

syndrome (AIDS) is marked by the patient's CD4⁺ T cell count. This targeting of CD4⁺ T cells by the virus is also what results in the inability of infected patients to successfully mount productive immune responses against various pathogens, including opportunistic pathogens.

[8] Targeting the virus with various pharmacological classes of drugs prevents viral resistance and has shown a significant efficacy in infected patients, but requires high levels of adherence by patients to ensure its complete efficacy. In fact, non-adherence can result in the emergence of drug-resistant strains, leading to further difficulties in effectively managing and treating both the disease and subsequent complications in patients.

[9] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY

[10] The present application in one example provides an anti-CD4 immune cell receptor ("anti-CD4 D1 immune cell receptor") comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 1 ("D1") of CD4 ("anti-CD4 D1 moiety"), a transmembrane domain, and an intracellular signaling domain. In some examples, the CD4 binding moiety is a single domain antibody (sdAb), an scFv, a Fab', a (Fab')₂, an Fv, or a peptide ligand.

[10a] In one aspect, the present disclosure refers to an anti-CD4 immune cell receptor comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 1 ("D1") of CD4 ("anti-CD4 D1 moiety"), a transmembrane domain, and an intracellular signaling domain.

[11] In some examples according to one or more of the above examples of the anti-CD4 D1 immune cell receptors, the CD4 binding moiety competes for binding with a reference antibody that specifically binds to an epitope within D1 of CD4 ("anti-CD4 D1 antibody"). In some examples, the CD4 binding moiety binds to an epitope in D1 of CD4 that overlaps with the epitope of a reference anti-CD4 D1 antibody. In some examples, the CD4 binding moiety comprises the same heavy chain and light chain CDR sequences as those of a reference anti-CD4 D1 antibody. In some examples, the CD4 binding moiety comprises the same heavy chain variable domain (VH) and light chain variable domain (VL) sequences as those of a reference anti-CD4 D1 antibody.

[12] In some examples according to one or more of the above examples of the anti-CD4 D1 immune cell receptors, the reference anti-CD4 D1 antibody comprises a heavy chain CDR1 (HC-CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 (HC-CDR2) comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain CDR3 (HC-CDR3) comprising the amino acid sequence of SEQ ID NO: 3, a light chain CDR1 (LC-CDR1)

comprising the amino acid sequence of SEQ ID NO: 4, a light chain CDR2 (LC-CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a light chain CDR3 (LC-CDR3) comprising the amino acid sequence of SEQ ID NO: 6. In some examples, the reference anti-CD4 D1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:7 and a VL comprising the amino acid sequence of SEQ ID NO:8.

[13] In some examples according to one or more of the above examples of the anti-CD4 D1 immune cell receptors, the reference anti-CD4 D1 antibody comprises a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 9, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 10, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 11, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 12, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 13, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 14. In some examples, the reference anti-CD4 D1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:15 and a VL comprising the amino acid sequence of SEQ ID NO: 16.

[14] In some examples according to one or more of the above examples of the anti-CD4 D1 immune cell receptors, the reference anti-CD4 D1 antibody comprises a heavy chain CDR1 (HC-CDR1) comprising the amino acid sequence of SEQ ID NO: 17, a heavy chain CDR2 (HC-CDR2) comprising the amino acid sequence of SEQ ID NO: 18, a heavy chain CDR3 (HC-CDR3) comprising the amino acid sequence of SEQ ID NO: 19, a light chain CDR1 (LC-CDR1) comprising the amino acid sequence of SEQ ID NO: 20, a light chain CDR2 (LC-CDR2) comprising the amino acid sequence of SEQ ID NO: 21, and a light chain CDR3 (LC-CDR3) comprising the amino acid sequence of SEQ ID NO: 22. In some examples, the reference anti-CD4 D1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 23 and a VL comprising the amino acid sequence of SEQ ID NO: 24.

