CLAIMS

1. A vector, comprising:
a base sequence encoding two types of short hairpin RNA (shRNA) which inhibit the expression of at least one gene that weakens the function of immune cells, and
a base sequence encoding a chimeric antigen receptor (CAR) or a monoclonal T cell receptor (mTCR).

2. The vector according to Claim 1, wherein the expression of the two types of shRNA is characterized in that they are respectively regulated by two different promoters.

3. The vector according to Claim 2, wherein the two promoters are RNA polymerase III promoters.

4. The vector according to Claim 2, wherein the two promoters are U6 promoters derived from different species.

5. The vector according to Claim 2, wherein the two promoters are oriented in different directions from each other on the vector.

6. The vector according to Claim 1, wherein the gene weakening the function of immune cells is an immune checkpoint receptor or ligand.

7. The vector according to Claim 6, wherein the immune checkpoint receptor or ligand is selected from a group consisting of PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG 3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK and 2B4.

8. The vector according to Claim 1, wherein the gene weakening the function of immune cells is selected from a group consisting of FAS, CD45, PP2A, SHIP1, SHIP2, DGK alpha, DGK zeta, Cbl-b, CD147, LRR1, TGFBR1, IL10R alpha, KLGR1, DNMT3A and A2aR.

9. The vector according to Claim 1, wherein the two types of shRNA target a single gene which weakens the function of immune cells, or wherein the two types of shRNA target different genes which weaken the function of immune cells.

10. The vector according to Claim 1, wherein the two types of shRNA target PD-1.

11. The vector according to Claim 1, wherein, of the two types of shRNA, i) one shRNA targets PD-1 and the second shRNA targets TIM-3, or ii) one shRNA targets PD-1 and the second shRNA targets TIGIT.

12. The vector according to Claim 1, wherein, of the two types of shRNA, the base sequence encoding one shRNA comprises a sequence selected from a group consisting of SEQ ID NOs: 2-219, and the base sequence encoding the second shRNA comprises a different sequence selected from the group consisting of SEQ ID Nos: 2-219.

13. The vector according to Claim 1, wherein the target of the CAR or mTCR is a human tumor antigen that exhibits increased expresssion in a cancer cell, cancer tissue, and/or tumor microenvironment, or is a mutated form of antigen found in a cancer cell, cancer tissue and/or tumor microenvironment.

14. The vector according to Claim 1, whether the vector comprises the base sequence of SEQ ID NO: 220 or 221.

15. The vector according to Claim 1, wherein the vector is a plasmid vector, a lentivirus vector, an adenovirus vector, an adeno-associated vector or a retrovirus vector.

16. An immune cell comprising the vector according to Claim 1, wherein expression of the one or more genes is reduced to 40% or less than that of expression in the absence of the shRNAs.

17. The immune cell according to Claim 16, wherein the immune cell is a human-derived T cell or natural killer (NK) cell.

18. A pharmaceutical composition comprising the immune cell according to any one of Claim 1-17.

19. The pharmaceutical composition according to Claim 18, for treatment of a patient in need of immune threapy, wherein the immune cell is originally obtained from the patient.

20. The pharmaceutical composition according to Claim 19, wherein the patient has a tumor or cancer in which the target, and/or an increase or variation in levels of the target, of the CAR or mTCR expressed in the immune cell is detected.

21. An immune cell comprising a genetically engineered antigen receptor that specifically binds to a target antigen and a genetic disruption agent reducing or capable of reducing the expression in the immune cell of a gene that weakens the function of the immune cell.

22. The immune cell of claim 21, wherein the genetically engineered antigen receptor is a chimeric antigen receptor (CAR) or a T cell receptor (TCR).

23. The immune cell of claim 22, wherein the genetically engineered antigen receptor is a CAR.

24. The immune cell of claim 23, wherein the CAR comprises an extracellular antigen recognition domain, a transmembrane domain, and an intracellular signal transduction domain.

25. The immune cell of claim 24, wherein the extracellular antigen recognition domain of the CAR specifically binds to the target antigen.

26. The immune cell of claim 24, wherein the intracellular signal transduction domain of the CAR comprises an intracellular domain of a CD3 zeta (CD3ζ) chain.

27. The immune cell of claim 26, wherein the intracellular signal transduction domain of the CAR further comprises a costimulatory molecule.

28. The immune cell of claim 27, wherein the costimulatory molecule is selected from the group consisting of ICOS, 0X40, CD137 (4-1BB), CD27, and CD28.

