

[0005] A need exists to identify novel and improved therapies for treating STEAP1 related diseases and disorders.

SUMMARY

[0006] The disclosure relates to engineered immune cells (such as CARs or TCRs), antigen binding molecules (including but not limited to, antibodies, scFvs, heavy and/or light chains, and CDRs of these antigen binding molecules) with specificity to STEAP1.

[0007] Chimeric antigen receptors of the disclosure typically comprise: (i) a STEAP1 specific antigen binding molecule, (ii) one or more costimulatory domain, and (iii) one or more activating domain. It will be appreciated that each domain may be heterogeneous, thus comprised of sequences derived from different protein chains.

[0007a] In one aspect, the present disclosure refers to chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, a costimulatory domain, and an activating domain that is a signaling domain of CD3 zeta, wherein the antigen binding molecule comprises: a) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:89, SEQ ID NO:90, and SEQ ID NO:91, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:94, SEQ ID NO:95, and SEQ ID NO:96, respectively; or b) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:104, SEQ ID NO:105, and SEQ ID NO:106, respectively; or c) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:114, SEQ ID NO:115, and SEQ ID NO:116, respectively; or d) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:119, SEQ ID NO:120, and SEQ ID NO:121, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126, respectively; or e) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:129, SEQ ID NO:130, and SEQ ID NO:131, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino

acid sequences SEQ ID NO:134, SEQ ID NO:135, and SEQ ID NO:136, respectively; or f) a variable heavy chain region comprising complementary determining regions (“CDRs”) 1, 2, and 3 with amino acid sequences SEQ ID NO:139, SEQ ID NO:140, and SEQ ID NO:141, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:144, SEQ ID NO:145, and SEQ ID NO:146, respectively; or g) a VH region of SEQ ID NO: 88 and a VL region of SEQ ID NO:93, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 89, a variable heavy chain CDR2 of SEQ ID NO: 90, and a variable heavy chain CDR3 of SEQ ID NO: 91, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 94, a variable light chain CDR2 of SEQ ID NO: 95, and a variable light chain CDR3 of SEQ ID NO: 96; or h) a VH region of SEQ ID NO:88 and a VL region of SEQ ID NO:93; or i) a VH region of SEQ ID NO: 98 and a VL region of SEQ ID NO:103, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 99, a variable heavy chain CDR2 of SEQ ID NO: 100, and a variable heavy chain CDR3 of SEQ ID NO: 101, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 104, a variable light chain CDR2 of SEQ ID NO: 105, and a variable light chain CDR3 of SEQ ID NO: 106; or j) a VH region of SEQ ID NO:98 and a VL region of SEQ ID NO:103; or k) a VH region of SEQ ID NO: 108 and a VL region of SEQ ID NO:113, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 109, a variable heavy chain CDR2 of SEQ ID NO: 110, and a variable heavy chain CDR3 of SEQ ID NO: 111, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 114, a variable light chain CDR2 of SEQ ID NO: 115, and a variable light chain CDR3 of SEQ ID NO: 116; or l) a VH region of SEQ ID NO:108 and a VL region of SEQ ID NO:113; or m) a VH region of SEQ ID NO: 118 and a VL region of the amino acid sequence of SEQ ID NO:123, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 119, a variable heavy chain CDR2 of SEQ ID NO: 120, and a variable heavy chain CDR3 of SEQ ID NO: 121, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 124, a variable light chain CDR2 of SEQ ID NO: 125, and a variable light chain CDR3 of SEQ ID NO: 126; or n) a VH region of SEQ ID NO:118 and a VL region of SEQ ID NO:123; or o) a VH region of SEQ ID NO: 128 and a VL region of SEQ ID NO:133, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 129, a variable heavy chain CDR2 of SEQ ID NO: 130, and a variable heavy chain CDR3 of SEQ ID NO: 131, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 134, a variable light chain CDR2 of SEQ ID NO: 135, and a variable light chain CDR3 of SEQ ID NO: 136; or p) a VH region of SEQ ID NO:128 and a VL region of SEQ ID NO:133; or q) a VH region of SEQ ID NO: 138 and a VL