[15] In some examples according to any of the above examples of the anti-CD4 D1 immune cell receptors, the CD4 binding moiety in the extracellular domain is fused to the transmembrane domain directly or indirectly. In some examples, the CD4 binding moiety in the extracellular domain is non-covalently bound to a polypeptide comprising the transmembrane domain. In some examples, the extracellular domain comprises i) a first polypeptide comprising the CD4 binding moiety and a first member of a binding pair; and ii) a second polypeptide comprising a second member of the binding pair, wherein the first member

and the second member bind to each other, and wherein the second member is fused to the transmembrane domain directly or indirectly.

[16] In some examples according to any of the above examples of the anti-CD4 D1 immune cell receptors, the immune cell receptor is monospecific.

[17] In some examples according to any of the above examples of the anti-CD4 D1 immune cell receptors, the immune cell receptor is multispecific. In some examples, the extracellular domain comprises a second antigen binding moiety specifically recognizing a second antigen. In some examples, the second antigen binding moiety is an sdAb, an scFv, a Fab', a (Fab')₂, an Fv, or a peptide ligand. In some examples, the CD4 binding moiety and the second antigen binding moiety are linked in tandem. In some examples, the CD4 binding moiety is N-terminal to the second antigen binding moiety. In some examples, the CD4 binding moiety is C-terminal to the second antigen binding moiety. In some examples, the CD4 binding moiety and the second antigen binding moiety are linked via a linker. In some examples, the second antigen binding moiety specifically binds to an antigen on the surface of a T cell. In some examples, the second antigen is CCR5.

[18] In some examples according to any of the above examples of the anti-CD4 D1 immune cell receptors, the immune cell receptor is a chimeric antigen receptor ("CAR"). In some examples, the transmembrane domain is derived from a molecule selected from the group consisting of CD8 α , CD4, CD28, 4-1BB, CD80, CD86, CD152 and PD1. In some examples, the transmembrane domain is derived from CD8 α . In some examples, the intracellular signaling domain comprises a primary intracellular signaling domain derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d. In some examples, the primary intracellular signaling domain is derived from CD3 ζ . In some examples, the intracellular signaling domain comprises a co-stimulatory signaling domain. In some examples, the co-stimulatory signaling domain is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD40, PD-1, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD4OLG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, DAP10, DAP12, CD83, ligands of CD83 and combinations thereof. In some examples, the co-stimulatory signaling domain comprises a cytoplasmic domain of 4-1BB. In some examples, the anti-CD4 immune cell receptor further comprising a hinge domain located between the C-terminus of the extracellular

domain and the N-terminus of the transmembrane domain. In some examples, the hinge domain is derived from CD8 α or IgG4 CH2-CH3.

[19] In some examples according to any of the above examples of the anti-CD4 D1 immune cell receptors, the immune cell receptor is a chimeric T cell receptor ("cTCR"). In some examples, the 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 . In some examples, the transmembrane domain is derived from the transmembrane domain of CD3 ϵ . In some examples, the intracellular 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 . In some examples, the intracellular signaling domain is derived from the intracellular signaling domain of CD3 ϵ . In some examples, the transmembrane domain and intracellular signaling domain are derived from the same TCR subunit. In some examples, the anti-CD4 immune cell receptor further comprising at least a portion of an extracellular domain of a TCR subunit. In some examples, the extracellular domain is fused to the N-terminus of CD3 ϵ ("eTCR").

[20] The present application in another example provides a composition comprising one or more nucleic acids encoding any one of the above anti-CD4 D1 immune cell receptors, wherein the anti-CD4 immune cell receptor comprising an extracellular domain comprising an anti-CD4 D1 moiety.

[20a] In one aspect, the present disclosure refers to a composition comprising one or more nucleic acids encoding the anti-CD4 immune cell receptor disclosed herein.

