

What is claimed is:

1. An isolated nucleic acid encoding a chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

- a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;
- b) a transmembrane domain; and
- c) an intracellular activating domain, wherein the transmembrane domain is located between the

ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

the HCDR1 sequence is GFNIKDTYIH (SEQ ID NO:131);

the HCDR2 sequence is X₁IYPTNGYTX₂YADSVKG (SEQ ID NO:137); and

the HCDR3 sequence is WGGDGFYAMDY (SEQ ID NO:133);

and the ASTR comprises a light chain variable region including three CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

the LCDR1 sequence is RASQDVNTX₃VA (SEQ ID NO:142);

the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and

the LCDR3 sequence is QXX₄YTTTPPT (SEQ ID NO:143),

wherein X₁ is R or K, X₂ is R or E, X₃ is A or D, and X₄ is H, D or E;

and wherein the combination of X₁, X₂, X₃, and X₄ in the ASTR is other than R, R, A, and H, respectively.

2. A chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

- a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;
- b) a transmembrane domain; and
- c) an intracellular activating domain, wherein the transmembrane domain is located between the

ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

the HCDR1 sequence is GFNIKDTYIH (SEQ ID NO:131);

the HCDR2 sequence is X₁IYPTNGYTX₂YADSVKG (SEQ ID NO:137); and

the HCDR3 sequence is WGGDGFYAMDY (SEQ ID NO:133);

and the ASTR comprises a light chain variable region including three CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

the LCDR1 sequence is RASQDVNTX₃VA (SEQ ID NO:142);
 the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and
 the LCDR3 sequence is QXX₄YTPPT (SEQ ID NO:143),
 wherein X₁ is R or K, X₂ is R or E, X₃ is A or D, and X₄ is H, D or E;
 and wherein the combination of X₁, X₂, X₃, and X₄ in the ASTR is other than R, R, A, and H,
 respectively.

3. A delivery suspension, comprising a population of genetically modified T cells and/or NK cells suspended in a delivery solution, wherein the genetically modified T cells and/or NK cells comprise a nucleic acid encoding a chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

- a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;
- b) a transmembrane domain; and

c) an intracellular activating domain, wherein the transmembrane domain is located between the ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

- the HCDR1 sequence is GFNIKDTYIH (SEQ ID NO:131);
- the HCDR2 sequence is X₁IYPTNGYTX₂YADSVKG (SEQ ID NO:137); and
- the HCDR3 sequence is WGGDGFYAMDY (SEQ ID NO:133);

and the ASTR comprises a light chain variable region including three CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

- the LCDR1 sequence is RASQDVNTX₃VA (SEQ ID NO:142);
- the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and
- the LCDR3 sequence is QXX₄YTPPT (SEQ ID NO:143),
- wherein X₁ is R or K, X₂ is R or E, X₃ is A or D, and X₄ is H, D or E;
- and wherein the combination of X₁, X₂, X₃, and X₄ in the ASTR is other than R, R, A, and H,

respectively.

4. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the combination of X₁, X₂, X₃, and X₄ is R, R, D, and H, respectively; R, R, A, and D, respectively; R, R, A, and E, respectively; K, R, A, and H, respectively; or R, E, A, and H, respectively, wherein the heavy chain variable region and the light chain variable region are separated by a linker between 5 and 50 amino acids in length, and wherein the sequence of the heavy chain variable region is at

least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

5. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the combination of X₁, X₂, X₃, and X₄ is R, R, D, and H, respectively; R, R, A, and D, respectively; or R, R, A, and E, respectively, wherein the heavy chain variable region and the light chain variable region are separated by a linker between 5 and 50 amino acids in length, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

6. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the combination of X₁, X₂, X₃, and X₄ is K, R, A, and H, respectively; or R, E, A, and H, respectively, wherein the heavy chain variable region and the light chain variable region are separated by a linker between 5 and 50 amino acids in length, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

7. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein said CAR is a conditionally active CAR having increased anti-HER2 CAR activity at a pH of 6.7 compared to a pH of 7.4.

