

[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.

~~In one aspect, the present disclosure refers to a chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises:~~

- a) ~~— a variable heavy chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:89, 99, 109, 119, 129, or 139; or~~
- b) ~~— a variable heavy chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:90, 100, 110, 120, 130, or 140; or~~
- e) ~~— a variable heavy chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:91, 101, 111, 121, 131, or 141; or~~
- d) ~~— a variable light chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:94, 104, 114, 124, 134, or 144; or~~
- e) ~~— a variable light chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:95, 105, 115, 125, 135, or 145; or~~
- f) ~~— a variable light chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ IDs:96, 106, 116, 126, 136, or 146; or~~
 - g) ~~— a variable heavy chain CDR1 comprising an amino acid sequence of a variable heavy chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - h) ~~— a variable heavy chain CDR2 comprising an amino acid sequence of a variable heavy chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - i) ~~— a variable heavy chain CDR3 comprising an amino acid sequence of a variable heavy chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - j) ~~— a variable light chain CDR1 comprising an amino acid sequence of a variable light chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - k) ~~— a variable light chain CDR2 comprising an amino acid sequence of a variable light chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - l) ~~— a variable light chain CDR3 comprising an amino acid sequence of a variable light chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~

m) ~~a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~

n) ~~a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.~~

~~[0007b] — In another aspect, the present disclosure refers to a polynucleotide encoding the chimeric antigen receptor as described herein. In another aspect, the present disclosure refers to a vector comprising the polynucleotide as described herein, wherein the vector 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. In another aspect, the present disclosure refers to an immune cell comprising the vector as described herein. In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising an immune cell as described herein.~~

~~[0007c] — In another aspect, the present disclosure refers to a chimeric antigen receptor comprising:~~

~~(a) a VH region of clone 2F3 and a VL region of clone 2F3;~~

~~(b) a VH region of clone 11C2 and a VL region of clone 11C2;~~

~~(c) a VH region of clone 1A1 and a VL region of clone 1A1;~~

~~(d) a VH region of clone 7A4 and a VL region of clone 7A4;~~

~~(e) a VH region of clone 7A5 and a VL region of clone 7A5; or~~

~~(f) a VH region of clone 14C1 and a VL region of clone 14C1,~~

~~— wherein the VH and VL region is linked by at least one linker.~~

~~[0007d] — In another aspect, the present disclosure refers to an immune cell comprising the chimeric antigen receptor as described herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the cell as described herein. In another aspect, the present disclosure refers to an isolated polynucleotide comprising a sequence encoding the chimeric antigen receptor as described herein. In yet another aspect, the present disclosure refers to an isolated polypeptide comprising the amino acid sequence of construct 2F3-CD28T-CD28-41BB, construct 2F3-CD28T-CD28, construct 2F3-CD28T-41BB, construct 2F3-C8K-CD28, construct 2F3-C8K-41BB, construct 11C2-CD28T-CD28-41BB, construct 11C2-CD28T-CD28, construct~~

~~11C2-CD28T-41BB, construct 11C2-C8K-CD28, construct 11C2-C8K-41BB, construct 1A1-CD28T-CD28-41BB, construct 1A1-CD28T-CD28, construct 1A1-CD28T-41BB, construct 1A1-C8K-CD28, construct 1A1-C8K-41BB, construct 7A4-CD28T-CD28-41BB, construct 7A4-CD28T-CD28, construct 7A4-CD28T-41BB, construct 7A4-C8K-CD28, construct 7A4-C8K-41BB, construct 7A5-CD28T-CD28-41BB, construct 7A5-CD28T-CD28, construct 7A5-CD28T-41BB, construct 7A5-C8K-CD28, construct 7A5-C8K-41BB, construct 14C1-CD28T-CD28-41BB, construct 14C1-CD28T-CD28, construct 14C1-CD28T-41BB, construct 14C1-C8K-CD28, or construct 14C1-C8K-41BB~~2F3-CD28.

