

WHAT IS CLAIMED IS:

1. An engineered immune cell comprising:
 - (i) a chimeric antigen receptor (CAR) comprising a CD2 targeting domain, a transmembrane domain, and an intracellular signaling domain; and
 - (ii) a genetic modification of a target CD2 nucleic acid sequence to downregulate endogenous CD2 expression in said cell.
2. The engineered immune cell of claim 1, wherein said genetic modification comprises genome editing using a system selected from the group consisting of CRISPR/Cas, zinc finger nucleases, TALENs, and meganucleases.
3. The engineered immune cell of claim 1, wherein said genetic modification comprises gene silencing using a system selected from the group consisting of short hairpin RNA, double-stranded RNA, sdRNA, short inhibitory RNA, and microRNA.
4. The engineered immune cell of claim 2, wherein the CRISPR/Cas system comprises a guide RNA corresponding to a nucleic acid sequence selected from the group consisting of SEQ ID NOS:44-47.
5. The engineered immune cell of any one of claims 1–4, wherein said CD2 targeting domain comprises a scFv comprising a variable heavy chain (V_H) sequence having at least 90% sequence identity to SEQ ID NO:18 and a variable light chain (V_L) sequence having at least 90% sequence identity to SEQ ID NO:19.
6. The engineered immune cell of any one of claims 1–4, wherein said CD2 targeting domain comprises a scFv comprising variable heavy chain (V_H) sequence having at least 90% sequence identity to SEQ ID NO:20 and a variable light chain (V_L) sequence having at least 90% sequence identity to SEQ ID NO:21.
7. The engineered immune cell of any one of claims 1–6, wherein said transmembrane domain comprises a hinge-transmembrane domain of CD8 α .

8. The engineered immune cell of any one of claims 1–7, wherein said intracellular signaling domain comprises one or more selected from the group consisting of a 4-1BB signaling domain, a CD28 signaling domain, an OX40 signaling domain, and a CD3 ζ signaling domain.

9. The engineered immune cell of any one of claims 1–8, wherein said CAR is an anti-CD2-4-1BB-CD3 ζ CAR comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO:5.

10. The engineered immune cell of any one of claims 1–9, wherein said engineered immune cell induces cytotoxicity of CD2+ cells.

11. The engineered immune cell of any one of claims 1–10, wherein said engineered immune cell proliferates at a substantially equivalent rate as a comparable immune cell.

12. The engineered immune cell of any one of claims 1–11, wherein said engineered immune cell is an allogeneic cell.

13. The engineered immune cell of any one of claims 1–11, wherein said engineered immune cell is an autologous cell.

14. The engineered immune cell of any one of claims 1–11, wherein said engineered immune cell is an engineered T cell.

15. The engineered immune cell of any one of claims 1–11, wherein said engineered immune cell is an engineered gamma-delta T cell.

16. The engineered immune cell of any one of claims 1–11, wherein said engineered immune cell is an engineered NK cell.

17. The engineered immune cell of any one of claims 1–16, further comprising a blocking polypeptide comprising a single chain variable fragment (scFv) linked to the N-terminus of a cellular localizing domain,

wherein said scFv binds to a cell surface molecule, wherein said cellular localizing domain comprises an amino acid sequence selected from the group consisting of an endoplasmic

reticulum (ER) retention sequence, a Golgi retention sequence, and a proteosome localizing sequence, and wherein said blocking polypeptide remains intracellularly within said engineered cell and binds the endogenous cell surface molecule within the engineered cell.

18. The engineered immune cell of claim 17, wherein said ER retention sequence comprises an amino acid sequence selected from the group consisting of KDEL (SEQ ID NO:24), KKXX (SEQ ID NO:26), and KKMP (SEQ ID NO:27), wherein X is any amino acid; or said Golgi retention sequence is selected from the group consisting of YGRL (SEQ ID NO:40), YQRL (SEQ ID NO:41), YKGL (SEQ ID NO:42), and YXXL (SEQ ID NO:43), wherein X is any amino acid.

19. The engineered immune cell of claim 17 or 18, wherein said blocking polypeptide further comprises a transmembrane domain linked between said scFv and either said ER retention sequence domain comprising KKMP or KKTN or said Golgi retention sequence domain comprising YGRL, YQRL, YKGL, wherein said transmembrane domain is a transmembrane domain selected from any one of the group consisting of CD8 α , CD8 β , 4-1BB, CD28, CD34, CD4, Fc ϵ RI γ , CD16, OX40, CD3 ζ , CD3 ϵ , CD3 γ , CD3 δ , TCR α , CD32, CD64, VEGFR2, FAS, and FGFR2B.

20. The engineered immune cell of any one of claims 17–19, wherein said transmembrane domain comprises a hinge-transmembrane domain of CD8 α .

21. A pharmaceutical composition comprising at least one of the engineered immune cell of any one of claims 1–20, or an isolated population of the engineered immune cell of any one of claims 1–20.

22. A pharmaceutical composition comprising at least one of the engineered immune cell of any one of claims 1-20, or an isolated population of the engineered immune cell of any one of claims 1-20, for use in therapy.

23. Use of a therapeutically effective amount of a composition comprising the engineered immune cell of any one of claims 1–20 in the preparation of a medicament for treating cancer in a subject in need thereof, wherein the medicament is to be administered to the subject, thereby treating cancer in the subject in need thereof.

24. The use of claim 23, wherein the composition further comprises a pharmaceutically acceptable carrier.
25. The use of claim 23 or 24, wherein the cancer is a T-cell malignancy or a CD2 associated cancer.
26. The use of any one of claims 23-25, wherein said T-cell malignancy or said CD2 associated cancer is selected from the group consisting of T cell leukemia T cell lymphoma, T-cell acute lymphoblastic leukemia (T-ALL), early T-cell progenitor acute lymphoblastic leukemia (ETP-ALL), T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, cutaneous T-cell lymphomas (CTCL), any subtype of CTCL, mycosis fungoides, Sézary syndrome, primary cutaneous gamma-delta T-cell lymphoma, a malignancy with the T lineage subsets of Non-Hodgkin's lymphoma (NHL), peripheral T-cell lymphoma (PTCL) not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma.
27. The use of any one of claims 23-26, wherein said administration is by any one selected from the group consisting of intravenous infusion, intra-arterial infusion, intraperitoneal infusion, direct injection into tumor and/or perfusion of tumor bed after surgery, implantation at a tumor site in an artificial scaffold, and intrathecal administration.
28. An expression vector composition comprising an expression vector comprising a polynucleotide encoding said CAR of any one of claims 1-20.
29. An expression vector composition comprising one or more expression vectors comprises a polynucleotide for a guide RNA complementary to the human CD2 gene, and a polynucleotide encoding a Cas protein, wherein the polynucleotide for the guide RNA comprises any one selected from the group consisting of SEQ ID NOS:44-47.
30. An expression vector composition comprising an expression vector comprising a polynucleotide encoding said blocking polypeptide of any one of claims 17-20.

31. An in-vitro method for producing an engineered immune cell of any one of claims 1–20, the method comprising: introducing the expression vector composition of claim 28, and the expression vector composition of claim 29 into an immune cell.

32. The method of claim 31, further comprising introducing the expression vector composition of claim 30 into said immune cell.

33. The method of claim 31 or 32, wherein introducing comprises concomitantly or sequentially introducing the expression vector compositions into said immune cell.