

WHAT IS CLAIMED IS:

1. An isolated nucleic acid sequence encoding
 - a) a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain specific for a cell surface antigen; and
 - b) an armoring molecule, wherein the armoring molecule counters immunosuppression of a cell in a tumor microenvironment when expressed on a surface of the cell.
2. The isolated nucleic acid sequence of claim 1, wherein the antigen-binding domain comprises an antibody or antigen-binding fragment thereof.
3. The isolated nucleic acid sequence of claim 2, wherein the antigen-binding domain is a Fab or a single chain variable fragment (scFv).
4. The isolated nucleic acid sequence of claim 3, wherein the antigen-binding domain is an scFv comprising the nucleic acid sequence of SEQ ID NO: 33 or SEQ ID NO: 34.
5. The isolated nucleic acid sequence according to any of the preceding claims further encoding a transmembrane domain, a costimulatory domain, and a signal domain.
6. The isolated nucleic acid sequence of claim 5, wherein the transmembrane domain comprises a CD28 transmembrane domain.
7. The isolated nucleic acid sequence of claim 5, wherein the costimulatory domain comprises one or more of CD28, 4-1BB, CD3zeta, OX-40, ICOS, CD27, GITR, and MyD88/CD40 costimulatory domains.
8. The isolated nucleic acid sequence of claim 5, wherein the costimulatory domain comprises one or more of CD28, 4-1BB, and CD3zeta costimulatory domains.

9. The isolated nucleic acid sequence of claim 5, wherein the signal domain comprises a sequence encoding a CSFR2 signal peptide.
10. The isolated nucleic acid sequence according to any of the preceding claims a sequence encoding further comprising a hinge/spacer domain.
11. The isolated nucleic acid sequence of claim 10, wherein the hinge/spacer domain is an IgG4P hinge/spacer.
12. The isolated nucleic acid sequence of claim 1, wherein the armoring molecule is hypoxia-inducible factor 1 α (HIF-1 α) dominant negative (HIF1 α DN).
13. The isolated nucleic acid sequence of claim 12, wherein HIF1 α DN is encoded by the nucleic acid sequence of SEQ ID NO: 46.
14. The isolated nucleic acid of claim 1, wherein the cell surface antigen comprises one or more of CD10, CD16, CD19, CD20, CD22, CD123, CD30, CD34, CD47, CD56, CD80, CD86, CD117, CD133, CD138, CD171, CD37, CD38, CD5, CD7, CD79, 5T4, AFP, AXL, BCMA, B7H3, CDH3, CDH6, CLDN6, CLDN18, CLL-1, CMV, CS1, DLL3, DR5, FBP, GD2, GFRA1, GPA33, GPC3, IL-1-RAP, IL17RA, ITGB7, EBV, ERBB1/EGFR, ERBB2/Her-2, ERBB3, ERBB4, cMet, EGFR vIII, FAP, FOLR1, CEA, CEACAM6, EphA2, HSV-1, HSV-2, HTLV, HPV16-E6, HPV16-E7, IL13Ra2, Ig κ chain, LGR5, LMP1, LeY, LRP8, MG7, MR1, NRCAM, PMEL, NKG2D ligand, PRAME, PRLR, PVR, ROR1, ROR2, SSX2, STEAP1, STEAP2, TACI, TIM3, TRBC1, VEGFR-2, EPCAM1, VCAM1, VIPR2, MAGE-A1, MAGE-A3, MAGE-A4, mesothelin (MSLN), MUC1, MUC16, NY-ESO-1, WT1, PDL1, CAIX, CD70, PSMA, and PSCA.
15. A vector, comprising a nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain specific for a cell surface antigen and an armoring molecule, wherein the nucleic acid sequence comprises SEQ ID NO: 46.