~~[0007e]~~ — In a further aspect, the present disclosure refers to a vector encoding the polypeptide as described herein. In a further aspect, the present disclosure refers to an immune cell comprising the polypeptide as described herein. In a further aspect, the present disclosure 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 a variable heavy chain CDR3 comprising the amino acid sequence of a variable heavy chain CDR3 of clone 2F3, clone 11C2, clone 1A1, clone 7A4, clone 7A5, or clone 14C1. In a further aspect, the present disclosure refers to isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), said CAR or TCR comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises:

- a. ~~a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; and/or~~
- b. ~~a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.~~

~~[0007f]~~ — In another aspect, the present disclosure 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 heavy chain comprises CDR1 (SEQ ID NO:89), CDR2 (SEQ ID NO:90), and CDR3 (SEQ ID NO:91) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:94), CDR2 (SEQ ID NO:95), and CDR3 (SEQ ID NO:96), or wherein the antigen binding molecule heavy chain

~~comprises CDR1 (SEQ ID NO:99), CDR2 (SEQ ID NO:100), and CDR3 (SEQ ID NO:101) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:104), CDR2 (SEQ ID NO:105), and CDR3 (SEQ ID NO:106), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:109), CDR2 (SEQ ID NO:110), and CDR3 (SEQ ID NO:111) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:114), CDR2 (SEQ ID NO:115), and CDR3 (SEQ ID NO:116), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:119), CDR2 (SEQ ID NO:120), and CDR3 (SEQ ID NO:121) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:124), CDR2 (SEQ ID NO:125), and CDR3 (SEQ ID NO:126), wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:129), CDR2 (SEQ ID NO:130), and CDR3 (SEQ ID NO:131) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:134), CDR2 (SEQ ID NO:135), and CDR3 (SEQ ID NO:136), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:139), CDR2 (SEQ ID NO:140), and CDR3 (SEQ ID NO:141) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:144), CDR2 (SEQ ID NO:145), and CDR3 (SEQ ID NO:146).~~

~~[0007g] — In yet another aspect, the present disclosure refers to the polynucleotide as described herein; or the polypeptide as described herein; or the chimeric antigen receptor as described herein; or the cell as described herein or the pharmaceutical composition as described herein for use in therapy. In yet another aspect, the present disclosure refers to use of the polynucleotide as described herein; or the polypeptide as described herein; or the chimeric antigen receptor as described herein; or the cell as described herein; or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or disorder 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 144 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

- g) 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.
- ~~a) a variable heavy chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:89, 99, 109, 119, 129, or 139; or~~
- ~~b) a variable heavy chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:90, 100, 110, 120, 130, or 140; or~~
- ~~c) a variable heavy chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:91, 101, 111, 121, 131, or 141; or~~
- ~~d) a variable light chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:94, 104, 114, 124, 134, or 144; or~~
- ~~e) a variable light chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:95, 105, 115, 125, 135, or 145; or~~
- ~~f) a variable light chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ IDs:96, 106, 116, 126, 136, or 146; or~~
- ~~g) a variable heavy chain CDR1 comprising an amino acid sequence of a variable heavy chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
- ~~h) a variable heavy chain CDR2 comprising an amino acid sequence of a variable heavy chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~

- ~~i) a variable heavy chain CDR3 comprising an amino acid sequence of a variable heavy chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - ~~j) a variable light chain CDR1 comprising an amino acid sequence of a variable light chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - ~~k) a variable light chain CDR2 comprising an amino acid sequence of a variable light chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - ~~l) a variable light chain CDR3 comprising an amino acid sequence of a variable light chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - ~~m) a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or~~
 - ~~n) a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.~~
- ~~2. The chimeric antigen receptor according to claim 1 further comprising at least one costimulatory domain or activating domain, wherein the costimulatory domain is a signaling region of CD28, 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 I 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, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT-AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.~~
- ~~3. The chimeric antigen receptor according to claim 2 wherein the CD28 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid~~

~~residues from the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:8 or the CD8 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:14.~~

~~4.2.~~ The chimeric antigen receptor according to claim ~~2-1~~ wherein the activating domain comprises ~~CD3 or CD3 zeta~~, wherein the CD3 zeta comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.

