

CLAIMS

WHAT IS CLAIMED IS:

1. An antigen receptor, comprising (I) a first polypeptide chain that comprises an extracellular domain comprising a T cell receptor (TCR) beta chain or an antigen-binding fragment thereof, a transmembrane domain, and a cytoplasmic domain, and (II) a second polypeptide chain that comprises an extracellular domain comprising a TCR alpha chain or an antigen-binding fragment thereof, a transmembrane domain, and a cytoplasmic domain, wherein

the TCR beta chain and the TCR alpha chain form an antigen binding site, and

the cytoplasmic domain of the first polypeptide chain or of the second polypeptide chain comprises:

0, 1, or 2 copies of a cytoplasmic domain of a human 4-1BB or a fragment thereof, or

0, 1, or 2 copies of a cytoplasmic domain of human CD3zeta or a fragment thereof, or

0, 1, or 2 copies of a cytoplasmic domain of human CD3epsilon or a fragment thereof, or

0, 1, or 2 copies of a cytoplasmic domain of human CD28 or a fragment thereof.

2. The antigen receptor of claim 1, wherein the first polypeptide chain is substantially different from the second polypeptide chain in one or more of the transmembrane domain, and the cytoplasmic domain.

3. The antigen receptor of claim 1, comprising 1 or 2 copies of the cytoplasmic domain of a human 4-1BB.

4. The antigen receptor of claim 3, comprising 1 or 2 copies of the cytoplasmic domain of human CD3zeta.

5. The antigen receptor of claim 3 or 4, comprising 1 or 2 copies of the cytoplasmic domain of human CD28.

6. The antigen receptor of claim 1 or 2, comprising only 1 copy of the cytoplasmic domain of human 4-1BB, 1 copy of the cytoplasmic domain of human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta.

7. The antigen receptor of claim 1 or 2, comprising only one copy of the transmembrane domain of CD28, one copy of the transmembrane domain of CD8, one copy of the cytoplasmic domain of human 4-1BB, one copy of the cytoplasmic domains of human CD28, and one copy of the cytoplasmic domain of human CD3zeta.

8. The antigen receptor of claim 1 or 2, comprising two copies of the cytoplasmic domain of human 4-1BB, two copies of the cytoplasmic domain of human CD28, and two copies of the cytoplasmic domain of human CD3zeta.
9. The antigen receptor of claim 8, wherein
- the cytoplasmic domain of the first polypeptide chain comprises 1 copy of the cytoplasmic domain of human 4-1BB, 1 copy of the cytoplasmic domain of human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta, and
- the cytoplasmic domain of the second polypeptide chain comprises 1 copy of the cytoplasmic domain of human 4-1BB, 1 copy of the cytoplasmic domain of human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta.
10. The antigen receptor of claim 1 or 2, wherein
- the first polypeptide chain comprises 1 copy of the transmembrane domain of human CD28, 1 copy of the cytoplasmic domain human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta, and
- the second polypeptide chain comprises 1 copy of the transmembrane domain of human CD8, and 1 copy of the cytoplasmic domain human 4-1BB.
11. The antigen receptor of claim 1 or 2, wherein
- the first polypeptide chain comprises 1 copy of the transmembrane domain of human CD8, 1 copy of the cytoplasmic domain human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta, and
- the second polypeptide chain comprises 1 copy of the transmembrane domain of human CD8, 1 copy of the cytoplasmic domain human 4-1BB, and 1 copy of the cytoplasmic domain of human CD3zeta.
12. The antigen receptor of claim 1 or 2, wherein
- the first polypeptide chain comprises 1 copy of the transmembrane domain of human CD8, 2 copies of the cytoplasmic domain human CD28, and 1 copy of the cytoplasmic domain of human CD3zeta, and
- the second polypeptide chain comprises 1 copy of the transmembrane domain of human CD8, 2 copies of the cytoplasmic domain human 4-1BB, and 1 copy of the cytoplasmic domain of human CD3zeta.
13. The antigen receptor of any one of claims 1-12, wherein the transmembrane domain of the first or the second polypeptide chain comprises one selected from the group consisting of a transmembrane domain of CD8 and a transmembrane domain of CD28.

