

Claims

1. A $\gamma\delta$ T cell comprising at least one vector, the at least one vector directing the expression of a chimeric antigen receptor (CAR) and a survival factor, wherein the CAR comprises an extracellular domain comprising chlorotoxin, ~~a functional variant of chlorotoxin having at least about 90% sequence identity to SEQ ID NO: 1~~, a transmembrane domain and at least one intracellular signaling domain; and wherein the survival factor is a polypeptide that confers resistance to a chemotherapeutic agent.
2. The $\gamma\delta$ T cell of claim 1, wherein the intracellular signaling ~~is selected from the group consisting of:~~ comprises CD3 ζ , MB1 chain, B29, FcRIII, or FcRI, ~~and or a combinations~~ of the foregoing.
3. The $\gamma\delta$ T cell of claim 1 wherein ~~the CAR comprises an intracellular signaling and the intracellular signaling domain comprises only CD3 ζ .~~
4. The $\gamma\delta$ T cell of any one of claims 1 to 3, wherein the ~~CAR further~~ intracellular signaling domain comprises a costimulatory domain.
5. The $\gamma\delta$ T cell of claim 4, wherein the costimulatory domain comprises a functional signaling domain of a polypeptide 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, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRP1), CD160, CD19, CD4, CD8 α , CD8 β , IL2R β , IL2R γ , IL7R α , 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, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, and NKG2D.
6. A $\gamma\delta$ T cell comprising at least one vector, the at least one vector directing the expression of a chimeric antigen receptor (CAR) and a survival factor, wherein the CAR comprises an extracellular domain comprising chlorotoxin, ~~a functional variant of chlorotoxin having at~~

~~least about 90% sequence identity to SEQ ID NO: 1,~~ and a transmembrane domain, and wherein the survival factor is a polypeptide that confers resistance to a chemotherapeutic agent.

7. The $\gamma\delta$ T cell of any one of claims 1 to 6, wherein the transmembrane domain is selected from the group consisting of: T-cell receptor alpha chain, T-cell receptor beta chain, T-cell receptor zeta chain, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, KIRDS2, OX40, CD2, CD27, LFA-1, ICOS, 4-1BB, GITR, CD40, BAFFR, HVEM, SLAMF7, NKp80, CD160, CD19, IL2R β , IL2R γ , IL7R α , ITGA1, 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, DNAM1, SLAMF4, CD84, CD96, CEACAM1, CRTAM, Ly9, CD160, PSGL1, CD100, SLAMF6, SLAM, BLAME, SELPLG, LTBR, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, and NKG2C.
8. The $\gamma\delta$ T cell of any one of claims 1 to 7, wherein the CAR further comprises an extracellular spacer.
9. The $\gamma\delta$ T cell of claim 8, wherein the extracellular spacer comprises all or a portion of a hinge region of human IgD or human IgG1 and optionally all or a portion of an immunoglobulin heavy chain constant region from human IgG1.
10. The $\gamma\delta$ T cell of any one of claims 1 to 9, wherein the CAR further comprises a flexible linker.
11. The $\gamma\delta$ T cell of claim 10, wherein the flexible linker has the sequence of SEQ ID NO: 2 or SEQ ID NO: 3, present from 1 to 10 copies.
12. The $\gamma\delta$ T cell of any one of claims 1 to 7, wherein the CAR further comprises a flexible linker and an extracellular spacer.
13. The $\gamma\delta$ T cell of claim 12, wherein the flexible linker has the sequence of SEQ ID NO: 2 or SEQ ID NO: 3, present from 1 to 10 copies.
14. The $\gamma\delta$ T cell of any one of claims 1 to 13, wherein a single vector directs the expression of the CAR, the survival factor, and a stress-induced antigen receptor, wherein the stress-induced antigen receptor is NKG2D.
15. The $\gamma\delta$ T cell of any one of claims 1 to 13, wherein the $\gamma\delta$ T cell naturally expresses a stress-induced antigen receptor, wherein the stress-induced antigen receptor is NKG2D.

- ~~16.~~ The $\gamma\delta$ T cell of claim ~~14~~ or claim ~~15~~, wherein the stress induced antigen receptor is an NKG2D receptor.
- ~~17.~~ The $\gamma\delta$ T cell of any one of claims ~~1~~ to ~~16~~, wherein the survival factor allows the $\gamma\delta$ T cell to survive in a treatment environment created by the chemotherapeutic agent.
- ~~18.~~16. The $\gamma\delta$ T cell of ~~claim 17~~ any one of the preceding claims, wherein the chemotherapeutic agent is selected from the group consisting of: trimethotrexate, temozolomide, raltitrexed, S-(4-Nitrobenzyl)-6-thioinosine, 6-benzylguanine, nitrosoureas, fotemustine, cytarabine, camptothecin, doxorubicin, melphalan, and any combination of the foregoing.
- ~~19.~~17. The $\gamma\delta$ T cell of any one of claims ~~1~~ to ~~18~~16, wherein the survival factor is selected from the group consisting of: *O*⁶-Methylguanine-DNA methyltransferase, multidrug resistance protein 1, 5' nucleotidase II, dihydrofolate reductase and thymidylate synthase.
- ~~20.~~18. The $\gamma\delta$ T cell of any one of claims ~~1~~ to ~~19~~17, wherein the $\gamma\delta$ T cell is isolated.
- ~~21.~~19. The $\gamma\delta$ T cell of claim ~~6~~, wherein the $\gamma\delta$ T cell lacks an intracellular signaling domain.
- ~~22.~~20. A pharmaceutical composition comprising a $\gamma\delta$ T cell of any one of claims ~~1~~ to ~~21~~19 and a pharmaceutically acceptable carrier.
- ~~23.~~21. The pharmaceutical composition of claim ~~22~~20, wherein the $\gamma\delta$ T cells are present at greater than or equal to 60% of the total cell population of the composition as determined by flow cytometry.
- ~~24.~~22. The pharmaceutical composition of claim ~~22~~20 or ~~23~~21, wherein the extracellular domain comprises chlorotoxin and the survival factor is *O*⁶-Methylguanine-DNA methyltransferase.
- ~~25.~~23. The pharmaceutical composition of any one of claims ~~22~~20 to ~~24~~22 for use in treating cancer, wherein the composition is for administration concurrently with the chemotherapeutic agent, or after administration of the chemotherapeutic agent, or any combination thereof.
- ~~26.~~24. The pharmaceutical composition of ~~25~~23, wherein the cancer is selected from the group consisting of glioma, melanoma, neuroblastoma, medulloblastoma, or small cell lung carcinoma.
- ~~27.~~25. The pharmaceutical composition of claim ~~26~~24, wherein the cancer is glioblastoma.

28.26. The pharmaceutical composition of claim ~~24~~22, wherein the chemotherapeutic agent is temozolomide.