

What is claimed is:

1. An invention not claimed in any divisional application. ~~A cell (e.g., a population of cells), e.g., an immune effector cell, expressing a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein the cell has altered expression and/or function of a Tet2-associated gene (e.g., one or more Tet2-associated genes).~~

2. The cell of claim 1, wherein the cell has reduced or eliminated expression and/or function of a Tet2-associated gene.

3. The cell of claim 1 or 2, wherein the cell has increased or activated expression and/or function of a Tet2-associated gene.

4. The cell of any of the preceding claims, wherein the cell has reduced or eliminated expression and/or function of a first Tet2-associated gene, and increased or activated expression and/or function of a second Tet2-associated gene.

5. The cell of any of the preceding claims, wherein the cell further has reduced or eliminated expression and/or function of Tet2.

6. The cell of any of the preceding claims, wherein the Tet2-associated gene comprises one or more (e.g., 2, 3, 4, 5, or all) genes chosen from IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

7. The cell of claim 6, wherein the cell has reduced or eliminated expression and/or function of one or more (e.g., 2, 3, 4, 5, or all) genes chosen from IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

8. The cell of any of claims 1-4, wherein the Tet2-associated gene comprises one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 8.

9. The cell of claim 8, wherein the cell has reduced or eliminated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 8, Column B.

10. The cell of claim 8 or 9, wherein the cell has increased or activated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 8, Column A.

11. The cell of any of claims 1-4, wherein the Tet2-associated gene comprises one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 9, Column D.

12. The cell of claim 11, wherein the cell has reduced or eliminated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 9, Column D.

13. The cell of claim 11 or 12, wherein the cell has increased or activated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 9, Column D.

14. The cell of any of claims 1-4, wherein the Tet2-associated gene comprises one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes in a pathway (e.g., one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pathways) chosen from Table 9, Column A.

15. The cell of claim 14, wherein the cell has reduced or eliminated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 9, Column A.

16. The cell of claim 14 or 15, wherein the cell has increased or activated expression and/or function of one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) genes chosen from Table 9, Column A.

17. The cell of any of claims 14-16, wherein the pathway is chosen from one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or all) of:

- (1) a leukocyte differentiation pathway;
- (2) a pathway of positive regulation of immune system process;
- (3) a transmembrane receptor protein tyrosine kinase signaling pathway;
- (4) a pathway of regulation of anatomical structure morphogenesis;
- (5) a pathway of TNFA signaling via NFkB;
- (6) a pathway of positive regulation of hydrolase activity;
- (7) a wound healing pathway;
- (8) an alpha-beta T cell activation pathway;
- (9) a pathway of regulation of cellular component movement;
- (10) an inflammatory response pathway;
- (11) a myeloid cell differentiation pathway;
- (12) a cytokine production pathway;
- (13) a pathway of downregulation in UV response;
- (14) a pathway of negative regulation of multicellular organismal process;
- (15) a blood vessel morphogenesis pathway;

- (16) a NFAT dependent transcription pathway;
(17) a pathway of positive regulation of apoptotic process;
(18) a hypoxia pathway;
(19) a pathway of upregulation by KRAS signaling; or
(20) a pathway of stress activated protein kinase signaling cascade.

18. The cell of claim 17, wherein the one or more genes associated with a leukocyte differentiation pathway are chosen from Table 9, Row 1.

19. The cell of claim 17, wherein the one or more genes associated with a pathway of positive regulation of immune system process are chosen from Table 9, Row 56.

20. The cell of claim 17, wherein the one or more genes associated with a transmembrane receptor protein tyrosine kinase signaling pathway are chosen from Table 9, Row 85.

21. The cell of claim 17, wherein the one or more genes associated with a pathway of regulation of anatomical structure morphogenesis are chosen from Table 9, Row 128.

22. The cell of claim 17, wherein the one or more genes associated with a pathway of TNFA signaling via NFkB are chosen from Table 9, Row 134.

23. The cell of claim 17, wherein the one or more genes associated with a pathway of positive regulation of hydrolase activity are chosen from Table 9, Row 137.

24. The cell of claim 17, wherein the one or more genes associated with a wound healing pathway are chosen from Table 9, Row 141.

25. The cell of claim 17, wherein the one or more genes associated with a alpha-beta T cell activation pathway are chosen from Table 9, Row 149.

26. The cell of claim 17, wherein the one or more genes associated with a pathway of regulation of cellular component movement are chosen from Table 9, Row 180.