14. The antigen receptor of any one of claims 1-13, wherein the antigen binding site binds to a tumor antigen, or a tumor-related antigen (TAA), or a viral antigen in the context of MHC(HLA) restricted fashion, or wherein the extracellular domains, when expressed on a cell, bind to a tumor antigen, or a TAA, or a viral antigen, in the context of MHC(HLA) restricted fashion.
15. The antigen receptor of claim 14, wherein the tumor antigen is NY-ESO-1.
16. A fusion protein comprising the first polypeptide chain and the second polypeptide chain recited in any one of claims 1-15, wherein the first polypeptide chain and second polypeptide chain are linked by a protein linker sequence or a self-cleaving peptide sequence.
17. The fusion protein of claim 16, wherein the self-cleaving peptide sequence comprise a P2A, E2A, F2A or T2A sequence.
18. An isolated nucleic acid or a set of isolated nucleic acids encoding the antigen receptor of any one of claims 1-15 or the fusion protein of claims 16-17.
19. The isolated nucleic acid or a set of isolated nucleic acids of claim 18, comprising
- (I) a first nucleic acid sequence encoding the first polypeptide chain containing a first polypeptide segment of at least 10 amino acids in length and
 - (II) a second nucleic acid sequence encoding the second polypeptide chain containing a second polypeptide segment of at least 10 amino acids in length, wherein
- the first polypeptide segment is at least 90% identical to the second polypeptide segment, and
 - the first nucleic acid sequence and the second nucleic acid sequence contain at least one non-identical codon within the codons that encode identical amino acid residues in the first polypeptide segment and the second polypeptide segment.
20. The isolated nucleic acid or nucleic acids of claim 19, wherein (a) the first polypeptide chain and the second polypeptide chain comprise an identical polypeptide sequence of greater than 10 amino acids in length; and (b) the first nucleic acid sequence and the second nucleic acid sequence contain at least one non-identical codon within the codons that encode the identical polypeptide sequence of the first and second nucleic acid sequences.
21. The isolated nucleic acid or nucleic acids of any one of claims 19-20, wherein at least 2% of the codons are non-identical.
22. The isolated nucleic acid or nucleic acids of any one of claims 19-21, wherein the first nucleic acid sequence and the second nucleic acid sequence are less than 98% identical within the codons.

23. The isolated nucleic acid or nucleic acids of any one of claims 19-22, wherein the first nucleic acid sequence and the second nucleic acid sequence contain at least one non-identical codon within the codons that encode one or more selected from the group consisting of:
- (a) the TCR beta chain or an antigen-binding fragment thereof,
 - (b) the TCR alpha chain or an antigen-binding fragment thereof,
 - (c) the transmembrane domain of human CD8,
 - (d) the transmembrane domain of human CD28,
 - (e) the cytoplasmic domain of human CD3zeta or a fragment thereof,
 - (f) the cytoplasmic domain of human CD3epsilon or a fragment thereof,
 - (g) the cytoplasmic domain of human CD28 or a fragment thereof, and
 - (h) the cytoplasmic domain of human 4-1BB or a fragment thereof.
24. The isolated nucleic acid or nucleic acids of claim 23, wherein the isolated nucleic acid encode one selected from the group consisting of SEQ ID NOs: 9, 64, 10, 11, and 32-41.
25. The isolated nucleic acid or nucleic acids of claim 24, wherein the isolated nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs: 12, 65, 13, 14, and 54-63.
26. The isolated nucleic acid of any one of claims 19-24, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked via a nucleic acid sequence comprising an internal ribosomal entry site (IRES), an IRES DNA fragment.
27. A vector comprising the isolated nucleic acid or nucleic acids of any one of claims 18-26.
28. The vector of claim 27, wherein the vector is an expression vector.
29. The vector of claim 28, wherein the vector is a viral vector.
30. A cell comprising the antigen receptor of any one of claims 1-15, or the fusion protein of claims 16-17, or the isolated nucleic acid or nucleic acids of any one of claims 18-26, or the vector of any one of claims 27-29.
31. The cell of claim 30, wherein the cell is a T cell.
32. A pharmaceutical composition comprising (i) the isolated nucleic acid of any one of claims 18-26, or the vector of any one of claims 27-29, or the cell of any one of claims 30-31, and (ii) a pharmaceutically acceptable carrier.
33. A method of treating a tumor, or a viral infection disease, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 32.