

WHAT IS CLAIMED IS:

1. An antibody that specifically binds LRP5, comprising a light chain variable region and/or a heavy chain variable region, the heavy chain variable region comprising complementarity determining regions CDR-H1, CDR-H2 and CDR-H3, the light chain variable region comprising complementarity determining region CDR-L1, CDR-L2 and CDR-L3, wherein the amino acid sequences of said CDRs comprise or consist of CDR sequences selected from: CDR sequence sets of anti-LRP5 antibodies: LRP5 - A7, LRP5 - A9, LRP5 - C5, LRP5 - C12, LRP5 - D9, LRP5 - E5, LRP5 - G2, LRP5 - G9, LRP5 - G10, LRP5 - G11, LRP5 - H3, LRP5 - H5, LRP5 - H9, LRP5 - R3O_D3, LRP5 - R3_E8, LRP5 - R3O_G6.
2. The antibody of claim 1 wherein the amino acid sequences of said CDRs comprise or consist of sequences selected from the sequences as set forth below:

CDR-H1 is selected from the group consisting of LSYYIM, ISYSYI, LSYSIM, ISSYSI, ISYSYI, IYSYSI, LSYYIM, FSSSSI, LYYYYI, LSYSSI, IYSYI, LLYSSM and FSSSSI;

CDR-H2 is selected from the group consisting of SIYPYGYTY, SSSYGYTY, SISSYGYTY, SIYSSYGTS, SIYSSYGYTY, SIYPYSSYTS, SIYSSYGYTY, SIYPSYGYTY, SISPYYGYTS, SISSYGYTS, SIYSYGYTY, SISSYGYTY, SISSYGYTY SISSYGYTS, and YISPYYGYTS;

CDR-H3 is selected from the group consisting of HGAM, TVRGSKKPYFSGWAM, SSYYSSVSSSVYAL, TVRGSKKPYFSGWAM, HYSFFYAM, YAVYFPGYYWGM, WSHVSGHYSGM, WGAYHSSGYGM, GGSGVSHYGSVYYSSWWAL, AAPYGYGYYSYAM, SGYGWYAM, GYWA, SYPAM, SWAM; YWAL, GWGSPASAGYYGL, SSYYSSVSSSVYAL, TVRGSKKPYFSGWAM and TVRGSKKPYFSGWAM;

CDR-L1 is SVSSA;

CDR-L2 is SASSLYS; and

CDR-L3 is selected from the group consisting of AWGWGLF, VHYPYSLI, YQYGLI, FSHVSLI, ASYSPI, YHYLYLF, ASYAPI, SSSSPI, SSYSLI, GVSLI, YWFLI, PVGHYGYPI, SSYSPI, YWAYYSPI, VSYYPLI, SSYSLI, and VHYPYSLI.
3. The antibody of claim 2, wherein the antibody comprises a heavy chain variable region comprising:
 - i) a heavy chain amino acid sequence as set forth in Table 2;
 - ii) an amino acid sequence with at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to the heavy chain amino acid sequence as set forth in Table 2, wherein the CDR sequences are a CDR sequence set as set forth in Table 1, or

iii) a conservatively substituted amino acid sequence of i) wherein the CDR sequences are a CDR sequence set as set forth in Table.

4. The antibody of any one of claims 2 to 3, wherein the antibody comprises a light chain variable region comprising:

- 5 i) a light chain amino acid sequence as set forth in Table 2,
ii) an amino acid sequence with at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to the light chain amino acid sequence as set forth in Table 2, wherein the CDR sequences are a CDR sequence set as set forth in Table 1, or
10 iii) a conservatively substituted amino acid sequence of i) wherein the CDR sequences are a CDR sequence set as set forth in Table 1.

5. The antibody of any one of claims 1 to 4, wherein the CDR sequences are a full CDR sequence set selected from an antibody identified in Table 1.

6. The antibody of any one of claims 1 to 5, wherein the antibody cross-reacts
15 with LRP6.

7. The antibody of claim 1, wherein the CDR sequences comprise a light chain CDR sequence set or a heavy chain CDR sequence set selected from an antibody identified in Table 1.

8. The antibody of any one of claims 1 to 7, wherein the antibody specifically binds
20 LRP5.

9. The antibody of claim 8, wherein the CDR sequences are a CDR sequence set of an antibody selected from antibodies LRP5 - A7, LRP5 - A9, LRP5 - C5, LRP5 - C12, LRP5 - D9, LRP5 - E5, LRP5 - G2, LRP5 - G9, LRP5 - G10, LRP5 - G11, LRP5 - H3, LRP5 - H5, LRP5 - H9, LRP5 - R3O_D3, LRP5 - R3_E8, LRP5 - R3O_G6.