27. The cell of claim 17, wherein the one or more genes associated with an inflammatory response pathway are chosen from Table 9, Row 197.

28. The cell of claim 17, wherein the one or more genes associated with a myeloid cell differentiation pathway are chosen from Table 9, Row 206.

29. The cell of claim 17, wherein the one or more genes associated with a cytokine production pathway are chosen from Table 9, Row 221.

30. The cell of claim 17, wherein the one or more genes associated with a pathway of downregulation in UV response are chosen from Table 9, Row 233.

31. The cell of claim 17, wherein the one or more genes associated with a pathway of negative regulation of multicellular organismal process are chosen from Table 9, Row 235.

32. The cell of claim 17, wherein the one or more genes associated with a blood vessel morphogenesis pathway are chosen from Table 9, Row 237.

33. The cell of claim 17, wherein the one or more genes associated with a NFAT dependent transcription pathway are chosen from Table 9, Row 243.

34. The cell of claim 17, wherein the one or more genes associated with a pathway of positive regulation of apoptotic process are chosen from Table 9, Row 250.

35. The cell of claim 17, wherein the one or more genes associated with a hypoxia pathway are chosen from Table 9, Row 256.

36. The cell of claim 17, wherein the one or more genes associated with a pathway of upregulation by KRAS signaling are chosen from Table 9, Row 258.

37. The cell of claim 17, wherein the one or more genes associated with a pathway of stress-activated protein kinase signaling cascade are chosen from Table 9, Row 260.

38. The cell of claim 1 or 2, wherein the Tet2 associated gene comprises a gene (e.g., one or more genes) associated with a central memory phenotype.

39. The cell of claim 38, wherein the central memory phenotype is a central memory T cell phenotype.

40. The cell of claim 38 or 39, wherein the central memory phenotype comprises a higher expression level of CCR7 and/or CD45RO, compared to the expression level of CCR7 and/or CD45RO in a naïve cell (e.g., a naïve T cell).

41. The cell of any of claims 38-40, wherein the central memory phenotype comprises a lower expression level of CD45RA, compared to the expression level of CD45RA in a naïve cell (e.g., a naïve T cell).

42. The cell of any of claims 38-41, wherein the central memory phenotype comprises enhanced antigen-dependent proliferation of the cell.

43. The cell of any of claims 38-42, wherein the central memory phenotype comprises a reduced expression level of IFN- γ and/or CD107a, e.g., when the cell is activated with an anti-CD3 or anti-CD28 antibody.

44. The cell of any of the preceding claims, wherein the cell comprises a modulator (e.g., an inhibitor or an activator) of the Tet2-associated gene.

45. The cell of claim 41, wherein the modulator (e.g., inhibitor or activator) is (1) a gene editing system targeted to one or more sites within the Tet2-associated gene or a regulatory element thereof; (2) a nucleic acid encoding one or more components of said gene editing system; or (3) a combination thereof.

46. The cell of claim 45, wherein the gene editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, and a meganuclease system.

47. The cell of claim 45 or 46, wherein the gene editing system binds to a target sequence in an early exon or intron of the Tet2-associated gene.

48. The cell of any of claims 45-47, wherein the gene editing system binds a target sequence of the Tet2-associated gene, and the target sequence is upstream of exon 4, e.g., in exon 1, exon 2, or exon 3.

49. The cell of any of claims 45-48, wherein the gene editing system binds to a target sequence in a late exon or intron of the Tet2-associated gene.

50. The cell of any of claims 45-49, wherein the gene editing system binds a target sequence of the Tet2-associated gene, and the target sequence is downstream of a preantepenultimate exon, e.g., is in an antepenultimate exon, a penultimate exon, or a last exon.

51. The cell of any of claims 45-50, wherein the gene editing system is a CRISPR/Cas system comprising a gRNA molecule comprising a targeting sequence which hybridizes to a target sequence of the Tet2-associated gene.

52. The cell of claim 44, wherein the modulator (e.g., inhibitor) is an siRNA or shRNA specific for the Tet2-associated gene, or nucleic acid encoding said siRNA or shRNA.

53. The cell of claim 52, wherein the siRNA or shRNA comprises a sequence complementary to a sequence of an mRNA of the Tet2-associated gene.