29. The immune cell of claim 28, wherein the costimulatory molecule is CD137 (4-1BB).

30. The immune cell of claim 28, wherein the costimulatory molecule is CD28.

31. The immune cell of claim 22, wherein the genetically engineered antigen receptor is a TCR.

32. The immune cell of claim 31, wherein the TCR is a monoclonal TCR (mTCR).

33. The immune cell of claim 31 or 32, wherein the target antigen is expressed in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

34. The immune cell of claim 33, wherein the target antigen is selected from the group consisting of:
5T4 (Trophoblast glycoprotein), 707-AP, 9D7, AFP (α-fetoprotein), AlbZIP (androgen-induced bZIP), HPG1 (human prostate specific gene-1), α5β1-Integrin, α5β6-Integrin, α -methylacyl-coenzyme A racemase, ART-4 (ADPribosyltransferase-4), B7H4 (v-set domain-containing T-cell activation inhibitor 1), BAGE-1 (B melanoma antigen-1), BCL-2 (B-cell CLL/lymphoma-2), BING-4 (WD repeat domain 46), CA 15-3/CA 27-29 (mucin 1), CA 19-9 (cancer antigen 19-9), CA 72-4 (cancer antigen 72-4), CA125 (cancer antigen 125), calreticulin, CAMEL (CTL-recognized antigen on melanoma), CASP-8 (caspase 8), cathepsin B, cathepsin L, CD19 (cluster of differentiation 19), CD20, CD22, CD25, CD30, CD33, CD4, CD52, CD55, CD56, CD80, CEA (carcinoembryonic antigen SG8), CLCA2 (chloride channel accessory 2), CML28 (chronic myelogenous leukemia tumor antigen 28), Coactosin-like protein, Collagen XXIII, COX-2 (cyclooxygenase-2), CT-9/BRD6 (cancer/testis antigen 9), Cten (c-terminal tensin-like protein), cyclin B1, cyclin D1, cyp-B, CYPB1 (cytochrome p450 family 1 subfamily b member 1), DAM-10/MAGE-B1 (melanoma-associated antigen B1), DAM-6/MAGE-B2, EGFR/Her1 (epidermal growth factor receptor), EMMPRIN (basigin), EpCam, EphA2 (EPH receptor A2), EphA3, ErbB3 (Erb-B2 receptor tyrosine kinase 3), EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), FGF-5 (fibroblast growth factor 5), FN (fibronectin), Fra-1 (Fosrelated antigen-1), G250/CAIX (carbonic anhydrase 9), GAGE-1 (G antigen-1), GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7b, GAGE-8, GDEP (gene differentially expressed in prostate), GnT-V (gluconate kinase), gp100 (melanocytes lineage-specific antigen GP100),