[21] The present application in another example provides an engineered immune cell ("anti-CD4 D1 engineered immune cell") comprising any one of the above anti-CD4 D1 immune cell receptors or the above nucleic acid compositions. In some examples, the immune cell is a T cell. In some examples, the immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer (NK) cell, a natural killer T (NK-T) cell, and a $\gamma\delta$ T cell. In some examples, the engineered immune cell further comprises a co-receptor. In some examples, the co-receptor is a chemokine receptor. In some examples, the chemokine receptor is CXCR5. In some examples, the engineered immune cell further comprises an anti-HIV antibody. In some examples, the anti-HIV antibody is a broadly neutralizing antibody. In some examples, the broadly neutralizing antibody is selected from the group consisting of VRC01, PGT-121, 3BNC117, 10-1074, N6, VRC07, VRC07-523, eCD4-IG, 10E8, 10E8v4, PG9, PGDM 1400, PGT151, CAP256.25, 35022, and 8ANC195.

[21a] In one aspect, the present disclosure refers to an engineered immune cell comprising the anti-CD4 immune cell receptor disclosed herein, or the composition disclosed herein.

[22] In some examples, the present application provides a pharmaceutical composition ("anti-CD4 D1 pharmaceutical composition") comprising the anti-CD4 D1 engineered immune cell of any one of the examples described above.

[22a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the engineered immune cell disclosed herein.

[23] In some examples, the present application provides a method of treating an individual having a cancer, comprising administering to the individual an effective amount of the anti-CD4 D1 pharmaceutical composition described above, wherein the engineered immune cells are autologous to the individual. In some examples, the cancer is T cell lymphoma. In some examples, the method further comprises administering to the individual a second anticancer agent. In some examples, the second anti-cancer agent is selected from the group consisting of CD70 targeting drugs, TRBC1, CD30 targeting drugs, CD37 targeting drugs and CCR4 targeting drugs.

[23a] In one aspect, the present disclosure refers to use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating an individual having a cancer or an infectious disease, wherein: (i) the extracellular domain of the anti-CD4 immune receptor comprising an anti-CD4 D1 moiety, wherein the engineered immune cells are autologous to the individual; or (ii) the extracellular domain of the anti-CD4 immune receptor comprising an anti-CD4 D2/D3 moiety, wherein the engineered immune cells are autologous to the individual.

[24] In some examples, the present application provides a method of treating an individual having an infectious disease, comprising administering to the individual an effective amount of the anti-CD4 D1 pharmaceutical composition described above, wherein the engineered immune cells are autologous to the individual. In some examples, the infectious disease is an infection by a virus selected from the group consisting of HIV and HTLV. In some examples, the infectious disease is HIV. In some examples, the method further comprises administering to the individual a second anti-infectious disease agent. In some examples, the second anti-infectious disease agent is selected from the group consisting of anti-retroviral drugs, broad neutralization antibodies, toll-like receptor agonists, latency reactivation agents, CCR5 antagonist, immune stimulator, and a vaccine.

[25] Also provides are anti-CD4 D1 immune receptors, engineered immune cells, or compositions according to any one of the examples described above for use in treating a cancer or an infectious disease (*e.g.*, HIV), and use of anti-CD4 D1 immune receptors, engineered immune cells, or compositions according to any one of the examples described above in the preparation of a medicament for treating a cancer or an infectious disease (*e.g.*, HIV).

[26] One example of the present application provides an anti-CD4 immune cell receptor ("anti-CD4 D2/D3 immune cell receptor") comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 2 ("D2") and/or Domain 3 ("D3") of CD4 ("anti-CD4 D2/D3 moiety"), a transmembrane domain, and an intracellular signaling domain. In some examples, the CD4 binding moiety specifically binds

to an epitope within D2 of CD4. In some examples, the CD4 binding moiety specifically binds to an epitope within D3 of CD4. In some examples, the CD4 binding moiety specifically binds to an epitope that bridges D2 and D3 of CD4. In some examples, the CD4 binding moiety is an sdAb, an scFv, a Fab', a (Fab')₂, an Fv, or a peptide ligand that specifically binds to D2 and/or D3 of CD4.