54. The cell of claim 44, wherein the modulator (e.g., inhibitor or activator) is a small molecule.

55. The cell of claim 44, wherein the modulator (e.g., inhibitor or activator) is a protein.

56. The cell of claim 55, wherein the modulator (e.g., inhibitor) is a dominant negative binding partner of a protein encoded by the Tet2-associated gene, or a nucleic acid encoding said dominant negative binding partner.

57. The cell of claim 55, wherein the modulator (e.g., inhibitor) is a dominant negative (e.g., catalytically inactive) variant of a protein encoded by the Tet2-associated gene, or a nucleic acid encoding said dominant negative variant.

58. The cell of any of the preceding claims, wherein the cell comprises an inhibitor of a first Tet2-associated gene and an activator of a second Tet2-associated gene.

59. The cell of any of the preceding claims, wherein the cell further comprises an inhibitor of Tet2.

60. The cell of any of the preceding claims, wherein the antigen binding domain binds to a tumor antigen is selected from a group consisting of: TSHR, CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1, CD33, EGFRvIII, GD2, GD3, BCMA, Tn Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, PRSS21,

VEGFR2, LewisY, CD24, PDGFR beta, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe^x, GM3, TGS5, HMWMAA, o-acetyl GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1a, MAGE-A1, legumain, HPV-E6,E7, MAGE-A1, ETV6-AML, sperm protein 17, XAGE1, Tie-2, MAD-CT-1, MAD-CT-2, Fos-related antigen-1, p53, p53 mutant, prostatein, survivin and telomerase, PCTA-1/Galectin-8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2-ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1.

61. The cell of claim 60, wherein the tumor antigen is CD19.

62. The cell of any of the preceding claims, wherein the antigen-binding domain is an antibody or antibody fragment as described in, e.g., WO2012/079000 or WO2014/153270.

63. The cell of any of the preceding claims, wherein the transmembrane domain comprises: an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 12, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 12; or the sequence of SEQ ID NO: 12.

64. The cell of any of the preceding claims, wherein the antigen-binding domain is connected to the transmembrane domain by a hinge region, wherein said hinge region comprises SEQ ID NO: 2 or SEQ ID NO: 6, or a sequence with 95-99% identity thereof.

65. The cell of any of the preceding claims, wherein the intracellular signaling domain comprises a primary signaling domain and/or a costimulatory signaling domain, wherein the primary signaling domain comprises a functional signaling domain of a protein chosen from CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCER1G), FcR beta (Fc Epsilon R1b), CD79a, CD79b, Fc gamma RIIa, DAP10, or DAP12.

66. The cell of claim 65, wherein the primary signaling domain comprises: an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20, or a sequence with 95-99% identity

to an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20; or the amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20.

67. The cell of any of the preceding claims, wherein the intracellular signaling domain comprises a costimulatory signaling domain, or a primary signaling domain and a costimulatory signaling domain, wherein the costimulatory signaling domain comprises a functional signaling domain of a protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CD86, ICAM-1, GITR, BAFTR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R 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, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, 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, NKp44, NKp30, NKp46, and NKG2D.

68. The cell of claim 67, wherein the costimulatory signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16.

69. The cell of claim 67 or 68, wherein the costimulatory signaling domain comprises a sequence of SEQ ID NO: 14 or SEQ ID NO: 16.

70. The cell of any of the preceding claims, wherein the intracellular domain comprises the sequence of SEQ ID NO: 14 or SEQ ID NO: 16, and the sequence of SEQ ID NO: 18 or SEQ ID NO: 20, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

71. The cell of any of the preceding claims, further comprising a leader sequence comprises the sequence of SEQ ID NO: 2.

72. The cell of any of the preceding claims, wherein the cell is an immune effector cell (e.g., a population of immune effector cells).

73. The cell of claim 72, wherein the immune effector cell is a T cell or an NK cell.

74. The cell of claim 72 or 73, wherein the immune effector cell is a T cell.

75. The cell of claim 73 or 74, wherein the T cell is a CD4⁺ T cell, a CD8⁺ T cell, or a combination thereof.

76. The cell of any of the preceding claims, wherein the cell is a human cell.

77. The cell of any of the preceding claims, wherein the cell comprises an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

78. The cell of claim 77, wherein the inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 is (1) a gene editing system targeted to one or more sites within an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene or a regulatory element thereof; (2) a nucleic acid encoding one or more components of said gene editing system; or (3) a combination thereof.

79. The cell of claim 78, wherein the gene editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, and a meganuclease system.

