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.

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.

Claims:

1. An isolated antibody or fragment thereof that binds to an inactive state of a HER receptor, wherein the antibody blocks both ligand-dependent and ligand-independent signal transduction.

2. The isolated antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof stabilizes the HER receptor in an inactive state.

3. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER receptor, and wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

4. The isolated antibody or fragment thereof of claim 3, wherein the antibody or fragment thereof binds to the inactive state of the HER receptor.

5. The isolated antibody or fragment thereof of claim 4, wherein the antibody or fragment thereof stabilizes the HER receptor in the inactive state.

6. The isolated antibody or fragment thereof of claim 2, wherein the HER receptor is selected from the group consisting of HER1, HER2, HER3 and HER4.

7. The isolated antibody or fragment thereof of claim 3, wherein the antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chimeric antibody, a humanized antibody, and a synthetic antibody.

8. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER receptor, wherein binding of the antibody stabilizes the HER receptor in an inactive state, and wherein a HER ligand can concurrently bind to a ligand binding site on the HER receptor.

9. The isolated antibody or fragment thereof of claim 8, wherein HER ligand binding to the ligand binding site fails to induce a conformational change in the HER receptor to an active state.

10. The isolated antibody or fragment thereof of claim 8, wherein HER ligand binding to the ligand binding site fails to activate signal transduction.

11. The isolated antibody or fragment thereof of claim 8, wherein the HER ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, neuregulin 3, neuregulin 4, betacellulin, heparin-binding epidermal growth factor, epiregulin, epidermal growth factor, amphiregulin, and transforming growth factor alpha.

12. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER receptor, wherein binding of the antibody stabilizes the HER receptor in an inactive state such that the HER receptor fails to dimerize with a co-receptor to form a receptor-receptor complex.

13. The isolated antibody or fragment thereof of claim 12, wherein the failure to form a receptor-receptor complex prevents activation of signal transduction.

14. The isolated antibody or fragment thereof of claim 12, wherein signal transduction is ligand-independent signal transduction.

15. The isolated antibody or fragment thereof of claim 12, wherein signal transduction is ligand-dependent signal transduction.

16. An isolated antibody or fragment thereof that binds to an inactive conformation of a HER3 receptor, wherein the antibody blocks both ligand-dependent and ligand-independent signal transduction.

17. The isolated antibody or fragment thereof of claim 16, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state.

18. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

19. The isolated antibody or fragment thereof of claim 18, wherein the antibody or fragment thereof binds to the inactive state of the HER3 receptor.

20. The isolated antibody or fragment thereof of claim 18, wherein the antibody or fragment thereof stabilizes the HER3 receptor in the inactive state.

21. The isolated antibody or fragment thereof of claim 18, wherein the antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chimeric antibody, a humanized antibody, and a synthetic antibody.

22. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody stabilizes the HER3 receptor in an inactive state, and wherein a HER3 ligand can concurrently bind to a ligand binding site on the HER3 receptor.

23. The isolated antibody or fragment thereof of claim 22, wherein HER3 ligand binding to the ligand binding site fails to induce a conformational change in the HER3 receptor to an active state.

24. The isolated antibody or fragment thereof of claim 22, wherein the HER3 ligand binding to the ligand binding site fails to activate signal transduction.

25. The isolated antibody or fragment thereof of claim 22, wherein the HER3 ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, betacellulin, heparin-binding epidermal growth factor, and epiregulin.

26. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

27. The isolated antibody or fragment thereof of claim 26, wherein the antibody or fragment thereof binds to the inactive state of the HER3 receptor.

28. The isolated antibody or fragment thereof of claim 27, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state.

29. An isolated antibody or fragment thereof that binds a conformational epitope of HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein the antibody or fragment thereof binds to the inactive HER3 receptor, and wherein the antibody or fragment blocks both ligand-dependent and ligand-independent signal transduction.

30, The isolated antibody or fragment thereof of claim 28, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state.

31. The isolated antibody of claim 29, wherein the conformational epitope comprises amino acid residues 265-277, 315 (of domain 2), 571, 582-584, 596-597, 600-602, 609-615 (of domain 4), or a subset thereof.

32. The isolated antibody of claim 29, wherein the VH of the antibody or fragment thereof binds to at least one of the following HER3 residues: Asn266, Lys267, Leu268, Thr269, Gln271, Glu273, Pro274, Asn275, Pro276, His277, Asn315, Asp571, Pro583, His584, Ala596, Lys597.

33. The isolated antibody of claim 29, wherein the VL of the antibody or fragment thereof binds to at least one of the following HER3 residues: Tyr265, Lys267, Leu268, Phe270, Gly582, Pro583, Lys597, Ile600, Lys602, Glu609, Arg611, Pro612, Cys613, His614, Glu615.

34. An isolated antibody or fragment thereof that recognizes a conformational epitope of first HER receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the first HER receptor, wherein binding of the antibody or fragment thereof to the first HER receptor in the absence of a HER receptor ligand reduces ligand-independent formation of a first HER receptor-second HER receptor protein complex in a cell which expresses first HER receptor and second HER receptor.

35. The isolated antibody or fragment thereof of claim 34, wherein antibody or fragment thereof stabilizes first HER receptor in an inactive state such that the first HER receptor fails to dimerize with the second HER receptor to form a first HER receptor-second HER receptor protein complex.

36. The isolated antibody or fragment thereof of claim 35, wherein the failure to form a first HER receptor-second HER receptor protein complex prevents activation of signal transduction.

37. The isolated antibody or fragment thereof of claim 35, wherein the first HER is selected from the group consisting of HER1, HER2, HER3, and HER4.

38. The isolated antibody or fragment thereof of claim 35, wherein the second HER is selected from the group consisting of HER1, HER2, HER3, and HER4.

39. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody or fragment thereof to the HER3 receptor in the absence of a HER3 ligand reduces ligand-independent formation of a HER2-HER3 protein complex in a cell which expresses HER2 and HER3.

40. The isolated antibody or fragment thereof of claim 39, wherein antibody or fragment thereof stabilizes the HER3 receptor in an inactive state such that the HER3 receptor fails to dimerize with the HER2 receptor to form a HER2-HER3 protein complex.

41. The isolated antibody or fragment thereof of claim 40, wherein the failure to form a HER2-HER3 protein complex prevents activation of signal transduction.