GPC3 (glypican3), HAGE (helical antigen), HAST-2 (sulfotransferase family 1A member 1), hepsin, Her2/neu/ErbB2 (Erb-B2 receptor tyrosine kinase 2), HERV-K-MEL, HNE (medullasin), homeobox NKX 3.1, HOM-TES-14/SCP-1, HOM-TES-85, HPV-E6, HPVE7, HST-2 (sirtuin-2), hTERT, iCE (caspase 1), IGF-1R (insulin like growth factor-1 receptor), IL-13Ra2 (interleukin-13 receptor subunit α 2), IL-2R (interleukin-2 receptor), IL-5 (interleukin-5), immature laminin receptor, kallikrein 2, kallikrein 4, Ki67, KIAA0205 (lysophosphatidylglycerol acyltransferase 1), KK-LC-1 (kita-kyushu lung cancer antigen-1), KM-HN-1, LAGE-1 (L antigen family member-1), Livin, MAGE-A1, MAGE-A10, MAGE-A12, MAGEA2, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A9, MAGE-B1, MAGE-B10, MAGE-B16, MAGEB17, MAGE-B2, MAGE-B3, MAGE-B4, MAGE-B5, MAGE-B6, MAGE-C1, MAGE-C2, MAGE-C3, MAGE-D1, MAGE-D2, MAGE-D4, MAGE-E1, MAGE-E2, MAGE-F1, MAGE-H1, MAGEL2 (melanoma antigen family L2), mammaglobin A, MART-1/Melan-A (melanoma antigen recognized by T-cells-1), MART-2, matrix protein 22, MC1R (melanocortin 1 receptor), M-CSF (macrophage colony-stimulating factor), Mesothelin, MG50/PXDN (peroxidasin), MMP 11 (matrix metalloprotease 11), MN/CA IX-antigen (carbonic anhydrase 9), MRP-3 (multidrug resistance-associated protein-3), MUC1 (mucin 1), MUC2, NA88-A (VENT-like homeobox 2 pseudogene 1), N-acetylglucos-aminyltransferase-V, Neo-PAP (Neo-poly (A) polymerase), NGEP (new gene expressed in prostate), NMP22 (nuclear matrix protein 22), NPM/ALK (nucleophosmin), NSE (neuron-specific enolase), NY-ESO-1, NY-ESO-B, OA1 (osteoarthritis QTL 1), OFA-iLRP (oncofetal antigen immature laminin receptor protein), OGT (O-GlcNAc transferase), OS-9 (endoplasmic reticulum lectin), osteocalcin, osteopontin, p15 (CDK inhibitor 2B), p53, PAGE-4 (P antigen family member-4), PAI-1 (plasminogen activator inhibitor-1), PAI-2, PAP (prostatic acid phosphatase), PART-1 (prostate androgen-regulated transcript 1), PATE (prostate and testis expressed 1), PDEF (prostate-derived Ets factor), Pim-1-Kinase (proviral integration site 1), Pin1 (Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1), POTE (expressed in prostate, ovary, testis, and placenta), PRAME (preferentially expressed antigen in melanoma), prostein, proteinase-3, PSA (prostate-specific antigen), PSCA (prostate stem cell antigen), PSGR (prostate-specific G-protein coupled receptor), PSM, PSMA (prostate specific membrane antigen), RAGE-1 (renal tumor carcinoma antigen), RHAMM/CD168, RU1 (renal ubiquitous protein 1), RU2, SAGE (sarcoma antigen), SART-1 (squamous cell carcinoma antigen recognized by T-cells-1), SART-2, SART-3, Sp17 (sperm protein 17), SSX-1 (SSX family member 1), SSX-2/HOM-MEL-40, SSX-4, STAMP-1 (STEAP2 metalloreductase), STEAP, survivin, survivin-213, TA-90 (tumor associated antigen-90),

TAG-72 (tumor associated glycoprotein-72), TARP (TCRγ alternate reading frame protein), TGFb (transforming growth factor β), TGFbR11 (transforming growth factor β receptor 11), TGM-4 (transglutaminase 4), TRAG-3 (taxol resistance associated gene 3), TRG (T-cell receptor γ locus), TRP-1 (transient receptor potential-1), TRP-2/6b, TRP-2/INT2, Trp-p8, Tyrosinase, UPA (U-plasminogen activator), VEGF (vascular endothelial growth factor A), VEGFR-2/FLK-1, and WT1 (wilms tumor 1).

35. The immune cell of claim 35, wherein the target antigen is CD19 or CD22.

36. The immune cell of claim 36, wherein the target antigen is CD19.

37. The immune cell of any of claims 34-36, wherein the target antigen is a cancer antigen whose expression is increased in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

38. The immune cell of claim 33, wherein the target antigen is selected from the group consisting of:
α-actinin-4/m, ARTC1/m, bcr/abl, beta-Catenin/m, BRCA1/m, BRCA2/m, CASP-5/m, CASP-8/m, CDC27/m, CDK4/m, CDKN2A/m, CML66, COA-1/m, DEK-CAN, EFTUD2/m, ELF2/m, ETV6-AML1, FN1/m, GPNMB/m, HLA-A*0201-R170I, HLA-A11/m, HLA-A2/m, HSP70-2M, KIAA0205/m, K-Ras/m, LDLR-FUT, MART2/m, ME1/m, MUM-1/m, MUM-2/m, MUM-3/m, Myosin class 1/m, neo-PAP/m, NFYC/m, N-Ras/m, OGT/m, OS-9/m, p53/m, Pml/RARa, PRDX5/m, PTPRX/m, RBAF600/m, SIRT2/m, SYTSSX-1, SYT-SSX-2, TEL-AML1, TGFbRII, and TPI/m; and
wherein the target antigen is a cancer antigen that is a mutated form of antigen expressed in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

39. The immune cell of any of claims 21-38, wherein expression of the gene that weakens the function of the immune cell causes one or more of the following:
i) inhibition of proliferation of the immune cell;
ii) induction of cell death of the immune cell;
iii) inhibition of the ability of the immune cell to recognize the target antigen and/or undergo activation;

iv) induction of differentiation of the immune cell into a cell that does not induce immune response to the target antigen;

v) decreased reactios of the immune cell to a molecule which promotes immune response of the immune cell; or

vi) increased reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

40. The immune cell of claim 39, wherein the gene that weakens the function of the immune cell is selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG 3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, 2B4, FAS, CD45, PP2A, SHP1, SHP2, DGK alpha, DGK zeta, Cbl-b, Cbl-c, CD148, LRR1, TGFBR1, IL10RA, KLGR1, DNMT3A, and A2aR.