80. The cell of claim 78 or 79, wherein the gene editing system binds to a target sequence in an early exon or intron of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene.

81. The cell of any of claims 78-80, wherein the gene editing system binds a target sequence of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene, and the target sequence is upstream of exon 4, e.g., in exon1, exon2, or exon3, e.g. in exon 3.

82. The cell of any of claims 78-81, wherein the gene editing system binds to a target sequence in a late exon or intron of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene.

83. The cell of any of claims 78-82, wherein the gene editing system binds a target sequence of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene, and the target sequence is downstream of a preantepenultimate exon, e.g., is in an antepenultimate exon, a penultimate exon, or a last exon.

84. The cell of any of claims 78-83, wherein the gene editing system is a CRISPR/Cas system comprising a gRNA molecule comprising a targeting sequence which hybridizes to a target sequence of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene.

85. The cell of claim 84, wherein the inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 is an siRNA or shRNA specific for IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1, or nucleic acid encoding said siRNA or shRNA.

86. The cell of claim 85, wherein the siRNA or shRNA comprises a sequence complementary to a sequence of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 mRNA.

87. The cell of claim 77, wherein the inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 is a small molecule.

88. The cell of claim 77, wherein the inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 is a protein, e.g., is a dominant negative binding partner of a protein encoded by an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene, or a nucleic acid encoding said dominant negative binding partner.

89. The cell of claim 77, wherein the inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 is a protein, e.g., is a dominant negative (e.g., catalytically inactive) variant of a protein encoded by an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene, or a nucleic acid encoding said dominant negative variant.

90. A method of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell of any of the preceding claims, e.g., a CAR19-expressing cell (e.g., CTL019 or CTL119), comprising a step of altering (e.g., decreasing or increasing) expression and/or function of a Tet2-associated gene (e.g., one or more Tet2-associated genes) in said cell, wherein the Tet2-associated gene is chosen from one or more (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

91. The method of claim 90 or 91, comprising altering (e.g., decreasing) expression and/or function of one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

92. The method of any of claims 90-92, further comprising altering (e.g., decreasing) expression and/or function of Tet2.

93. A method of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell of any of the preceding claims, e.g., a CAR19-expressing cell (e.g., CTL019 or CTL119), comprising a step of contacting said cell with a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

(i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;

(ii) one or more genes listed in Table 8;

(iii) one or more genes listed in Table 9, Column D;

(iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or

(v) one or more genes associated with a central memory phenotype.

94. The method of claim 93, wherein said step comprises contacting said cells with an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

95. The method of claim 93 or 94, wherein the inhibitor is selected from the group consisting of: (1) a gene editing system targeted to one or more sites within the Tet2-associated gene, or a regulatory element thereof; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of the Tet2-associated gene; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) encoded by the Tet2-associated gene, or a binding partner of a protein encoded by the Tet2-associated gene; (4) a small molecule that inhibits expression and/or function of the Tet2-associated gene; (5) a nucleic acid encoding any of (1)-(3); and (6) any combination of (1)-(5).

96. The method of any of claims 93-95, further comprising contacting said cell with an inhibitor of Tet2.

97. The method of any of claims 93-96, wherein said contacting occurs *ex vivo*.

98. The method of any of claims 93-97, wherein the contacting occurs *in vivo*.

99. The method of claim 98, wherein the contacting occurs *in vivo* prior to delivery of nucleic acid encoding a CAR into the cell.

100. The method of claim 98, wherein the contacting occurs *in vivo* after the cells have been administered to a subject in need thereof.

101. A method for treating a cancer in a subject, the method comprising administering to said subject an effective amount of the cell of any of claims 1-91.

102. The method of claim 101, further comprising administering to said subject a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from one or more (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

103. The method of claim 101 or 102, further comprising administering to said subject an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

104. The method of any of claims 101-103, further comprising administering to said subject an inhibitor of Tet2.

105. A cell for use in a method of treating a subject in need thereof, the method comprising administering to said subject an effective amount of the cell of any of claims 1-91.

106. The cell for use of claim 105, wherein the method further comprises administering to said subject a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

107. The cell for use of claim 105 or 106, wherein the method further comprises administering to said subject an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

108. The cell for use of any of claims 105-107, wherein the method further comprises administering to said subject an inhibitor of Tet2.

