The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Claims:

1. An isolated bivalent antibody or a bivalent fragment thereof to a low density lipoprotein-related protein 6 (LRP6) that potentiates a Wnt signal by clustering one or more LRP6 receptors in the presence of an unblocked LRP6 binding protein.

2. The isolated bivalent antibody or a bivalent fragment thereof of claim 2, wherein the antibody clusters one or more LRP6 receptors by binding to a Propeller region selected from the group consisting of Propeller 1 and Propeller 3.

3. The isolated bivalent antibody or fragment thereof of claim 2, wherein the LRP6 binding protein is a Wnt binding protein selected from the group consisting of Wnt 1, Wnt 3, and Wnt 3a.

4. An isolated monovalent antibody or monovalent fragment thereof to a low density lipoprotein-related protein 6 (LRP6) that avoids potentiation of a Wnt signal by clustering one or more LRP6 receptors in the presence of an unblocked LRP6 binding protein.

5. An isolated antibody or fragment thereof to a low density lipoprotein-related protein 6 (LRP6) protein, having a dissociation (K_D) of at least 1 x 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, 10^{13} M^{-1}, wherein the antibody or fragment thereof is monovalent or bivalent.

6. The isolated antibody or fragment thereof of claim 5, wherein the antibody or fragment thereof inhibits a canonical Wnt pathway as measured by in vitro binding to human LRP6 in a Solution Equilibrium Titration assay with a K_D of 0.001nM-1μM, and wherein the antibody or fragment thereof is monovalent or bivalent.

7. An isolated antibody or fragment thereof to a low density lipoprotein-related protein 6 (LRP6) protein that inhibits a phosphorylation of LRP6 as assessed by a Wnt ligand induced phosphorylation assay, wherein the antibody or fragment thereof is monovalent or bivalent.

8. An isolated antibody or fragment thereof to a low density lipoprotein-related protein 6 (LRP6) protein that inhibits a canonical Wnt pathway as measured by in vitro binding to human LRP6 in a Solution Equilibrium Titration (SET) assay with a EC_{50} of less than or equal to 300 μM, wherein the antibody or fragment thereof is monovalent or bivalent.

9. An antibody or fragment thereof to LRP6 protein, that cross competes with an antibody described in Table 1, wherein the antibody or fragment thereof is monovalent or bivalent.

10. An antibody or fragment thereof, that binds to the same epitope as an antibody described in Table 1, wherein the antibody or fragment thereof is monovalent or bivalent .

11. The antibody of claims 1, 4, 9, or 10, wherein said antibody is a monoclonal antibody.

12. The antibody of claim 11, wherein said antibody is a human or humanized antibody.

13. The antibody of claim 11, wherein said antibody is a chimeric antibody.

14. The antibody of claim 11, wherein said antibody comprises a human heavy chain constant region and a human light chain constant region.

15. The antibody of claim 11, wherein said antibody is a single chain antibody.

16. The antibody of claim 11, wherein said antibody is a Fab fragment.

17. The antibody of claim 11, wherein said antibody is a scFv.

18. The antibody of claim 11 binds to both human LRP6 and cynomologus LRP6.

19. The antibody of claim 11 is an IgG isotype.

20. The antibody of claim 11, wherein said antibody comprises a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

21. An isolated antibody or fragment thereof to LRP6 comprising 1, 2, 3, 4, 5, or 6 CDRs of any of the antibodies in Table 1, wherein the antibody or fragment thereof is monovalent or bivalent.

22. An isolated antibody or fragment thereof to LRP6 comprising a heavy chain CDR3 selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 25, SEQ and SEQ ID NO: 43, wherein the antibody or fragment thereof is monovalent or bivalent.

23. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 44, SEQ ID NO: 60, and SEQ ID NO: 62 and a VL selected from the group

consisting of SEQ ID NO: 13, SEQ ID NO: 33, SEQ ID NO: 35, SEQ ID NO: 43, SEQ ID NO: 59, and SEQ ID NO: 61, wherein the antibody or fragment thereof is monovalent or bivalent.

24. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 14 and a VL comprising SEQ ID NO: 13, wherein the antibody or fragment thereof is monovalent or bivalent.

25. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 34 and a VL comprising SEQ ID NO: 33, wherein the antibody or fragment thereof is monovalent or bivalent.

26. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 36 and a VL comprising SEQ ID NO: 35, wherein the antibody or fragment thereof is monovalent or bivalent.

27. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 44 and a VL comprising SEQ ID NO: 43, wherein the antibody or fragment thereof is monovalent or bivalent.

28. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 36 and a VL comprising SEQ ID NO: 35, wherein the antibody or fragment thereof is monovalent or bivalent.

29. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 60 and a VL comprising SEQ ID NO: 59, wherein the antibody or fragment thereof is monovalent or bivalent.

30. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 61 and a VL comprising SEQ ID NO: 62, wherein the antibody or fragment thereof is monovalent or bivalent.

31. An isolated antibody or fragment thereof, comprising at least one heavy chain CDR sequence that is identical to SEQ ID NO: 1, 2, 3, 21, 22, 23, 47, 48, and 49, wherein the antibody binds to human LRP6 protein.

32. An isolated monovalent monoclonal antibody, or fragment thereof, comprising at least one light chain CDR sequence that is identical to SEQ ID NO: 4, 5, 6, 24, 25, 26 50,

51 and 52, wherein the antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

33. An isolated antibody or fragment thereof, comprising at least one heavy chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 1, 2, 3, 21, 22, 23, 47, 48, and 49, 47, 48, and 49, wherein the antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

34. An isolated antibody or fragment thereof, comprising at least one light chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 4, 5, 6, 24, 25, 26 50, 51 and 52, wherein the antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

35. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the antibody or fragment thereof is monovalent or bivalent.

36. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 21; a heavy chain variable region CDR2 of SEQ ID NO: 22; a heavy chain variable region CDR3 of SEQ ID NO: 23; a light chain variable region CDR1 of SEQ ID NO: 24; a light chain variable region CDR2 of SEQ ID NO: 25; and a light chain variable region CDR3 of SEQ ID NO: 26, wherein the antibody or fragment thereof is monovalent or bivalent.

37. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 47; a heavy chain variable region CDR2 of SEQ ID NO: 48; a heavy chain variable region CDR3 of SEQ ID NO: 49; a light chain variable region CDR1 of SEQ ID NO: 50; a light chain variable region CDR2 of SEQ ID NO: 51; and a light chain variable region CDR3 of SEQ ID NO: 52, wherein the antibody or fragment thereof is monovalent or bivalent.

38. A fragment of an antibody of anyone of the previous claim that binds to LRP6 selected from the group consisting of; Fab, $F(ab_2)$', $F(ab)_2$', ScFV, VHH, VH, VL, dAbs, wherein the fragment is monovalent or bivalent.

39. A pharmaceutical composition comprising an antibody or fragment thereof selected from claims 1-38 and a pharmaceutically acceptable carrier, wherein the antibody or fragment thereof is monovalent or bivalent.

40. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region identity to SEQ ID NO: 14, 34, 36, 44, 60, and 62.

41. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region identity to SEQ ID NO: 13, 33, 35, 43, 59 and 61.

42. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region having at least 98% sequence identity to SEQ ID NO: 14, 34, 36, 44, 60, and 62.

43. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region having at least 98% sequence identity to SEQ ID NO: 13, 33, 35, 43, 59 and 61.

44. A vector comprising the nucleic acid of claims 40-43.

45. An isolated antibody or fragment thereof to LRP6 comprising a CDR3 selected from the group consisting of SEQ ID NO: 69, SEQ ID NO: 93, and SEQ ID NO: 115, wherein the antibody or fragment thereof is monovalent or bivalent.