42. An isolated antibody or fragment thereof that recognizes a conformational epitope of first HER receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the first HER receptor, wherein binding of the antibody or fragment thereof to the first HER receptor in the presence of a HER ligand reduces ligand-dependent formation of a first HER receptor-second HER receptor protein complex in a cell which expresses first HER receptor and second HER receptor.

43. The isolated antibody or fragment thereof of claim 42, wherein antibody or fragment thereof stabilizes the first HER receptor in an inactive state such that the HER receptor fails to dimerize with the second HER receptor in the presence of a first HER ligand to form a first HER receptor- second HER receptor protein complex.

44. The isolated antibody or fragment thereof of claim 43, wherein the failure to form a first HER receptor- second HER receptor protein complex prevents activation of signal transduction.

45. The isolated antibody or fragment thereof of claim 42, wherein the HER ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, neuregulin 3, neuregulin 4, betacellulin, heparin-binding epidermal growth factor, epiregulin, epidermal growth factor, amphiregulin, and transforming growth factor alpha.

46. The isolated antibody or fragment thereof of claim 42, wherein the first HER is selected from the group consisting of HER1, HER2, HER3, and HER4.

47. The isolated antibody or fragment thereof of claim 42, wherein the second HER is selected from the group consisting of HER1, HER2, HER3, and HER4.

48. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody or fragment thereof to the HER3 receptor in the presence of a HER3 ligand reduces ligand-dependent formation of a HER2-HER3 protein complex in a cell which expresses HER2 and HER3.

49. The isolated antibody or fragment thereof of claim 48, wherein antibody or fragment thereof stabilizes the HER3 receptor in an inactive state such that the HER3 receptor fails to dimerize with the HER2 receptor in the presence of a HER3 ligand to form a HER2-HER3 protein complex.

50. The isolated antibody or fragment thereof of claim 49, wherein the failure to form a HER2-HER3 protein complex prevents activation of signal transduction.

51. The isolated antibody or fragment thereof of claim 48, wherein ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, betacellulin, heparin-binding epidermal growth factor, and epiregulin.

52. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as assessed by HER3 ligand-independent phosphorylation assay.

53. The isolated antibody or fragment thereof of claim 52, wherein the HER3 ligand-independent phosphorylation assay uses HER2 amplified cells, wherein the HER2 amplified cells are SK-Br-3 cells.

54. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as assessed by HER3 ligand-dependent phosphorylation assay.

55. The isolated antibody or fragment thereof of claim 54, wherein the HER3 ligand-dependent phosphorylation assay uses stimulated MCF7 cells in the presence of neuregulin (NRG).

56. An isolated antibody or fragment thereof to a HER3 receptor, 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}.

57. The isolated antibody or fragment thereof of claim 56, wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as measured by an in vitro phosphorylation assay selected from the group consisting of phospho-HER3 and phospho-Akt.

58. An isolated ntibody or fragment thereof to HER3 receptor, that cross-competes with an antibody described in Table 1.

59. An isolated antibody or fragment thereof, that binds to the same conformational epitope as an antibody described in Table 1.

60. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody is selected from the group consisting of a monoclonal antibody, chimeric antibody. a single chain antibody, an Fab, and an scFv.

61. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody is a human.

62. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody comprises a human heavy chain constant region and a human light chain constant region.

63. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody or fragment binds to both human HER3 and cynomologus HER3.

64. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody or fragment is an IgG isotype.

65. The isolated antibody or fragment thereof of any of the above claims, wherein the antibody comprises a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

66. An isolated antibody or fragment thereof to HER3 receptor comprising 1, 2, 3, 4, 5, or 6 CDRs calculated by Kabat or Chothia of any of the antibodies in Table 1.

67. An isolated antibody or fragment thereof to HER3 receptor comprising a heavy chain CDR3 selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 10, SEQ ID NO: 22, SEQ ID NO: 28, SEQ ID NO: 40, SEQ ID NO: 46, SEQ ID NO: 58, SEQ ID NO: 64, SEQ ID NO: 76, SEQ ID NO: 82, SEQ ID NO: 94, SEQ ID NO: 100, SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 148, SEQ ID NO: 166, SEQ ID NO: 184, SEQ ID NO: 202, SEQ ID NO: 220, SEQ ID NO: 238, SEQ ID NO: 256, SEQ ID NO: 274, SEQ ID NO: 292, SEQ ID NO: 310, SEQ ID NO: 328, SEQ ID NO: 346, and SEQ ID NO: 364.

68. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 15 and a VL comprising SEQ ID NO: 14, or an amino acid sequence with 97-99% identity thereof.

69. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 33 and a VL comprising SEQ ID NO: 32, or an amino acid sequence with 97-99% identity thereof.

70. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 51 and a VL comprising SEQ ID NO: 50, or an amino acid sequence with 97-99% identity thereof.

71. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 69 and a VL comprising SEQ ID NO: 68, or an amino acid sequence with 97-99% identity thereof.

72. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 87 and a VL comprising SEQ ID NO: 86, or an amino acid sequence with 97-99% identity thereof.

73. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 105 and a VL comprising SEQ ID NO: 104, or an amino acid sequence with 97-99% identity thereof.

74. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 123 and a VL comprising SEQ ID NO: 122, or an amino acid sequence with 97-99% identity thereof.

75. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 141 and a VL comprising SEQ ID NO: 140, or an amino acid sequence with 97-99% identity thereof.

76. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 159 and a VL comprising SEQ ID NO: 158, or an amino acid sequence with 97-99% identity thereof.

77. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 177 and a VL comprising SEQ ID NO: 176, or an amino acid sequence with 97-99% identity thereof.

78. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 195 and a VL comprising SEQ ID NO: 194, or an amino acid sequence with 97-99% identity thereof.

79. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 213 and a VL comprising SEQ ID NO: 212, or an amino acid sequence with 97-99% identity thereof.

80. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 231 and a VL comprising SEQ ID NO: 230, or an amino acid sequence with 97-99% identity thereof.

81. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 249 and a VL comprising SEQ ID NO: 248, or an amino acid sequence with 97-99% identity thereof.

82. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 267 and a VL comprising SEQ ID NO: 266, or an amino acid sequence with 97-99% identity thereof.

83. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 285 and a VL comprising SEQ ID NO: 284, or an amino acid sequence with 97-99% identity thereof.

84. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 303 and a VL comprising SEQ ID NO: 302, or an amino acid sequence with 97-99% identity thereof.

85. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 321 and a VL comprising SEQ ID NO: 320, or an amino acid sequence with 97-99% identity thereof.

86. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 339 and a VL comprising SEQ ID NO: 338, or an amino acid sequence with 97-99% identity thereof.

87. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 357 and a VL comprising SEQ ID NO: 356, or an amino acid sequence with 97-99% identity thereof.

88. An isolated antibody or fragment thereof to HER3 receptor which antibody comprises a VH comprising SEQ ID NO: 375 and a VL comprising SEQ ID NO: 374, or an amino acid sequence with 97-99% identity thereof.

89 . An isolated antibody or fragment thereof comprising a variable heavy chain sequence having SEQ ID NO: 493.

90. An isolated antibody or fragment thereof comprising a variable light chain sequence having SEQ ID NO: 494.

91. An isolated antibody or fragment thereof comprising a variable heavy chain sequence having SEQ ID NO: 493 and a variable light chain sequence having SEQ ID NO: 494.

92. An isolated antibody or fragment thereof to HER3 receptor with a variant heavy chain variable region comprising CDR1, CDR2, and CDR3, wherein the variant has at least one to four amino acid changes in one of CDR1, CDR2, or CDR3.

93. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 2; CDR2 of SEQ ID NO: 3; CDR3 of SEQ ID NO: 4; a light chain variable region CDR1 of SEQ ID NO: 5; CDR2 of SEQ ID NO: 6; and CDR3 of SEQ ID NO: 7.

94. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 20; CDR2 of SEQ ID NO: 21; CDR3 of SEQ ID NO: 22; a light chain variable region CDR1 of SEQ ID NO: 23; CDR2 of SEQ ID NO: 24; and CDR3 of SEQ ID NO: 25.

95. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 38; CDR2 of SEQ ID NO: 39; CDR3 of SEQ ID NO: 40; a light chain

variable region CDR1 of SEQ ID NO: 41; CDR2 of SEQ ID NO: 42; and CDR3 of SEQ ID NO: 43.

96. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 56; CDR2 of SEQ ID NO: 57; CDR3 of SEQ ID NO: 58; a light chain variable region CDR1 of SEQ ID NO: 59; CDR2 of SEQ ID NO: 60; and CDR3 of SEQ ID NO: 61.

97. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 74; CDR2 of SEQ ID NO: 75; CDR3 of SEQ ID NO: 76; a light chain variable region CDR1 of SEQ ID NO: 77; CDR2 of SEQ ID NO: 78; and CDR3 of SEQ ID NO: 79.

98. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 92; CDR2 of SEQ ID NO: 93; CDR3 of SEQ ID NO: 94; a light chain variable region CDR1 of SEQ ID NO: 95; CDR2 of SEQ ID NO: 96; and CDR3 of SEQ ID NO: 97.

99. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 110; CDR2 of SEQ ID NO: 111; CDR3 of SEQ ID NO: 112; a light chain variable region CDR1 of SEQ ID NO: 113; CDR2 of SEQ ID NO: 114; and CDR3 of SEQ ID NO: 115.

100. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 128; CDR2 of SEQ ID NO: 129; CDR3 of SEQ ID NO: 130; a light chain variable region CDR1 of SEQ ID NO: 131; CDR2 of SEQ ID NO: 132; and CDR3 of SEQ ID NO: 133.

101. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 146; CDR2 of SEQ ID NO: 147; CDR3 of SEQ ID NO: 148; a light chain variable region CDR1 of SEQ ID NO: 149; CDR2 of SEQ ID NO: 150; and CDR3 of SEQ ID NO: 151.

102. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 164; CDR2 of SEQ ID NO: 165; CDR3 of SEQ ID NO: 166; a light chain variable region CDR1 of SEQ ID NO: 167; CDR2 of SEQ ID NO: 168; and CDR3 of SEQ ID NO: 169.

103. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 182; CDR2 of SEQ ID NO: 183; CDR3 of SEQ ID NO: 184; a light chain variable region CDR1 of SEQ ID NO: 185; CDR2 of SEQ ID NO: 186; and CDR3 of SEQ ID NO: 187.

104. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 200; CDR2 of SEQ ID NO: 201; CDR3 of SEQ ID NO: 202; a light chain variable region CDR1 of SEQ ID NO: 203; CDR2 of SEQ ID NO: 204; and CDR3 of SEQ ID NO: 205.

105. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 218; CDR2 of SEQ ID NO: 219; CDR3 of SEQ ID NO: 220; a light chain variable region CDR1 of SEQ ID NO: 221; CDR2 of SEQ ID NO: 222; and CDR3 of SEQ ID NO: 223.

106. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 236; CDR2 of SEQ ID NO: 237; CDR3 of SEQ ID NO: 238; a light chain variable region CDR1 of SEQ ID NO: 239; CDR2 of SEQ ID NO: 240; and CDR3 of SEQ ID NO: 241.

107. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 254; CDR2 of SEQ ID NO: 255; CDR3 of SEQ ID NO: 256; a light chain variable region CDR1 of SEQ ID NO: 257; CDR2 of SEQ ID NO: 258; and CDR3 of SEQ ID NO: 259.

108. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 272; CDR2 of SEQ ID NO: 273; CDR3 of SEQ ID NO: 274; a light chain variable region CDR1 of SEQ ID NO: 275; CDR2 of SEQ ID NO: 276; and CDR3 of SEQ ID NO: 277.

109. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 290; CDR2 of SEQ ID NO: 291; CDR3 of SEQ ID NO: 292; a light chain variable region CDR1 of SEQ ID NO: 293; CDR2 of SEQ ID NO: 294; and CDR3 of SEQ ID NO: 295.

110. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 308; CDR2 of SEQ ID NO: 309; CDR3 of SEQ ID NO: 310; a light

chain variable region CDR1 of SEQ ID NO: 311; CDR2 of SEQ ID NO: 312; and CDR3 of SEQ ID NO: 313.

111. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 326; CDR2 of SEQ ID NO: 327; CDR3 of SEQ ID NO: 328; a light chain variable region CDR1 of SEQ ID NO: 329; CDR2 of SEQ ID NO: 330; and CDR3 of SEQ ID NO: 331.

112. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 344; CDR2 of SEQ ID NO: 345; CDR3 of SEQ ID NO: 346; a light chain variable region CDR1 of SEQ ID NO: 347; CDR2 of SEQ ID NO: 348; and CDR3 of SEQ ID NO: 349.

113. An isolated antibody or fragment thereof, comprising a heavy chain variable region CDR1 of SEQ ID NO: 362; CDR2 of SEQ ID NO: 363; CDR3 of SEQ ID NO: 364; a light chain variable region CDR1 of SEQ ID NO: 365; CDR2 of SEQ ID NO: 366; and CDR3 of SEQ ID NO: 367.

114. A fragment of an antibody of anyone of the previous claim that binds to HER3 selected from the group consisting of; Fab, $F(ab_2)'$, $F(ab)_2'$, scFv, VHH, VH, VL, dAbs.

115. A pharmaceutical composition comprising an antibody or fragment thereof selected from any one of the previous claims and a pharmaceutically acceptable carrier.

116. The pharmaceutical composition of claim 115, further comprising an additional therapeutic agent.

117. The pharmaceutical composition of claim 116, wherein the additional therapeutic agent is selected from the group consisting of an HER1 inhibitor, a HER2 inhibitor, a HER3 inhibitor, a HER4 inhibitor, an mTOR inhibitor and a PI3 Kinase inhibitor.

118. The pharmaceutical composition of claim 117, wherein the additional therapeutic agent is a HER1 inhibitor selected from the group consisting of Matuzumab (EMD72000), Erbitux®/Cetuximab, Vectibix® /Panitumumab, mAb 806, Nimotuzumab, Iressa® /Gefitinib, CI-1033 (PD183805), Lapatinib (GW-572016), Tykerb® /Lapatinib Ditosylate, Tarceva® / Erlotinib HCL (OSI-774), PKI-166, and Tovok®; a HER2 inhibitor selected from the group consisting of Pertuzumab, Trastuzumab, MM-111, neratinib, lapatinib or lapatinib ditosylate /Tykerb®; a HER3 inhibitor selected from the group consisting of, MM-121, MM-111,

IB4C3, 2DID12 (U3 Pharma AG), AMG888 (Amgen), AV-203(Aveo), MEHD7945A (Genentech) and small molecules that inhibit HER3; and a HER4 inhibitor.

119. The pharmaceutical composition of claim 117, wherein the additional therapeutic agent is an mTOR inhibitor selected from the group consisting of Temsirolimus/Torisel®, ridaforolimus / Deforolimus, AP23573, MK8669, everolimus /Affinitor® .

120. The pharmaceutical composition of claim 117, wherein the additional therapeutic agent is a PI3 Kinase inhibitor selected from the group consisting of GDC 0941, BEZ235, BMK120 and BYL719.

121. A method of treating a cancer comprising selecting a subject having an HER3 expressing cancer, administering to the subject an effective amount of a composition comprising an antibody or fragment thereof selected from any one of the previous claims.

122. The method of claim 121, wherein the subject is a human.

123. A method of treating a cancer mediated by a HER signalling pathway comprising selecting a subject having an HER3 expressing cancer, administering to the subject an effective amount of a composition comprising an antibody or fragment thereof selected from any one of the previous claims, wherein the cancer is selected from the group consisting of breast cancer, colorectal cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, pancreatic cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors , schwannoma, head and neck cancer, bladder cancer, esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma.

124. The method of claim 123, wherein said cancer is breast cancer.

125. A method of treating a cancer comprising selecting a subject having an HER3 expressing cancer, administering to said subject an effective amount of a composition comprising an a combination of antibodies or fragments thereof disclosed in Table 1 that binds to HER3.

126. A method of treating a cancer comprising selecting a subject having an HER3 expressing cancer, administering to said subject an effective amount of a composition

comprising an antibody or fragment thereof that binds to HER3 and inhibits HER3 ligand-dependent signal transduction and ligand-independent signal transduction.

127. An antibody or fragment thereof of any one of the previous claims for use as a medicament.

128. An antibody or fragment thereof of any one of the previous claims for use in the treatment of a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway selected from the group consisting of breast cancer, colorectal cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, pancreatic cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors, schwannoma, head and neck cancer, bladder cancer, esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma.

129. An antibody having VH of SEQ ID NO: 15 and VL of SEQ ID NO: 14 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

130. An antibody having VH of SEQ ID NO: 33 and VL of SEQ ID NO: 32 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

131. An antibody having VH of SEQ ID NO: 51 and VL of SEQ ID NO: 50 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

132. An antibody having VH of SEQ ID NO: 69 and VL of SEQ ID NO: 68 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

133. An antibody having VH of SEQ ID NO: 87 and VL of SEQ ID NO: 86 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

134. An antibody having VH of SEQ ID NO: 105 and VL of SEQ ID NO: 104 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

135. An antibody having VH of SEQ ID NO: 123 and VL of SEQ ID NO: 122 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

136. An antibody having VH of SEQ ID NO: 141 and VL of SEQ ID NO: 140 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

137. An antibody having VH of SEQ ID NO: 151 and VL of SEQ ID NO: 158 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

138. An antibody having VH of SEQ ID NO: 177 and VL of SEQ ID NO: 176 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

139. An antibody having VH of SEQ ID NO: 195 and VL of SEQ ID NO: 194 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

140. An antibody having VH of SEQ ID NO: 213 and VL of SEQ ID NO: 212 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

141. An antibody having VH of SEQ ID NO: 231 and VL of SEQ ID NO: 230 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

142. An antibody having VH of SEQ ID NO: 249 and VL of SEQ ID NO: 248 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

143. An antibody having VH of SEQ ID NO: 267 and VL of SEQ ID NO: 266 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

144. An antibody having VH of SEQ ID NO: 285 and VL of SEQ ID NO: 284 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

145. An antibody having VH of SEQ ID NO: 303 and VL of SEQ ID NO: 302 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

146. An antibody having VH of SEQ ID NO: 321 and VL of SEQ ID NO: 320 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

147. An antibody having VH of SEQ ID NO: 339 and VL of SEQ ID NO: 338 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

148. An antibody having VH of SEQ ID NO: 357 and VL of SEQ ID NO: 356 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

149. An antibody having VH of SEQ ID NO: 375 and VL of SEQ ID NO: 374 for use in treating a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway.