41. The immune cell of claim 39, wherein the gene that weakens the function of the immune cell increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

42. The immune cell of claim 41, wherein the gene that increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell encodes an immune checkpoint receptor or ligand.

43. The immune cell of claim 42, wherein the immune checkpoint receptor or ligand is selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG 3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, and 2B4.

44. The immune cell of any of claims 21-43, wherein the genetic disruption agent reduces the expression of a gene in the immune cell that weakens the function of the immune cell by at least 30, 40, 50, 60, 70, 80, 90, or 95 % as compared to the immune cell in the absence of the genetic disruption agent.

45. The immune cell of claim 44, wherein the genetic disruption agent reduces the expression of a gene that increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

46. The immune cell of claim 45, wherein the genetic disruption agent reduces the expression of a gene that encodes an immune checkpoint receptor or ligand.

47. The immune cell of claim 46, wherein the genetic disruption agent reduces the expression of a gene selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, and 2B4.

48. The immune cell of any of claims 45-47, wherein the genetic disruption agent reduces the expression of the gene that weakens the function of the immune cell by RNA interference (RNAi).

49. The immune cell of claim 48, wherein more than one genetic disruption agents reduce the expression of the gene that weakens the function of the immune cell in the immune cell by RNAi.

50. The immune cell of claim 49, wherein the genetic disruption agents target a single gene which weakens the function of the immune cell, or wherein different genetic disruption agents target different genes which weaken the function of the immune cell, for example, wherein a first genetic disruption agent targets a first gene and a second genetic disruption agent targets a second gene.

51. The immune cell of any of claims 48-50, wherein the RNAi is mediated by a short hairpin RNA (shRNA).

52. The immune cell of claim 51, wherein the RNAi is mediated by more than one shRNA.

53. The immune cell of claim 52, wherein the RNAi is mediated by two shRNAs.

54. The immune cell of any of claims 52-53, wherein two shRNAs target PD-1.

55. The immune cell of any of claims 52-53, wherein a first shRNA targets PD-1 and a second shRNA targets TIM-3.

56. The immune cell of any of claims 52-53, wherein a first shRNA targets PD-1 and a second shRNA targets CTLA-4.

57. The immune cell of any of claims 52-53, wherein a first shRNA targets PD-1 and a second shRNA targets LAG-3.

58. The immune cell of any of claims 52-53, wherein a first shRNA targets PD-1 and a second shRNA targets TIGIT.

59. The immune cell of any of claims 51-58, wherein the immune cell comprises nucleotide sequences that encode a shRNA.

60. The immune cell of claim 59, wherein the immune cell comprises nucleotide sequences that encode more than one shRNA.

61. The immune cell of claim 59, wherein the immune cell comprises nucleotide sequences that encode two shRNAs.

62. The immune cell of any of claims 59-61, wherein the nucleotide sequence encoding the shRNA(s) comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2-219 and 238-267.

63. The immune cell of any of claims 59-62, wherein the nucleotide sequence encoding the shRNA(s) is present on a vector.

64. The immune cell of any of claim 63, wherein the expression of different shRNAs is regulated by different promoters.

65. The immune cell of claim 64, wherein the expression of two different shRNA is regulated by two different promoters.

66. The immune cell of claim 65, wherein the two different promoters are RNA polymerase III promoters.

67. The immune cell of claim 66, wherein the two promoters are U6 promoters.

68. The immune cell of claim 67, wherein the U6 promoters derived from different species.

69. The immune cell of any of claims 65-68, wherein the two promoters are oriented in different directions from each other.

70. The immune cell of any of claims 21-69, wherein the genetically engineered antigen receptor and the genetic disruption agent(s) are each expressed from a vector.

71. The immune cell of claim 70, wherein the genetically engineered antigen receptor and the genetic disruption agent(s) are expressed from the same vector.