46. An isolated antibody or fragment thereof to LRP6 comprising a heavy chain CDR1 selected from the group consisting of SEQ ID NO: 69, SEQ ID NO: 93, and SEQ ID NO: 115; a CDR2 selected from the group consisting of SEQ ID NO: 70, SEQ ID NO: 94, and SEQ ID NO: 116; and a CDR3 selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 95, and SEQ ID NO: 117, wherein the antibody or fragment thereof is monovalent or bivalent.

47. An isolated antibody or fragment thereof to LRP6 comprising a light chain CDR1 selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 96, and SEQ ID NO: 118; a CDR2 selected from the group consisting of SEQ ID NO: 73, SEQ ID NO: 97, and SEQ ID NO: 119; and a CDR3 selected from the group consisting of SEQ ID NO: 74, SEQ ID NO: 98, and SEQ ID NO: 120, wherein the antibody or fragment thereof is monovalent or bivalent.

48. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH selected from the group consisting of SEQ ID NO: 82, SEQ ID NO: 89, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 128, SEQ ID NO: 130, and SEQ ID NO: 138; and a VL selected from the group consisting of SEQ ID NO: 81, SEQ ID NO: 90, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 127, SEQ ID NO: 129, and SEQ ID NO: 137, wherein the antibody or fragment thereof is monovalent or bivalent.

49. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 82 and a VL comprising SEQ ID NO: 81, wherein the antibody or fragment thereof is monovalent or bivalent.

50. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 90 and a VL comprising SEQ ID NO: 89, wherein the antibody or fragment thereof is monovalent or bivalent.

51. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 106 and a VL comprising SEQ ID NO: 105, wherein the antibody or fragment thereof is monovalent or bivalent.

52. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 108 and a VL comprising SEQ ID NO: 107, wherein the antibody or fragment thereof is monovalent or bivalent.

53. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 128 and a VL comprising SEQ ID NO: 127, wherein the antibody or fragment thereof is monovalent or bivalent.

54. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 128 and a VL comprising SEQ ID NO: 127, wherein the antibody or fragment thereof is monovalent or bivalent.

55. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 130 and a VL comprising SEQ ID NO: 129, wherein the antibody or fragment thereof is monovalent or bivalent.

56. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 138 and a VL comprising SEQ ID NO: 137, wherein the antibody or fragment thereof is monovalent or bivalent.

57. An isolated antibody or fragment thereof, comprising at least one heavy chain CDR sequence that is identical to SEQ ID NO: 69, 70, 71, 93, 94, 95, 115, 116, and 117, wherein said antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

58. An isolated antibody or fragment thereof, comprising at least one light chain CDR sequence that is identical to SEQ ID NO: 72, 73, 74, 96, 97, 98, 118, 119, and 120, wherein said antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

59. An isolated antibody or fragment thereof, comprising at least one heavy chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 70, 71, 93, 94, 95, 115, 116, and 117, wherein said antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

60. An isolated antibody or fragment thereof, comprising at least one light chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 72, 73, 74, 96, 97, 98, 118, 119, and 120, wherein said antibody binds to human LRP6 protein, wherein the antibody or fragment thereof is monovalent or bivalent.

61. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74, wherein the antibody or fragment thereof is monovalent or bivalent.

62. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 93; a heavy chain variable region CDR2 of SEQ ID NO: 94; a heavy chain variable region CDR3 of SEQ ID NO: 95; a light chain variable region CDR1 of SEQ ID NO: 96; a light chain variable region CDR2 of SEQ ID NO: 97; and a light chain variable region CDR3 of SEQ ID NO: 98, wherein the antibody or fragment thereof is monovalent or bivalent.

63. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 115; a heavy chain variable region CDR2 of SEQ ID NO: 116; a heavy chain variable region CDR3 of SEQ ID NO: 117; a light chain variable region

CDR1 of SEQ ID NO: 118; a light chain variable region CDR2 of SEQ ID NO: 119; and a light chain variable region CDR3 of SEQ ID NO: 120, wherein the antibody or fragment thereof is monovalent or bivalent.

