

CLAIMS

What is claimed:

1. A nucleic acid encoding a chimeric antigen receptor (CAR) for binding HER2, said CAR comprising:
 - a) an antigen-specific targeting region (ASTR) that 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 QQX4YTTPPT (SEQ ID NO:143),wherein the combination of X1, X2, X3, and X4 in the ASTR is K, R, A, and H; K, E, A, and H; R, R, D, and H; K, E, D, and H; R, R, A, and D; R, R, D, and D; K, R, D, and D; K, E, D, and D; R, R, A, and E; K, E, A, and E; K, R, D, and E; or K, E, D, and E.
2. A chimeric antigen receptor (CAR) polypeptide for binding HER2, wherein the CAR is encoded by the nucleic acid of claim 1.
3. A replication incompetent recombinant retroviral particle, comprising the nucleic acid of claim 1.
4. A modified T cell, , wherein:
 - a) the modified T cell comprises the nucleic acid of claim 1, or
 - b) a recombinant nucleic acid vector is associated with the modified T cell, wherein the recombinant nucleic acid vector comprises the nucleic acid of claim 1,wherein the nucleic acid of claim 1 is operably linked to a promoter.
5. The nucleic acid of claim 1, the CAR of claim 2, the replication incompetent recombinant retroviral particle of claim 3, or the modified T cell or NK cell of claim 4, 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; or K, R, A, and H, respectively.

6. The nucleic acid of any one of claims 1 or 5, the CAR of any one of claims 2 or 5, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5, or the modified T cell of any one of claims 4-5, wherein the sequence of the heavy chain variable region is at least 90% identical to SEQ ID NO:119.

7. The nucleic acid of any one of claims 1 or 5-6, the CAR of any one of claims 2 or 5-6, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-6, or the modified T cell of any one of claims 4-6, wherein the sequence of the light chain variable region is at least 90% identical to SEQ ID NO:122.

8. The nucleic acid of any one of claims 1 or 5-7, the CAR of any one of claims 2 or 5-7, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-7, or the modified T cell of any one of claims 4-7, wherein the ASTR is a single-chain variable antibody fragment

9. The nucleic acid of any one of claims 1 or 5-8, the CAR of any one of claims 2 or 5-8, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-8, or the modified T cell of any one of claims 4-8, wherein the heavy and light chains are separated by a linker, and wherein the linker is between 5 and 50 amino acids in length.

10. The nucleic acid of any one of claims 1 or 5-8, the CAR of any one of claims 2 or 5-8, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-8, or the modified T cell or NK cell of any one of claims 4-8, wherein the heavy chain variable region and the light chain variable region are separated by a linker, and wherein the linker comprises one of the sequences of SEQ ID NOs:1, 63-71, 144, 152, or 249.

11. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the heavy chain is N-terminal to the light chain.

12. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the light chain is N-terminal to the heavy chain.

13. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the ASTR comprises the amino acid sequence of any one of SEQ ID NOs:157, 160, 171, or 175.

14. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the ASTR comprises the amino acid sequence of any one of SEQ ID NOs:158, 161, 164-165, 167, or 176.

15. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the ASTR comprises the amino acid sequence of any one of SEQ ID NOs:159, 162, 168-170, or 173-174.

16. The nucleic acid of any one of claims 1 or 5-10, the CAR of any one of claims 2 or 5-10, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-10, or the modified T cell of any one of claims 4-10, wherein the ASTR comprises the amino acid sequence of any one of SEQ ID NOs:163, 166, or 177-178.

17. The nucleic acid of any one of claims 1 or 5-16, the CAR of any one of claims 2 or 5-16, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-16, or the modified T cell of any one of claims 4-16, wherein the CAR further comprises a stalk domain, and wherein the CAR comprises from amino terminus to carboxy terminus, the ASTR, the stalk domain, the transmembrane domain, and the intracellular activating domain.

18. The nucleic acid, CAR, or modified T cell of claim 17, wherein the stalk domain is a CD8 stalk domain.

19. The nucleic acid, CAR, or modified T cell of claim 18, wherein the CAR comprises the amino acid sequence of SEQ ID NO:24.

20. The nucleic acid of any one of claims 1 or 5-19, the CAR of any one of claims 2 or 5-19, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-19, or the modified T cell of any one of claims 4-19, wherein the CAR further comprises a co-stimulatory domain, wherein the CAR comprises from amino terminus to carboxy terminus, the ASTR, the stalk domain, the transmembrane domain, the co-stimulatory domain, and the intracellular activating domain, and wherein the co-stimulatory domain comprises 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 both a CD28 co-stimulatory domain and a CD137 co-stimulatory domain.

21. The nucleic acid, CAR, or modified T cell of claim 20, wherein the co-stimulatory domain is the CD137 co-stimulatory domain, wherein the CD137 co-stimulatory domain comprises the amino acid sequence of SEQ ID NO:53.

22. The nucleic acid of any one of claims 1 or 5-21, the CAR of any one of claims 2 or 5-21, the replication incompetent recombinant retroviral particle of any one of claims 3 or 5-21, or the modified T cell of any one of claims 4-21, wherein the intracellular activating domain comprises the amino acid sequence of SEQ ID NO:28.