8. The isolated nucleic acid, the CAR, or the delivery suspension of claim 7, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

9. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

10. The isolated nucleic acid, the CAR, or the delivery suspension of claim 9, wherein the heavy chain variable region (HCVR) comprises an HCVR framework region having a sequence at least 90% identical to the HCVR framework region formed by residues 1-25, residues 36-49, residues 67-98, and residues 110-120 of SEQ ID NO:119, and the light chain variable region (LCVR) comprises an LCVR

framework region having a sequence at least 90% identical to the LCVR framework region formed by residues 1-23, residues 35-49, residues 57-88, and residues 98-107 of SEQ ID NO:122.

11. The isolated nucleic acid, the CAR, or the delivery suspension of claim 10, wherein the heavy chain variable region (HCVR) framework region comprises residues 1-25, residues 36-49, residues 67-98, and residues 110-120 of SEQ ID NO:119 and wherein the light chain variable region (LCVR) comprises residues 1-23, residues 35-49, residues 57-88, and residues 98-107 of SEQ ID NO:122.

12. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein an antibody or fragment thereof, having the heavy chain and the light chain of the ASTR exhibits an increased binding to HER2 at a pH of 6.7 compared to a pH of 7.4.

13. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the ASTR binds to the same epitope of HER2 as an antibody or a single-chain variable antibody fragment comprising the antibody heavy chain variable region of SEQ ID NO:119 and the antibody light chain variable region of SEQ ID NO:122.

14. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the ASTR is an antibody selected from a single-chain antibody, an Fab fragment, an Fab' fragment, an (Fab')₂ fragment, an Fv fragment, and a divalent single-chain antibody or a diabody.

15. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the ASTR is a single-chain variable fragment comprising a heavy chain variable region and a light chain variable region.

16. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 15, wherein the heavy and light chains are separated by a linker, and wherein the linker is between 5 and 50 amino acids in length.

17. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the heavy chain variable region and the light chain variable region are separated by a linker, and wherein the linker comprises one of SEQ ID NOs:1, 63-71, 144, 152, or 249.

18. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the heavy chain is N-terminal to the light chain, and wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

19. The isolated nucleic acid of claim 4, the chimeric antigen receptor, or the delivery suspension of claim 4, wherein the heavy chain is N-terminal to the light chain.

20. The isolated nucleic acid of claim 5, the chimeric antigen receptor, or the delivery suspension of claim 5, wherein the heavy chain is N-terminal to the light chain.

21. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the light chain is N-terminal to the heavy chain.

22. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 4, wherein the light chain is N-terminal to the heavy chain.

23. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 5, wherein the light chain is N-terminal to the heavy chain.

24. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the chimeric antigen receptor further comprises a stalk domain and a co-stimulatory domain, and wherein the chimeric antigen receptor comprises from amino terminus to carboxy terminus, the ASTR, the stalk domain, the transmembrane domain, the co-stimulatory domain, and the intracellular activating domain.

25. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 24, wherein the intracellular activating domain is a CD3Z activating domain and wherein the co-stimulatory domain is an ICA co-stimulatory domain, a CD28 co-stimulatory domain, a CD137 co-stimulatory domain, or comprises both a ICA co-stimulatory domain and a CD137 co-stimulatory domain, or a CD28 co-stimulatory domain and a CD137 co-stimulatory domain.

26. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 24, wherein the stalk domain is a CD8 stalk domain or a CD28 stalk domain, wherein the transmembrane

domain is a CD8 transmembrane domain or a CD28 transmembrane domain, wherein the intracellular activating domain is a CD3Z activating domain, and wherein the co-stimulatory domain is a CD137 co-stimulatory domain, a CD28 co-stimulatory domain, or an ICA co-stimulatory domain.

27. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 26, wherein the co-stimulatory domain is a CD137 co-stimulatory domain.

28. The isolated nucleic acid of claim 1, the chimeric antigen receptor of claim 2, or the delivery suspension of claim 3, wherein the CAR further comprises a recognition domain.

29. The isolated nucleic acid, the chimeric antigen receptor, or the delivery suspension of claim 28, wherein the recognition domain is recognized by a regulatory authority-approved antibody.

30. The isolated nucleic acid the chimeric antigen receptor, or the delivery suspension of claim 28, wherein the recognition domain is at least 20 contiguous amino acids of EGFR.

31. The isolated nucleic acid, the CAR, or the delivery suspension of claim 7, wherein said anti-HER2 CAR activity is activation of T cells upon incubation with HER2 expressing target cells.

