ ID NO: 8, an LC-CDR2 having an amino acid sequence of SEQ ID NO: 9 and an LC-CDR3 having an amino acid sequence of SEQ ID NO: 10. In certain embodiments, the light chain variable region comprises an LC-CDR1 has an amino acid sequence of SEQ ID NO: 8 with a mutation at amino acid residues NS, an LC-CDR2 having an amino acid sequence of SEQ ID NO: 9 and an LC-CDR3 having an amino acid sequence of SEQ ID NO: 10. In certain embodiments, the LC-CDR1 has an amino acid sequence selected from SEQ ID NOs: 20, 22, 24, 26, 28, 30, 32, 34,

[00153] In certain embodiments, the LILRB4 antibody has a CDR sequence as listed in **Table 1** below.

[00154] **Table 1. CDR sequences of the anti-LILRB4 antibodies**

Antibody VH/VL #	CDR1	CDR2	CDR3
H7	SEQ ID NO: 5 GFSLS ~~S~~ SYW	SEQ ID NO: 6 IDSGSVGIT	SEQ ID NO: 7 ARHGD ~~N~~ WALDL
K3	SEQ ID NO: 8 QSINSW	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
H7m1	SEQ ID NO: 5 GFSLS ~~S~~ SYW	SEQ ID NO: 6 IDSGSVGIT	SEQ ID NO: 12 ARHGD ~~N~~ VALDL
H7m2	SEQ ID NO: 5 GFSLS ~~S~~ SYW	SEQ ID NO: 6 IDSGSVGIT	SEQ ID NO: 14 ARHGD ~~N~~ YALDL
H7m3	SEQ ID NO: 5 GFSLS ~~S~~ SYW	SEQ ID NO: 6 IDSGSVGIT	SEQ ID NO: 16 ARHGD ~~N~~ FALDL
H7m4	SEQ ID NO: 5 GFSLS ~~S~~ SYW	SEQ ID NO: 6 IDSGSVGIT	SEQ ID NO: 18 ARHGD ~~N~~ QALDL
K3m1	SEQ ID NO: 20 QSIVSW	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m2	SEQ ID NO: 22 QSIDS ~~W~~	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m3	SEQ ID NO: 24 QSIES ~~W~~	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m4	SEQ ID NO: 26 QSIQ ~~S~~ W	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m5	SEQ ID NO: 28 QSISS ~~W~~	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m6	SEQ ID NO: 30 QSITS ~~W~~	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m7	SEQ ID NO: 32 QSINQ ~~W~~	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV
K3m8	SEQ ID NO: 34QSIN ~~V~~ W	SEQ ID NO: 9 KASTLAS	SEQ ID NO: 10 HGYIRGD ~~L~~ DNV

[00155] The heavy chain and light chain variable region amino acid sequences of the anti-LILRB4 antibodies above are provided below.

H7 (SEQ ID NO: 1)

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSSSYWISWVRQAPGKGLEWIGSIDSGSVGITYYATWVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCCARHGDNWALDLWGQGLVTVSS

K3 (SEQ ID NO: 3)

DIQMTQSPSTLSASVGDRVTITCRASQSINSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

H7m1 (SEQ ID NO: 11)

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSSSYWISWVRQAPGKGLEWIGSIDSGSVGITYYATWVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCCARHGDNVALDLWGQGLVTVSS

H7m2 (SEQ ID NO: 13)

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSSSYWISWVRQAPGKGLEWIGSIDSGSVGITYYATWVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCCARHGDNYALDLWGQGLVTVSS

H7m3 (SEQ ID NO: 15)

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSSSYWISWVRQAPGKGLEWIGSIDSGSVGITYYATWVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCCARHGDNFALDLWGQGLVTVSS

H7m4 (SEQ ID NO: 17)

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSSSYWISWVRQAPGKGLEWIGSIDSGSVGITYYATWVKG
RFTISRDN SKNTLYLQMNSLRAEDTAVYYCCARHGDNQALDLWGQGLVTVSS

K3m1 (SEQ ID NO: 19)

DIQMTQSPSTLSASVGDRVTITCRASQSIVSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K3m2 (SEQ ID NO: 21)

DIQMTQSPSTLSASVGDRVTITCRASQSIDSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K3m3 (SEQ ID NO: 23)

DIQMTQSPSTLSASVGDRVTITCRASQSIESWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K3m4 (SEQ ID NO: 25)

DIQMTQSPSTLSASVGDRVTITCRASQSIQSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K3m5 (SEQ ID NO: 27)

