

CLAIMS

1. An engineered immune cell comprising:

1) a chimeric receptor (CR) comprising: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain, wherein the CR antigen binding domain comprises a CD4 binding moiety and a CCR5 binding moiety linked in tandem, or a CD4 binding moiety and a CXCR4 binding moiety linked in tandem; or

2) a) a chimeric receptor (CR) comprising: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain, and

b) a chimeric co-receptor (CCOR) comprising: i) a CCOR antigen binding domain specifically recognizing a CCOR target antigen; ii) a CCOR transmembrane domain; and iii) an intracellular CCOR co-stimulatory domain,

wherein the CR target antigen is CCR5 or CXCR4 and the CCOR target antigen is CD4, or

wherein the CR target antigen is CD4 and the CCOR target antigen is CCR5 or CXCR4.

2. The engineered immune cell of claim 1, further comprising one or more co-receptors (“COR”) selected from the group consisting of CXCR5, $\alpha 4\beta 7$, and CCR9.

3. An engineered immune cell comprising:

a) a chimeric receptor (CR) comprising: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain, wherein the CR target antigen is selected from the group consisting of CCR5, CXCR4 and CD4; and

b) one or more co-receptors (“COR”) selected from the group consisting of CXCR5, $\alpha 4\beta 7$, and CCR9.

4. An engineered immune cell comprising:

1) a nucleic acid encoding a chimeric receptor (CR) comprising: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain, wherein the CR antigen binding domain comprises a CD4 binding moiety and a CCR5 binding moiety linked in tandem, or a CD4 binding moiety and a CXCR4 binding moiety linked in tandem; or

2) a) a first nucleic acid encoding a chimeric receptor (CR), wherein the CR comprises: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain; and

b) a second nucleic acid encoding a chimeric co-receptor (CCOR), wherein the CCOR comprises: i) a CCOR antigen binding domain specifically recognizing a CCOR target antigen; ii) a CCOR transmembrane domain; and iii) an intracellular CCOR co-stimulatory signaling domain;

wherein the CR target antigen is CCR5 or CXCR4 and the CCOR target antigen is CD4, or

wherein the CR target antigen is CD4 and the CCOR target antigen is CCR5 or CXCR4.

5. The engineered immune cell of claim 4, further comprising one or more nucleic acid(s) encoding one or more co-receptors ("COR") selected from the group consisting of CXCR5, $\alpha 4\beta 7$, and CCR9.

6. An engineered immune cell comprising:

a) a nucleic acid encoding a chimeric receptor (CR), wherein the CR comprises: i) a CR antigen binding domain specifically recognizing a CR target antigen; ii) a CR transmembrane domain, and iii) an intracellular CR signaling domain, wherein the CR target antigen is selected from the group consisting of CCR5, CXCR4 and CD4, and

b) one or more nucleic acid(s) encoding one or more co-receptors ("COR") selected from the group consisting of CXCR5, $\alpha 4\beta 7$, and CCR9.

7. The engineered immune cell of any one of claims 1-6, wherein the CR is a chimeric antigen receptor ("CAR").

8. The engineered immune cell of claim 7, wherein the CR transmembrane is derived from CD8 α , the intracellular CR signaling domain is derived from CD3 ζ , and the CR optionally further comprises an intracellular CR co-stimulatory domain.

9. The engineered immune cell of any one of claims 1-6, wherein the CR is a chimeric T cell receptor ("cTCR").

10. The engineered immune cell of claim 9, wherein the CR transmembrane domain is derived from the transmembrane domain of a TCR subunit selected from the group consisting of TCR α , TCR β , TCR γ , TCR δ , CD3 γ , CD3 ϵ , and CD3 δ , and/or the intracellular CR signaling domain is derived from the intracellular signaling domain of a TCR subunit selected from the group

consisting of TCR α , TCR β , TCR γ , TCR δ , CD3 γ , CD3 ϵ , and CD3 δ , and optionally the CR further comprises a portion of an extracellular domain of a TCR subunit.

11. The engineered immune cell of any one of claims 1, 2, 4, 5, and 7-10, wherein the CCOR transmembrane domain comprises one or more transmembrane domains derived from CD28, CD3 ϵ , CD3 ζ , CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, or CD154, and the intracellular CCOR co-stimulatory domain is a portion of the intracellular domain of a co-stimulatory molecule selected from the group consisting of CD28, 4-1BB (CD137), CD27, OX40, CD27, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD40LG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, CD83, and a ligand that specifically binds with CD83.

12. The engineered immune cell of any one of claims 1-11, wherein the engineered immune cell is modified to reduce or eliminate expression of CCR5 within the cell.

13. The engineered immune cell of any one of claims 1-12, wherein the engineered immune cell is modified to express an anti-HIV antibody, wherein the anti-HIV antibody is a broadly neutralizing antibody.

14. The engineered immune cell of any one of claims 1-13, wherein the CR antigen binding domain is scFv or sdAb, and/or the CCOR antigen binding domain is scFv or sdAb.

15. The engineered immune cell of any one of claims 1-14, wherein the engineered immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer cell, a $\gamma\delta$ T cell and a natural killer T cell.

16. The engineered immune cell of any one of claims 1-15, comprising a nucleotide sequence encoding any one of SEQ ID NOs: 13-19, 22-26, 29, 78 and 79.

17. A pharmaceutical composition comprising the engineered immune cell of any one of claims 1-16 and a pharmaceutically acceptable carrier.

18. Use of an effective amount of the pharmaceutical composition of claim 17 in manufacture of a medicament for treating an infectious disease or a cancer.

19. The use of claim 18, wherein the infectious disease is an infection by a virus selected from the group consisting of HIV and HTLV, preferably wherein the infectious disease is HIV.

20. The use of claim 18, wherein the cancer is T cell lymphoma.