32. The isolated nucleic acid, the CAR, or the delivery suspension of claim 31, wherein the activation of T cells is determined by analyzing one or more of increased expression of T cell activation biomarkers by T cells, cytokine production by T cells, proliferation of T cells, and target cell killing by T cells, wherein said CAR activity is measured in an *in vitro* assay wherein a source of HER2-expressing target cells and on-test CAR-T cells transduced with either the isolated nucleic acid of claim 1 or an isolated nucleic acid encoding the CAR of claim 6, are incubated together in an assay medium for an effective time for performing the assay.

33. The isolated nucleic acid of claim 1, the CAR of claim 2 or the delivery suspension of claim 3, wherein:

the combination of X₁, X₂, X₃, and X₄ is R, R, D, and H, respectively, the heavy chain variable region peptide is encoded by nucleic acid sequence SEQ ID NO:145, and the light chain variable region is encoded by nucleic acid sequence SEQ ID NO:149;

the combination of X₁, X₂, X₃, and X₄ is R, R, A, and D, respectively, the heavy chain variable region peptide is encoded by nucleic acid sequence SEQ ID NO:145, and the light chain variable region is encoded by nucleic acid sequence SEQ ID NO:150; or

the combination of X₁, X₂, X₃, and X₄ is R, R, A, and E, respectively, the heavy chain variable region peptide is encoded by nucleic acid sequence SEQ ID NO:145, and the light chain variable region is encoded by nucleic acid sequence SEQ ID NO:151.

34. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein:

the combination of X₁, X₂, X₃, and X₄ is K, R, A, and H, respectively, the light chain variable region is encoded by SEQ ID NO:148 and the heavy chain variable region is encoded by nucleic acid sequence SEQ ID NO:146; or

the combination of X₁, X₂, X₃, and X₄ is R, E, A, and H, respectively, the light chain variable region is encoded by SEQ ID NO:148 and the heavy chain variable region is encoded by nucleic acid sequence SEQ ID NO:147.

35. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the ASTR is any one of SEQ ID NOs.157-236.

36. The isolated nucleic acid of claim 1, the CAR of claim 2, or the delivery suspension of claim 3, wherein the ASTR is any one of SEQ ID NOs:157-178.

37. An isolated recombinant T cell or NK cell, comprising a genome comprising one or more nucleic acid sequences operably linked to a promoter active in T cells and/or NK cells, wherein the one or more nucleic acid sequences comprise the isolated nucleic acid of claim 1.

38. The isolated recombinant T cell or NK cell of claim 37 or the delivery suspension of claim 3, wherein the CAR is operably linked to the promoter and the nucleic acid sequence encoding the CAR further encodes a recognition domain, wherein nucleic acids encoding the recognition domain are separated from nucleic acids encoding the CAR by a ribosomal skip sequence.

39. An expression vector comprising the isolated nucleic acid of claim 1 and a promoter that is active in T cells and/or NK cells that is operably linked to the nucleic acid sequence encoding the CAR.

40. The expression vector of claim 39, wherein the expression vector is a replication incompetent retroviral particle.

41. The expression vector of claim 40, wherein the expression vector is a lentiviral vector.

42. A use of a replication incompetent recombinant retroviral particle in the manufacture of a kit for treating a human having a HER2+ cancer, wherein use of the kit comprises: administering to the human having the HER2+ cancer, a dose of T cells and/or NK cells comprising the nucleic acid of claim 1 or 58, or one to four containers of the delivery suspension of claim 3 or 60.

43. A method of treating a human having a HER2+ cancer, the method comprising administering to the human having the HER2+ cancer, an effective dose of T cells and/or NK cells comprising the nucleic acid of claim 1 or 58, or one to four containers of the delivery suspension of claim 3 or 60.

44. A use of a replication incompetent recombinant retroviral particle in the manufacture of a kit for generating a persisting population of genetically modified T cells in a human having a HER2+ cancer, wherein use of the kit comprises: administering to the human having the HER2+ cancer, T cells and/or NK cells comprising the nucleic acid of claim 1 or 58, or one to four containers of the delivery suspension of claim 3 or 60, wherein the persisting population of genetically modified T cells persists in the human for at least 21 days after administration.

45. A method of generating a persisting population of genetically modified T cells in a human having a HER2+ cancer, the method comprising administering to the human having the HER2+ cancer, T cells and/or NK cells comprising the nucleic acid of claim 1 or 58, or one to four containers of the delivery suspension of claim 3 or 60,

wherein the persisting population of genetically modified T cells persists in the human for at least 21 days after administration.