72. The immune cell of any of claims 70-71, wherein the vector is a plasmid vector or a viral vector.

73. The immune cell of claim 72, wherein the viral vector is a lentivirus vector, adenovirus vector or adeno-associated viral vector.

74. The immune cell of claim 73, wherein the lentivirus vector is a retrovirus vector.

75. The immune cell of any of claims 21-74, wherein the immune cell is selected from the group consisting of a T cell and a natural killer (NK) cell.

76. The immune cell of claim 75, wherein the immune cell is a T cell.

77. The immune cell of claim 76, wherein the T cell is a CD4+ T cell or a CD8+ T cell.

78. The immune cell of any of claim 76 or 77, wherein the immune cell comprises nucleotide sequences that encode two shRNAs and a CAR or mTCR on the same vector.

79. The immune cell of claim 78, wherein the two shRNA are each regulated by two different RNA polymerase III promoters oriented in different directions from each other.

80. The immune cell of claim 79, wherein the CAR targets CD19, the first shRNA targets PD-1, and the second shRNA targets TIGIT.

81. A method of producing an immune cell comprising introducing into an immune cell, simultaneously or sequentially in any order:
(1) a gene encoding a genetically engineered antigen receptor that specifically binds to a target antigen; and
(2) a genetic disruption agent, wherein the genetic disruption agent, or expression theref, reduces or is capable of reducing expression in the immune cell of a gene that weakens the function of the immune cell,
thereby producing an immune cell in which a genetically engineered antigen receptor is expressed and expression of a gene that weakens the function of the immune cell is reduced.

82. The method of claim 81, wherein the genetically engineered antigen receptor is a chimeric antigen receptor (CAR) or a T cell receptor (TCR).

83. The method of claim 82, wherein the genetically engineered antigen receptor is a CAR.

84. The method of claim 83, wherein the CAR comprises an extracellular antigen recognition domain, a transmembrane domain, and an intracellular signal transduction domain.

85. The method of claim 84, wherein the extracellular antigen recognition domain of the CAR specifically binds to the target antigen.

86. The method of claim 84, wherein the intracellular signal transduction domain of the CAR comprises an intracellular domain of a CD3 zeta (CD3ζ) chain.

87. The method of claim 86, wherein the intracellular signal transduction domain of the CAR further comprises a costimulatory molecule.

88. The method of claim 87, wherein the costimulatory molecule is selected from the group consisting of ICOS, 0X40, CD137 (4-1BB), CD27, and CD28.

89. The method of claim 88, wherein the costimulatory molecule is CD137 (4-1BB).

90. The method of claim 88, wherein the costimulatory molecule is CD28.

91. The method of claim 82, wherein the genetically engineered antigen receptor is a TCR.

92. The method of claim 91, wherein the TCR is a monoclonal TCR (mTCR).

93. The method of any of claims 81-92, wherein the target antigen is expressed in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

94. The method of claim 93, wherein the target antigen is selected from the group consisting of: 5T4 (Trophoblast glycoprotein), 707-AP, 9D7, AFP (α-fetoprotein), AlbZIP (androgen-induced bZIP), HPG1 (human prostate specific gene-1), α5β1-Integrin, α5β6-Integrin, α -methylacyl-coenzyme A racemase, ART-4 (ADPribosyltransferase-4), B7H4 (v-set domain-containing T-cell activation inhibitor 1), BAGE-1 (B melanoma antigen-1), BCL-2 (B-cell CLL/lymphoma-2), BING-4 (WD repeat domain 46), CA 15-3/CA 27-29 (mucin 1), CA 19-9 (cancer antigen 19-9), CA 72-4 (cancer antigen 72-4), CA125 (cancer antigen 125), calreticulin, CAMEL (CTL-recognized antigen on melanoma), CASP-8 (caspase 8), cathepsin B, cathepsin L, CD19 (cluster of differentiation 19), CD20, CD22, CD25, CD30, CD33, CD4, CD52, CD55, CD56, CD80, CEA (carcinoembryonic antigen SG8), CLCA2 (chloride channel accessory 2), CML28 (chronic myelogenous leukemia tumor antigen 28), Coactosin-like protein, Collagen XXIII, COX-2 (cyclooxygenase-2), CT-9/BRD6 (cancer/testis antigen 9), Cten (c-terminal tensin-like protein), cyclin B1, cyclin D1, cyp-B, CYPB1 (cytochrome p450 family 1 subfamily b member 1), DAM-10/MAGE-B1 (melanoma-associated antigen B1), DAM-6/MAGE-B2, EGFR/Her1 (epidermal growth factor receptor), EMMPRIN (basigin), EpCam, EphA2 (EPH receptor A2), EphA3, ErbB3 (Erb-B2 receptor tyrosine kinase 3), EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), FGF-5 (fibroblast growth factor 5), FN (fibronectin), Fra-1 (Fosrelated antigen-1), G250/CAIX (carbonic anhydrase 9), GAGE-1 (G antigen-1), GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7b, GAGE-8, GDEP (gene differentially expressed in prostate), GnT-V (gluconate kinase), gp100 (melanocytes lineage-specific antigen GP100), GPC3 (glypican3), HAGE (helical antigen), HAST-2 (sulfotransferase family 1A member 1), hepsin, Her2/neu/ErbB2 (Erb-B2 receptor tyrosine kinase 2), HERV-K-MEL, HNE