64. A combination of a monoclonal antibody or fragment thereof selected from the group consisting of any one of the antibodies in claims 35-37 with any one of the antibodies in claims 65-63, wherein the antibody or fragment thereof is monovalent.

65. A combination of a monoclonal antibody or fragment thereof selected from the group consisting of any one of the antibodies in claims 35-37 with any one of the antibodies in claims 65-63, wherein the antibody or fragment thereof is bivalent.

66. A fragment of the antibody of any previous claim that binds with LRP6 selected from the group consisting of; Fab, $F(ab_2)'$, $F(ab)_2'$, ScFV, VHH, VH, VL, dAbs, wherein the fragment is monovalent or bivalent.

67. A pharmaceutical composition comprising antibody selected from claims 45-63 and a pharmaceutically acceptable carrier, wherein the antibody is monovalent or bivalent.

68. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region selected from the group consisting of SEQ ID NO: 82, 89, 106, 108, 128, 130, and 138.

69. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region selected from the group consisting of SEQ ID NO: 81, 90, 105, 107, 127, 129, and 137.

70. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region having at least 98% sequence identity to SEQ ID NO: 82, 89, 106, 108, 128, 130, and 138.

71. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region having at least 98% sequence identity to SEQ ID NO: 81, 90, 105, 107, 127, 129, and 137.

72. A vector comprising the nucleic acid of claims 68-71.

73. A method of treating a cancer comprising selecting a subject having an LRP6 expressing cancer, administering to said subject an effective amount of a composition

comprising an antibody or fragment thereof selected from claims 1-38 and 45-65, wherein the antibody or fragment thereof is monovalent or bivalent.

74. The method of claim 73, wherein the subject is a human.

75. A method of treating a cancer mediated by a canonical Wnt signaling pathway comprising selecting a subject having an LRP6 expressing cancer, administering to the subject an effective amount of a composition comprising an antibody or fragment thereof selected from claims 1-39 and 45-66, wherein said antibody or fragment thereof is monovalent or bivalent, and wherein said cancer is selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma.

76. The method of claim 75, wherein said cancer is breast cancer.

77. A method of treating a cancer comprising selecting a subject having an LRP6 expressing cancer, administering to said subject an effective amount of a composition comprising an antibody or fragment thereof that binds to a propeller 1 region of LRP6 in combination with an antibody or fragment thereof that binds to a propeller 3 region of LRP6, wherein the antibody or fragment thereof is monovalent or bivalent.

78. A method of treating a cancer comprising selecting a subject having an LRP6 expressing cancer, administering to said subject an effective amount of a composition comprising an antibody or fragment thereof that binds to LRP6 and inhibits Wnt1 signalling by LRP6 in combination with an antibody or fragment thereof that binds to LRP6 and inhibits Wnt3 signalling by LRP6, wherein the antibodies or fragments thereof are monovalent or bivalent.

79. Use of an antibody or fragment thereof of any one of the previous claims in the manufacture of a medicament for the treatment of a cancer mediated by a canonical Wnt signaling pathway selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma, wherein the antibody or fragment thereof is monovalent or bivalent.

80. An antibody having VH of SEQ ID NO: 14 and VL of SEQ ID NO: 13 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

81. An antibody having VH of SEQ ID NO: 34 and VL of SEQ ID NO: 36 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

82. An antibody having VH of SEQ ID NO: 36 and VL of SEQ ID NO: 35 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

83. An antibody having VH of SEQ ID NO: 44 and VL of SEQ ID NO: 43 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

84. An antibody having VH of SEQ ID NO: 60 and VL of SEQ ID NO: 59 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

85. An antibody having VH of SEQ ID NO: 62 and VL of SEQ ID NO: 61 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

86. An antibody having VH of SEQ ID NO: 82 and VL of SEQ ID NO: 81 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

87. An antibody having VH of SEQ ID NO: 90 and VL of SEQ ID NO: 89 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

88. An antibody having VH of SEQ ID NO: 106 and VL of SEQ ID NO: 105 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