46. The use of claim 42 or claim 44, or the method of claim 43 or claim 45, wherein the HER2+ cancer is breast cancer, gastric cancer, esophageal cancer, ovarian cancer, endometrial cancer, lung cancer, or urothelial bladder cancer.

47. The use of claim 42 or claim 44, or the method of claim 43 or claim 45, wherein the human received prior trastuzumab therapy.

48. The use of claim 42 or claim 44, or the method of claim 43 or claim 45, wherein the dose is effective for reducing the size of a HER2+ tumor in the human.

49. The use of claim 42 or claim 44, or the method of claim 43 or claim 45, wherein between 1×10^4 cells/kg and 1×10^9 cells/kg of the genetically modified T cells and/or NK cells are administered to the human, and wherein the genetically modified T cells and/or NK cells are autologous cells.

50. A method for making a conditionally activatable T cell or NK cell, wherein the method comprises genetically modifying the T cell or NK cell with an expression vector comprising a promoter operably linked to the isolated nucleic acid of claim 1.

51. An *ex vivo* method for making conditionally activatable T cells and/or NK cells, wherein the method comprises:

a) enriching peripheral blood mononuclear cells (PBMCs) to isolate PBMCs comprising T cells and/or NK cells from isolated blood;

b) transducing the activated T cells and/or NK cells with replication incompetent recombinant retroviral particles under effective conditions, thereby producing genetically modified T cells and/or NK cells, wherein the replication incompetent recombinant retroviral particles each comprise a retroviral genome comprising one or more nucleic acid sequences operatively linked to a promoter active in T cells and/or NK cells, wherein the one or more nucleic acid sequences comprises the isolated nucleic acid of claim 1; and

d) optionally expanding the genetically modified T cells and/or NK cells, thereby making the conditionally activatable T cells and/or NK cells.

52. The method of claim 51, wherein the method further comprises harvesting the genetically modified T cells and/or NK cells.

53. The method of claim 52, further comprising administering the harvested genetically modified T cells and/or NK cells to a mammalian subject.

54. A population of modified T cells produced by a method of claim 51.

55. The delivery suspension of claim 3, wherein the delivery solution is 5 to 100 ml of a cryopreservative infusion solution.

56. The delivery solution of claim 55, wherein the delivery suspension is contained inside an infusion bag.

57. The delivery suspension of claim 55 or claim 56, comprising between 1×10^4 and 1×10^{10} genetically modified T cells and/or NK cells in suspension in a cryopreservative delivery solution.

58. An isolated nucleic acid encoding a chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

- a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;
- b) a transmembrane domain; and
- c) an intracellular activating domain, wherein the transmembrane domain is located between the ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

the HCDR1 sequence is GFX₁IKDTYIH (SEQ ID NO:138);

the HCDR2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO:141); and

the HCDR3 sequence is WGGDGFYX₈MDY (SEQ ID NO:140);

and the ASTR can include a light chain variable region that includes three CDRs, said CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

the LCDR1 RASQDVNTX₉VA (SEQ ID NO:142);

the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and

the LCDR3 sequence is QQX₁₀YTPPT (SEQ ID NO:143),

wherein X₁ is N or W, X₂ is R or K, X₃ is Y, D, or K, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E, X₈ is A or E, X₉ is A or D, and X₁₀ is H, D, or E;

and wherein the combination of X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, and X₁₀ in the ASTR is other than N, R, Y, N, G, T, R, A, A, and H respectively.

59. A chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

- a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;
- b) a transmembrane domain; and

c) an intracellular activating domain, wherein the transmembrane domain is located between the ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

the HCDR1 sequence is GFX₁IKDTYIH (SEQ ID NO:138);

the HCDR2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO:141); and

the HCDR3 sequence is WGGDGFYX₈MDY (SEQ ID NO:140);

and the ASTR can include a light chain variable region that includes three CDRs, said CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

the LCDR1 RASQDVNTX₉VA (SEQ ID NO:142);

the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and

the LCDR3 sequence is QQX₁₀YTTPPT (SEQ ID NO:143),

wherein X₁ is N or W, X₂ is R or K, X₃ is Y, D, or K, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E, X₈ is A or E, X₉ is A or D, and X₁₀ is H, D, or E;

and wherein the combination of X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, and X₁₀ in the ASTR is other than N, R, Y, N, G, T, R, A, A, and H respectively.