(medullasin), homeobox NKX 3.1, HOM-TES-14/SCP-1, HOM-TES-85, HPV-E6, HPVE7, HST-2 (sirtuin-2), hTERT, iCE (caspase 1), IGF-1R (insulin like growth factor-1 receptor), IL-13Ra2 (interleukin-13 receptor subunit α 2), IL-2R (interleukin-2 receptor), IL-5 (interleukin-5), immature laminin receptor, kallikrein 2, kallikrein 4, Ki67, KIAA0205 (lysophosphatidylglycerol acyltransferase 1), KK-LC-1 (kita-kyushu lung cancer antigen-1), KM-HN-1, LAGE-1 (L antigen family member-1), Livin, MAGE-A1, MAGE-A10, MAGE-A12, MAGEA2, MAGE-A3, MAGE-A4, MAGE-A6, MAGE-A9, MAGE-B1, MAGE-B10, MAGE-B16, MAGEB17, MAGE-B2, MAGE-B3, MAGE-B4, MAGE-B5, MAGE-B6, MAGE-C1, MAGE-C2, MAGE-C3, MAGE-D1, MAGE-D2, MAGE-D4, MAGE-E1, MAGE-E2, MAGE-F1, MAGE-H1, MAGEL2 (melanoma antigen family L2), mammaglobin A, MART-1/Melan-A (melanoma antigen recognized by T-cells-1), MART-2, matrix protein 22, MC1R (melanocortin 1 receptor), M-CSF (macrophage colony-stimulating factor), Mesothelin, MG50/PXDN (peroxidasin), MMP 11 (matrix metalloprotease 11), MN/CA IX-antigen (carbonic anhydrase 9), MRP-3 (multidrug resistance-associated protein-3), MUC1 (mucin 1), MUC2, NA88-A (VENT-like homeobox 2 pseudogene 1), N-acetylglucos-aminyltransferase-V, Neo-PAP (Neo-poly (A) polymerase), NGEP (new gene expressed in prostate), NMP22 (nuclear matrix protein 22), NPM/ALK (nucleophosmin), NSE (neuron-specific enolase), NY-ESO-1, NY-ESO-B, OA1 (osteoarthritis QTL 1), OFA-iLRP (oncofetal antigen immature laminin receptor protein), OGT (O-GlcNAc transferase), OS-9 (endoplasmic reticulum lectin), osteocalcin, osteopontin, p15 (CDK inhibitor 2B), p53, PAGE-4 (P antigen family member-4), PAI-1 (plasminogen activator inhibitor-1), PAI-2, PAP (prostatic acid phosphatase), PART-1 (prostate androgen-regulated transcript 1), PATE (prostate and testis expressed 1), PDEF (prostate-derived Ets factor), Pim-1-Kinase (proviral integration site 1), Pin1 (Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1), POTE (expressed in prostate, ovary, testis, and placenta), PRAME (preferentially expressed antigen in melanoma), prostein, proteinase-3, PSA (prostate-specific antigen), PSCA (prostate stem cell antigen), PSGR (prostate-specific G-protein coupled receptor), PSM, PSMA (prostate specific membrane antigen), RAGE-1 (renal tumor carcinoma antigen), RHAMM/CD168, RU1 (renal ubiquitous protein 1), RU2, SAGE (sarcoma antigen), SART-1 (squamous cell carcinoma antigen recognized by T-cells-1), SART-2, SART-3, Sp17 (sperm protein 17), SSX-1 (SSX family member 1), SSX-2/HOM-MEL-40, SSX-4, STAMP-1 (STEAP2 metalloreductase), STEAP, survivin, survivin-213, TA-90 (tumor associated antigen-90), TAG-72 (tumor associated glycoprotein-72), TARP (TCRγ alternate reading frame protein), TGFb (transforming growth factor β), TGFbR11 (transforming growth factor β receptor 11),