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K3m6 (SEQ ID NO: 29)

DIQMTQSPSTLSASVGDRVTITCRASQSITSWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K4m7 (SEQ ID NO: 31)

DIQMTQSPSTLSASVGDRVTITCRASQSINQWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

K4m8 (SEQ ID NO: 33)

DIQMTQSPSTLSASVGDRVTITCRASQSINVWLAWYQQKPGKAPKLLIYKASTLASGVPSRFSGSGSG
TEFTLTISSLQPDDFATYYCQHGYIRGDLDNVFGGGTKVEIK

[00156] In certain embodiments, the antibodies and antigen-binding fragments thereof provided herein comprise suitable framework region (FR) sequences, as long as the antibodies and antigen-binding fragments thereof can specifically bind to LILRB4. The CDR sequences provided in Table 1 can be grafted to any suitable FR sequences of any suitable species such as mouse, human, rat, rabbit, among others, using suitable methods known in the art such as recombinant techniques.

[00157] In certain embodiments, the antibodies and antigen-binding fragments thereof provided herein are humanized. A humanized antibody or antigen-binding fragment is desirable in its reduced immunogenicity in human. A humanized antibody is chimeric in its variable regions, as non-human CDR sequences are grafted to human or substantially human FR sequences. Humanization of an antibody or antigen-binding fragment can be essentially performed by substituting the non-human (such as murine) CDR genes for the corresponding human CDR genes in a human immunoglobulin gene (see, for example, Jones et al., Nature (1986) 321:522-525; Riechmann et al., Nature (1988) 332:323-327; Verhoeyen et al., Science (1988) 239:1534-1536).

[00158] Suitable human heavy chain and light chain variable domains can be selected to achieve this purpose using methods known in the art. In an illustrative example, “best-fit”

WHAT IS CLAIMED IS:

1. An isolated anti-LILRB4 antibody or an antigen-binding fragment thereof, comprising:
 - a) a heavy chain variable region comprising a heavy chain complementarity determining region (HC-CDR) 1 having an amino acid sequence of SEQ ID NO: 5, an HC-CDR2 having an amino acid sequence of SEQ ID NO: 6 and an HC-CDR3 having an amino acid sequence of SEQ ID NO: 7; and
 - b) a light chain variable region comprising a light chain complementarity determining region (LC-CDR) 1 having an amino acid sequence of SEQ ID NO: 28, an LC-CDR2 having an amino acid sequence of SEQ ID NO: 9 and an LC-CDR3 having an amino acid sequence of SEQ ID NO: 10.
2. The antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region has an amino acid sequence of SEQ ID NO: 1 or at least about 90% identical to SEQ ID NO: 1; and wherein the light chain variable region has an amino acid sequence of SEQ ID NO: 27 or at least about 90% identical to SEQ ID NO: 27.
3. The antibody or antigen-binding fragment thereof of any of the preceding claims, further comprising an immunoglobulin constant region.
4. The antibody or antigen-binding fragment thereof of claim 3, wherein the immunoglobulin constant region is a constant region of I.
5. The antibody or antigen-binding fragment thereof of claim 3, wherein the immunoglobulin constant region is a constant region of human IgG.
6. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is humanized.
7. The antibody or antigen-binding fragment thereof of claim 1, which is a diabody, a scFv, a scFv dimer, a BsFv, a dsFv, a (dsFv)₂, a dsFv-dsFv', an Fv fragment, a Fab, a Fab', a F(ab')₂, a bispecific antibody, a ds diabody, or a bivalent antibody.
8. The antibody or antigen-binding fragment thereof of any of the preceding claims linked to one or more conjugate moieties; wherein the conjugate moiety comprises a clearance-

modifying agent, a toxin, a detectable label, a chemotherapeutic agent, a cytokine, or purification moiety.

9. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any of the preceding claims, and a pharmaceutically acceptable carrier.
10. An isolated polynucleotide encoding the antibody or antigen-binding fragment thereof of claims 1-8.
11. A vector comprising the isolated polynucleotide of claim 10.
12. A host cell comprising the vector of claim 11.
13. A method of expressing the antibody or antigen-binding fragment thereof of any one of claims 1-8, comprising culturing the host cell of claim 12 under the condition at which the vector of claim 11 is expressed.
14. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof of any one of claims 1-8 or the pharmaceutical composition of claim 9 in the manufacture of a medication for treating or ameliorating the effect of a cancer in a subject, wherein the subject is human and wherein the cancer is selected from the group consisting of lymphocytic leukemia, acute myeloid leukemia (AML), acute lymphocytic/lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), B acute lymphocytic leukemia (Pre-B ALL), B-cell leukemia, and chronic lymphoblastic leukemia (CLL).
15. The use of claim 14, wherein the antibody or an antigen-binding fragment thereof is to be administered intravenously, intra-arterially, intra-tumorally, or subcutaneously.
16. The use of claim 14 or 15, further comprising to be administered to the subject one or more drugs selected from the group consisting of an anthracycline, a daunorubicin, a cytarabine, a hypomethylating agent, a combination of daunorubicin and cytarabine, a daunorubicin and cytarabine liposome for injection, an azacytidine, a decitabine, an all-trans-retinoic acid (ATRA), an arsenic, an arsenic trioxide, a histamine dihydrochloride, an interleukin-

