1. A chimeric antigen receptor (CAR) polypeptide, comprising a ligand binding domain, a transmembrane domain, an intracellular signaling domain, and a co-stimulatory signaling region, wherein the co-stimulatory signaling region comprises a mutated form of a cytoplasmic domain of CD28 that enhances CAR-T cell fusion.

2. The polypeptide of claim 1, wherein the co-stimulatory signaling region comprises a cytoplasmic domain of CD28 lacking a YMNM subdomain, or having a null mutation in the YMNM subdomain.

3. The polypeptide of claim 1 or 2, wherein the co-stimulatory signaling region comprises a cytoplasmic domain of CD28 lacking a PRRP subdomain, or having a null mutation in the PRRP subdomain.

4. The polypeptide of any one of claims 1 to 3, where in the co-stimulatory signaling region comprises a cytoplasmic domain of CD28 lacking a PYAP subdomain, or having a null mutation in the PYAP subdomain.

5. The polypeptide of any one of claims 1 to 4, wherein the CAR polypeptide is defined by the formula:

SP–TAA–HG–TM– CSR–ISD; or
SP– TAA – HG–TM–ISD–3/CSR

wherein “SP” represents a signal peptide,

wherein “TAA” represents a tumor associated antigen-binding region,

wherein “HG” represents and optional hinge domain,

wherein “TM” represents a transmembrane domain,

wherein “CSR” represents the co-stimulatory signaling region,

wherein “ISD” represents an intracellular signaling domain, and

wherein “-“ represents a bivalent linker.

6. The polypeptide of any one of claims 1 to 5, wherein the intracellular signaling domain comprises a CD3 zeta (CD3ζ) signalling domain.

7. The polypeptide of any one of claims 1 to 6, wherein the mutated form of the cytoplasmic domain of CD28 reduces CAR-T cell exhaustion.

8. An isolated nucleic acid sequence encoding the recombinant polypeptide of any one of claims 1 to 7.

9. A vector comprising the isolated nucleic acid sequence of claim 8.

10. A cell comprising he vector of claim 9.

11. The cell of claim 10, wherein the cell is selected from the group consisting of an αβT cell, γδT cell, a Natural Killer (NK) cells, a Natural Killer T (NKT) cell, a B cell, an innate lymphoid cell (ILC), a cytokine induced killer (CIK) cell, a cytotoxic T lymphocyte (CTL), a lymphokine activated killer (LAK) cell, a regulatory T cell, or any combination thereof.

12. The cell of claim 11, wherein the cell exhibits an anti-tumor immunity when the antigen binding domain of the CAR binds to TAA.

13. Use of an effective amount of an immune effector cell genetically modified to express the CAR polypeptide of any one of claims 1 to 7, in the manufacturing of a medicament for the treatment of an anti-tumor immunity in a mammal with a TAA-expressing cancer.

14. The use of claim 13, wherein the immune effector cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), and a regulatory T cell.

15. The use of claim 13 or 14, further comprising administering to the subject a checkpoint inhibitor.

16. The use of claim 15, wherein the checkpoint inhibitor comprises an anti-PD-1 antibody, anti-PD-L1 antibody, anti-CTLA-4 antibody, or a combination thereof.