TGM-4(transglutaminase 4), TRAG-3 (taxol resistance associated gene 3), TRG (T-cell receptor γ locus), TRP-1 (transient receptor potential-1), TRP-2/6b, TRP-2/INT2, Trp-p8, Tyrosinase, UPA (U-plasminogen activator), VEGF (vascular endothelial growth factor A), VEGFR-2/FLK-1, and WT1 (wilms tumor 1).

95. The method of claim 95, wherein the target antigen is CD19 or CD22.

96. The method of claim 96, wherein the target antigen is CD19.

97. The method of any of claims 94-96, wherein the target antigen is a cancer antigen, wherein the cancer antigen is an antigen whose expression is increased in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

98. The method of claim 93, wherein the target antigen is selected from the group consisting of: α-actinin-4/m, ARTC1/m, bcr/abl, beta-Catenin/m, BRCA1/m, BRCA2/m, CASP-5/m, CASP-8/m, CDC27/m, CDK4/m, CDKN2A/m, CML66, COA-1/m, DEK-CAN, EFTUD2/m, ELF2/m, ETV6-AML1, FN1/m, GPNMB/m, HLA-A*0201-R170I, HLA-A11/m, HLA-A2/m, HSP70-2M, KIAA0205/m, K-Ras/m, LDLR-FUT, MART2/m, ME1/m, MUM-1/m, MUM-2/m, MUM-3/m, Myosin class 1/m, neo-PAP/m, NFYC/m, N-Ras/m, OGT/m, OS-9/m, p53/m, Pml/RARa, PRDX5/m, PTPRX/m, RBAF600/m, SIRT2/m, SYTSSX-1, SYT-SSX-2, TEL-AML1, TGFbRII, and TPI/m; and
wherein the target antigen is a cancer antigen, wherein the cancer antigen is a mutated form of antigen expressed in or on the surface of a cancer cell, a cancer tissue, and/or a tumor microenvironment.

99. The method of any of claims 81-98, wherein expression of the gene that weakens the function of the immune cell causes one or more of the following:
i) inhibition of proliferation of the immune cell;
ii) induction of cell death of the immune cell;
iii) inhibition of the ability of the immune cell to recognize the target antigen and/or to get activated;
iv) induction of differentiation of the immune cell into a cell that does not induce immune response to the target antigen;

v) decreased reaction of the immune cell to a molecule which promotes immune response of the immune cell; or

vi) increased reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

100. The method of claim 99, wherein the gene that weakens the function of the immune cell is selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG 3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, 2B4, FAS, CD45, PP2A, SHP1, SHP2, DGK alpha, DGK zeta, Cbl-b, Cbl-c, CD148, LRR1, TGFBR1, IL10RA, KLGR1, DNMT3A, and A2aR.

101. The method of claim 99, wherein the gene that weakens the function of the immune cell increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

102. The method of claim 101, wherein the gene that increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell encodes an immune checkpoint receptor or ligand.

103. The method of claim 102, wherein the immune checkpoint receptor or ligand is selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG 3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, and 2B4.

104. The method of any of claims 81-103, wherein the genetic disruption agent reduces the expression of a gene in the immune cell that weakens the function of the immune cell by at least 30, 40, 50, 60, 70, 80, 90, or 95 % as compared to the immune cell in the absence of the genetic disruption agent(s).

105. The method of claim 104, wherein the genetic disruption agent reduces the expression of a gene that increases reaction of the immune cell to a molecule which suppresses immune response of the immune cell.

106. The method of claim 105, wherein the genetic disruption agent reduces the expression of a gene that encodes an immune checkpoint receptor or ligand.

107. The method of claim 106, wherein the genetic disruption agent reduces the expression of a gene selected from the group consisting of: PD1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3 or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, CD96, MerTK, and 2B4.

108. The method of any of claims 105-107, wherein the genetic disruption agent reduces the expression of the gene that weakens the function of the immune cell by RNA interference (RNAi).

109. The method of claim 108, wherein more than one genetic disruption agents reduce the expression of the gene that weakens the function of the immune cell in the immune cell by RNAi.