- 2, an aldesleukin, a gemtuzumab ozogamicin, a midostaurin, a clofarabine, a decitabine, an ivosidenib, an enasidenib, a glasdegib, an epacadostat, a BCL-2 inhibitor, a venetoclax, oxaliplatin, an ibrutinib, an acalabrutinib, a zanubrutinib, a PD-1 antibody, a PD-L1 antibody, a CTLA-4 antibody, a LAG3 antibody, an ICOS antibody, a TIGIT antibody, a TIM3 antibody, a CD40 antibody, a 4-1BB antibody, a CD47 antibody, a SIRP1 α antibody or fusions protein, an antagonist of E-selectin, an alkylating agent, a nitrosourea agent, an antimetabolite, an antitumor antibiotic, an alkaloid derived from a plant, a hormone therapy medicine, and/or a hormone antagonist.
17. A *in vitro* method of activating a T cell, comprising contacting the T cell with an antibody or an antigen-binding fragment thereof of any one of claims 1-8.
18. The method of claim 17, wherein the method comprises contacting the T cell with the antibody or an antigen-binding fragment thereof of any one of claims 1-8 in the presence of a cancerous cell, wherein the cancerous cell increases antigen-presenting activity.
19. A method of detecting a cancer cell or cancer stem cell in a sample from a subject, wherein the sample is a body fluid or biopsy, comprising:
- (a) contacting the sample from the subject with an antibody or an antigen-binding fragment thereof of any one of claims 1-8; and
 - (b) detecting binding of said antibody to the cancer cell or the cancer stem cell in said sample from the subject.
20. The method of claim 19, wherein the sample is blood, sputum, tears, saliva, mucous, serum, urine or feces.
21. The method of claim 19, wherein said detecting further comprises:
- (c) performing steps (a) and (b) a second time or additional times and determining a change in detection levels as compared to the first time.
22. The method of claim 19, wherein detection comprises immunohistochemistry, flow cytometry or FACS, immunoassays or Western blot.
23. The method of claim 22, wherein the immunoassays include ELISA or RIA.

24. A kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1-8, useful in detecting LILRB4.
25. A chimeric antigen receptor (CAR) protein, comprising:
- a) a heavy chain variable region comprising an HC-CDR1 having an amino acid sequence of SEQ ID NO: 5, an HC-CDR2 having an amino acid sequence of SEQ ID NO: 6 and an HC-CDR3 having an amino acid sequence of SEQ ID NO: 7; and
 - b) a light chain variable region comprising an LC-CDR1 having an amino acid sequence of SEQ ID NO: 28, an LC-CDR2 having an amino acid sequence of SEQ ID NO: 9 and an LC-CDR3 having an amino acid sequence of SEQ ID NO: 10.
26. The CAR protein of claim 25, wherein the heavy chain variable region has an amino acid sequence of SEQ ID NO: 1 or at least about 90% identical to SEQ ID NO: 1; and wherein the light chain variable region has an amino acid sequence of SEQ ID NO: 27 or at least about 90% identical to SEQ ID NO: 27.
27. The CAR protein of claim 25, comprising a single- chain variable fragment (scFv) having an amino acid sequence identical to SEQ ID NOs: 66 or 68, or at least 85%, 90%, 95% or 99% identical to SEQ ID NOs: 66 or 68.
28. The CAR protein of claim 25, further comprising a CD8 α transmembrane domain or a CD28 transmembrane domain.
29. The CAR protein of claim 25, further comprising a 4-1BB intracellular co-stimulatory signaling domain, a CD28 intracellular co-stimulatory signaling domain or a CD3 ζ intracellular T cell signaling domain.
30. A polynucleotide molecule encoding a CAR protein according to any one of claims 25-29.
31. The polynucleotide molecule of claim 30, further comprising a promoter active in eukaryotic cells.
32. An engineered cell comprising the polynucleotide molecule of claim 30, wherein the engineered cell is a T cell, an NK cell.