of SEQ ID NO:143, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 139, a variable heavy chain CDR2 of SEQ ID NO: 140, and a variable heavy chain CDR3 of SEQ ID NO: 141, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 144, a variable light chain CDR2 of SEQ ID NO: 145, and a variable light chain CDR3 of SEQ ID NO: 146; or r) a VH region of SEQ ID NO:138 and a VL region of SEQ ID NO:143; and at least one costimulatory domain, wherein the costimulatory domain is a CD28 costimulatory domain which comprises a sequence of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 4 in combination with SEQ ID NO: 6 or SEQ ID NO: 8; or a CD8 costimulatory domain which comprises a sequence of SEQ ID NO: 14, or SEQ ID NO: 14 in combination with SEQ ID NO: 8, or SEQ ID NO:14 in combination with SEQ ID NO:16; or a 4-1BB costimulatory domain which comprises a sequence of SEQ ID NO:16, or SEQ ID NO:16 in combination with SEQ ID NO:8; or SEQ ID NO:16 in combination with SEQ ID NO:14 and SEQ ID NO:8.

In another aspect, the present invention refers to polynucleotide encoding the chimeric antigen receptor of the present disclosure.

In yet another aspect, the present invention refers to a vector comprising the polynucleotide of the present disclosure.

In another aspect, the present invention refers to an immune cell comprising the vector of the present disclosure.

In another aspect, the present invention refers to a pharmaceutical composition comprising an immune cell of the present disclosure.

In another aspect, the present invention refers to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, or 76.

In yet another aspect, the present invention refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises the sequence of SEQ ID NO: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, or 75.

In yet another aspect, the present invention refers to the use of the polynucleotide according to the present disclosure; or the polypeptide according to the present disclosure; or the chimeric antigen

receptor according to the present disclosure; or the cell according to the present disclosure; or the pharmaceutical composition according to the present disclosure in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0008] In some examples, the disclosure relates to a chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises at least one of: (a) a variable heavy chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NOs:89, 99, 109, 119, 129, or 139 by not more than 3, 2, 1, or 0 amino acid residues; (b) a variable heavy chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NOs:90, 100, 110, 120, 130, or 140 by not more than 3, 2, 1, or 0 amino acid residues; (c) a variable heavy chain CDR3 comprising an amino acid sequence differing from that of SEQ ID NOs:91, 101, 111, 121, 131, or 141 by not more than 3, 2, 1, or 0 amino acid residues; (d) a variable light chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NOs:94, 104, 114, 124, 134, or 14 by not more than 3, 2, 1, or 0 amino acid residues; (e) a variable light chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NOs:95, 105, 115, 125, 135, or 145 by not more than 3, 2, 1, or 0 amino acid residues; (f) a variable light chain CDR3 comprising an amino acid sequence differing from that of SEQ IDs:96, 106, 116, 126, 136, or 146 by not more than 3, 2, 1, or 0 amino acid residues.

[0009] In other examples, the chimeric antigen receptor further comprises at least one costimulatory domain. In further examples, the chimeric antigen receptor further comprises at least one activating domain.

[0010] In certain examples the costimulatory domain is a signaling region of CD28, CD28T, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, Programmed Death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2,

What is Claimed

1. A chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, a costimulatory domain, and an activating domain that is a signaling domain of CD3 zeta, wherein the antigen binding molecule comprises:
 - a) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:89, SEQ ID NO:90, and SEQ ID NO:91, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:94, SEQ ID NO:95, and SEQ ID NO:96, respectively; or
 - b) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:104, SEQ ID NO:105, and SEQ ID NO:106, respectively; or
 - c) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:114, SEQ ID NO:115, and SEQ ID NO:116, respectively; or
 - d) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:119, SEQ ID NO:120, and SEQ ID NO:121, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:124, SEQ ID NO:125, and SEQ ID NO:126, respectively; or
 - e) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:129, SEQ ID NO:130, and SEQ ID NO:131, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:134, SEQ ID NO:135, and SEQ ID NO:136, respectively; or
 - f) a variable heavy chain region comprising complementary determining regions ("CDRs") 1, 2, and 3 with amino acid sequences SEQ ID NO:139, SEQ ID NO:140, and SEQ ID NO:141, respectively, and a variable light chain region comprising CDRs 1, 2, and 3 with amino acid sequences SEQ ID NO:144, SEQ ID NO:145, and SEQ ID NO:146, respectively; or