25 10. The antibody of any one of claims 1 to 9, which blocks binding of a Wnt ligand to a Wnt3a binding site of LRP5.

11. The antibody of any one of claims 1 to 9, blocks binding of a Wnt ligand to a non-Wnt3a binding site of LRP5.

30 12. The antibody of any one of claims 1 to 11, wherein the antibody is a monoclonal antibody.

13. The antibody of any one of claims 1 to 12, wherein the antibody is a humanized antibody.
14. The antibody of any one of claims 1 to 13, wherein the antibody is a single chain antibody.
- 5 15. The antibody of any one of claims 1 to 14, wherein the antibody is an antibody binding fragment selected from Fab, Fab', F(ab')₂, scFv, dsFv, ds-scFv, dimers, nanobodies, minibodies, diabodies, and multimers thereof.
16. The antibody of any one of claims 1 to 14, wherein the antibody is a bi-specific antibody.
- 10 17. The antibody of any one of claims 1 to 14, wherein the antibody is a bi-specific antibody that further binds to FZD receptor.
18. The antibody of any one of claims 1 to 17, comprising a non-natural glycosylation pattern.
19. The antibody of any one of claims 1 to 17, comprising a cysteine substitution
15 or addition, e.g., in the constant region or a framework region.
20. An immunoconjugate comprising the antibody of any one of claims 1 to 17, and a detectable label or cytotoxic agent.
21. The immunoconjugate of claim 20, comprising a cytotoxic agent selected from maytansinoid, auristatin, dolastatin, tubulysin, cryptophycin, pyrrolobenzodiazepine (PBD)
20 dimer, indolinobenzodiazepine dimer, alpha-amanitin, trichothene, SN-38, duocarmycin, CC1065, calicheamincin, an enediyne antibioatic, taxane, doxorubicin derivatives, anthracycline and stereoisomers, azanofide, isosteres, analogs or derivatives thereof.
22. A nucleic acid molecule encoding the antibody of any one of claims 1 to 17.
23. The nucleic acid molecule of claim 22, wherein one or more of the CDR
25 sequences is/are encoded by a nucleic acid in Table 2.
24. The nucleic acid molecule of claim 22, wherein the antibody comprises a heavy chain variable region encoded by a nucleic acid comprising:
- i) a heavy chain nucleic acid sequence as set forth in Table 2;
- ii) a nucleotide sequence with at least 50%, at least 60%, at least 70%, at least
30 80%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to the heavy

chain nucleic acid sequence as set forth in Table 2, wherein the CDR sequences are a CDR sequence set as set forth in Table 1, or

iii) a codon degenerate nucleic acid sequence of i) wherein the CDR sequences are a CDR sequence set as set forth in Table 1.

5 **25.** The nucleic acid molecule of claim **22**, wherein the antibody comprises a light chain variable region encoded by a nucleic acid comprising:

i) a light chain nucleic acid sequence as set forth in Table 2,

ii) a nucleic acid sequence with at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, at least 95%, at least 98% or at least 99% sequence identity to the
10 light chain nucleic acid sequence as set forth in Table 2, wherein the CDR sequences are a CDR sequence set as set forth in Table 1, or

iii) a codon degenerate nucleic acid sequence of i) wherein the CDR sequences are a CDR sequence set as set forth in Table 1.

15 **26.** A vector comprising an expression control sequence operatively linked to the nucleic acid of any one of claims **22** to **25**.

27. A host cell comprising recombinant nucleic acid molecule comprising an expression control sequence operatively linked to the nucleic acid of any of claims **22** to **26**.

28. The host cell of claim **27**, that is a Chinese Hamster Ovary (CHO) cell.

29. A host cell comprising the vector of claim **26**.

20 **30.** A method for making an anti-LRP5 antibody comprising culturing a host cell of any one of claims **27** to **29**.

31. A composition comprising the antibody of any one or more of claims **1** to **17**, immunoconjugate of any one of claims **20** to **21**, the nucleic acid molecule of any one of claims **22** to **25**, the vector of claim **26**, or host cell of claim **29**, optionally with a suitable diluent.

25 **32.** The composition of claim **31**, wherein the composition comprises one or more antibodies or immunoconjugates, optionally wherein the composition is a pharmaceutical composition.

33. A kit comprising the antibody of any one or more of claims **1** to **17**, immunoconjugate of any one of claims **20** to **21**, the nucleic acid molecule of any one of claims
30 **22** to **25**, the vector of claim **26**, or host cell of any one of claims **27** to **29**.