~~5. The chimeric antigen receptor according to claim 1 wherein the costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:2 and the activating domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.~~

~~6.3.~~ A polynucleotide encoding the chimeric antigen receptor of claim 1.

~~4. A vector comprising the polynucleotide of claim 3.~~

~~7.5.~~ A The vector according comprising the polynucleotide of to claim ~~64~~ which, wherein the ~~vector~~ 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.

~~8.6.~~ An immune cell comprising the vector of claim ~~47~~.

~~9.7.~~ The immune cell according to claim ~~68~~, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

~~10.8.~~ The immune cell according to claim ~~97~~, wherein the cell is an autologous T cell.

~~11.9.~~ The immune cell according to claim ~~97~~, wherein the cell is an allogeneic T cell.

~~10.~~ The immune cell of claim ~~86~~, wherein the vector is introduced into a cell that is isolated from a patient's body ~~or donor's body~~ or that is grown from a sample taken from a patient's body ~~or donor's body~~.

~~12.11.~~ 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.

~~13.12.~~ A pharmaceutical composition comprising an immune cell of claim ~~86~~.

~~14. A chimeric antigen receptor comprising:~~

~~(a) a VH region of clone 2F3 and a VL region of clone 2F3;~~

~~(b) a VH region of clone 11C2 and a VL region of clone 11C2;~~

- ~~(c) a VH region of clone 1A1 and a VL region of clone 1A1;~~
 - ~~(d) a VH region of clone 7A4 and a VL region of clone 7A4;~~
 - ~~(e) a VH region of clone 7A5 and a VL region of clone 7A5; or~~
 - ~~(f) a VH region of clone 14C1 and a VL region of clone 14C1,~~
 - ~~— wherein the VH and VL region is linked by at least one linker.~~
- ~~15. The chimeric antigen receptor according to claim 14, wherein the linker comprises the scFv G4S linker or the scFv Whitlow linker.~~
- ~~16. The chimeric antigen receptor according to claim 15, further comprising a costimulatory domain or an activating domain, wherein the costimulatory domain is a signaling region of CD28, 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 I 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, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT-AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.~~
- ~~17. An immune cell comprising the chimeric antigen receptor of claim 14.~~
- ~~18. A pharmaceutical composition comprising the cell of claim 17.~~
- ~~19. An isolated polynucleotide comprising a sequence encoding the chimeric antigen receptor of claim 14.~~
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.

~~20. construct 2F3-CD28T-CD28-41BB, construct 2F3-CD28T-CD28, construct 2F3-CD28T-41BB, construct 2F3-C8K-CD28, construct 2F3-C8K-41BB, construct 11C2-CD28T-CD28-41BB, construct 11C2-CD28T-CD28, construct 11C2-CD28T-41BB, construct 11C2-C8K-CD28, construct 11C2-C8K-41BB, construct 1A1-CD28T-CD28-41BB, construct 1A1-CD28T-CD28, construct 1A1-CD28T-41BB, construct 1A1-C8K-CD28, construct 1A1-C8K-41BB, construct 7A4-CD28T-CD28-41BB, construct 7A4-CD28T-CD28, construct 7A4-CD28T-41BB, construct 7A4-C8K-CD28, construct 7A4-C8K-41BB, construct 7A5-CD28T-CD28-41BB, construct 7A5-CD28T-CD28, construct 7A5-CD28T-41BB, construct 7A5-C8K-CD28, construct 7A5-C8K-41BB, construct 14C1-CD28T-CD28-41BB, construct 14C1-CD28T-CD28, construct 14C1-CD28T-41BB, construct 14C1-C8K-CD28, or construct 14C1-C8K-41BB~~~~2F3-CD28.~~

~~21.14.~~ A vector encoding the polypeptide of claim ~~13~~20.