16. A cell comprising the vector of claim 15 or the isolated nucleic acid of any of claims 1-14.
17. A cell, comprising:
a nucleic acid sequence encoding a chimeric antigen receptor (CAR), and
a HIF1 α DN armoring molecule expressed on a surface of the cell.
18. The cell of claim 17, wherein the CAR comprises an antigen-binding domain, a transmembrane domain, a costimulatory domain, and a signal domain.
19. The cell of claim 18, wherein the antigen-binding domain is a Fab or a single chain variable fragment (scFv).
20. A cell, comprising:
an anti-GPC3 chimeric antigen receptor (CAR) comprising an antigen binding domain, wherein the antigen binding domain comprises an antibody, Fab, or an scFv comprising a heavy chain variable region (VH) and a light chain variable region (VL),
wherein the VH comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a CDR2 comprising the amino acid sequence of SEQ ID NO: 38, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 39, and
wherein the VL comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 40 or SEQ ID NO: 43, a CDR2 comprising the amino acid sequence of SEQ ID NO: 41 or SEQ ID NO: 44, and a CDR3 comprising the amino acid sequence of SEQ ID NO: 42 or SEQ ID NO: 45; and
a HIF1 α DN armoring molecule.
21. The cell of claim 20, wherein the VH comprises the amino acid sequence of SEQ ID NO: 27 or SEQ ID NO: 29.

22. The cell of claim 20-21, wherein the VL comprises the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 30.

23. The cell of any of claims 20-22, wherein the HIF1 α DN armoring molecule comprises the amino acid sequence of SEQ ID NO: 47.

24. The cell of any of claims 16-23, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), and a regulatory T cell.

25. Use of a cell in the manufacture of a medicament for a method of treating cancer, comprising wherein the cell is to be administered :

— administering to a subject in need thereof a cell, wherein the cell comprises

- a) a chimeric antigen receptor (CAR) specific for a cell surface antigen, and
- b) an armoring molecule, wherein the armoring molecule counters

immunosuppression of the cell in a tumor microenvironment of the cancer.

26. The ~~method~~use of claim 25, wherein the cell surface antigen is one or more of CD10, CD16, CD19, CD20, CD22, CD123, CD30, CD34, CD47, CD56, CD80, CD86, CD117, CD133, CD138, CD171, CD37, CD38, CD5, CD7, CD79, 5T4, AFP, AXL, BCMA, B7H3, CDH3, CDH6, CLDN6, CLDN18, CLL-1, CMV, CS1, DLL3, DR5, FBP, GD2, GFRA1, GPA33, GPC3, IL-1-RAP, IL17RA, ITGB7, EBV, ERBB1/EGFR, ERBB2/Her-2, ERBB3, ERBB4, cMet, EGFR vIII, FAP, FOLR1, CEA, CEACAM6, EphA2, HSV-1, HSV-2, HTLV, HPV16-E6, HPV16-E7, IL13Ra2, Ig κ chain, LGR5, LMP1, LeY, LRP8, MG7, MR1, NRCAM, PMEL, NKG2D ligand, PRAME, PRLR, PVR, ROR1, ROR2, SSX2, STEAP1, STEAP2, TACI, TIM3, TRBC1, VEGFR-2, EPCAM1, VCAM1, VIPR2, MAGE-A1, MAGE-A3, MAGE-A4, mesothelin (MSLN), MUC1, MUC16, NY-ESO-1, WT1, PDL1, CAIX, CD70, PSMA, and PSCA.

27. The ~~method~~use of claim 26, wherein the armoring molecule is a HIF1 α DN armoring molecule.

28. The ~~method~~use of claim 27, ~~wherein the medicament is capable of further comprising~~ inhibiting tumor growth, inducing tumor regression, and/or prolonging survival of the subject.
29. The ~~method~~use of claim 25, wherein the cell is an autologous cell.
30. The ~~method~~use of claim 29, wherein the autologous cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), and a regulatory T cell.
31. The ~~method~~use of any of claims 25-30, wherein the cancer is a solid tumor.
32. The ~~method~~use of claim 31, wherein the cancer is hepatocellular carcinoma, non-small cell lung cancer, ovarian cancer, and/or squamous cell lung carcinoma.
33. The ~~method~~use of claim 32, wherein the cancer is hepatocellular carcinoma.
34. The ~~use~~method of any of claims 26-33, ~~wherein further comprising administering to the subject~~ a therapeutically effective amount of an anticancer antibody and/or a chemotherapeutic component is to be administered to the subject.