110. The method of claim 109, wherein the genetic disruption agents target a single gene which weakens the function of the immune cell, or target different genes which weaken the function of the immune cell wherein a first genetic disruption agent targets a first gene and a second genetic disruption agent targets a second gene, or in any combination thereof.

111. The method of any of claims 108-110, wherein the RNAi is mediated by a short hairpin RNA (shRNA).

112. The method of claim 111, wherein the RNAi is mediated by more than one shRNA.

113. The method of claim 112, wherein the RNAi is mediated by two shRNAs.

114. The method of claim 112 or 113, wherein two shRNAs target PD-1.

115. The method of claim 112 or 113, wherein a first shRNA targets PD-1 and a second shRNA targets TIM-3.

116. The method of claim 112 or 113, wherein a first shRNA targets PD-1 and a second shRNA targets CTLA-4.

117. The method of claim 112 or 113, wherein a first shRNA targets PD-1 and a second shRNA targets LAG-3.

118. The method of claim 112 or 113, wherein a first shRNA targets PD-1 and a second shRNA targets TIGIT.

119. The method of any of claims 111-118, wherein the immune cell comprises nucleotide sequences that encode a shRNA.

120. The method of claim 119, wherein the immune cell comprises nucleotide sequences that encode more than one shRNA.

121. The method of claim 119, wherein the immune cell comprises nucleotide sequences that encode two shRNAs.

122. The method of any of claims 119-121, wherein the nucleotide sequences encoding the shRNA(s) comprise sequences selected from the group consisting of SEQ ID NOs: 2-219 and 238-267.

123. The method of any of claims 119-122, wherein the nucleotide sequences encoding the shRNA is present on a vector.

124. The method of any of claim 123, wherein the expression of different shRNAs is respectively regulated by different promoters.

125. The method of claim 124, wherein the expression of two different shRNAs is respectively regulated by two different promoters.

126. The method of claim 125, wherein the two different promoters are RNA polymerase III promoters.

127. The method of claim 126, wherein the two promoters are U6 promoters.

128. The method of claim 127, wherein the U6 promoters derive from different species.

129. The method of any of claims 125-128, wherein the two promoters are oriented in different directions from each other.

130. The method of any of claims 81-129, wherein the genetically engineered antigen receptor and the genetic disruption agent(s) are each expressed from a vector.

131. The method of claim 130, wherein the genetically engineered antigen receptor and the genetic disruption agent(s) are expressed from the same vector.

132. The method of any of claims 130-131, wherein the vector is a plasmid vector or a viral vector.

133. The method of claim 132, wherein the viral vector is a lentivirus vector, adenovirus vector ot adeno-associated viral vector.

134. The method of claim 133, wherein the lentivirus vector is a retrovirus vector.

135. The method of any of claims 81-134, wherein the immune cell is selected from the group consisting of a T cell and a natural killer (NK) cell.

136. The method of claim 135, wherein the immune cell is a T cell.

137. The method of claim 136, wherein the T cell is a CD4+ T cell or a CD8+ T cell.

138. The method of claim 136 or 137, wherein the immune cell comprises nucleotide sequences that encode two shRNAs and a CAR on the same vector.

139. The method of claim 138, wherein the two shRNAs are each regulated by two different RNA polymerase III promoters oriented in different directions from each other.

140. The method of claim 139, wherein the CAR targets CD19, the first shRNA targets PD-1, and the second shRNA targets TIGIT.

141. A composition comprising the immune cell of any of claims 21-80.

142. A pharmaceutical composition comprising the immune cell of any of claims 21-80 and a pharmaceutically acceptable carrier.

143. A method of treatment comprising administering to a subject having a disease or condition in need of immune therapy the immune cell of any of claims 21-80 or the composition of claim 141 or 142.

144. The method of claim 143, wherein the genetically engineered antigen receptor specifically binds to an antigen associated with the disease or the condition.

145. The method of claim 143 or 144, wherein the disease or the condition is a cancer, *e.g.*, a tumor.

146. The immune cell of any of claims 21-80 or the composition of claims 141-142 for use in treating a disease or a condition.

147. Use of the immune cell of any of claims 21-80 or the composition of claims 121-122 in the manufacture of a medicament for treating a disease or a condition.

148. The immune cells or the composition of claim 146 or the use of claim 147, wherein the genetically engineered antigen receptor specifically binds to an antigen associated with the disease or the condition.

149. The use, composition, or immune cell of claim 147 or claim 148, wherein the disease or the condition is a cancer, *e.g.* a tumor.