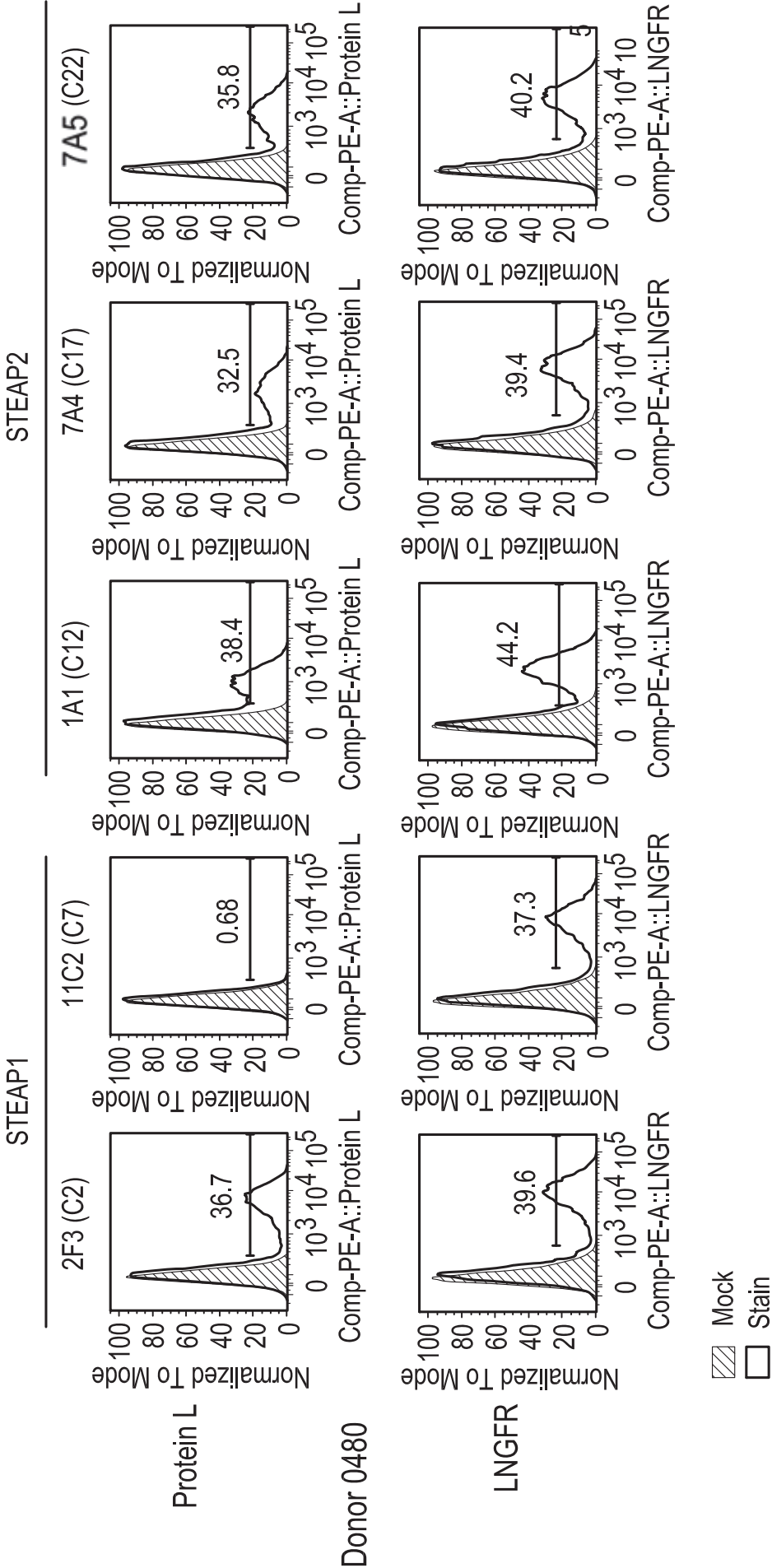
- g) a VH region of SEQ ID NO: 88 and a VL region of SEQ ID NO:93, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 89, a variable heavy chain CDR2 of SEQ ID NO: 90, and a variable heavy chain CDR3 of SEQ ID NO: 91, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 94, a variable light chain CDR2 of SEQ ID NO: 95, and a variable light chain CDR3 of SEQ ID NO: 96; or
- h) a VH region of SEQ ID NO:88 and a VL region of SEQ ID NO:93; or
- i) a VH region of SEQ ID NO: 98 and a VL region of SEQ ID NO:103, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 99, a variable heavy chain CDR2 of SEQ ID NO: 100, and a variable heavy chain CDR3 of SEQ ID NO: 101, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 104, a variable light chain CDR2 of SEQ ID NO: 105, and a variable light chain CDR3 of SEQ ID NO: 106; or
- j) a VH region of SEQ ID NO:98 and a VL region of SEQ ID NO:103; or
- k) a VH region of SEQ ID NO: 108 and a VL region of SEQ ID NO:113, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 109, a variable heavy chain CDR2 of SEQ ID NO: 110, and a variable heavy chain CDR3 of SEQ ID NO: 111, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 114, a variable light chain CDR2 of SEQ ID NO: 115, and a variable light chain CDR3 of SEQ ID NO: 116; or
- l) a VH region of SEQ ID NO:108 and a VL region of SEQ ID NO:113; or
- m) a VH region of SEQ ID NO: 118 and a VL region of the amino acid sequence of SEQ ID NO:123, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 119, a variable heavy chain CDR2 of SEQ ID NO: 120, and a variable heavy chain CDR3 of SEQ ID NO: 121, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 124, a variable light chain CDR2 of SEQ ID NO: 125, and a variable light chain CDR3 of SEQ ID NO: 126; or
- n) a VH region of SEQ ID NO:118 and a VL region of SEQ ID NO:123; or
- o) a VH region of SEQ ID NO: 128 and a VL region of SEQ ID NO:133, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 129, a variable heavy chain CDR2 of SEQ ID NO: 130, and a variable heavy chain CDR3 of SEQ ID NO: 131, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 134, a variable light chain CDR2 of SEQ ID NO: 135, and a variable light chain CDR3 of SEQ ID NO: 136; or
- p) a VH region of SEQ ID NO:128 and a VL region of SEQ ID NO:133; or