89. An antibody having VH of SEQ ID NO: 108 and VL of SEQ ID NO: 107 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

90. An antibody having VH of SEQ ID NO: 128 and VL of SEQ ID NO: 127 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

91. An antibody having VH of SEQ ID NO: 130 and VL of SEQ ID NO: 129 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

92. An antibody having VH of SEQ ID NO: 138 and VL of SEQ ID NO: 137 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

93. An antibody having VH of SEQ ID NO: 14 and VL of SEQ ID NO: 13 for use as a drug, wherein the antibody is monovalent or bivalent.

94. An antibody having VH of SEQ ID NO: 34 and VL of SEQ ID NO: 33 for use as a drug, wherein the antibody is monovalent or bivalent.

95. An antibody having VH of SEQ ID NO: 36 and VL of SEQ ID NO: 35 for use as a drug, wherein the antibody is monovalent or bivalent.

96. An antibody having VH of SEQ ID NO: 44 and VL of SEQ ID NO: 43 for use as a drug, wherein the antibody is monovalent or bivalent.

97. An antibody having VH of SEQ ID NO: 60 and VL of SEQ ID NO: 59 for use as a drug, wherein the antibody is monovalent or bivalent.

98. An antibody having VH of SEQ ID NO: 62 and VL of SEQ ID NO: 61 for use as a drug, wherein the antibody is monovalent or bivalent.

99. An antibody having VH of SEQ ID NO: 82 and VL of SEQ ID NO: 81 for use as a drug, wherein the antibody is monovalent or bivalent.

100. An antibody having VH of SEQ ID NO: 90 and VL of SEQ ID NO: 89 for use as a drug, wherein the antibody is monovalent or bivalent.

101. An antibody having VH of SEQ ID NO: 106 and VL of SEQ ID NO: 105 for use as a drug, wherein the antibody is monovalent or bivalent.

102. An antibody having VH of SEQ ID NO: 108 and VL of SEQ ID NO: 107 for use as a drug, wherein the antibody is monovalent or bivalent.

103. An antibody having VH of SEQ ID NO: 128 and VL of SEQ ID NO: 127 for use as a drug, wherein the antibody is monovalent or bivalent.

104. An antibody having VH of SEQ ID NO: 130 and VL of SEQ ID NO: 129 for use as a drug, wherein the antibody is monovalent or bivalent.

105. An antibody having VH of SEQ ID NO: 138 and VL of SEQ ID NO: 137 for use as a drug, wherein the antibody is monovalent or bivalent.

106. An antibody or fragment thereof of claims 1-38 and 45-66, for use as a medicament.

107. An antibody or fragment thereof of claims 1-38 and 45-66, for use as a medicament for treatment of an LRP6 expressing cancer.

108. An antibody or fragment thereof of claims 1-38 and 45-66, for use as a medicament for treatment of an LRP6 expressing cancer, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, and melanoma.

Claims

1. An isolated bivalent antibody or a bivalent fragment thereof to a low density lipoprotein-related protein 6 (LRP6) that potentiates a Wnt signal by clustering one or more LRP6 receptors in the presence of an unblocked LRP6 binding protein, wherein the antibody or fragment thereof cross competes with an antibody selected from the group consisting of MOR08168, MOR08545 and MOR06475, as described in Table 1.

2. The isolated bivalent antibody or a bivalent fragment thereof of claim 1, wherein the antibody clusters one or more LRP6 receptors by binding to a Propeller region selected from the group consisting of Propeller 1 and Propeller 3.

3. The isolated bivalent antibody or fragment thereof of claim 1 or 2, wherein the LRP6 binding protein is a Wnt binding protein selected from the group consisting of Wnt 1, Wnt 3, and Wnt 3a.

