Acute leukemia relapses can, in some cases, be treated with donor lymphocyte infusions from the original stem cell donor. This graft-versus-leukemia (GVL) effect of donor lymphocyte infusion, however, is often accompanied by graft-versus-host disease (GVHD), causing serious mortality and morbidity and is not always effective. If GVL could be selectively increased without enhancing immune responses against normal tissues (graft-versus-host disease, GVHD), post-HCT relapses might be prevented.

Certain minor H antigens are expressed on leukemic stem cells and blasts (*see, e.g.,* Bleakley and Riddell, *Nat. Rev. Cancer* 4:371-380, 2004; Bleakley *et al.*, *Blood* 115:4923-4933, 2010; Bleakley and Riddell, *Immunol. Cell. Biol.* 89:396-407, 2011; van der Harst *et al.*, *Blood* 83:1060-1066, 1994; Bonnet *et al.*, *Proc. Natl. Acad. Sci. USA* 96:8639-8644, 1999; Hambach *et al.*, *Leukemia* 20:371-374, 2006), and have been targeted using cancer-specific T cells. In a small clinical trial of minor H antigen-targeted T cell immunotherapy in patients with post-HCT relapse, clinical responses were observed in some patients (Warren *et al.*, *Blood* 115:3869-3878, 2010). Technical advances in genetic modification of T cells and growing knowledge of T cell biology means that therapeutic doses of antigen-specific T cells can now be prepared efficiently, given to patients, and persist and exert potent anti-tumor effects *in vivo* (Heemskerk *et al., J. Exp. Med.* 199:885-894, 2004; Morgan *et al., Science* 314:126-129, 2006; Griffioen *et al., Haematologica* 93:1535-131543, 2008; Ochi *et al., J. Biomed. Biotechnol.* 2010:5212248, 2010; Schmitt *et al., Hum. Gene Ther.* 20:1240-1248, 2009; Stromnes *et al., Immunol Rev.* 257:145-164, 2014). However, there is a need for cell-based therapies that target leukemia-associated antigens. Presently disclosed embodiments address these needs and provide other related advantages.

SUMMARY

In one aspect, the present disclosure refers to an engineered immune cell, comprising a heterologous polynucleotide encoding a binding protein that includes: (a) a TCR α chain variable (Vα) domain comprising a CDR3 amino acid sequence of SEQ ID NO:88, a CDR2 amino acid sequence of SEQ ID NO:136, and a CDR1 amino acid sequence of SEQ ID NO:135, and; (b) a TCR β-chain variable (Vβ) domain comprising a CDR3 amino acid sequence of SEQ ID NO:14, a CDR2 amino acid sequence of SEQ

ID NO:134, and a CDR1 amino acid sequence of SEQ ID NO:133, wherein the encoded binding protein is capable of specifically binding to a peptide containing an HA-1^H antigen and does not bind to a peptide that does not contain an HA-1^H antigen.

In another aspect, the present disclosure refers to an engineered immune cell, comprising a heterologous transgene polynucleotide comprising or consisting of the nucleotide sequence of SEQ ID NO:85.

In another aspect, the present disclosure refers to a composition, comprising an engineered immune cell of claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

In yet another aspect, the present disclosure refers to an engineered immune cell, comprising a heterologous polynucleotide encoding a binding protein that includes: (a) a TCR α-chain variable (Vα) domain, wherein the encoded Vα domain (i) comprises a CDR3 amino acid sequence of SEQ ID NO: 88, and (ii) has at least about 90% sequence identity to the Vα domain amino acid sequence of SEQ ID NO:4 or 99, provided that the encoded Vα domain comprises no change in amino acid sequence of CDR1 and CDR2, and; (b) a TCR β-chain variable (Vβ) domain, wherein encoded the Vβ domain (i) comprises a CDR3 amino acid sequence of SEQ ID NO: 14, and (ii) has at least about 90% sequence identity to the amino acid sequence of SEQ ID NOs: 3 or 98, provided that the encoded Vβ domain comprises no change in amino acid sequence of CDR1 and CDR2, wherein the encoded binding protein is capable of specifically binding to a peptide containing an HA-1^H antigen and does not bind to a peptide that does not contain an HA-1^H antigen.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts a process used to isolate and characterize HA-1^H-specific T cell clones of the present disclosure. (Top left of Figure 1) To isolate HA-1^H-specific T cells, $CD8^+$ cells were primed with dendritic cells (DCs) pulsed with $HA1^H$ peptide (VL**H**DDLLEA; SEQ ID NO:1) and expanded in microcultures. (Middle left) Following 12 days of incubation in CTL media containing IL-12 and IL-15, aliquots of the T cells were evaluated in a split well microcytotoxicity assay, where T2 cells were

CLAIMS

What is claimed is:

1. An engineered immune cell, comprising a heterologous polynucleotide encoding a binding protein that includes:

(a) a TCR α-chain variable (V_α) domain comprising a CDR3 amino acid sequence of SEQ ID NO:88, a CDR2 amino acid sequence of SEQ ID NO:136, and a CDR1 amino acid sequence of SEQ ID NO:135, and;

(b) a TCR β-chain variable (V_β) domain comprising a CDR3 amino acid sequence of SEQ ID NO:14, a CDR2 amino acid sequence of SEQ ID NO:134, and a CDR1 amino acid sequence of SEQ ID NO:133,

wherein the encoded binding protein is capable of specifically binding to a peptide containing an HA-1^H antigen and does not bind to a peptide that does not contain an HA-1^H antigen.