~~22.15.~~ An immune cell comprising the polypeptide of claim ~~14~~20.

~~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.

~~23.~~—a variable heavy chain CDR3 comprising the amino acid sequence of a variable heavy chain CDR3 of clone 2F3, clone 11C2, clone 1A1, clone 7A4, clone 7A5, or clone 14C1.

~~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.

24. ~~An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), said CAR or TCR comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises:~~
- ~~a. a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; and/or~~
 - ~~b. a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.~~
25. ~~The polynucleotide according to claim 24 further comprising an activating domain, wherein the activating domain is CD3 or CD3 zeta.~~
26. ~~The polynucleotide according to claim 25 wherein the CD3 zeta comprises the amino acid sequence set forth in SEQ ID NO:9.~~
27. ~~The polynucleotide according to claim 24 further comprising a costimulatory domain, wherein the costimulatory domain is a signaling region of CD28, 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 I 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, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDI Id, ITGAE, CD103, ITGAL, CDI Ia, LFA-1, ITGAM, CDI Ib, ITGAX, CDI Ic, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT-AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.~~
28. ~~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 heavy chain comprises CDR1 (SEQ ID NO:89), CDR2 (SEQ ID NO:90), and CDR3 (SEQ ID NO:91) and the antigen binding molecule light chain comprises~~

~~CDR1 (SEQ ID NO:94), CDR2 (SEQ ID NO:95), and CDR3 (SEQ ID NO:96), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:99), CDR2 (SEQ ID NO:100), and CDR3 (SEQ ID NO:101) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:104), CDR2 (SEQ ID NO:105), and CDR3 (SEQ ID NO:106), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:109), CDR2 (SEQ ID NO:110), and CDR3 (SEQ ID NO:111) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:114), CDR2 (SEQ ID NO:115), and CDR3 (SEQ ID NO:116), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:119), CDR2 (SEQ ID NO:120), and CDR3 (SEQ ID NO:121) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:124), CDR2 (SEQ ID NO:125), and CDR3 (SEQ ID NO:126), wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:129), CDR2 (SEQ ID NO:130), and CDR3 (SEQ ID NO:131) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:134), CDR2 (SEQ ID NO:135), and CDR3 (SEQ ID NO:136), or wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:139), CDR2 (SEQ ID NO:140), and CDR3 (SEQ ID NO:141) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:144), CDR2 (SEQ ID NO:145), and CDR3 (SEQ ID NO:146).~~

~~29.25.~~ The polynucleotide according to ~~claim~~ any one of claims ~~6, 19, 3~~ or ~~23-28~~19; or the polypeptide according to claim 2013; or the chimeric antigen receptor according to any one of claims ~~1-5, or 14-16~~2; or the cell according to any one of claims ~~86-12, 17, or 22~~11; or the pharmaceutical composition according to ~~any one of claims 13 or 18~~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.

~~30.27.~~ Use of the polynucleotide according to any one of claims ~~63 or, 19, or 23-28~~3; or the polypeptide according to claim 2013; or the chimeric antigen receptor according to any one of claims ~~1-52, or 14-16~~2; or the cell according to any one of claims ~~86-1211, 17, or 22~~11; or the pharmaceutical composition according to ~~any one of claims 13 or 18~~claim 12 in the manufacture of a medicament for treating ~~a disease or disorder~~cancer in a subject in need thereof.

~~31. The use according to claim 29, wherein the disease or disorder is cancer.~~

~~32.28.~~ The use according to claim 30-27 wherein the cancer is prostate cancer.

~~33.29.~~ The use according to claim ~~31~~28, wherein the cancer is metastatic castration resistant prostate cancer.