- q) a VH region of SEQ ID NO: 138 and a VL of SEQ ID NO:143, with the proviso that the VH region comprises a variable heavy chain CDR1 of SEQ ID NO: 139, a variable heavy chain CDR2 of SEQ ID NO: 140, and a variable heavy chain CDR3 of SEQ ID NO: 141, and the VL region comprises a variable light chain CDR1 of SEQ ID NO: 144, a variable light chain CDR2 of SEQ ID NO: 145, and a variable light chain CDR3 of SEQ ID NO: 146; or
 - r) a VH region of SEQ ID NO:138 and a VL region of SEQ ID NO:143;
and at least one costimulatory domain, wherein the costimulatory domain is a CD28 costimulatory domain which comprises a sequence of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 4 in combination with SEQ ID NO: 6 or SEQ ID NO: 8; or a CD8 costimulatory domain which comprises a sequence of SEQ ID NO: 14, or SEQ ID NO: 14 in combination with SEQ ID NO: 8, or SEQ ID NO:14 in combination with SEQ ID NO:16; or a 4-1BB costimulatory domain which comprises a sequence of SEQ ID NO:16, or SEQ ID NO:16 in combination with SEQ ID NO:8; or SEQ ID NO:16 in combination with SEQ ID NO:14 and SEQ ID NO:8.
2. The chimeric antigen receptor according to claim 1 wherein the CD3 zeta comprises the sequence of SEQ ID NO:10.
 3. A polynucleotide encoding the chimeric antigen receptor of claim 1.
 4. A vector comprising the polynucleotide of claim 3.
 5. The vector according to claim 4 which is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.
 6. An immune cell comprising the vector of claim 4.
 7. The immune cell according to claim 6, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
 8. The immune cell according to claim 7, wherein the cell is an autologous T cell.
 9. The immune cell according to claim 7, wherein the cell is an allogeneic T cell.
 10. The immune cell of claim 6, wherein the vector is introduced into a cell that is isolated from a patient's body or that is grown from a sample taken from a patient's body.
 11. The immune cell of claim 6, wherein the vector is introduced into a cell that is isolated from a donor's body or that is grown from a sample taken from a donor's body.
 12. A pharmaceutical composition comprising an immune cell of claim 6.