[26a] In one aspect, the present disclosure refers to an anti-CD4 immune cell receptor comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 2 ("D2") and/or Domain 3 ("D3") of CD4 ("anti-CD4 D2/D3 moiety"), a transmembrane domain, and an intracellular signaling domain.

[27] In some examples according to one or more of the above examples of the anti-CD4 D2/D3 immune cell receptors, the CD4 binding moiety competes for binding with a reference antibody specifically binding to an epitope within D2 and/or D3 of CD4 ("anti-CD4 D2/D3 antibody"). In some examples, the CD4 binding moiety binds to an epitope within D2 and/or D3 of CD4 that overlaps with the epitope of a reference anti-CD4 D2/D3 antibody. In some examples, the CD4 binding moiety comprises the same heavy chain and light chain CDR sequences as those of a reference anti-CD4 D2/D3 antibody. In some examples, the CD4 binding moiety comprises the same VH and VL sequences as those of a reference anti-CD4 D2/D3 antibody.

[28] In some examples according to one or more of the above examples of the anti-CD4 D2/D3 immune cell receptors, the reference anti-CD4 D2/D3 antibody comprises a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 26, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 29, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 30. In some examples, the reference anti-CD4 D2/D3 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:31 and a VL comprising the amino acid sequence of SEQ ID NO:32.

[29] In some examples according to one or more of the above examples of the anti-CD4 D2/D3 immune cell receptors, the reference anti-CD4 D2/D3 antibody comprises a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 47, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 48, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 50, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 51. In some examples, the reference anti-CD4 D2/D3 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:52 and a VL comprising the amino acid sequence of SEQ ID NO:53.

[30] In some examples according to one or more of the above examples of the anti-CD4 D2/D3 immune cell receptors, the reference anti-CD4 D2/D3 antibody comprises a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 56, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 59, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 60. In some examples, the reference anti-CD4 D2/D3 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:61 and a VL comprising the amino acid sequence of SEQ ID NO:62.

[31] In some examples according to any of the above examples of the anti-CD4 D2/D3 immune cell receptors, the CD4 binding moiety in the extracellular domain is fused to the transmembrane domain directly or indirectly. In some examples, the CD4 binding moiety in the extracellular domain is non-covalently bound to a polypeptide comprising the transmembrane domain. In some examples, the extracellular domain comprises i) a first polypeptide comprising the CD4 binding moiety and a first member of a binding pair; and ii) a second polypeptide comprising a second member of the binding pair, wherein the first member and the second member bind to each other, and wherein the second member is fused to the transmembrane domain directly or indirectly. In some examples, the CD4 binding moiety is fused to a polypeptide comprising the transmembrane domain.

[32] In some examples according to any of the above examples of the anti-CD4 D2/D3 immune cell receptors, the immune cell receptor is monospecific.

[33] In some examples according to any of the above examples of the anti-CD4 D2/D3 immune cell receptors, the immune cell receptor is multispecific. In some examples, the extracellular domain comprises a second antigen binding moiety specifically recognizing a second antigen. In some examples, the second antigen binding moiety is an sdAb, an scFv, a Fab', a (Fab')₂, an Fv, or a peptide ligand. In some examples, the CD4 binding moiety and the second antigen binding moiety are linked in tandem. In some examples, the CD4 binding moiety is N-terminal to the second antigen binding moiety. In some examples, the CD4 binding moiety is C-terminal to the second antigen binding moiety. In some examples, the CD4 binding moiety and the second antigen binding moiety are linked via a linker. In some examples, the second antigen binding moiety specifically binds to an antigen on the surface of a T cell. In some examples, the second antigen is CCR5.