4. An isolated monovalent antibody or monovalent fragment thereof to a low density lipoprotein-related protein 6 (LRP6) that avoids potentiation of a Wnt signal by clustering one or more LRP6 receptors in the presence of an unblocked LRP6 binding protein, wherein the antibody or fragment thereof cross competes with an antibody selected from the group consisting of MOR08168, MOR08545 and MOR06475, as described in Table 1.

5. The isolated antibody or fragment thereof of claim 4, having a dissociation (K_D) selected from less than 1 x 10^7 M^{-1}, 10^8 M, 10^9 M, 10^{10} M, 10^{11} M, 10^{12} M, 10^{13} M, wherein the antibody or fragment thereof binds human LRP6.

6. The isolated antibody or fragment thereof of claim 5, wherein the antibody or fragment thereof inhibits a canonical Wnt pathway as measured by in vitro binding to human LRP6 in a Solution Equilibrium Titration assay with a K_D of 0.001nM-1μM.

7. The isolated antibody or fragment thereof of claim 5, wherein the antibody or fragment inhibits a phosphorylation of LRP6 as assessed by a Wnt ligand induced phosphorylation assay.

8. The isolated antibody or fragment thereof of claim 5, wherein the antibody or fragment inhibits a canonical Wnt pathway as measured by in vitro binding to human LRP6 in a Solution Equilibrium Titration (SET) assay with a EC_{50} of less than or equal to 300 μM.

9. An isolated bivalent or monovalent antibody or fragment thereof to a low density lipoprotein-related protein 6 (LRP6) that cross competes with an antibody selected from the group consisting of MOR08168, MOR08545 and MOR06475, as described in Table 1.

10. The isolated antibody or fragment thereof of any one of claims 1 to 5, that binds to the same epitope as an antibody selected from the group consisting of MOR08168, MOR08545 and MOR06475, as described in Table 1.

11. The isolated antibody or fragment thereof of any one of claims 1 to 5, wherein the antibody or fragment is selected from a monoclonal antibody, a human antibody or humanized antibody, a chimeric antibody, a single chain antibody, a Fab fragment, and an scFv.

12. The isolated antibody or fragment thereof of claim 11, wherein the antibody or fragment binds to both human LRP6 and cynomologus LRP6.

13. The antibody of claim 11, wherein the antibody is an IgG isotype.

14. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising 1, 2, 3, 4, 5, or 6 CDRs of the antibodies in Table 1 selected from the group consisting of MOR08168, MOR08545 and MOR06475.

15. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising one or more of a heavy chain CDR3 comprising SEQ ID NO: 3, a light chain CDR2 comprising SEQ ID NO: 25, and a VL comprising SEQ ID NO: 43.

16. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH selected from the group consisting of SEQ ID NO: 14, SEQ ID NO: 34, SEQ ID NO: 36 and SEQ ID NO: 44 and a VL selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 33, SEQ ID NO: 35 and SEQ ID NO: 43.

17. An isolated antibody or fragment thereof to LRP6 which antibody comprises a VH comprising SEQ ID NO: 14 and a VL comprising SEQ ID NO: 13, wherein the antibody or fragment thereof is monovalent or bivalent.

18. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 34 and a VL comprising SEQ ID NO: 33.

19. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 36 and a VL comprising SEQ ID NO: 35.

20. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 44 and a VL comprising SEQ ID NO: 43.

21. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 36 and a VL comprising SEQ ID NO: 35.

22. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one heavy chain CDR sequence that is identical to SEQ ID NO: 1, 2, 3, 21, 22 and 23, wherein the antibody binds to human LRP6 protein.

23. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one light chain CDR sequence that is identical to SEQ ID NO: 4, 5, 6, 24, 25 and 26, wherein the antibody binds to human LRP6 protein.

24. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one heavy chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 1, 2, 3, 21, 22 and 23, wherein the antibody binds to human LRP6 protein.

25. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one light chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 4, 5, 6, 24, 25 and 26, wherein the antibody binds to human LRP6 protein.

26. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6, wherein the antibody or fragment thereof is monovalent or bivalent.

27. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising a heavy chain variable region CDR1 of SEQ ID NO: 21; a heavy chain variable region CDR2 of SEQ ID NO: 22; a heavy chain variable region CDR3 of SEQ ID NO: 23; a light chain variable region CDR1 of SEQ ID NO: 24; a light chain variable region CDR2 of SEQ ID NO: 25; and a light chain variable region CDR3 of SEQ ID NO: 26.

28. A pharmaceutical composition comprising an antibody or fragment thereof selected from claims 1 to 27 and a pharmaceutically acceptable carrier.

29. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a heavy chain variable region identity to SEQ ID NO: 14, 34, 36 and 44.

30. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a light chain variable region identity to SEQ ID NO: 13, 33, 35 and 43.

31. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a heavy chain variable region having at least 98% sequence identity to SEQ ID NO: 14, 34, 36 and 44.

32. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a light chain variable region having at least 98% sequence identity to SEQ ID NO: 13, 33, 35 and 43.

33. A vector comprising the nucleic acid of any one of claims 29 to 32.

34. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising a heavy chain CDR1 of SEQ ID NO: 69.

35. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising a heavy chain CDR1 of SEQ ID NO: 69; a heavy chain CDR2 of SEQ ID NO: 70; and a heavy chain CDR3 of SEQ ID NO: 71.

36. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising a light chain CDR1 of SEQ ID NO: 72; a light chain CDR2 of SEQ ID NO: 73; and a light chain CDR3 of SEQ ID NO: 74.

37. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH selected from the group consisting of SEQ ID NO: 82 and SEQ ID NO: 89; and a VL selected from the group consisting of SEQ ID NO: 81 and SEQ ID NO: 90.

38. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 82 and a VL comprising SEQ ID NO: 81.

39. The isolated antibody or fragment thereof of any one of claims 1 to 5, which antibody comprises a VH comprising SEQ ID NO: 84 and a VL comprising SEQ ID NO: 90.

40. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one heavy chain CDR sequence that is identical to SEQ ID NO: 69, 70 and 71, wherein said antibody binds to human LRP6 protein.

41. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one light chain CDR sequence that is identical to SEQ ID NO: 72, 73 and 74.

42. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one heavy chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 69, 70 and 71, wherein said antibody binds to human LRP6 protein.

43. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising at least one light chain CDR sequence having at least 95% sequence identity to SEQ ID NO: 72, 73 and 74, wherein said antibody binds to human LRP6 protein.

44. The isolated antibody or fragment thereof of any one of claims 1 to 5, comprising a heavy chain variable region CDR1 of SEQ ID NO: 69; a heavy chain variable region CDR2 of SEQ ID NO: 70; a heavy chain variable region CDR3 of SEQ ID NO: 71; a light chain variable region CDR1 of SEQ ID NO: 72; a light chain variable region CDR2 of SEQ ID NO: 73; and a light chain variable region CDR3 of SEQ ID NO: 74.

45. A combination of a monoclonal antibody or fragment thereof selected from the group consisting of any one of the antibodies in claims 26 or 27 with any one of the antibodies in claim 44, wherein the antibody or fragment thereof is monovalent.

46. A combination of a monoclonal antibody or fragment thereof selected from the group consisting of any one of the antibodies in claims 26 or 27 with any one of the antibodies in claim 44, wherein the antibody or fragment thereof is bivalent.

47. A pharmaceutical composition comprising antibody selected from any one of claims 34 to 44 and a pharmaceutically acceptable carrier, wherein the antibody is monovalent or bivalent.

48. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a heavy chain variable region selected from the group consisting of SEQ ID NO: 82 and 89.

49. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a light chain variable region selected from the group consisting of SEQ ID NO: 81 and 90.

50. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a heavy chain variable region having at least 98% sequence identity to SEQ ID NO: 82 and 89.

