

CLAIMS

1. An engineered immune cell expressing:
 - i) an antigen receptor, and
 - ii) an antibody binding PD-L1;
- 5 wherein the antibody comprises
 - i) the variable heavy chain (VH) CDR sequences CDR-H1, CDR-H2 and CDR-H3 as set forth in SEQ ID NOs: 6, 7, and 8, respectively, and
 - ii) the variable light chain (VL) CDR sequences CDR-L1, CDR-L2 and CDR-L3 as set forth in SEQ ID NOs: 3, 4, and 5, respectively; and
- 10 wherein said immune cell is a T cell or a Natural Killer T (NKT) cell.
2. The engineered immune cell of claim 1, wherein the antibody is humanized.
3. The engineered immune cell of claims 1 or 2, wherein the immune cell is a NKT cell.
- 15 4. The engineered immune cell of claims 1 or 2, wherein said T cell is a cytotoxic T lymphocyte (CTL), a regulatory T lymphocyte, an inflammatory T-lymphocytes, a helper T-lymphocyte or a gamma-delta T cell.
- 20 5. The engineered immune cell of claim 4, wherein said T cell is a CD4⁺ or CD8⁺ or a mixed population of CD4⁺ and CD8⁺ cells.
- 25 6. The engineered immune cell of any one of the preceding claims, wherein said antigen receptor is a chimeric antigen receptor (CAR), said CAR comprising a cytoplasmic domain, a transmembrane domain and an extracellular domain.
7. The engineered immune cell of claim 6, wherein said transmembrane domain is a CD3 zeta, CD4, a CD28, a CD8 alpha or a 4-1BB transmembrane domain.

8. The engineered immune cell of claim 6 or 7, wherein the CAR further comprises one or more costimulatory domains.

9. The engineered immune cell of any of claims 1-5, wherein said antigen receptor is a T-cell receptor (TCR), such as an endogenous TCR or an engineered TCR.

10. The engineered immune cell of any one of the preceding claims, wherein said antigen receptor is recombinantly expressed.

11. The engineered immune cell of any one of the preceding claims, wherein said antibody is a full-length immunoglobulin or an antibody derivative, wherein the antibody derivative is selected from the group consisting of Fab, Fab', scFab, scFv, Fv fragment, diabody, single-chain diabody (scDb), a linear dimeric scDb (LD-scDb), circular dimeric scDb (CD-scDb), tandem di-scFv, tandem scFv, tandem tri-scFv, tri(a)body, bispecific Fab2, di-miniantibody, tetrabody, scFv-Fc-scFv fusion, scFv-Fc fusion, di-diabody, scFab-Fc, scFab-Fc-scFab, IgG-scFab, scFab-dsscFv, Fv2-Fc, IgG-scFv fusion (such as bsAb, BslAb, Bs2Ab, Bs3Ab, TslAb, Ts2Ab, and Knob-into-Holes (KiHs)).

12. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises a functional Fc domain.

13. The engineered immune cell of any one of claims 1 to 11, wherein said antibody does not comprise a Fc domain.

14. The engineered immune cell of claim 13, wherein said antibody is an antibody fragment selected from the group consisting of Fab, Fab', scFab, scFv, Fv fragment, dAb, diabody, single-chain diabody (scDb).

15. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises
 - i) at least one VH sequence of SEQ ID NO. : 2, and/or
 - ii) at least one VL sequence of SEQ ID NO.: 1.
- 5 16. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises SEQ ID NO. : 9.
17. The engineered immune cell of any one of the preceding claims, comprising
 - i) at least one VH framework sequence of SEQ ID NO. : 2, and/or
 - 10 ii) at least one VL framework sequence of SEQ ID NO. : 1.
18. The engineered immune cell of any one of the preceding claims, wherein said antibody is secreted by the cell and/or expressed on its surface, for example is secreted.
- 15 19. The engineered immune cell of any one of the preceding claims, wherein the cell further expresses one or more cytokine, preferably human cytokine, such as IL-2, IL-4, IL-7, IL-12, IL-15, IL-21 and/or MIP-1 alpha, and/or
further expresses one or more antibodies targeting an immune inhibitory molecule, such as transforming growth factor-beta (TGF- β), IL-10, Fas, CD47, CTLA-4, Tim-3, LAG-3, and ligands thereof.
- 20 20. The engineered immune cell of any one of the preceding claims, wherein the antigen receptor binds to an antigen that is expressed by a tumor or a pathogen.
- 25 21. The engineered immune cell of any one of the preceding claims, wherein the antigen is selected from the group consisting of GD2, WT-1, 5T4, GPC3, CSPG4, MUC16, MUC1, CA1X, CEA, CDS, CD7, CD 10, CD19, CD20, CD22, CD23, CD30, CD33, CD34, CD38,