2. The engineered immune cell of claim 1, wherein the encoded binding protein is capable of specifically binding to a HA-1^H peptide:HLA complex.

3. The engineered immune cell of claim 2, wherein the HLA comprises HLA-A*0201.

4. The engineered immune cell of claim 1, further comprising a heterologous polynucleotide encoding:

(a) a safety switch protein;

(b) a selection marker;

(c) a CD8 co-receptor β-chain; and/or

(d) a CD8 co-receptor α-chain.

5. The engineered immune cell of claim 1, wherein

the encoded Vβ domain has at least 90% identity to the amino acid sequence of SEQ ID NO: 3 or 98, and the encoded Vα domain has at least 90% identity to the amino acid sequence of SEQ ID NO:4 or 99.

6. The engineered immune cell of claim 5, wherein

the encoded Vβ domain comprises the amino acid sequence of SEQ ID NO: 3 or 98, and the encoded Vα domain comprises the amino acid sequence of SEQ ID NO: 4 or 99.

7. The engineered immune cell of claim 1, wherein the encoded binding protein comprises a TCR α-chain having at least 90% identity to the amino acid sequence of SEQ ID NO: 30 or 111.

8. The engineered immune cell of claim 1, wherein the encoded binding protein comprises a TCR β-chain having at least 90% identity to the amino acid sequence of SEQ ID NO: 29 or 110.

9. The engineered immune cell of claim 1, wherein the encoded binding protein comprises:

(i) a TCR β-chain comprising or consisting of the amino acid sequence of SEQ ID NO: 29, and a TCR α-chain comprising or consisting of the amino acid sequence of SEQ ID NO: 30; or

(ii) a TCR β-chain comprising or consisting of the amino acid sequence of SEQ ID NO: 110, and a TCR α-chain comprising or consisting of the amino acid sequence of SEQ ID NO:111.

10. The engineered immune cell of claim 9, wherein the (i) heterologous polynucleotide encoding the TCR α-chain and the (ii) heterologous polynucleotide encoding the TCR β-chain are contained in a single open reading frame, wherein the

single open reading frame further comprises a polynucleotide encoding a self-cleaving peptide disposed between (i) and (ii).

11. The engineered immune cell of claim 10, wherein the encoded binding protein comprises the amino acid sequence of SEQ ID NO:54.

12. An engineered immune cell, comprising a heterologous transgene polynucleotide comprising or consisting of the nucleotide sequence of SEQ ID NO:85.

13. The engineered immune cell of claim 1, wherein the immune cell is a T cell, a NK cell, or a NK-T cell.

14. The engineered immune cell of claim 1, wherein the peptide containing an HA-1^{H} antigen comprises the amino acid sequence VLHDDLLEA (SEQ ID NO:66).

15. The engineered immune cell of claim 1, wherein the Vα domain is encoded by a TRAV21 gene, and the Vβ domain is encoded by a TRBV7-9 gene.

16. The engineered immune cell of claim 15, wherein the TRAV21 gene comprises TRAV21*02 and the TRBV7-9 gene comprises TRB7*03.

17. The engineered immune cell of claim 15, wherein the heterologous polynucleotide encoding a binding protein further comprises a TRAJ40*01 gene, a TRBD1*01 gene, and a TRBJ1-4*01 gene.

18. A composition, comprising an engineered immune cell of claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

19. An engineered immune cell, comprising a heterologous polynucleotide encoding a binding protein that includes:

(a) a TCR α-chain variable (Vα) domain, wherein the encoded Vα domain

(i) comprises a CDR3 amino acid sequence of SEQ ID NO: 88, and

(ii) has at least about 90% sequence identity to the Vα domain amino acid sequence of SEQ ID NO:4 or 99, provided that the encoded Vα domain comprises no change in amino acid sequence of CDR1 and CDR2, and;

(b) a TCR β-chain variable (Vβ) domain, wherein encoded the Vβ domain

(i) comprises a CDR3 amino acid sequence of SEQ ID NO: 14, and

(ii) has at least about 90% sequence identity to the amino acid sequence of SEQ ID NOs: 3 or 98, provided that the encoded Vβ domain comprises no change in amino acid sequence of CDR1 and CDR2,

wherein the encoded binding protein is capable of specifically binding to a peptide containing an HA-1^H antigen and does not bind to a peptide that does not contain an HA-1^H antigen.