51. A nucleic acid comprising a nucleotide sequence encoding a polypeptide of any one of claims 1 to 5, comprising a light chain variable region having at least 98% sequence identity to SEQ ID NO: 81 and 90.

52. A vector comprising the nucleic acid of any one of claims 48 to 51.

53. Use of the antibody or fragment thereof of any one of claims 1 to 27 and 34 to 44 in the manufacture of a medicament for the treatment of cancer, wherein the antibody or fragment thereof is monovalent or bivalent.

54. Use of an antibody or fragment thereof of any one of claims 1 to 27 and 34 to 44 in the manufacture of a medicament for the treatment of a cancer mediated by a canonical Wnt signaling pathway selected from the group consisting of breast cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, bladder cancer, gastric cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous

cell carcinoma, and melanoma, wherein the antibody or fragment thereof is monovalent or bivalent.

55. Use of claim 54, wherein said cancer is breast cancer.

56. Use of an antibody having VH of SEQ ID NO: 14 and VL of SEQ ID NO: 13 in the manufacture of a medicament for treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

57. Use of the antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 34 and VL of SEQ ID NO: 33 in the manufacture of a medicament for treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

58. Use of the antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 36 and VL of SEQ ID NO: 35 for use in treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

59. Use of the antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 44 and VL of SEQ ID NO: 43 in the manufacture of a medicament for treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

60. Use of the antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 82 and VL of SEQ ID NO: 81 in the manufacture of a medicament for treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

61. Use of the antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 89 and VL of SEQ ID NO: 90 in the manufacture of a medicament for treating a cancer mediated by a canonical Wnt signaling pathway, wherein the antibody is monovalent or bivalent.

62. An antibody having VH of SEQ ID NO: 14 and VL of SEQ ID NO: 13 for use as a drug, wherein the antibody is monovalent or bivalent.

63. The antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 34 and VL of SEQ ID NO: 33 for use as a drug, wherein the antibody is monovalent or bivalent.

64. The antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 36 and VL of SEQ ID NO: 35 for use as a drug, wherein the antibody is monovalent or bivalent.

65. An antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 44 and VL of SEQ ID NO: 43 for use as a drug, wherein the antibody is monovalent or bivalent.

66. The antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 82 and VL of SEQ ID NO: 81 for use as a drug, wherein the antibody is monovalent or bivalent.

67. The antibody of any one of claims 1 to 5 having VH of SEQ ID NO: 89 and VL of SEQ ID NO: 90 for use as a drug, wherein the antibody is monovalent or bivalent.

68. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 7; a heavy chain variable region CDR2 of SEQ ID NO: 8; a heavy chain variable region CDR3 of SEQ ID NO: 9; a light chain variable region CDR1 of SEQ ID NO: 10; a light chain variable region CDR2 of SEQ ID NO: 11; and a light chain variable region CDR3 of SEQ ID NO: 12, wherein the antibody or fragment thereof is monvalent or bivalent.

69. The isolated antibody or fragment thereof of any one of claims 1-5, comprising a heavy chain variable region CDR1 of SEQ ID NO: 27; a heavy chain variable region CDR2 of SEQ ID NO: 28; a heavy chain variable region CDR3 of SEQ ID NO: 29; a light chain variable region CDR1 of SEQ ID NO: 30; a light chain variable region CDR2 of SEQ ID NO: 31; and a light chain variable region CDR3 of SEQ ID NO: 32, wherein the antibody or fragment thereof is monovalent or bivalent.

70. The isolated antibody or fragment thereof of any one of claims 1-5, comprising a

heavy chain variable region CDR1 of SEQ ID NO: 75; a heavy chain variable region CDR2 of SEQ ID NO: 76; a heavy chain variable region CDR3 of SEQ ID NO: 77; a light chain variable region CDR1 of SEQ ID NO: 78; a light chain variable region CDR2 of SEQ ID NO: 79; and a light chain variable region CDR3 of SEQ ID NO: 80, wherein the antibody or fragment thereof is monovalent or bivalent.