CD41, CD44, CD49f, CD56, CD70, CD74, CD133, CD138, CD123, cytomegalovirus (CMV) proteins such as pp65 or IE-1, human papillomavirus (HPV) proteins such as E6 or E7, Epstein-Barr virus (EBV) proteins such as EBNA-1, LMP-1, LMP-2, or BARF-1, ADV proteins such as hexon, EGP-2, EGP-40, EpCAM, erb-B2, erb-B3, erb-B4, FBP, Fetal acetylcholine receptor, folate receptor-a, GD3, Her-1, HER-2, HER2-HER3 in combination or HER1-HER2 in combination, hTERT, IL- 13R~a2, K-light chain, DR, LeY, LI cell adhesion molecule, MAGE-A1, MAGE-A4, MAGE-A10, Mesothelin, NKG2D ligands, NY-ESO-1, PSCA, PSMA, ROR1, TAG-72, VEGF-R2, EGFR, EGFRvIII, mutated p53, mutated ras, mutated raf, mutated RAC1, bcr/abl fusions, c-Met, alphafetoprotein, CA-125, MUC-1, epithelial tumor antigen, prostate-specific antigen, melanoma-associated antigen, folate binding protein, HIV-1 envelope glycoprotein gpl20, HIV-1 envelope glycoprotein gp41, meothelin, HERV-K, or ERBB2.

22. A nucleic acid encoding the antigen receptor and the antibody according to any one of the preceding claims.

23. An expression vector comprising a nucleic acid encoding the antigen receptor and/or the antibody of any one of claims 1 to 21.

24. The expression vector of claim 23, being a lentiviral, a retroviral, an adenoviral, an Adeno-Associated Virus (AAV), a plasmid, a transposon, and insertion sequence, or an artificial chromosomal vector.

25. The expression vector of claim 23 or 24, being a multicistronic vector, such as a bicistronic vector.

26. The expression vector of any one of claims 23 to 25, comprising at least one IRES sequence and/or at least one self-cleaving sequence, such as a 2A sequence.

27. The expression vector of any one of claims 23 to 26, further comprising a safety switch, for example an inducible suicide switch.

28. A cloning vector comprising the nucleic acid of claim 22.

29. A method of generating an immune cell according to any one of claims 1 to 21, comprising the steps of:

(a) Providing an immune cell,

(b) Introducing into said cell at least one nucleic acid encoding said antigen receptor and at least one nucleic acid encoding said antibody; and

(c) Expressing said nucleic acids by said cell.

30. The method of claim 29, wherein step (b) comprises introducing the expression vector of any one of claims 23 to 27 into said cell.

31. The method of claim 29 or 30, further comprising the step of:

(i) Introducing into said cell at least one other antigen receptor having different antigen specificity than the antigen receptor of claim 29; and/or introducing into said cell at least one other antibody having a different antigen specificity than the antibody of claim 29.

32. A pharmaceutical composition comprising

i) an effective amount of the engineered immune cell of any one of claims 1 to 21 or of the expression vector of any one of claims 23 to 27, and

ii) a pharmaceutically acceptable excipient.

33. The engineered immune cell of any one of claims 1 to 21, the expression vector of any one of claims 23 to 27 or the pharmaceutical composition of claim 32 for use in therapy.

34. The engineered immune cell, the expression vector or the pharmaceutical composition of claim 33, wherein therapy is in combination with one or more therapies selected from the group of antibodies therapy, chemotherapy, cytokines therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.

35. Use of the engineered immune cell of any one of claims 1 to 21, the expression vector of any one of claims 23 to 27 or the pharmaceutical composition of claim 32 in the manufacture of a medicament for the treatment of a pre-malignant or malignant cancer condition, such as NSCLC (non small cell lung carcinoma), urothelial cancer, melanoma, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, ovarian cancer, gastrointestinal cancer, hepatocellular cancer, glioma, breast cancer, lymphoma, small cell lung carcinoma, myelodysplastic syndromes, prostate cancer, bladder cancer, cervical cancer, non clear cell kidney cancer, colorectal cancer, sarcomas, colon cancer, kidney cancer, lung cancer, pancreatic cancer or gastric cancer, skin cancer, uterine cancer, glioblastoma, neuroblastoma, sarcoma, head and neck cancer, leukemia, carcinoma, Merkel cell carcinoma or renal cell carcinoma (RCC), blood cancer, multiple myeloma, lymphoblastic leukemia (ALL), B cell leukemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and ovarian cancer; pathogen infection, or an autoimmune disorder.
36. A kit for treatment of cancer, pathogen infection, an autoimmune disorder comprising the engineered immune cell of any one of claims 1 to 21 or the expression vector of any one of claims 23 to 27, and written instructions for use.
37. The kit of claim 36, further comprising a safety switch, such as an inducible suicide switch.
38. The engineered immune cell of claim 8, wherein the one or more costimulatory domains are selected from the group consisting of CD28, 4-1BB (CD137), ICOS, OX40 (CD134), and functional fragments thereof, respectively.