FIG. 2

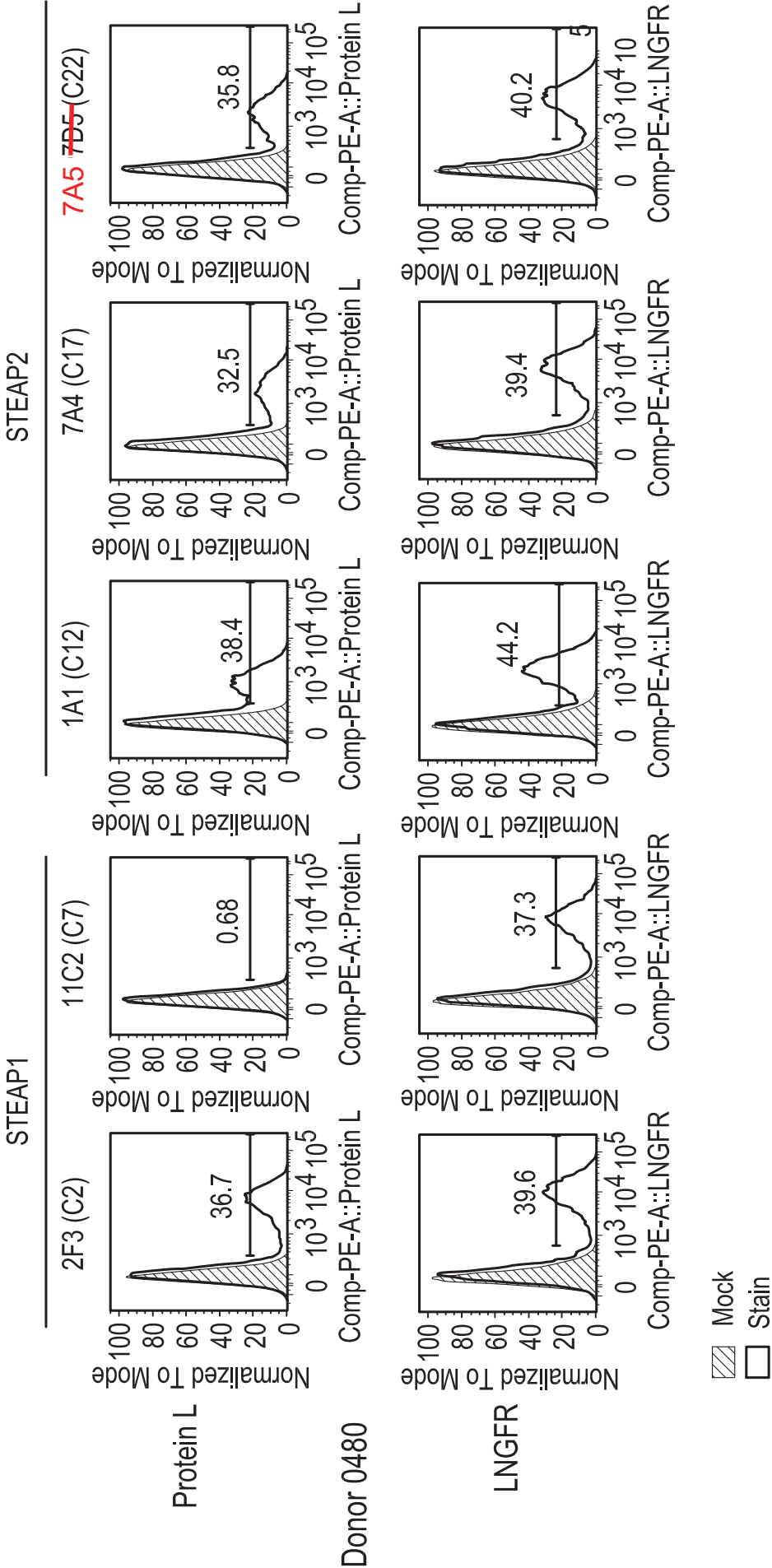