- 34.** A method of detecting LRP5 expression, the method comprising contacting a sample comprising one or more cells with one or more antibody or immunoconjugate of any one of claims **1** to **21** under conditions permissive for forming an antibody:cell complex and detecting the presence of any antibody complex.
- 5 **35.** The method of claim **34**, wherein the detection is by immunofluorescence.
- 36.** The method of claim **34**, wherein the detection is by flow cytometry.
- 37.** The method of any one of claims **34** to **36**, wherein the method is for detecting LRP4 expression and the antibody or immunoconjugate comprises a CDR sequence set corresponding to an antibody selected from LRP5 - A7, LRP5 - A9, LRP5 - C5, LRP5 - C12,
10 LRP5 - D9, LRP5 - E5, LRP5 - G2, LRP5 - G9, LRP5 - G10, LRP5 - G11, LRP5 - H3, LRP5 - H5, LRP5 - H9, LRP5 - R3O_D3, LRP5 - R3_E8, LRP5 - R3O_G6.
- 38.** A method of inhibiting Wnt ligand binding to an LRP5 receptor, disrupting a Wnt signaling pathway, inhibiting Wnt-induced transcriptional activity, inhibiting activation of disheveled, promoting preservation of the beta-catenin destruction complex, promoting
15 accumulation of beta-catenin or inhibiting growth of a cell, the method comprising contacting a cell expressing a LRP5 receptor with an antibody or immunoconjugate of any one of claims **1** to **21**.
- 39.** The method of claim **38**, wherein the antibody or immunoconjugate blocks binding of a Wnt ligand to a Wnt3a binding site of LRP5.
- 20 **40.** The method of claim **38**, wherein the antibody or immunoconjugate blocks binding of a Wnt ligand to a non-Wnt3a binding site of LRP5.
- 41.** The method of claim **38**, wherein the antibody or immunoconjugate comprises a CDR sequence set corresponding to an antibody selected from the group consisting of LRP5 - A7, LRP5 - A9, LRP5 - C5, LRP5 - C12, LRP5 - D9, LRP5 - E5, LRP5 - G2, LRP5 - G9,
25 LRP5 - G10, LRP5 - G11, LRP5 - H3, LRP5 - H5, LRP5 - H9, LRP5 - R3O_D3, LRP5 - R3_E8, LRP5 - R3O_G6.
- 42.** A method of treating cancer in a subject in need thereof comprising administering to the subject an effective amount of a pharmaceutical composition comprising an antibody or an immunoconjugate of any one of claims **1** to **21**.

- 43.** The method of claim **42**, wherein the cancer is selected from colon, lung, breast ovarian, endometrial, pancreas, stomach, liver, adrenocortical carcinoma and osteoblastoma cancer cells.
- 44.** The method of claim **42**, wherein the cancer is selected from acute myeloid
5 leukemia, prostate cancer, glioblastoma, bladder cancer and cervical cancer.
- 45.** The method of claim **42**, comprising administering to the subject first and second antibodies or antibody conjugates of any one of claims 1 to **21**, wherein the first blocks binding of a Wnt ligand to a Wnt3a binding site of LRP5, and the second blocks binding of a Wnt ligand to a non-Wnt3a binding site of LRP5.
- 46.** The method of claim **45**, wherein the first antibody or immunoconjugate
10 comprises a CDR sequence set selected from antibodies of Epitope Group 2.
- 47.** The method of claim **42**, wherein the antibody or immunoconjugate that specifically binds LRP5 in at least one assay, and inhibits Wnt3a- induced signaling in at least one assay, optionally wherein the antibody or immunoconjugate is the antibody or
15 immunoconjugate of any one of claims **1** to **21**.
- 48.** The method of claim **42**, wherein the antibody or immunoconjugate comprises a CDR sequence set corresponding to an antibody selected from the group consisting of LRP5 - A7, LRP5 - A9, LRP5 - C5, LRP5 - C12, LRP5 - D9, LRP5 - E5, LRP5 - G2, LRP5 - G9, LRP5 - G10, LRP5 - G11, LRP5 - H3, LRP5 - H5, LRP5 - H9, LRP5 - R3O_D3, LRP5 - R3_E8,
20 LRP5 - R3O_G6.
- 49.** A method of potentiating the signaling activity of Wnt-ligand binding to a Wnt3a binding site of LRP5 comprising contacting a cell expressing LRP5 with an antibody that blocks binding of Wnt ligands to the non-Wnt3a binding site of LRP5.
- 50.** A method of potentiating the signaling activity of Wnt-ligand binding to a non-
25 Wnt3a binding site of LRP5 by contacting a cell expressing LRP5 with an antibody that blocks binding of Wnt ligands to the Wnt3a binding site of LRP5.
- 51.** The method of any of claims **49** or **50**, performed *in vitro*.
- 52.** The method of any of claims **49** or **50**, performed *in vivo*.