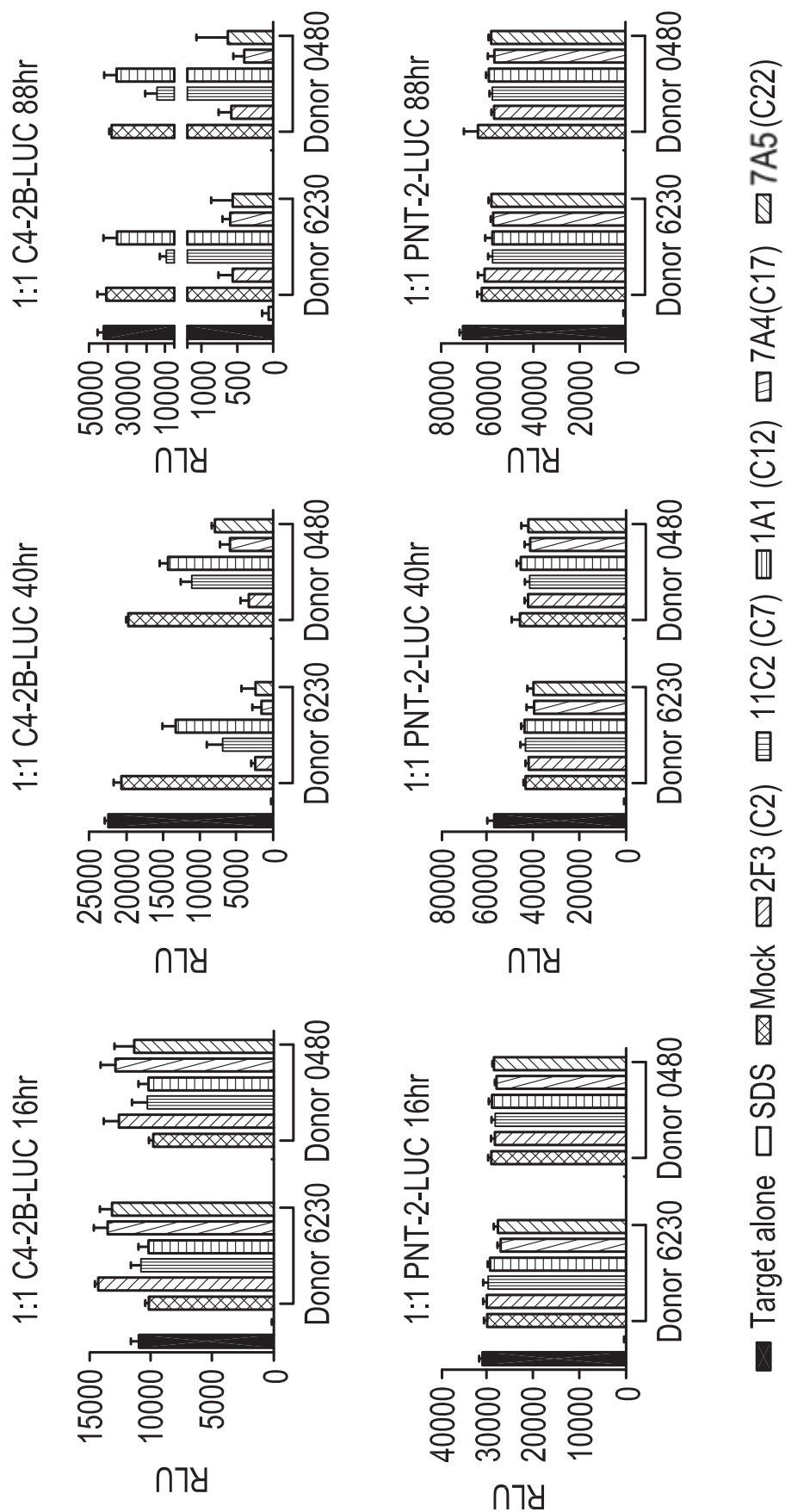
13. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, or 76.
14. A vector encoding the polypeptide of claim 13.
15. An immune cell comprising the polypeptide of claim 14.
16. The immune cell according to claim 15, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
17. The immune cell of claim 16 wherein the T cell is an autologous T cell.
18. The immune cell of claim 16 wherein the T cell is an allogeneic T cell.
19. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises the sequence of SEQ ID NO: 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, or 75.
20. A vector comprising the polynucleotide of claim 19.
21. An immune cell comprising the vector of claim 20.
22. The immune cell of claim 21, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
23. The immune cell of claim 22 wherein the T cell is an autologous T cell.
24. The immune cell of claim 22 wherein the T cell is an allogeneic T cell.
25. The polynucleotide according to any one of claims 3 or 19; or the polypeptide according to claim 13; or the chimeric antigen receptor according to any one of claims 1-2; or the cell according to any one of claims 6-11; or the pharmaceutical composition according to claim 12 for use in therapy.
26. The vector according to claim 5, wherein the lentiviral vector is a pGAR vector having SEQ ID NO:147.
27. Use of the polynucleotide according to any one of claims 3 or 19; or the polypeptide according to claim 13; or the chimeric antigen receptor according to any one of claims 1-2; or the cell according to any one of claims 6-11; or the pharmaceutical composition according to claim 12 in the manufacture of a medicament for treating cancer in a subject in need thereof.
28. The use according to claim 27 wherein the cancer is prostate cancer.

