CLAIMS

1. A cell comprising a first chimeric antigen receptor (CAR) and a second CAR, each of which comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the antigen binding domain of said first CAR binds to a B-Cell antigen and the antigen binding domain of said second CAR binds to a tumor antigen other than a B-Cell antigen, for use in a method of treating cancer in a subject wherein said method comprises administering the cell to the subject, wherein said administering of the cell enhances proliferation of the cell in the subject compared to administering a cell expressing the second CAR which does not express the first CAR.

2. A first chimeric antigen receptor (CAR) comprising: an antigen binding domain that binds to a B-Cell antigen, a transmembrane domain, and an intracellular signaling domain,

for use in a method of enhancing the anti-tumor efficacy of a cell expressing a second CAR in the treatment of cancer in a subject,

wherein the method comprises administering to the subject a cell comprising said first CAR and said second CAR,

wherein said second CAR comprises: an antigen binding domain that binds to a tumor antigen other than a B-Cell antigen, a transmembrane domain, and an intracellular signaling domain, and

wherein said method increases the proliferation of said cell compared to a cell expressing said second CAR which does not express said first CAR.

3. The cell or CAR for use according to claim 1 or 2, wherein

(i) the tumor antigen other than a B-Cell antigen is:

  (a) a solid tumor antigen;

  (b) a myeloid tumor antigen; or

  (c) an antigen of a hematological tumor not of B-cell lineage; or

(ii) the cancer is a solid tumor or a hematological tumor not of B-cell lineage, optionally wherein said subject has a tumor characterized as glioblastoma, ovarian cancer, lung cancer, prostate cancer, colorectal cancer, pancreatic cancer, breast carcinoma, adenocarcinoma or mesothelioma.

4. The cell or CAR for use according to any one of claims 1-3, wherein said B-Cell antigen is selected from the group consisting of CD19, CD5, CD10, CD20, CD21, CD22, CD23, CD24, CD25, CD27, CD30, CD34, CD37, CD38, CD40, CD53, CD69, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD86, CD123, CD135, CD138, CD179, CD269, Flt3, ROR1, BCMA, FcRn5, FcRn2, CS-1, CXCR4, 5, 7, IL-7/3R, IL7/4/3R, and IL4R.

5. The cell or CAR for use according to any one of claims 1-4, wherein

(a) said B-Cell antigen is CD19, optionally wherein:

(i) said antigen binding domain of said first CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any heavy chain binding domain amino acid sequence listed in Table 6, Table 7 or Table 9;

(ii) said antigen binding domain of said first CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any light chain binding domain amino acid sequence listed in Table 6, Table 8 or Table 9;

(iii) said antigen binding domain of said first CAR comprises: the amino acid sequence of any light chain variable region listed in Table 6 or Table 9; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the light chain variable regions provided in Table 6 or Table 9; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable regions provided in Table 6 or Table 9;

(iv) said antigen binding domain of said first CAR comprises: the amino acid sequence of any heavy chain variable region listed in Table 6 or Table 9; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable regions provided in Table 6 or Table 9; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable regions provided in Table 6 or Table 9;

(v) said antigen binding domain of said first CAR comprises a polypeptide having the amino acid sequence of any light chain variable region listed in Table 6 or Table 9, and the amino acid sequence of any heavy chain variable region listed in Table 6 or Table 9;

(vi) said antigen binding domain of said first CAR comprises a polypeptide having a sequence of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, or SEQ ID NO: 112; or

(vii) the first CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, and SEQ ID NO: 281; or

(b) said B-Cell antigen is BCMA, optionally wherein:

(i) said antigen binding domain of said first CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any heavy chain binding domain amino acid sequence listed in Table 12 or 13;

(ii) said antigen binding domain of said first CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any light chain binding domain amino acid sequence listed in Table 12 or 13;

(iii) said antigen binding domain of said first CAR comprises: the amino acid sequence of any light chain variable region listed in Table 12 or 13; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the light chain variable regions provided in Table 12 or 13; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable regions provided in Table 12 or 13;

(iv) said antigen binding domain of said first CAR comprises: the amino acid sequence of any heavy chain variable region listed in Table 12 or 13; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable regions provided in Table 12 or 13; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable regions provided in Table 12 or 13;

(v) said antigen binding domain of said first CAR comprises a polypeptide having the amino acid sequence of any light chain variable region listed in Table 12 or 13, and the amino acid sequence of any heavy chain variable region listed in Table 12 or 13;

