

CLAIMS

1. A pharmaceutical composition, ~~comprising wherein the pharmaceutical composition comprises~~ modified T cells, ~~the modified T-cells comprising an antigen-binding molecule, wherein expression and/or function of one or more proteins in the modified T-cell has been increased or enhanced comprising a first nucleic acid encoding a chimeric antigen receptor (CAR), and the one or more proteins comprise a second nucleic acid encoding therapeutic agents IL-6, and IFN γ , or a combination thereof and comprising SEQ ID NO: 469.~~
2. The pharmaceutical composition of claim 1, wherein the modified T cells express and secrete the ~~one or more proteins~~ therapeutic agents IL-6 and IFN γ in response to activation of the modified T cells, ~~hypoxia, or a combination thereof.~~
3. The pharmaceutical composition of claim 1, wherein IL-6 is human IL-6, and IFN γ is human IFN γ .
4. The pharmaceutical composition of claim 1, wherein the modified T cells comprise an exogenous polynucleotide encoding the one or more proteins.
5. The pharmaceutical composition of claim 4, wherein the exogenous polynucleotide is present in the modified T cell in a recombinant DNA construct, in an mRNA, or in a viral vector.
6. ~~3.~~ The pharmaceutical composition of claim 4, ~~wherein the exogenous polynucleotide comprises a polynucleotide~~ modified T cells comprise nucleic acid sequences encoding SEQ ID NOS: 287 and a polynucleotide ~~encoding SEQ ID NO: 328.~~
7. The pharmaceutical composition of claim 4, wherein the exogenous polynucleotide comprises a promoter comprising a binding site for a transcription modulator that modulates the expression and/or secretion of IL-6, IFN γ , or a combination thereof, in the modified cell.
8. The pharmaceutical composition of claim 7, wherein the transcription modulator comprises Hif1a, NFAT, FOXP3, or NFkB.
9. The pharmaceutical composition of claim 1, wherein the antigen-binding molecule and the one or more proteins are produced in the form of a polyprotein, which is cleaved to generate separate the antigen-binding molecule and the one or more proteins, and there is a cleavable moiety between the antigen-binding molecule and the one or more proteins.
10. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises modified T cells engineered to express IL-12.
11. The pharmaceutical composition of claim 10, wherein the modified T cells express and secrete IL-12 in response to activation of the modified T cells, hypoxia, or a combination thereof.
12. The pharmaceutical composition of claim 10, wherein the pharmaceutical composition comprises modified T cells engineered to express a chimeric antigen receptor (CAR) binding a solid tumor antigen.

~~13.4.~~ The pharmaceutical composition of claim 1, wherein the antigen-binding molecule is a CAR that comprises an extracellular domain, a transmembrane domain, and an intracellular domain, the extracellular domain binding an antigen.

~~14.~~ The pharmaceutical composition of claim ~~13~~, wherein the CAR binds 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, 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, or IGLL1.

~~15.5.~~ The pharmaceutical composition of claim ~~13~~ 4, wherein the intracellular domain comprises a co-stimulatory domain that comprises an intracellular domain of a co-stimulatory molecule 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, and a combination thereof. a ligand that specifically binds with CD83, CDS, 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.

~~16.6.~~ The pharmaceutical composition of claim ~~13~~ 4, wherein the CAR binds a B-cell antigen selected from the group consisting of is CD19, CD22, CD20, BCMA, CD5, CD7, CD2, CD16, CD56, CD30, CD14, CD68, CD11b, CD18, CD169, CD1c, CD33, CD38, CD138, and CD13.

7. The pharmaceutical composition of claim 1, wherein the therapeutic agents IL-6 and IFN γ are present in the modified T cells in a recombinant DNA construct, in an mRNA, or in a viral vector.

8. The pharmaceutical composition of claim 1, wherein the modified T cells further comprises a nucleic acid sequence comprising a binding site for a transcription modulator that modulates secretion of therapeutic agents IL-6 or IFN γ .

9. The pharmaceutical composition of claim 1, wherein SEQ ID NO: 469 drives expression and secretion of the therapeutic agents IL6 and IFN γ .

10. The pharmaceutical composition of claim 1, wherein the CAR and the therapeutic agents IL6 and IFN γ are produced in the form of a polyprotein, which is cleaved to generate separate CAR and therapeutic agent molecules, and there is a cleavable moiety between the CAR and the therapeutic agents IL-6 and IFN γ , the cleavable moiety comprising a 2A peptide, and the 2A peptide comprising P2A or T2A.

11. The pharmaceutical composition of claim 1, wherein the modified T cells comprise an additional CAR, and the additional CAR binds a solid tumor antigen.

12. The pharmaceutical composition of claim 11, wherein the solid tumor antigen is TSHR.

13. The pharmaceutical composition of claim 11, wherein the modified T cells comprise a dominant negative PD-1.

~~17. A pharmaceutical composition comprising a first population of CAR T cells binding a solid tumor antigen, and a second population of CAR T cells binding a B cell antigen, wherein expression of one or more cytokines of the second population of CAR cells has been enhanced, and the one or more cytokines comprising at least one of IL-6, IL-12, or IFN γ .~~

~~18. The pharmaceutical composition of any one of claims 1-17, wherein the modified T cells comprise SEQ ID NO: 532 or 533.~~

~~19. A method of inducing T cell response, enhancing T cell therapy, enhancing *in vivo* T cell expansion, and/or reducing M2 macrophages in a subject in need thereof, the method comprising administering an effective amount of the pharmaceutical composition of claim 1-18 to the subject, wherein the one or more proteins comprise IL-6, IL-12, IFN γ , or a combination thereof.~~