[34] In some examples according to any of the above examples of the anti-CD4 D2/D3 immune cell receptors, the immune cell receptor is a chimeric antigen receptor ("CAR"). In some examples, the transmembrane domain is derived from a molecule selected from the group consisting of CD8 α , CD4, CD28, 4-1BB, CD80, CD86, CD152 and PD1. In some examples, the transmembrane domain is derived from CD8 α . In some examples, the intracellular signaling domain comprises a primary intracellular signaling domain derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d. In some examples, the primary intracellular signaling domain is derived from CD3 ζ . In some examples, the intracellular signaling domain comprises a co-stimulatory signaling domain. In some examples, the co-stimulatory signaling domain is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD40, PD-1, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD4OLG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, DAP10, DAP12, CD83, ligands of CD83 and combinations thereof. In some examples, the co-stimulatory signaling domain comprises a cytoplasmic domain of 4-1BB. In some examples, the anti-CD4 immune cell receptor further comprising a hinge domain located between the C-terminus of the extracellular domain and the N-terminus of the transmembrane domain. In some examples, the hinge domain is derived from CD8 α or IgG4 CH2-CH3.

[35] In some examples according to any of the above examples of the anti-CD4 D2/D3 immune cell receptors, the immune cell receptor is a chimeric T cell receptor ("cTCR"). In some examples, the 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 . In some examples, the transmembrane domain is derived from the transmembrane domain of CD3 ϵ . In some examples, the intracellular 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 . In some examples, the intracellular signaling domain is derived from the intracellular signaling domain of CD3 ϵ . In some examples, the transmembrane domain and intracellular signaling domain are derived from the same TCR subunit. In some examples, the anti-CD4 immune cell receptor further comprising at least a portion of an extracellular domain of a TCR subunit. In some examples, the extracellular domain is fused to the N-terminus of CD3 ϵ ("eTCR").

[36] The present application in another example provides a composition comprising one or more nucleic acids encoding any one of the above anti-CD4 D2/D3 immune cell receptors, wherein the anti-CD4 immune cell receptor comprising an extracellular domain comprising an anti-CD4 D2/D3 moiety.

[37] The present application in another example provides an engineered immune cell ("anti-CD4 D2/D3 engineered immune cell") comprising any one of the above anti-CD4 D2/D3 immune cell receptors or the above nucleic acid compositions. In some examples, the immune cell is a T cell. In some examples, the immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer (NK) cell, a natural killer T (NK-T) cell, and a $\gamma\delta$ T cell. In some examples, the engineered immune cell further comprises a co-receptor. In some examples, the co-receptor is a chemokine receptor. In some examples, the chemokine receptor is CXCR5. In some examples, the engineered immune cell further comprises an anti-HIV antibody. In some examples, the anti-HIV antibody is a broadly neutralizing antibody. In some examples, the broadly neutralizing antibody is selected from the group consisting of VRC01, PGT-121, 3BNC117, 10-1074, N6, VRC07, VRC07-523, eCD4-IG, 10E8, 10E8v4, PG9, PGDM 1400, PGT151, CAP256.25, 35022, and 8ANC195.

[38] In some examples, the present application provides a pharmaceutical composition ("anti-CD4 D2/D3 pharmaceutical composition") comprising the anti-CD4 D2/D3 engineered immune cell of any one of the examples described above.

[39] In some examples, the present application provides a method of treating an individual having a cancer, comprising administering to the individual an effective amount of the anti-CD4 D2/D3 pharmaceutical composition described above, wherein the engineered immune cells are allogeneic to the individual. In some examples, the cancer is T cell lymphoma. In some examples, the method further comprises administering to the individual a second anti-cancer agent. In some examples, the second anti-cancer agent is selected from the group consisting of CD70 targeting drugs, TRBC1, CD30 targeting drugs, CD37 targeting drugs and CCR4 targeting drugs.