150. An antibody having VH of SEQ ID NO: 15 and VL of SEQ ID NO: 14 for use as a medicament.

151. An antibody having VH of SEQ ID NO: 33 and VL of SEQ ID NO: 32 for use as a medicament.

152. An antibody having VH of SEQ ID NO: 51 and VL of SEQ ID NO: 50 for use as a medicament.

153. An antibody having VH of SEQ ID NO: 69 and VL of SEQ ID NO: 68 for use as a medicament.

154. An antibody having VH of SEQ ID NO: 87 and VL of SEQ ID NO: 86 for use as a medicament.

155. An antibody having VH of SEQ ID NO: 105 and VL of SEQ ID NO: 104 for use as a medicament.

156. An antibody having VH of SEQ ID NO: 123 and VL of SEQ ID NO: 122 for use as a medicament.

157. An antibody having VH of SEQ ID NO: 141 and VL of SEQ ID NO: 140 for use as a medicament.

158. An antibody having VH of SEQ ID NO: 159 and VL of SEQ ID NO: 158 for use as a medicament.

159. An antibody having VH of SEQ ID NO: 177 and VL of SEQ ID NO: 176 for use as a medicament.

160. An antibody having VH of SEQ ID NO: 195 and VL of SEQ ID NO: 194 for use as a medicament.

161. An antibody having VH of SEQ ID NO: 213 and VL of SEQ ID NO: 212 for use as a medicament.

162. An antibody having VH of SEQ ID NO: 231 and VL of SEQ ID NO: 230 for use as a medicament.

163. An antibody having VH of SEQ ID NO: 249 and VL of SEQ ID NO: 248 for use as a medicament.

164. An antibody having VH of SEQ ID NO: 267 and VL of SEQ ID NO: 266 for use as a medicament.

165. An antibody having VH of SEQ ID NO: 285 and VL of SEQ ID NO: 284 for use as a medicament.

166. An antibody having VH of SEQ ID NO: 303 and VL of SEQ ID NO: 302 for use as a medicament.

167. An antibody having VH of SEQ ID NO: 321 and VL of SEQ ID NO: 320 for use as a medicament.

168. An antibody having VH of SEQ ID NO: 339 and VL of SEQ ID NO: 338 for use as a medicament.

169. An antibody having VH of SEQ ID NO: 357 and VL of SEQ ID NO: 356 for use as a medicament.

170. An antibody having VH of SEQ ID NO: 375 and VL of SEQ ID NO: 374 for use as a medicament.

171. Use of an antibody or fragment thereof of any one of the previous claims for the manufacture of a medicament for the treatment of a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway selected from the group consisting of breast cancer, colorectal cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, pancreatic cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors, schwannoma, head and neck cancer, bladder cancer, esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

2. The isolated antibody or fragment thereof of claim 1, wherein the antibody or fragment thereof binds to the inactive state of the HER3 receptor.

3. The isolated antibody or fragment thereof of claim 1 or claim 2, wherein the antibody or fragment thereof stabilizes the HER3 receptor in the inactive state.

4. The isolated antibody or fragment thereof of any one of claims 1 to 3, wherein the antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chimeric antibody, a humanized antibody, and a synthetic antibody.

5. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody stabilizes the HER3 receptor in an inactive state, and wherein a HER3 ligand can concurrently bind to a ligand binding site on the HER3 receptor.

6. The isolated antibody or fragment thereof of claim 5, wherein HER3 ligand binding to the ligand binding site fails to induce a conformational change in the HER3 receptor to an active state.

7. The isolated antibody or fragment thereof of claim 5 or claim 6, wherein the HER3 ligand binding to the ligand binding site fails to activate signal transduction.

8. The isolated antibody or fragment thereof of any one of claims 5 to 7, wherein the HER3 ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, betacellulin, heparin-binding epidermal growth factor, and epiregulin.

9. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or

fragment thereof blocks both ligand-dependent and ligand-independent signal transduction.

10. The isolated antibody or fragment thereof of claim 9, wherein the antibody or fragment thereof binds to the inactive state of the HER3 receptor.

11. The isolated antibody or fragment thereof of claim 9 or claim 10, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state.

12. An isolated antibody or fragment thereof that binds a conformational epitope of HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein the antibody or fragment thereof binds to the inactive HER3.

13. The isolated antibody or fragment thereof of claim 12, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state.

14. The isolated antibody of claim 12 or claim 13, wherein the conformational epitope comprises amino acid residues 265-277, 315 (of domain 2), 571, 582-584, 596-597, 600-602, 609-615 (of domain 4), or a subset thereof.

15. The isolated antibody of any one of claims 12 to 14, wherein the VH of the antibody or fragment thereof binds to at least one of the following HER3 residues: Asn266, Lys267, Leu268, Thr269, Gln271, Glu273, Pro274, Asn275, Pro276, His277, Asn315, Asp571, Pro583, His584, Ala596, Lys597.

16. The isolated antibody of any one of claims 12 to 15, wherein the VL of the antibody or fragment thereof binds to at least one of the following HER3 residues: Tyr265, Lys267, Leu268, Phe270, Gly582, Pro583, Lys597, Ile600, Lys602, Glu609, Arg611, Pro612, Cys613, His614, Glu615.

17. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody or fragment thereof to the HER3 receptor in the absence of a HER3 ligand reduces ligand-independent formation of a HER2-HER3 protein complex in a cell which expresses HER2 and HER3.

18. The isolated antibody or fragment thereof of claim 17, wherein antibody or fragment thereof stabilizes the HER3 receptor in an inactive state such that the HER3 receptor fails to dimerize with the HER2 receptor to form a HER2-HER3 protein complex.

19. The isolated antibody or fragment thereof of claim 18, wherein the failure to form a HER2-HER3 protein complex prevents activation of signal transduction.

20. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein binding of the antibody or fragment thereof to the HER3 receptor in the presence of a HER3 ligand reduces ligand-dependent formation of a HER2-HER3 protein complex in a cell which expresses HER2 and HER3.

21. The isolated antibody or fragment thereof of claim 20, wherein the antibody or fragment thereof stabilizes the HER3 receptor in an inactive state such that the HER3 receptor fails to dimerize with the HER2 receptor in the presence of a HER3 ligand to form a HER2-HER3 protein complex.

22. The isolated antibody or fragment thereof of claim 21, wherein the failure to form a HER2-HER3 protein complex prevents activation of signal transduction.