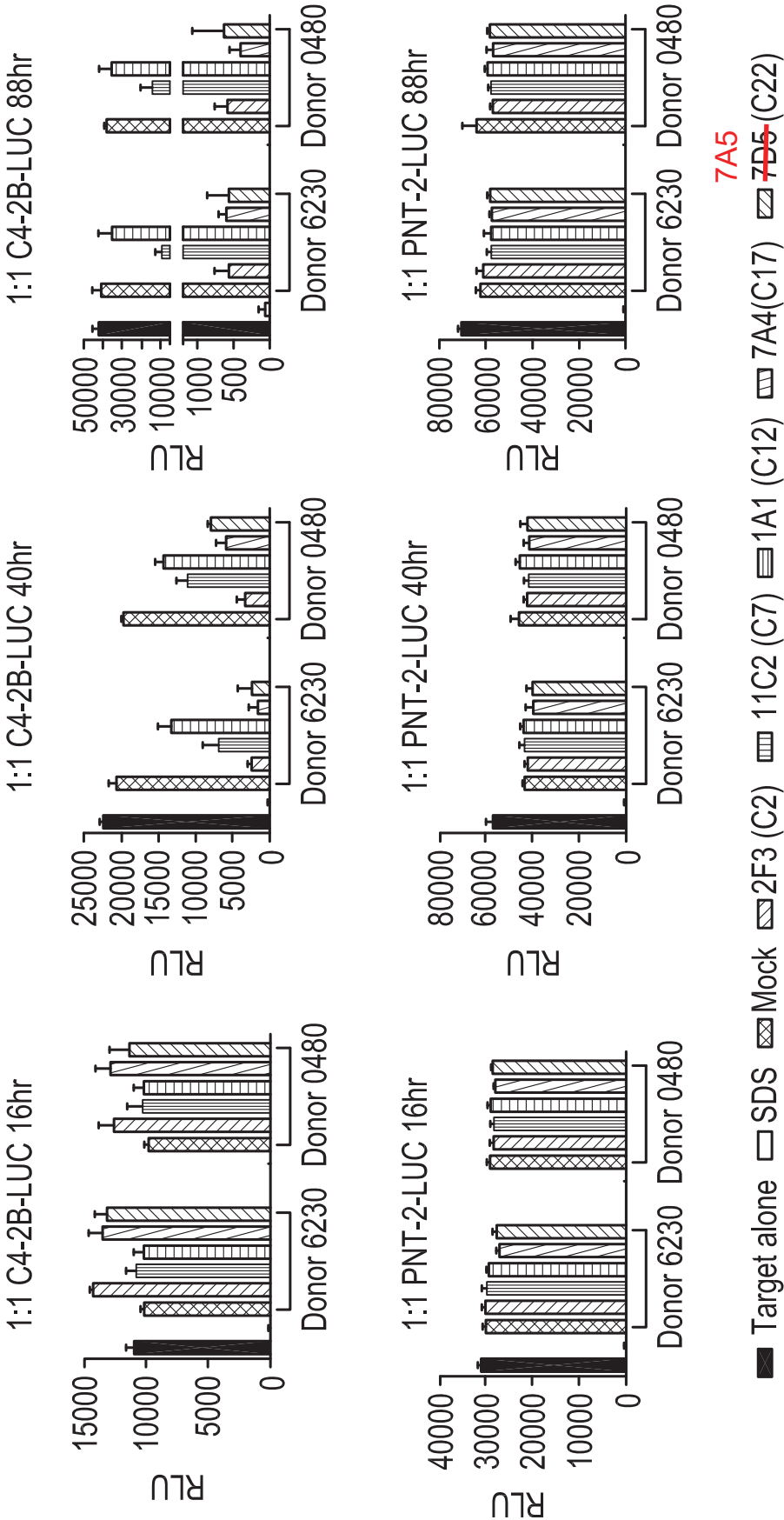