[40] In some examples, the present application provides a method of treating an individual having an infectious disease, comprising administering to the individual an effective amount of the anti-CD4 D2/D3 pharmaceutical composition described above, wherein the engineered immune cells are allogeneic to the individual. In some examples, the infectious

disease is an infection by a virus selected from the group consisting of HIV and HTLV. In some examples, the infectious disease is HIV. In some examples, the method further comprises administering to the individual a second anti-infectious disease agent. In some examples, the second anti-infectious disease agent is selected from the group consisting of anti-retroviral drugs, broad neutralization antibodies, toll-like receptor agonists, latency reactivation agents, CCR5 antagonist, immune stimulator, and a vaccine.

[41] Also provided are anti-CD4 D2/D3 immune receptors, engineered immune cells, or compositions according to any one of the examples described above for use in treating a cancer or an infectious disease (*e.g.*, HIV), and use of anti-CD4 D2/D3 immune receptors, engineered immune cells, or compositions according to any one of the examples described above in the preparation of a medicament for treating a cancer or an infectious disease (*e.g.*, HIV).

[42] Further provided are compositions, kits and articles of manufacture comprising any one of the anti-CD4 immune receptors or engineered immune cells described above.

BRIEF DESCRIPTION OF THE DRAWINGS

[43] FIG. 1A shows the structure of an exemplary anti-CD4 CAR, which comprises a CD4 binding moiety, a hinge region, a transmembrane domain, a co-stimulatory domain and a CD3 ζ signaling domain. The CD4 binding moiety can specifically recognize an epitope in Domain 1 of CD4 or an epitope in Domain 2 and/or 3 of CD4.

[44] FIG. 1B shows phenotypes of two different kinds of anti-CD4 CAR-T cells. The CAR in CAR-T No. 1 contains an scFv specifically recognizing an epitope in Domain 1 of CD4, and can kill the CD4⁺ cells in both CAR⁺ and CAR⁻ population. The CAR in CAR-T No. 2 contains an scFv specifically recognizing an epitope in domain 2 of CD4 and was not effective in killing the CAR⁺ target CD4⁺ cells.

[45] FIG. 2 shows domain mapping of anti-CD4 antibodies Ibalizumab, Tregalizumab, and Zanolimumab. Mouse CD4 substituted with five different domains of human CD4 were transiently expressed on HEK-293 T cells. The antibodies were used to detect these domains by flow cytometry. The Zanolimumab VH/VL was used to generate CAR-T No. 1, and Ibalizumab VH/VL was used to generate CAR-T No. 2. Tregalizumab VH/VL was used to generate CAR-T No. 3.

CLAIMS

What is claimed is:

1. An anti-CD4 immune cell receptor comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 1 (“D1”) of CD4 (“anti-CD4 D1 moiety”), a transmembrane domain, and an intracellular signaling domain.
2. The anti-CD4 immune cell receptor of claim 1, wherein:
 - (i) the CD4 binding moiety competes for binding with a reference antibody that specifically binds to an epitope within D1 of CD4 (“anti-CD4 D1 antibody”);
 - (ii) the CD4 binding moiety binds to an epitope in D1 of CD4 that overlaps with the epitope of a reference anti-CD4 D1 antibody;
 - (iii) the CD4 binding moiety comprises the same heavy chain and light chain CDR sequences as those of a reference anti-CD4 D1 antibody; and/or
 - (iv) the CD4 binding moiety comprises the same heavy chain variable domain (VH) and light chain variable domain (VL) sequences as those of a reference anti-CD4 D1 antibody.
3. The anti-CD4 immune cell receptor of claim 2, wherein the reference anti-CD4 D1 antibody comprises:
 - (i) a heavy chain CDR1 (HC-CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a heavy chain CDR2 (HC-CDR2) comprising the amino acid sequence of SEQ ID NO: 2, a heavy chain CDR3 (HC-CDR3) comprising the amino acid sequence of SEQ ID NO: 3, a light chain CDR1 (LC-CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a light chain CDR2 (LC-CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a light chain CDR3 (LC-CDR3) comprising the amino acid sequence of SEQ ID NO: 6;
 - (ii) a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 9, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 10, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 11, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 12, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 13, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 14; or
 - (iii) a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18, a HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, a LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22.

