

WHAT IS CLAIMED IS:

1. An engineered immune cell comprising:

(i) a CD2 blocking polypeptide comprising a single chain variable fragment (scFv) linked to the N-terminus of a cellular localizing domain,

wherein the scFv binds CD2, wherein the 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 CD2 blocking polypeptide remains intracellularly within said engineered cell and binds endogenous CD2 within the engineered immune cell; and

(ii) a chimeric antigen receptor (CAR) comprising a CD2 binding domain, a transmembrane domain, and a signaling domain.

2. The engineered immune cell of claim 1, wherein said scFv comprises a variable heavy chain (V_H) sequence having at least 90% sequence identity to SEQ ID NO:18 and comprising complementarity determining region (CDR) 1, CDR 2, and CDR 3 of SEQ ID NO:18 and a variable light chain (V_L) sequence having at least 90% sequence identity to SEQ ID NO:19 and comprising CDR 1, CDR 2, and CDR 3 of SEQ ID NO:19.

3. The engineered immune cell of claim 1, wherein the scFv comprises a variable heavy chain (V_H) sequence having at least 90% sequence identity to SEQ ID NO:20 and comprising CDR 1, CDR 2, and CDR 3 of SEQ ID NO:20 and a variable light chain (V_L) sequence having at least 90% sequence identity to SEQ ID NO:21 and comprising CDR 1, CDR 2, and CDR 3 of SEQ ID NO:21.

4. The engineered immune cell of any one of claims 1-3, 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.

5. The engineered immune cell of claim 4, wherein said CD2 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.

6. The engineered immune cell of claim 5, wherein said transmembrane domain comprises a hinge-transmembrane domain of CD8 α .

7. The engineered immune cell of any one of claims 1-6, wherein said CD2 blocking polypeptide (i) comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:2, and a scFv V_H sequence having complementarity determining region (CDR) 1, CDR 2, and CDR 3 of SEQ ID NO:18 and a scFv V_L sequence having CDR 1, CDR 2, and CDR 3 of SEQ ID NO:19; or (ii) comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:3 or SEQ ID NO:4, and a scFv V_H sequence having complementarity determining region (CDR) 1, CDR 2, and CDR 3 of SEQ ID NO:20 and a scFv V_L sequence having CDR 1, CDR 2, and CDR 3 of SEQ ID NO:21.

8. The engineered immune cell of any one of claims 1-7, wherein said CAR is an anti-CD2-4-1BB-CD3 ζ CAR.

9. The engineered immune cell of claim 8, wherein said anti-CD2-4-1BB-CD3 ζ CAR comprises an amino acid sequence having a sequence of 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 CD2 surface expression by said engineered immune cell is blocked or significantly reduced by the CD2 blocking polypeptide.

12. The engineered immune cell of claim 11, wherein said blockage of said CD2 surface expression by said engineered immune cell persists for at least 6 months.

13. The engineered immune cell of claim 11, wherein said blockage of said CD2 surface expression by said engineered immune cell persists for at least 12 months.

14. The engineered immune cell of any one of claims 1-13, wherein said engineered immune cell proliferates at a substantially equivalent rate as an otherwise identical immune cell which does not comprise said CD2 blocking polypeptide.

15. The engineered immune cell of any one of claims 1-14, wherein said engineered immune cell is an allogeneic cell.

16. The engineered immune cell of any one of claims 1-14, wherein said engineered immune cell is an autologous cell.

17. The engineered immune cell of any one of claims 1-16, wherein said engineered immune cell is an engineered T cell.

18. The engineered immune cell of any one of claims 1-16, wherein said engineered immune cell is an engineered gamma-delta T cell.

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

20. A pharmaceutical composition comprising at least one of the engineered immune cells of any one of claims 1-19.

21. A pharmaceutical composition comprising at least one of the engineered immune cells of any one of claims 1-19 for use in therapy.

22. Use of a therapeutic amount of a composition comprising the engineered immune cell of any one of claims 1-19 in the preparation of a medicament for treating a CD2 positive cancer in a subject in need thereof, wherein the medicament is to be administered to the subject, thereby treating the CD2 positive cancer in the subject in need thereof.

23. The use of claim 22, wherein the composition further comprises a pharmaceutically acceptable carrier.

24. The use of claim 22 or 23, wherein the CD2 positive cancer is a T-cell malignancy.

25. The use of claim 24, wherein said T-cell malignancy 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) and angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma.

26. The use of any one of claims 22-25, wherein said administration is by 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, or intrathecal administration.

27. A polynucleotide encoding said CD2 blocking polypeptide of any one of claims 1-7.

28. A polynucleotide encoding said CAR of claim 9.

29. An expression vector comprising the polynucleotide of claim 27.

30. An expression vector comprising the polynucleotide of claim 28.

31. The expression vector of claim 29, further comprising the polynucleotide of claim 28.

32. A host cell comprising the expression vectors of claims 29 and 30 or the expression vector of claim 31.

33. An in-vitro method for producing an engineered immune cell of any one of claims 1-19, the method comprising: introducing the polynucleotides of claims 27 and 28 into an immune cell.

34. An in-vitro method for producing an engineered immune cell of any one of claims 1-19, the method comprising: introducing the expression vectors of claims 29 and 30, or the expression vector of claim 32 into an immune cell.