FIG. 3



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FIG. 4

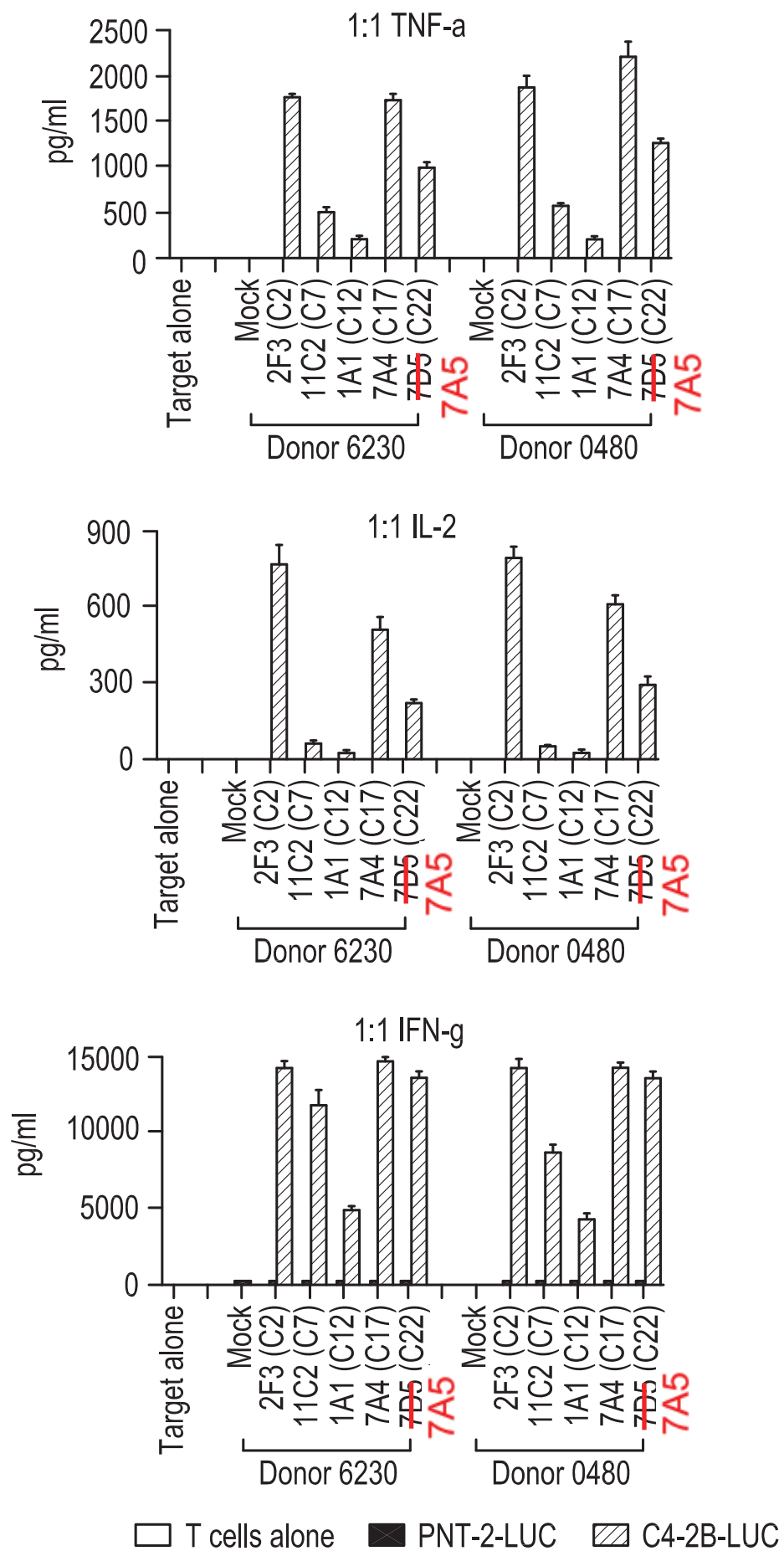


FIG. 5

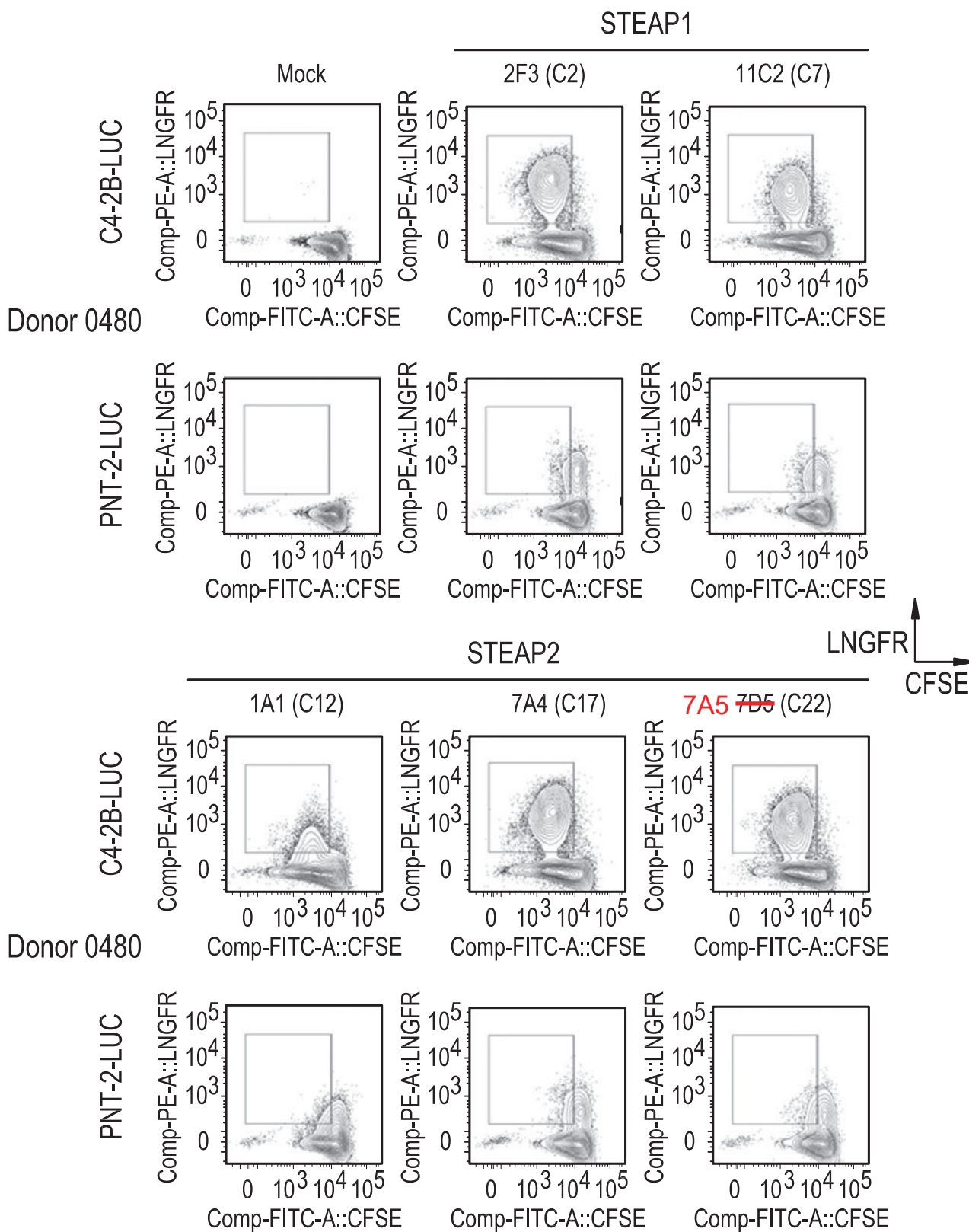


FIG. 5 Cont'd