60. A delivery suspension, comprising a population of genetically modified T cells and/or NK cells suspended in a delivery solution, wherein the genetically modified T cells and/or NK cells comprise a nucleic acid encoding a chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:

a) an antigen-specific targeting region (ASTR) that specifically binds to HER2 protein;

b) a transmembrane domain; and

c) an intracellular activating domain, wherein the transmembrane domain is located between the ASTR and the intracellular activating domain, and wherein the ASTR comprises a heavy chain variable region comprising three complementarity determining regions (CDRs), said CDRs having sequences HCDR1, HCDR2, and HCDR3, wherein:

the HCDR1 sequence is GFX₁IKDTYIH (SEQ ID NO:138);

the HCDR2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO:141); and

the HCDR3 sequence is WGGDGFYX₈MDY (SEQ ID NO:140);

and the ASTR can include a light chain variable region that includes three CDRs, said CDRs having sequences LCDR1, LCDR2, and LCDR3, wherein:

the LCDR1 RASQDVNTX₉VA (SEQ ID NO:142);

the LCDR2 sequence is SASFLYS (SEQ ID NO:135); and

the LCDR3 sequence is QQX₁₀YTTPPT (SEQ ID NO:143),

wherein X₁ is N or W, X₂ is R or K, X₃ is Y, D, or K, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E, X₈ is A or E, X₉ is A or D, and X₁₀ is H, D, or E;

and wherein the combination of wherein the combination of X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, and X₁₀ in the ASTR is other than N, R, Y, N, G, T, R, A, A, and H, respectively.

61. The isolated nucleic acid of claim 58, the CAR of claim 59, or the delivery suspension of claim 60, wherein the combination of X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, and X₁₀ is W, R, Y, N, G, T, R, A, A, and H (N028W), respectively; N, K, Y, N, G, T, R, A, A, and H (R050K), respectively; N, R, D, N, G, T, R, A, A, and H (Y052D), respectively; N, R, K, N, G, T, R, A, A, and H (Y052K), respectively; N, R, Y, A, G, T, R, A, A, and H (N055A), respectively; N, R, Y, N, K, T, R, A, A, and H (G056K), respectively; N, R, Y, N, G, D, R, A, A, and H (T058D), respectively; N, R, Y, N, G, T, E, A, A, and H (R059E), respectively; N, R, Y, N, G, T, R, E, A, and H (A106E), respectively; N, R, Y, N, G, T, R, R, D, and H (A032D), respectively; N, R, Y, N, G, T, R, A, A, and D (H091D), respectively; N, R, Y, N, G, T, R, A, A, and E (H091E), respectively; N, R, K, N, G, T, R, R, D, and H (Y052K/A032D), respectively; N, R, Y, N, K, T, R, R, D, and H (G056K/A032D), respectively; N, R, Y, N, G, D, R, D, A, and H (T058D/A032D), respectively; or N, R, Y, N, G, T, R, E, D, and H (A106E/A032D), respectively.

62. The isolated nucleic acid of claim 58, the CAR of claim 59, or the delivery suspension of claim 60, wherein said CAR is a conditionally active CAR having increased anti-HER2 CAR activity at a pH of 6.7 compared to a pH of 7.4.

63. The isolated nucleic acid of claim 58, the CAR of claim 59, or the delivery suspension of claim 60, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.

64. The isolated nucleic acid, the CAR, or the delivery suspension of claim 63, wherein the heavy chain variable region (HCVR) comprises a HCVR framework region having a sequence at least 90% identical to the HCVR framework region of SEQ ID NO: 119, and wherein light chain variable region (LCVR) comprises a framework region having a sequence at least 90% identical to the LCVR framework region of SEQ ID NO: 122.

65. The isolated nucleic acid, the CAR, or the delivery suspension of claim 64, wherein the heavy chain variable region (HCVR) framework region is identical to the HCVR framework region of SEQ ID

NO: 119 and wherein the light chain variable region (LCVR) framework region is identical to the LCVR of SEQ ID NO: 122.

66. The isolated nucleic acid, the CAR, or the delivery suspension of claim 62, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO: 119, and wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO: 122.