29. The use according to claim 28, wherein the cancer is metastatic castration resistant prostate cancer.

FIG. 2



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FIG. 4

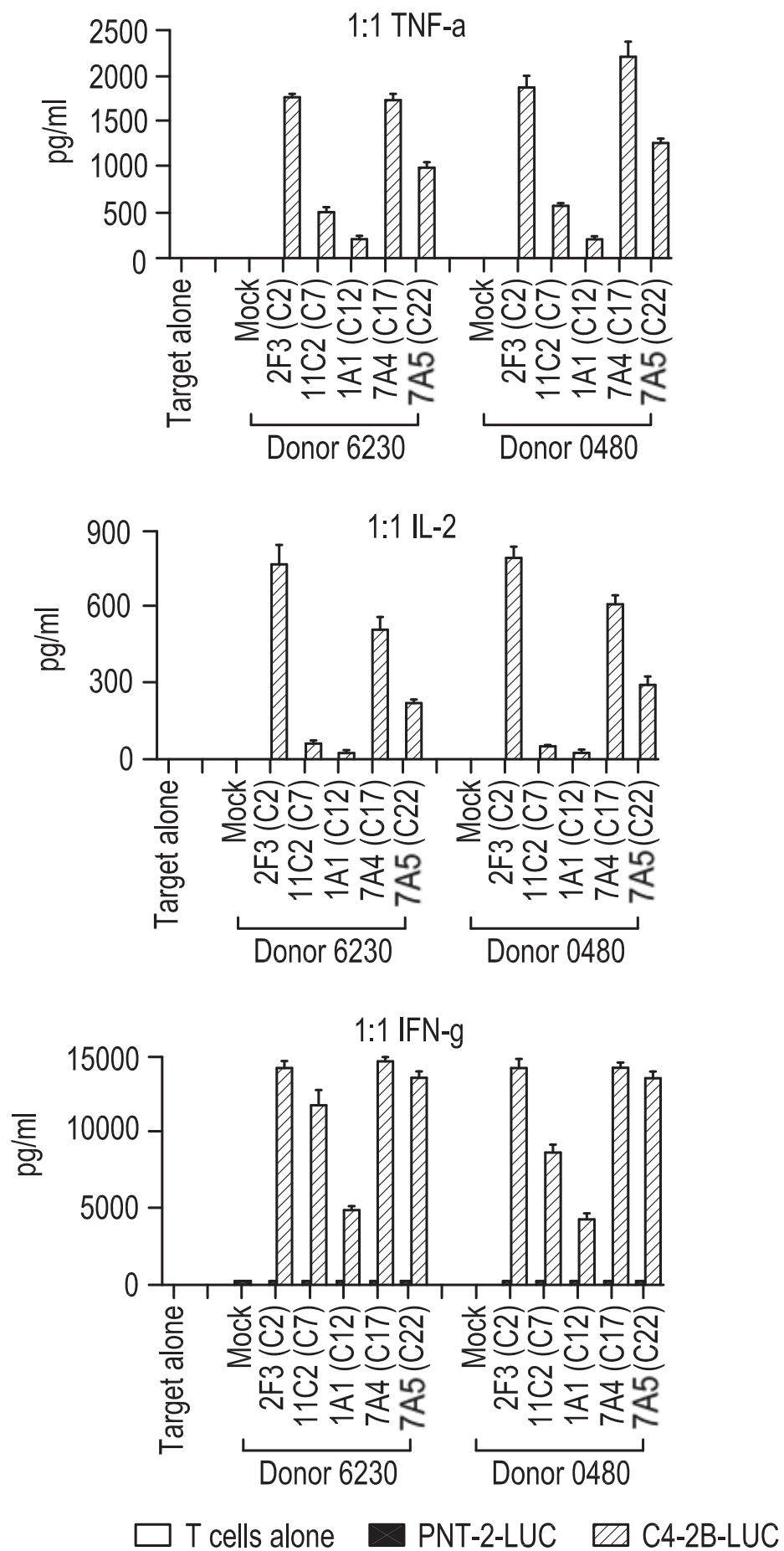


FIG. 5

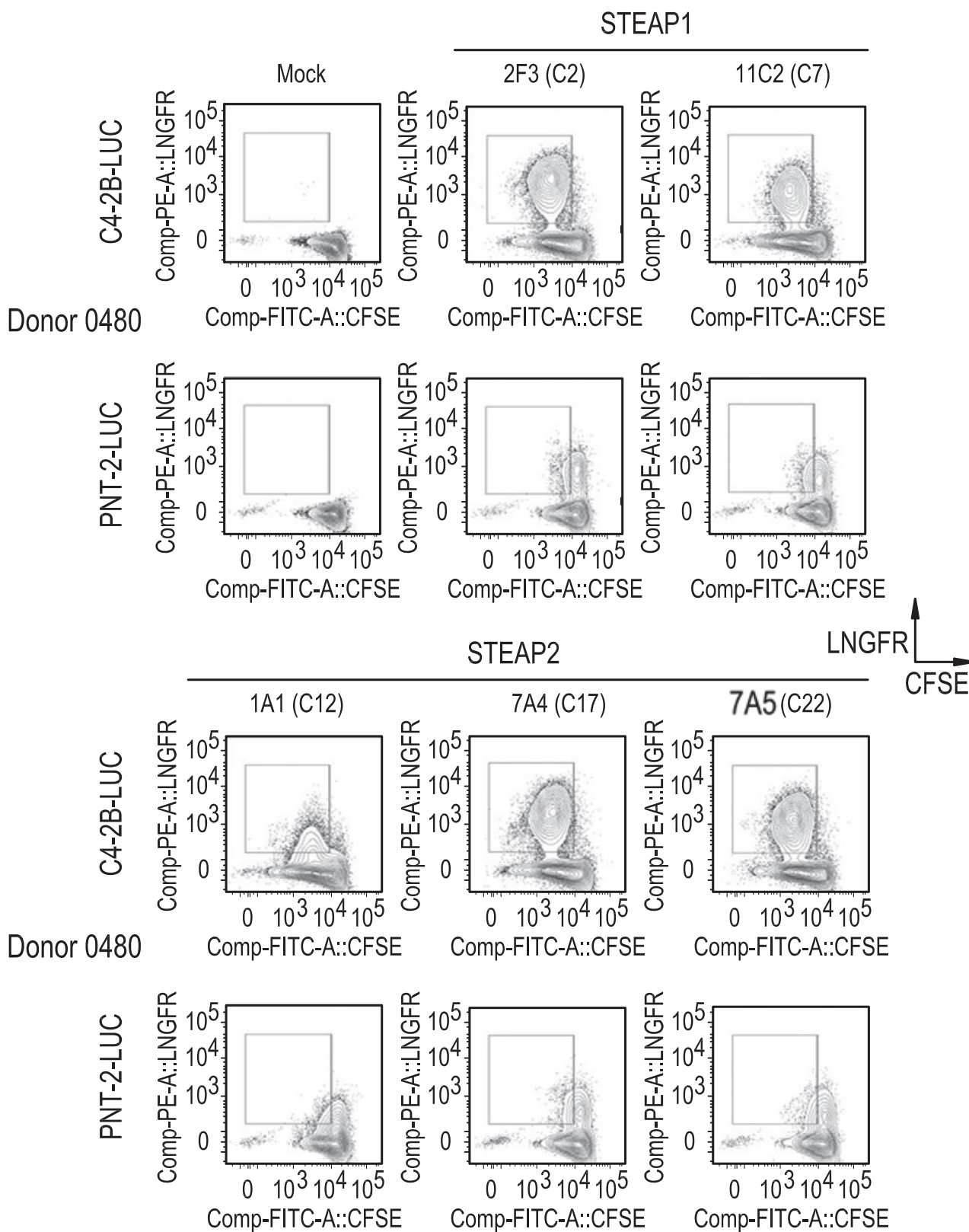


FIG. 5 Cont'd