(vi) said antigen binding domain of said first CAR comprises a polypeptide having a sequence of SEQ ID NO: 349; SEQ ID NO: 339, SEQ ID NO: 340; SEQ ID NO: 341; SEQ ID NO: 342; SEQ ID NO: 343; SEQ ID NO: 344, SEQ ID NO: 345, SEQ ID NO: 346, SEQ ID NO: 347, SEQ ID NO: 348, SEQ ID NO: 350, SEQ ID NO: 351, SEQ ID NO: 352, SEQ ID NO: 353, SEQ ID NO: 429, SEQ ID NO: 430, SEQ ID NO: 431, SEQ ID NO: 432, SEQ ID NO: 433, SEQ ID NO: 434, SEQ ID NO: 435, SEQ ID NO: 436, SEQ ID NO: 437, SEQ ID NO: 438, SEQ ID NO: 439, SEQ ID NO: 440, SEQ ID NO: 441, SEQ ID NO: 442, SEQ ID NO: 443, SEQ ID NO: 444, SEQ ID NO: 445, SEQ ID NO: 446, SEQ ID NO: 447, SEQ ID NO: 448, SEQ ID NO: 449, SEQ ID NO: 563, SEQ ID NO: 564, SEQ ID NO: 565 or SEQ ID NO: 566; or

(vii) the first CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 949, SEQ ID NO: 950, SEQ ID NO: 951, SEQ ID NO: 952, SEQ ID NO: 953, SEQ ID NO: 954, SEQ ID NO: 955, SEQ ID NO: 956, SEQ ID NO: 957, SEQ ID NO: 958, SEQ ID NO: 959, SEQ ID NO: 960, SEQ ID NO: 961, SEQ ID NO: 962, SEQ ID NO: 963, SEQ ID NO: 979, SEQ ID NO: 980, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 985, SEQ ID NO: 986, SEQ ID NO: 987, SEQ ID NO: 988, SEQ ID NO: 989, SEQ ID NO: 990, SEQ ID NO: 991, SEQ ID NO: 992, SEQ ID NO: 993, SEQ ID NO: 994, SEQ ID NO: 995, SEQ ID NO: 996, SEQ ID NO: 997, SEQ ID NO: 998, and SEQ ID NO: 999.

6. The cell or CAR for use according to any one of claims 1-5, wherein said second CAR binds a solid tumor antigen, wherein said solid tumor antigen is selected from the group consisting of EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFRα4, and a peptide of any of these antigens presented on MHC.

7. The cell or CAR for use according to claim 6, wherein

(a) said solid tumor antigen is EGFRvIII, optionally wherein:

(i) said antigen binding domain of said second CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any anti-EGFRvIII heavy chain binding domain amino acid sequence listed in Table 5;

(ii) said antigen binding domain of said second CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any anti-EGFRvIII light chain binding domain amino acid sequence listed in Table 5;

(iii) said antigen binding domain of said second CAR comprises: the amino acid sequence of any anti-EGFRvIII light chain variable region listed in Table 5; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the anti-EGFRvIII light chain variable regions provided in Table 5; or an amino acid sequence with 95-99% identity

to the amino acid sequence of any of the anti-EGFRvIII light chain variable regions provided in Table 5;

(iv) said antigen binding domain of said second CAR comprises: the amino acid sequence of any anti-EGFRvIII heavy chain variable region listed in Table 5; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the anti-EGFRvIII heavy chain variable regions provided in Table 5; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the anti-EGFRvIII heavy chain variable regions provided in Table 5;

(v) said antigen binding domain of said second CAR comprises a polypeptide having the amino acid sequence of any anti-EGFRvIII light chain variable region listed in Table 5, and the amino acid sequence of any anti-EGFRvIII heavy chain variable region listed in Table 5;

(vi) said antigen binding domain of said second CAR comprises a polypeptide having a sequence of any of SEQ ID NOS: 71-79; or

(vii) the second CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 1043, SEQ ID NO: 1049, SEQ ID NO: 1055, SEQ ID NO: 1061, SEQ ID NO: 1067, SEQ ID NO: 1073, SEQ ID NO: 1079, SEQ ID NO: 1085, SEQ ID NO: 1090, and SEQ ID NO: 1096; or

(b) said solid tumor antigen is mesothelin, optionally wherein:

(i) said antigen binding domain of said second CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any heavy chain binding domain amino acid sequence listed in Table 2 or 3;

(ii) said antigen binding domain of said second CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any light chain binding domain amino acid sequence listed in Table 2 or 4;

(iii) said antigen binding domain of said second CAR comprises: the amino acid sequence of any light chain variable region listed in Table 2; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the light chain variable regions provided in Table 2; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable regions provided in Table 2;

(iv) said antigen binding domain of said second CAR comprises: the amino acid sequence of any heavy chain variable region listed in Table 2; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable regions provided in Table 2; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable regions provided in Table 2;

(v) said antigen binding domain of said second CAR comprises a polypeptide having the amino acid sequence of any light chain variable region listed in Table 2, and the amino acid sequence of any heavy chain variable region listed in Table 2;

(vi) said antigen binding domain of said second CAR comprises a polypeptide having a sequence of any one of SEQ ID NOS: 46-70; or

(vii) the second CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, and SEQ ID NO: 306.

8. The cell or CAR for use according to any one of claims 1-7, wherein said administering of the cell results in partial or complete elimination of said cancer and, thereafter, continue to persist in said subject at a level greater than, or for a length of time longer than, otherwise identical cells that lack said first CAR.