109. A CAR-expressing cell therapy for use in a method of treating a subject in need thereof, the method comprising administering to said subject the CAR-expressing cell therapy and a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

110. The CAR-expressing cell therapy for use of claim 109, wherein the modulator is an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

111. The CAR-expressing cell therapy for use of claim 109 or 110, wherein the method further comprises administering to said subject an inhibitor of Tet2.

112. The CAR-expressing cell therapy for use of any of claims 109-111, wherein the subject receives a pre-treatment of the modulator (e.g., inhibitor), prior to the initiation of the CAR-expressing cell therapy.

113. The CAR-expressing cell therapy for use of any of claims 109-112, wherein the subject receives concurrent treatment with the modulator (e.g., inhibitor) and the CAR-expressing cell therapy.

114. The CAR-expressing cell therapy for use of any of claims 109-113, wherein the subject receives treatment with the modulator (e.g., inhibitor) post-CAR-expressing cell therapy.

115. The CAR-expressing cell therapy for use of any of claims 109-114, wherein the subject has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.

116. The CAR-expressing cell therapy for use of claim 115, wherein the cancer is a hematologic cancer or a solid tumor.

117. The CAR-expressing cell therapy for use of claim 115 or 116, wherein the cancer is a hematologic cancer chosen from one or more of chronic lymphocytic leukemia (CLL), acute

leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell or a large cell follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, or pre-leukemia.

118. The CAR-expressing cell therapy for use of claim 115 or 116, wherein the cancer is selected from the group consisting of colon cancer, rectal cancer, renal cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, and metastatic lesions of said cancers.

119. A method of treating a subject, the method comprising administering to said subject a modulator (e.g., an inhibitor or activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

(i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;

(ii) one or more genes listed in Table 8;

(iii) one or more genes listed in Table 9, Column D;

(iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or

(v) one or more genes associated with a central memory phenotype;

wherein said subject has received, is receiving, or is about to receive therapy comprising a CAR-expressing cell.

120. The method of claim 119, wherein the modulator is an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

121. The method of claim 119 or 120, further comprising administering to said subject an inhibitor of Tet2.

122. A modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) for use in the treatment of a subject, wherein the Tet2-associated gene is chosen from (e.g., 2, 3, 4, or all) of:
(i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
(ii) one or more genes listed in Table 8;
(iii) one or more genes listed in Table 9, Column D;
(iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
(v) one or more genes associated with a central memory phenotype, and wherein said subject has received, is receiving, or is about to receive therapy comprising a CAR-expressing cell.

123. The modulator for use of claim 122, wherein the modulator is an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

124. The modulator for use of claim 122 or 123, wherein subject has received, is receiving, or is about to receive an inhibitor of Tet2.

125. A method of manufacturing a CAR-expressing cell, comprising introducing a nucleic acid encoding a CAR into a cell such that said nucleic acid (or CAR-encoding portion thereof) integrates into the genome of the cell within a Tet2-associated gene (e.g., one or more Tet2-associated genes) (e.g., within an intron or exon of the Tet2-associated gene), such that expression and/or function of the Tet2-associated genes is altered (e.g., reduced or eliminated),

wherein the Tet2-associated gene is chosen from (e.g., 2, 3, 4, or all) of:

(i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;

(ii) one or more genes listed in Table 8;

(iii) one or more genes listed in Table 9, Column D;

(iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or

(v) one or more genes associated with a central memory phenotype.

126. The method of claim 125, wherein the Tet2-associated gene is chosen from IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

127. A method of manufacturing a CAR-expressing cell, comprising contacting said CAR-expressing cell *ex vivo* with a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

128. The method of claim 127, wherein the Tet2-associated gene is chosen from IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

129. A vector comprising sequence encoding a CAR and sequence encoding a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:

- (i) one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;
- (ii) one or more genes listed in Table 8;
- (iii) one or more genes listed in Table 9, Column D;
- (iv) one or more genes associated with one or more pathways listed in Table 9, Column A; or
- (v) one or more genes associated with a central memory phenotype.

130. The vector of claim 129, wherein the modulator (e.g., inhibitor) is a (1) a gene editing system targeted to one or more sites within the gene, or a regulatory element thereof; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of the Tet2-associated gene; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) encoded by the Tet2-associated gene, or a binding partner of a protein encoded by the Tet2-associated gene; and (4) a nucleic acid encoding any of (1) (3), or combinations thereof.