33. Use of a therapeutically effective amount of cells in accordance with claim 32 in the manufacture of a medicament for treating or ameliorating cancer in a subject in need thereof, wherein the cancer is selected from the group consisting of lymphocytic leukemia, acute myeloid leukemia (AML), acute lymphocytic/lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), B acute lymphocytic leukemia (Pre-B ALL), B-cell leukemia, and chronic lymphoblastic leukemia (CLL).
34. The use of claim 33, wherein said medicament is to be administered local to cancer site, regional to a cancer site, or systemically.
35. The use of claim 34, further comprising to be administered to said human subject a second cancer therapy.
36. The use of claim 35, wherein said second cancer therapy is chemotherapy, immunotherapy, radiotherapy, hormone therapy or surgery.
37. The use of claim 36, wherein said second cancer therapy is to be administered at the same time, before, or after the medicament.
38. The use of claim 34, further comprising to be administered to said human subject a second administration of an effective amount of one or more cells in accordance with claim 32.
39. The use of claim 33, wherein said cancer is metastatic, recurrent or drug-resistant cancer.
40. A bispecific antibody or antigen-binding fragment capable of binding to LILRB4 and CD3, comprising
- (a) a first antigen-binding region comprising a first light chain variable (V_L) domain and a first heavy chain variable (V_H) domain; and
 - (b) a second antigen-binding region comprising a second V_L domain and a second V_H domain,
- wherein the first antigen-binding region is capable of binding to LILRB4 and the second antigen-binding region is capable of binding to CD3, or vice versa, and wherein

- (a) the first V_H domain comprising a first HC-CDR 1 having an amino acid sequence of SEQ ID NO: 5, a first HC-CDR2 having an amino acid sequence of SEQ ID NO: 6 and a first HC-CDR3 having an amino acid sequence of SEQ ID NO: 7; and
 - (b) a first V_L domain comprising a first LC-CDR1 having an amino acid sequence of SEQ ID NO: 28, a first LC-CDR2 having an amino acid sequence of SEQ ID NO: 9 and a first LC-CDR3 having an amino acid sequence of SEQ ID NO: 10.
41. The bispecific antibody or antigen-binding fragment of claim 40, wherein the first V_L domain and the first heavy chain variable domain link to a first pair of constant domains, respectively, and wherein the second V_L domain and the second V_H domain link to a second pair of constant domains, respectively.
42. The bispecific antibody or antigen-binding fragment of claim 41, wherein
- (a) the first V_L domain links to a first light chain constant (C_L) domain, and the first V_H domain links to a first heavy chain constant domain 1 (C_H1), or
 - (b) the first V_L domain links to a first C_H1 domain, and the first V_H domain links to a first C_L domain.
43. The bispecific antibody or antigen-binding fragment of claim 42, wherein
- (a) the second V_L domain links to a second C_L domain, and the second V_H domain links to a second C_H1 domain, or
 - (b) the second V_L domain links to a second C_H1 domain, and the second V_H domain links to a second C_L domain, or
 - (c) the second V_L domain links to a T cell receptor (TCR) α chain constant domain, and the second V_H domain links to a TCR β chain constant domain, or
 - (d) the second V_L domain links to a TCR β chain constant domain, and the second V_H domain links to a TCR α chain constant domain.
44. The bispecific antibody or antigen-binding fragment of claim 40, wherein the first antigen-binding region and/or the second antigen-binding region is a single chain variable fragment (scFv).
45. The bispecific antibody or antigen-binding fragment of claim 40, further comprising a third antigen-binding region comprising a third V_L domain and a third V_H domain, wherein the

third antigen-binding region is capable of binding to LILRB4 or CD3.

46. The bispecific antibody or antigen-binding fragment of claim 45, wherein the third V_L domain and the third heavy chain variable domain link to a third pair of constant domains, respectively.
47. The bispecific antibody or antigen-binding fragment of claim 46, wherein
- (a) the third V_L domain links to a third C_L domain, and the third V_H domain links to a third C_{H1} domain, or
 - (b) the third V_L domain links to a third C_{H1} domain, and the third V_H domain links to a third C_L domain, or
 - (c) the third V_L domain links to a second TCR α chain constant domain, and the third V_H domain links to a second TCR β chain constant domain, or
 - (d) the third V_L domain links to a second TCR β chain constant domain, and the third V_H domain links to a second TCR α chain constant domain.