23. The isolated antibody or fragment thereof of any one of claims 20 to 22, wherein ligand is selected from the group consisting of neuregulin 1 (NRG), neuregulin 2, betacellulin, heparin-binding epidermal growth factor, and epiregulin.

24. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as assessed by HER3 ligand-independent phosphorylation assay.

25. The isolated antibody or fragment thereof of claim 24, wherein the HER3 ligand-independent phosphorylation assay uses HER2 amplified cells, wherein the HER2 amplified cells are SK-Br-3 cells.

26. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as assessed by HER3 ligand-dependent phosphorylation assay.

27. The isolated antibody or fragment thereof of claim 26, wherein the HER3 ligand-dependent phosphorylation assay uses stimulated MCF7 cells in the presence of neuregulin (NRG).

28. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, and wherein the antibody or fragment thereof has a dissociation (K_D) of at least 1 x 10^{-7} M, 1 x 10^{-8} M, 1 x 10^{-9} M, 1 x 10^{-10} M, 1 x 10^{-11} M, 1 x 10^{-12} M, and 1 x 10^{-13} M.

29. The isolated antibody or fragment thereof of claim 28, wherein the antibody or fragment thereof inhibits phosphorylation of HER3 as measured by an in vitro phosphorylation assay selected from the group consisting of phospho-HER3 and phospho-Akt.

30. An isolated antibody or fragment thereof to HER3 receptor, that cross-competes with an antibody described in Table 1.

31. An isolated antibody or fragment thereof, that binds to the same conformational epitope as an antibody described in Table 1.

32. The isolated antibody or fragment thereof of any one of claims 1 to 31, wherein the antibody is selected from the group consisting of a monoclonal antibody, chimeric antibody, a single chain antibody, an Fab, and an scFv.

33. The isolated antibody or fragment thereof of any one of claims 1 to 32, wherein the antibody is a human antibody.

34. The isolated antibody or fragment thereof of any one of claims 1 to 33, wherein the antibody comprises a human heavy chain constant region and a human light chain constant region.

35. The isolated antibody or fragment thereof of any one of claims 1 to 34, wherein the antibody or fragment binds to both human HER3 and cynomologus HER3.

36. The isolated antibody or fragment thereof of any one of claims 1 to 35, wherein the antibody or fragment is an IgG isotype.

37. The isolated antibody or fragment thereof of any one of claims 1 to 36, wherein the antibody comprises a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

38. An isolated antibody or fragment thereof to HER3 receptor comprising 1, 2, 3, 4, 5, or 6 CDRs calculated by Kabat or Chothia of any of the antibodies in Table 1.

39. An isolated antibody or fragment thereof to HER3 receptor comprising a heavy chain CDR3 selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 10, SEQ ID NO: 22, SEQ ID NO: 28, SEQ ID NO: 40, SEQ ID NO: 46, SEQ ID NO: 58, SEQ ID NO: 64, SEQ ID NO: 76, SEQ ID NO: 82, SEQ ID NO: 94, SEQ ID NO: 100, SEQ ID NO: 112, SEQ ID NO: 118, SEQ ID NO: 130, SEQ ID NO: 136, SEQ ID NO: 148, SEQ ID NO: 166, SEQ ID NO: 184, SEQ ID NO: 202, SEQ ID NO: 220, SEQ ID NO: 238, SEQ ID NO: 256, SEQ ID NO: 274, SEQ ID NO: 292, SEQ ID NO: 310, SEQ ID NO: 328, SEQ ID NO: 346, and SEQ ID NO: 364.

40. An isolated antibody or fragment thereof to HER3 receptor, wherein the antibody or fragment thereof comprises a VH and a VL selected from the group consisting of:
a) a VH comprising SEQ ID NO: 15 and a VL comprising SEQ ID NO: 14, or an amino acid sequence with 97-99% identity thereof;
b) a VH comprising SEQ ID NO: 33 and a VL comprising SEQ ID NO: 32, or an amino acid sequence with 97-99% identity thereof;
c) a VH comprising SEQ ID NO: 51 and a VL comprising SEQ ID NO: 50, or an amino acid sequence with 97-99% identity thereof;
d) a VH comprising SEQ ID NO: 69 and a VL comprising SEQ ID NO: 68, or an amino acid sequence with 97-99% identity thereof;
e) a VH comprising SEQ ID NO: 87 and a VL comprising SEQ ID NO: 86, or an amino acid sequence with 97-99% identity thereof;

f) a VH comprising SEQ ID NO: 105 and a VL comprising SEQ ID NO: 104, or an amino acid sequence with 97-99% identity thereof;

g) a VH comprising SEQ ID NO: 123 and a VL comprising SEQ ID NO: 122, or an amino acid sequence with 97-99% identity thereof;

h) a VH comprising SEQ ID NO: 141 and a VL comprising SEQ ID NO: 140, or an amino acid sequence with 97-99% identity thereof;

i) a VH comprising SEQ ID NO: 159 and a VL comprising SEQ ID NO: 158, or an amino acid sequence with 97-99% identity thereof;

j) a VH comprising SEQ ID NO: 177 and a VL comprising SEQ ID NO: 176, or an amino acid sequence with 97-99% identity thereof;

k) a VH comprising SEQ ID NO: 195 and a VL comprising SEQ ID NO: 194, or an amino acid sequence with 97-99% identity thereof;

l) a VH comprising SEQ ID NO: 213 and a VL comprising SEQ ID NO: 212, or an amino acid sequence with 97-99% identity thereof;

m) a VH comprising SEQ ID NO: 231 and a VL comprising SEQ ID NO: 230, or an amino acid sequence with 97-99% identity thereof;

n) a VH comprising SEQ ID NO: 249 and a VL comprising SEQ ID NO: 248, or an amino acid sequence with 97-99% identity thereof;

o) a VH comprising SEQ ID NO: 267 and a VL comprising SEQ ID NO: 266, or an amino acid sequence with 97-99% identity thereof;

p) a VH comprising SEQ ID NO: 285 and a VL comprising SEQ ID NO: 284, or an amino acid sequence with 97-99% identity thereof;

q) a VH comprising SEQ ID NO: 303 and a VL comprising SEQ ID NO: 302, or an amino acid sequence with 97-99% identity thereof;

r) a VH comprising SEQ ID NO: 321 and a VL comprising SEQ ID NO: 320, or an amino acid sequence with 97-99% identity thereof;.

s) a VH comprising SEQ ID NO: 339 and a VL comprising SEQ ID NO: 338, or an amino acid sequence with 97-99% identity thereof;

t) a VH comprising SEQ ID NO: 357 and a VL comprising SEQ ID NO: 356, or an amino acid sequence with 97-99% identity thereof; and

u) a VH comprising SEQ ID NO: 375 and a VL comprising SEQ ID NO: 374, or an amino acid sequence with 97-99% identity thereof.