4. The anti-CD4 immune cell receptor of claim 3, wherein the reference anti-CD4 D1 antibody comprises:
 - (i) a VH comprising the amino acid sequence of SEQ ID NO: 7 and a VL comprising the amino acid sequence of SEQ ID NO: 8;
 - (ii) a VH comprising the amino acid sequence of SEQ ID NO: 15 and a VL comprising the amino acid sequence of SEQ ID NO: 16; or
 - (iii) a VH comprising the amino acid sequence of SEQ ID NO: 23 and a VL comprising the amino acid sequence of SEQ ID NO: 24.
5. An anti-CD4 immune cell receptor comprising an extracellular domain comprising a CD4 binding moiety that specifically binds to an epitope within Domain 2 (“D2”) and/or Domain 3 (“D3”) of CD4 (“anti-CD4 D2/D3 moiety”), a transmembrane domain, and an intracellular signaling domain.
6. The anti-CD4 immune cell receptor of claim 5, wherein:
 - (i) the CD4 binding moiety competes for binding with a reference antibody specifically binding to an epitope within D2 and/or D3 of CD4 (“anti-CD4 D2/D3 antibody”);
 - (ii) the CD4 binding moiety binds to an epitope within D2 and/or D3 of CD4 that overlaps with the epitope of a reference anti-CD4 D2/D3 antibody;
 - (iii) the CD4 binding moiety comprises the same heavy chain and light chain CDR sequences as those of a reference anti-CD4 D2/D3 antibody; and/or
 - (iv) the CD4 binding moiety comprises the same VH and VL sequences as those of a reference anti-CD4 D2/D3 antibody.
7. The anti-CD4 immune cell receptor of claim 6, wherein the reference anti-CD4 D2/D3 antibody comprises:
 - (i) a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 26, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 27, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 29, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 30;
 - (ii) a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 47, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 48, LC-CDR1 comprising the amino acid sequence of SEQ ID

- NO: 49, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 50, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 51; or
- (iii) a HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 56, HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 57, LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 59, and a LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 60.
8. The anti-CD4 immune cell receptor of claim 7, wherein the reference anti-CD4 D2/D3 antibody comprises:
 - (i) a VH comprising the amino acid sequence of SEQ ID NO: 31 and a VL comprising the amino acid sequence of SEQ ID NO: 32;
 - (ii) a VH comprising the amino acid sequence of SEQ ID NO: 52 and a VL comprising the amino acid sequence of SEQ ID NO: 53; or
 - (iii) a VH comprising the amino acid sequence of SEQ ID NO: 61 and a VL comprising the amino acid sequence of SEQ ID NO: 62.
 9. The anti-CD4 immune cell receptor of any one of claims 1-8, wherein:
 - (i) the CD4 binding moiety in the extracellular domain is fused to the transmembrane domain directly or indirectly;
 - (ii) the CD4 binding moiety in the extracellular domain is non-covalently bound to a polypeptide comprising the transmembrane domain; or
 - (iii) the extracellular domain comprises i) a first polypeptide comprising the CD4 binding moiety and a first member of a binding pair; and ii) a second polypeptide comprising a second member of the binding pair, wherein the first member and the second member bind to each other, and wherein the second member is fused to the transmembrane domain directly or indirectly.
 10. The anti-CD4 immune cell receptor of any one of claims 1-9, wherein the immune cell receptor is multispecific.
 11. The anti-CD4 immune cell receptor of claim 1, wherein the extracellular domain further comprises a second antigen binding moiety specifically recognizing a second target molecule, and wherein the CD4 binding moiety and the second antigen binding moiety are linked in tandem, preferably wherein the extracellular domain comprises a second antigen

binding moiety specifically recognizing an antigen on the surface of a T cell, more preferably wherein the second antigen is CCR5.