9. A cell comprising a first chimeric antigen receptor (CAR) and a second CAR, each of which comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, wherein

(a) the antigen binding domain of said first CAR binds to CD19, wherein:

(i) said antigen binding domain of said first CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any heavy chain binding domain amino acid sequence listed in Table 6, Table 7 or Table 9;

(ii) said antigen binding domain of said first CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any light chain binding domain amino acid sequence listed in Table 6, Table 8 or Table 9;

(iii) said antigen binding domain of said first CAR comprises: the amino acid sequence of any light chain variable region listed in Table 6 or Table 9; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the light chain variable regions provided in Table 6 or Table 9; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the light chain variable regions provided in Table 6 or Table 9;

(iv) wherein said antigen binding domain of said first CAR comprises: the amino acid sequence of any heavy chain variable region listed in Table 6 or Table 9; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the heavy chain variable regions provided in Table 6 or Table 9; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the heavy chain variable regions provided in Table 6 or Table 9;

(v) said antigen binding domain of said first CAR comprises a polypeptide having the amino acid sequence of any light chain variable region listed in Table 6 or Table 9, and the amino acid sequence of any heavy chain variable region listed in Table 6 or Table 9;

(vi) said antigen binding domain of said first CAR comprises a polypeptide having a sequence of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, or SEQ ID NO: 112; or

(vii) the first CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, and SEQ ID NO: 281; and

(b) the antigen binding domain of said second CAR binds to EGFRvIII, wherein:

(i) said antigen binding domain of said second CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any anti-EGFRvIII heavy chain binding domain amino acid sequence listed in Table 5;

(ii) said antigen binding domain of said second CAR further comprises a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any anti-EGFRvIII light chain binding domain amino acid sequence listed in Table 5;

(iii) said antigen binding domain of said second CAR comprises: the amino acid sequence of any anti-EGFRvIII light chain variable region listed in Table 5; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the anti-EGFRvIII light chain variable regions provided in Table 5; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the anti-EGFRvIII light chain variable regions provided in Table 5;

(iv) said antigen binding domain of said second CAR comprises: the amino acid sequence of any anti-EGFRvIII heavy chain variable region listed in Table 5; an amino acid sequence having at least one, two or three modifications but not more than 20 or 10 modifications of the amino acid sequence of any of the anti-EGFRvIII heavy

chain variable regions provided in Table 5; or an amino acid sequence with 95-99% identity to the amino acid sequence of any of the anti-EGFRvIII heavy chain variable regions provided in Table 5;

(v) said antigen binding domain of said second CAR comprises a polypeptide having the amino acid sequence of any anti-EGFRvIII light chain variable region listed in Table 5, and the amino acid sequence of any anti-EGFRvIII heavy chain variable region listed in Table 5;

(vi) said antigen binding domain of said second CAR comprises a polypeptide having a sequence of any of SEQ ID NOS: 71-79; or

(vii) the second CAR comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 1043, SEQ ID NO: 1049, SEQ ID NO: 1055, SEQ ID NO: 1061, SEQ ID NO: 1067, SEQ ID NO: 1073, SEQ ID NO: 1079, SEQ ID NO: 1085, SEQ ID NO: 1090, and SEQ ID NO: 1096.

10. A cell comprising a first chimeric antigen receptor (CAR) and a second CAR, each of which comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the antigen binding domain of said first CAR binds to a B-Cell antigen and the antigen binding domain of said second CAR binds to a tumor antigen other than a B-Cell antigen, wherein

(i) the intracellular signaling domain of said first CAR comprises a costimulatory signaling domain, but not a primary signaling domain; and

(ii) the intracellular signaling domain of said second CAR comprises a costimulatory signaling domain and a primary signaling domain.

11. The cell of claim 9 or 10, wherein the cell shows enhanced proliferation or persistence in vivo, compared to an otherwise identical cell that lacks said first CAR.

12. The cell or CAR for use according to any one of claims 1-8, or the cell of any one of claims 9-11, wherein said intracellular signaling domain of said first or said second CAR comprises:

(i) one or more primary signaling domains, optionally wherein the primary signaling domains comprise a CD3-zeta stimulatory domain; and/or

(ii) one or more costimulatory signaling domains, optionally wherein said costimulatory signaling domain is an intracellular domain of a costimulatory protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CDS, CD7, CD287, LIGHT, NKG2C, NKG2D, SLAMF7, NKp80, NKp30, NKp44, NKp46, CD160, B7-H3, and a ligand that specifically binds with CD83, optionally wherein the costimulatory domain of both said first and said second CAR comprise an intracellular domain of 4-1BB; and/or an intracellular domain of CD28.

13. The cell or CAR for use according to any one of claims 1-8 or 12, or the cell of any one of claims 9-12, wherein the first CAR binds to CD19 and the second CAR binds to EGFRvIII.

14. A nucleic acid encoding the first CAR and the second CAR of any one of claims 1-13, optionally wherein the sequence of said first CAR and the sequence of said second CAR are separated by an independent ribosomal entry site, a promoter element, or a sequence encoding a T2A, P2A, E2A, or F2A element.

15. The cell of any one of claims 9-13 for use in a method of treating cancer.