41. An isolated antibody or fragment thereof that recognizes a conformational epitope of a HER3 receptor, wherein the conformational epitope comprises amino acid residues within domain 2 and domain 4 of the HER3 receptor, wherein the antibody or fragment comprises a variant heavy chain variable region comprising CDR1, CDR2, and CDR3, and wherein the variant has at least one to four amino acid changes in one of CDR1, CDR2, or CDR3.

42. An isolated antibody or fragment thereof, comprising heavy and light chain CDRs selected from the group consisting of:

a) a heavy chain variable region CDR1 of SEQ ID NO: 2; CDR2 of SEQ ID NO: 3; CDR3 of SEQ ID NO: 4; and a light chain variable region CDR1 of SEQ ID NO: 5; CDR2 of SEQ ID NO: 6; and CDR3 of SEQ ID NO: 7:

b) a heavy chain variable region CDR1 of SEQ ID NO: 20; CDR2 of SEQ ID NO: 21; CDR3 of SEQ ID NO: 22; and a light chain variable region CDR1 of SEQ ID NO: 23; CDR2 of SEQ ID NO: 24; and CDR3 of SEQ ID NO: 25;

c) a heavy chain variable region CDR1 of SEQ ID NO: 38; CDR2 of SEQ ID NO: 39; CDR3 of SEQ ID NO: 40; and a light chain variable region CDR1 of SEQ ID NO: 41; CDR2 of SEQ ID NO: 42; and CDR3 of SEQ ID NO: 43;

d) a heavy chain variable region CDR1 of SEQ ID NO: 56; CDR2 of SEQ ID NO: 57; CDR3 of SEQ ID NO: 58; and a light chain variable region CDR1 of SEQ ID NO: 59; CDR2 of SEQ ID NO: 60; and CDR3 of SEQ ID NO: 61;

e) a heavy chain variable region CDR1 of SEQ ID NO: 74; CDR2 of SEQ ID NO: 75; CDR3 of SEQ ID NO: 76; and a light chain variable region CDR1 of SEQ ID NO: 77; CDR2 of SEQ ID NO: 78; and CDR3 of SEQ ID NO: 79.

f) a heavy chain variable region CDR1 of SEQ ID NO: 92; CDR2 of SEQ ID NO: 93; CDR3 of SEQ ID NO: 94; and a light chain variable region CDR1 of SEQ ID NO: 95; CDR2 of SEQ ID NO: 96; and CDR3 of SEQ ID NO: 97;

g) a heavy chain variable region CDR1 of SEQ ID NO: 110; CDR2 of SEQ ID NO: 111; CDR3 of SEQ ID NO: 112and a light chain variable region CDR1 of SEQ ID NO: 113; CDR2 of SEQ ID NO: 114; and CDR3 of SEQ ID NO: 115;

h) a heavy chain variable region CDR1 of SEQ ID NO: 128; CDR2 of SEQ ID NO: 129; CDR3 of SEQ ID NO: 130; and a light chain variable region CDR1 of SEQ ID NO: 131; CDR2 of SEQ ID NO: 132; and CDR3 of SEQ ID NO: 133;

i) a heavy chain variable region CDR1 of SEQ ID NO: 146; CDR2 of SEQ ID NO: 147; CDR3 of SEQ ID NO: 148; and a light chain variable region CDR1 of SEQ ID NO: 149; CDR2 of SEQ ID NO: 150; and CDR3 of SEQ ID NO: 151;

j) a heavy chain variable region CDR1 of SEQ ID NO: 164; CDR2 of SEQ ID NO: 165; CDR3 of SEQ ID NO: 166; and a light chain variable region CDR1 of SEQ ID NO: 167; CDR2 of SEQ ID NO: 168; and CDR3 of SEQ ID NO: 169;

k) a heavy chain variable region CDR1 of SEQ ID NO: 182; CDR2 of SEQ ID NO: 183; CDR3 of SEQ ID NO: 184; and a light chain variable region CDR1 of SEQ ID NO: 185; CDR2 of SEQ ID NO: 186; and CDR3 of SEQ ID NO: 187;

l) a heavy chain variable region CDR1 of SEQ ID NO: 200; CDR2 of SEQ ID NO: 201; CDR3 of SEQ ID NO: 202; and a light chain variable region CDR1 of SEQ ID NO: 203; CDR2 of SEQ ID NO: 204; and CDR3 of SEQ ID NO: 205;

m) a heavy chain variable region CDR1 of SEQ ID NO: 218; CDR2 of SEQ ID NO: 219; CDR3 of SEQ ID NO: 220; and a light chain variable region CDR1 of SEQ ID NO: 221; CDR2 of SEQ ID NO: 222; and CDR3 of SEQ ID NO: 223;

n) a heavy chain variable region CDR1 of SEQ ID NO: 236; CDR2 of SEQ ID NO: 237; CDR3 of SEQ ID NO: 238; and a light chain variable region CDR1 of SEQ ID NO: 239; CDR2 of SEQ ID NO: 240; and CDR3 of SEQ ID NO: 241;

o) a heavy chain variable region CDR1 of SEQ ID NO: 254; CDR2 of SEQ ID NO: 255; CDR3 of SEQ ID NO: 256; and a light chain variable region CDR1 of SEQ ID NO: 257; CDR2 of SEQ ID NO: 258; and CDR3 of SEQ ID NO: 259;

p) a heavy chain variable region CDR1 of SEQ ID NO: 272; CDR2 of SEQ ID NO: 273; CDR3 of SEQ ID NO: 274; a light chain variable region CDR1 of SEQ ID NO: 275; CDR2 of SEQ ID NO: 276; and CDR3 of SEQ ID NO: 277;

q) a heavy chain variable region CDR1 of SEQ ID NO: 290; CDR2 of SEQ ID NO: 291; CDR3 of SEQ ID NO: 292; a light chain variable region CDR1 of SEQ ID NO: 293; CDR2 of SEQ ID NO: 294; and CDR3 of SEQ ID NO: 295;