12. The anti-CD4 immune cell receptor of any one of claims 1-11, wherein the immune cell receptor is a chimeric antigen receptor ("CAR").
13. The anti-CD4 immune cell receptor of claim 12, wherein:
 - (i) the transmembrane domain is derived from a molecule selected from the group consisting of CD8 α , CD4, CD28, 4-1BB, CD80, CD86, CD152 and PD1, optionally wherein the transmembrane domain is derived from CD8 α ; and/or
 - (ii) the intracellular signaling domain comprises a primary intracellular signaling domain derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d, optionally wherein the intracellular signaling domain comprises a primary intracellular signaling domain derived from CD3 ζ ; and/or
 - (iii) the intracellular signaling domain comprises a co-stimulatory signaling domain, optionally wherein the co-stimulatory signaling domain comprises a cytoplasmic domain of 4-1BB; and/or
 - (iv) the anti-CD4 immune cell receptor further comprises a hinge domain located between the C-terminus of the extracellular domain and the N-terminus of the transmembrane domain.
14. The anti-CD4 immune cell receptor of claim 13, further comprising a hinge domain located between the C-terminus of the extracellular domain and the N-terminus of the transmembrane domain, wherein the hinge domain is derived from CD8 α or IgG4 CH2-CH3.
15. The anti-CD4 immune cell receptor of any one of claims 1-11, wherein the immune cell receptor is a chimeric T cell receptor ("cTCR").
16. The anti-CD4 immune cell receptor of claim 15, wherein:
 - (i) the 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 , optionally wherein the transmembrane domain is derived from the transmembrane domain of CD3 ϵ ; and/or
 - (ii) the intracellular 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 , optionally wherein the intracellular signaling domain is derived from the intracellular signaling domain of CD3 ϵ ; and/or

- (iii) the transmembrane domain and intracellular signaling domain are derived from the same TCR subunit.
17. The anti-CD4 immune cell receptor of claim 15 or 16, further comprising at least a portion of an extracellular domain of a TCR subunit, optionally wherein the extracellular domain is fused to the N-terminus of CD3 ϵ ("eTCR").
 18. A composition comprising one or more nucleic acids encoding the anti-CD4 immune cell receptor of any one of claims 1-17.
 19. An engineered immune cell comprising the anti-CD4 immune cell receptor of any one of claims 1-17, or the composition of claim 18.
 20. The engineered immune cell of claim 19, wherein the immune cell is a T cell or a natural killer (NK) cell, optionally, wherein the T cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T (NK-T) cell, and a $\gamma\delta$ T cell.
 21. The engineered immune cell of claim 19 or 20, further comprising a co-receptor.
 22. The engineered immune cell of claim 22, wherein the co-receptor is a chemokine receptor.
 23. The engineered immune cell of claim 23, wherein the chemokine receptor is CXCR5.
 24. The engineered immune cell of any one of claims 19-23, further comprising an anti-HIV antibody, preferably wherein the anti-HIV antibody is a broadly neutralizing antibody, more preferably wherein the broadly neutralizing antibody is selected from the group consisting of VRC01, PGT-121, 3BNC117, 10-1074, N6, VRC07, VRC07-523, eCD4-IG, 10E8, 10E8v4, PG9, PGDM 1400, PGT151, CAP256.25, 35022, and 8ANC195.
 25. A pharmaceutical composition comprising the engineered immune cell of any one of claims 19-24.
 26. Use of the pharmaceutical composition of claim 18 in the manufacture of a medicament for treating an individual having a cancer or an infectious disease, wherein:
 - (i) the extracellular domain of the anti-CD4 immune receptor comprising an anti-CD4 D1 moiety, wherein the engineered immune cells are autologous to the individual; or
 - (ii) the extracellular domain of the anti-CD4 immune receptor comprising an anti-CD4 D2/D3 moiety, wherein the engineered immune cells are autologous to the individual.
 27. The use of claim 26, wherein the cancer is T cell lymphoma, wherein the infectious disease is an infection by a virus selected from the group consisting of HIV and HTLV.