

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, a chlorotoxin-like peptide, functional variant of the chlorotoxin-like peptide or a combination thereof, a transmembrane domain and at least one intracellular signaling domain.
2. The $\gamma\delta$ T cell of claim 1, wherein the intracellular signaling domain is present and is selected from the group consisting of: CD3 ζ , MB1 chain, B29, FcRIII, FcRI, and 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 comprises a costimulatory domain.
5. The $\gamma\delta$ T cell of claim 5, 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 (KLRF1), 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, a

chlorotoxin-like peptide, functional variant of the chlorotoxin-like peptide or a combination thereof, and a transmembrane domain.

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: 1 or SEQ ID NO: 2, 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: 1 or SEQ ID NO: 2, present from 1 to 10 copies.
14. The $\gamma\delta$ T cell of claim 13, 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.
15. The $\gamma\delta$ T cell of any one of claims 1 to 15, wherein a single vector directs the expression of the CAR and the survival factor.

16. The $\gamma\delta$ T cell of any one of claims 1 to 15, wherein a single vector directs the expression of the CAR, the survival factor, and a stress-related antigen.
17. The $\gamma\delta$ T cell of any one of claims 1 to 15, wherein the $\gamma\delta$ T cell naturally expresses a stress-induced antigen receptor.
18. The $\gamma\delta$ T cell of claim 16 or claim 17, wherein the stress-induced antigen receptor is an NKG2D receptor.
19. The $\gamma\delta$ T cell of any one of claims 1 to 18, wherein the survival factor allows the $\gamma\delta$ T cell to survive in a treatment environment created by an additional therapeutic treatment.
20. The $\gamma\delta$ T cell of claim 19, wherein the additional therapeutic treatment is a treatment with an agent selected from the group consisting of: trimethotrexate, temozolomide, raltitrexed, S-(4-Nitrobenzyl)-6-thioinosine, 6-benzylguanidine, nitrosoureas, fotemustine, cytarabine, camptothecin, and any combination of the foregoing.
21. The $\gamma\delta$ T cell of any one of claims 1 to 20, 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.
22. The $\gamma\delta$ T cell of any one of claims 1 to 21, wherein the $\gamma\delta$ T cell is isolated.
23. A $\gamma\delta$ T cell comprising a chimeric antigen receptor (CAR), wherein the CAR comprises an extracellular domain comprising chlorotoxin, a functional variant of chlorotoxin, a chlorotoxin-like peptide, a functional variant of the chlorotoxin-like peptide or a combination thereof, a transmembrane domain and an intracellular signaling domain comprising only CD3 ζ .
24. A $\gamma\delta$ T cell comprising a chimeric antigen receptor (CAR), wherein the CAR comprises an extracellular domain comprising chlorotoxin, a functional variant of chlorotoxin, a chlorotoxin-like peptide, a functional variant of the chlorotoxin-like peptide or a combination thereof, a transmembrane domain and lacks an intracellular signaling domain.
25. A pharmaceutical composition comprising a $\gamma\delta$ T cell of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.