r) a heavy chain variable region CDR1 of SEQ ID NO: 308; CDR2 of SEQ ID NO: 309; CDR3 of SEQ ID NO: 310; a light chain variable region CDR1 of SEQ ID NO: 311; CDR2 of SEQ ID NO: 312; and CDR3 of SEQ ID NO: 313;
s) a heavy chain variable region CDR1 of SEQ ID NO: 326; CDR2 of SEQ ID NO: 327; CDR3 of SEQ ID NO: 328; a light chain variable region CDR1 of SEQ ID NO: 329; CDR2 of SEQ ID NO: 330; and CDR3 of SEQ ID NO: 331;
t) a heavy chain variable region CDR1 of SEQ ID NO: 344; CDR2 of SEQ ID NO: 345; CDR3 of SEQ ID NO: 346; a light chain variable region CDR1 of SEQ ID NO: 347; CDR2 of SEQ ID NO: 348; and CDR3 of SEQ ID NO: 349; and .
u) a heavy chain variable region CDR1 of SEQ ID NO: 362; CDR2 of SEQ ID NO: 363; CDR3 of SEQ ID NO: 364; a light chain variable region CDR1 of SEQ ID NO: 365; CDR2 of SEQ ID NO: 366; and CDR3 of SEQ ID NO: 367.

43. A fragment of an antibody of any one of claims 1 to 42 that binds to HER3 selected from the group consisting of; Fab, $F(ab_2)$', $F(ab)_2$', scFv, VHH, VH, VL, dAbs.

44. A pharmaceutical composition comprising an antibody or fragment thereof of any one of claims 1 to 43 and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, further comprising an additional therapeutic agent.

46. The pharmaceutical composition of claim 45, wherein the additional therapeutic agent is selected from the group consisting of an HER1 inhibitor, a HER2 inhibitor, a HER3 inhibitor, a HER4 inhibitor, an mTOR inhibitor and a PI3 Kinase inhibitor.

47. The pharmaceutical composition of claim 46, wherein the additional therapeutic agent is a HER1 inhibitor selected from the group consisting of Matuzumab (EMD72000), Cetuximab, Panitumumab, mAb 806, Nimotuzumab, Gefitinib, CI-1033 (PD183805), Lapatinib (GW-572016), Lapatinib Ditosylate, Erlotinib HCL (OSI-774), and PKI-166; a HER2 inhibitor selected from the group consisting of Pertuzumab, Trastuzumab, MM-111, neratinib, lapatinib or lapatinib ditosylate; a HER3 inhibitor selected from the group consisting of, MM-121, MM-111, IB4C3, 2DID12 (U3 Pharma AG), AMG888 (Amgen), AV-203(Aveo), MEHD7945A (Genentech) and small molecules that inhibit HER3; and a HER4 inhibitor.

48. The pharmaceutical composition of claim 46, wherein the additional therapeutic agent is an mTOR inhibitor selected from the group consisting of Temsirolimus, ridaforolimus / Deforolimus, AP23573, MK8669, and everolimus.

49. The pharmaceutical composition of claim 46, wherein the additional therapeutic agent is a PI3 Kinase inhibitor selected from the group consisting of GDC 0941, BEZ235, BMK120 and BYL719.

50. Use of an antibody or fragment thereof for the manufacture of a medicament for treating a cancer mediated by a HER3 ligand dependent signal transduction or ligand independent signal transduction pathway, wherein the antibody or fragment thereof comprises a VH and VL selected from the group consisting of:

a) VH of SEQ ID NO: 15 and VL of SEQ ID NO: 14;

b) VH of SEQ ID NO: 33 and VL of SEQ ID NO: 32;

c) VH of SEQ ID NO: 51 and VL of SEQ ID NO: 50;

d) VH of SEQ ID NO: 69 and VL of SEQ ID NO: 68;

e) VH of SEQ ID NO: 87 and VL of SEQ ID NO: 86;

f) having VH of SEQ ID NO: 105 and VL of SEQ ID NO: 104;

g) having VH of SEQ ID NO: 123 and VL of SEQ ID NO: 122;

h) having VH of SEQ ID NO: 141 and VL of SEQ ID NO: 140;

i) having VH of SEQ ID NO: 159 and VL of SEQ ID NO: 158;

j) having VH of SEQ ID NO: 177 and VL of SEQ ID NO: 176;.

k) having VH of SEQ ID NO: 195 and VL of SEQ ID NO: 194;

l) having VH of SEQ ID NO: 213 and VL of SEQ ID NO: 212;

m) having VH of SEQ ID NO: 231 and VL of SEQ ID NO: 230;

n) having VH of SEQ ID NO: 249 and VL of SEQ ID NO: 248;

o) having VH of SEQ ID NO: 267 and VL of SEQ ID NO: 266;

p) having VH of SEQ ID NO: 285 and VL of SEQ ID NO: 284;

q) having VH of SEQ ID NO: 303 and VL of SEQ ID NO: 302;

r) having VH of SEQ ID NO: 321 and VL of SEQ ID NO: 320;

s) having VH of SEQ ID NO: 339 and VL of SEQ ID NO: 338;.

t) having VH of SEQ ID NO: 357 and VL of SEQ ID NO: 356; and

u) having VH of SEQ ID NO: 375 and VL of SEQ ID NO: 374.

51. Use of an antibody or fragment thereof of any one of claims 1 to 43 for the manufacture of a medicament for the treatment of a cancer mediated by a HER3 ligand-dependent signal transduction or ligand-independent signal transduction pathway selected from the group consisting of breast cancer, colorectal cancer, lung cancer, multiple myeloma, ovarian cancer, liver cancer, gastric cancer, pancreatic cancer, prostate cancer, acute myeloid leukemia, chronic myeloid leukemia, osteosarcoma, squamous cell carcinoma, peripheral nerve sheath tumors, schwannoma, head and neck cancer, bladder cancer, esophageal cancer, glioblastoma, clear cell sarcoma of soft tissue, malignant mesothelioma, neurofibromatosis, renal cancer, and melanoma.

52. Use of a combination of antibodies or fragments thereof disclosed in Table 1 that bind to HER3 for the manufacture of a medicament for treating cancer in a subject having a HER3 expressing cancer.