131. The vector of claim 129 or 130, wherein the modulator is an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.

132. The vector of any of claims 129-131, wherein the sequence encoding a CAR and the sequence encoding the inhibitor are separated by a 2A site.

133. A gene editing system that is specific for a sequence of a Tet2-associated gene (e.g., one or more Tet2-associated genes) or a regulatory element thereof, wherein the Tet2-associated gene is chosen from (e.g., 2, 3, 4, or all) of:

- (i) ~~one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;~~
(ii) ~~one or more genes listed in Table 8;~~
(iii) ~~one or more genes listed in Table 9, Column D;~~
(iv) ~~one or more genes associated with one or more pathways listed in Table 9, Column A; or~~
(v) ~~one or more genes associated with a central memory phenotype.~~

134. ~~The gene editing system of claim 133, wherein the gene editing system is specific for a sequence of an IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1 gene.~~

135. ~~The gene editing system of claim 133 or 134, wherein the gene editing system is a CRISPR/Cas gene editing system, a zinc finger nuclease system, a TALEN system, or a meganuclease system.~~

136. ~~The gene editing system of any of claims 133-135, wherein the gene editing system is a CRISPR/Cas gene editing system.~~

137. ~~The gene editing system of claim 136, comprising:
a gRNA molecule comprising a targeting sequence specific to a sequence of the Tet2-associated gene or a regulatory element thereof, and a Cas9 protein;
a gRNA molecule comprising a targeting sequence specific to a sequence of the Tet2-associated gene or a regulatory element thereof, and a nucleic acid encoding a Cas9 protein;
a nucleic acid encoding a gRNA molecule comprising a targeting sequence specific to a sequence of the Tet2-associated gene or a regulatory element thereof, and a Cas9 protein; or
a nucleic acid encoding a gRNA molecule comprising a targeting sequence specific to a sequence of the Tet2-associated gene or a regulatory element thereof, and a nucleic acid encoding a Cas9 protein.~~

138. ~~The gene editing system of any of claims 133-137, further comprising a template DNA.~~

139. ~~The gene editing system of claim 138, wherein the template DNA comprises nucleic acid sequence encoding a CAR, e.g., a CAR as described herein.~~

140. ~~A composition for the ex vivo manufacture of a CAR-expressing cell, comprising a modulator (e.g., an inhibitor or an activator) of a Tet2-associated gene (e.g., one or more Tet2-associated genes) chosen from (e.g., 2, 3, 4, or all) of:~~

- (i) ~~one or more of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1;~~
(ii) ~~one or more genes listed in Table 8;~~

- (iii) ~~one or more genes listed in Table 9, Column D;~~
- (iv) ~~one or more genes associated with one or more pathways listed in Table 9, Column A; or~~
- (v) ~~one or more genes associated with a central memory phenotype.~~

5 141. ~~The composition of claim 140, wherein the modulator is an inhibitor of IFNG, NOTCH2, CD28, ICOS, IL2RA, or PRDM1.~~

10 142. ~~The composition of claim 140 or 141, wherein the modulator (e.g., inhibitor) is a (1) a gene editing system targeted to one or more sites within the Tet2-associated gene or a regulatory element thereof; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of the Tet2-associated gene; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) encoded by the gene, or a binding partner of a protein encoded by the Tet2-associated gene; or (4) a nucleic acid encoding any of (1) (3), or combinations thereof.~~

15 143. ~~The composition of claim 142, further comprising an inhibitor of Tet2.~~

20 144. ~~A population of cells comprising one or more cells of any of claims 1-89, wherein the population of cells comprises a higher (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold higher) percentage of Tscm cells (e.g., CD45RA+CD62L+CCR7+ (optionally CD27+CD95+) T cells) than a population of cells which does not comprise one or more cells in which expression and/or function of a Tet2-associated gene (e.g., one or more Tet2-associated genes) in said cell has been reduced or eliminated.~~

25 145. ~~A population of cells comprising one or more cells of any of claims 1-89, wherein at least 50% (e.g., at least 60%, 70%, 80%, 85%, 90%, 95%, 97%, or 99%) of the population of cells have a central memory T cell phenotype.~~

30 146. ~~The population of cells of claim 145, wherein the central memory cell phenotype is a central memory T cell phenotype.~~

 147. ~~The population of cells of claim 145 or 146, wherein at least 50% (e.g., at least 60%, 70%, 80%, 85%, 90%, 95%, 97%, or 99%) of the population of cells express CD45RO and/or CCR7.~~