

CLAIMS

1. An engineered immune cell expressing:
 - i) an antigen receptor, and
 - 5 ii) an antibody blocking PD-L1.
2. The engineered immune cell of claim 1, wherein the antibody inhibits PD-L1 interaction with both CD80 and PD-1.
- 10 3. The engineered immune cell of claim 1 or 2, wherein the antibody is humanized.
4. The engineered immune cell of any one of the preceding claims, wherein said immune cell is
 - a T cell,
 - 15 a Natural Killer T (NKT) cell,
 - a Natural Killer (NK) cell
 - a human embryonic stem cell,
 - a hematopoietic stem cell (HSC) or
 - an induced pluripotent stem cell (iPS).
- 20 5. The engineered immune cell of any one of the preceding claims, 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.
- 25 6. The engineered immune cell of claims 4 or 5, wherein said T cell is a CD4+ or CD8+ or a mixed population of CD4+ and CD8+ cells.
7. The engineered immune cell of any one of the preceding claims, wherein said antigen receptor is a CAR, said CAR comprising a cytoplasmic domain, a transmembrane domain
- 30 and an extracellular domain.
8. The engineered immune cell of claim 7, wherein said transmembrane domain is a CD3 zeta, CD4, a CD28, a CD8 alpha or a 4-1BB transmembrane domain.

9. The engineered immune cell of any one of the preceding claims, wherein the CAR further comprises one or more costimulatory domains,
10. The engineered immune cell of any of claims 1-6, wherein said antigen receptor is a
5 TCR, such as an endogenous TCR or an engineered TCR.
11. The engineered immune cell of any one of the preceding claims, wherein said antigen receptor is recombinantly expressed.
- 10 12. The engineered immune cell of any one of the preceding claims, wherein said antibody is a full-length immunoglobulin or an antibody derivative.
13. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises a functional Fc domain.
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14. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises a Fc domain which is modified such that it does not induce cytotoxic immune responses or complement activation.
- 20 15. The engineered immune cell of any one of the preceding claims, wherein said antibody does not comprise a Fc domain.
16. The engineered immune cell of claim 15, wherein said antibody is an antibody fragment selected from the group consisting of Fab, Fab', scFab, scFv, Fv fragment,
25 nanobody, VHH, dAb, minimal recognition unit, diabody, single-chain diabody (scDb), BiTE or DART.
17. The engineered immune cell of any one of the preceding claims, wherein said antibody binds human PD-L1 with a KD of lower than 100 pM,
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18. The engineered immune cell of any one of the preceding claims, wherein said antibody comprises
- i) at least one of the variable heavy chain (VH) CDR sequences CDR-H1, CDR-H2 or CDR-H3 as set forth in SEQ ID NOs.: 6, 7, and 8, respectively, or variants thereof,

- ii) at least one of the variable light chain (VL) CDR sequences CDR-L1 , CDR-L2 or CDR-L3 as set forth in SEQ ID NOs.: 3, 4, and 5, respectively, or variants thereof.
19. The engineered immune cell of any one of the preceding claims, wherein said
5 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.
20. The engineered immune cell of any one of the preceding claims, wherein said
10 antibody comprises SEQ ID NO.: 9.
21. 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
- ii) at least one VL framework sequence of SEQ ID NO.: 1.
- 15 22. The engineered immune cell of any one of claims 1 to 11, wherein the antibody competes with the antibody of claims 17 to 19 for binding to PD-L1.
23. The engineered immune cell of any one of the preceding claims, wherein said
20 antibody is secreted by the cell and/or expressed on its surface, for example is secreted.
24. 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-1alpha, and/or
- 25 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
25. The engineered immune cell of any one of the preceding claims, wherein the antigen
30 receptor binds to an antigen that is expressed by or derived from a tumor or a pathogen.
26. 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, PSMA, 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 gp120, HIV-1 envelope glycoprotein gp41, meothelin, HERV-K, or ERBB2 ..

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

28. An expression vector comprising a nucleic acid encoding the antigen receptor and/or the antibody of any one of claims 1 to 26.

29. The expression vector of claim 28, being a lentiviral, a retroviral, an adenoviral, an Adeno-Associated Virus (AAV), a plasmid, a transposon, and insertion sequence, or an artificial chromosomal vector.

30. The expression vector of claim 28 or 29, being a multicistronic vector, such as a bicistronic vector.

31. The expression vector of any one of claims 28 to 30, comprising at least one IRES sequence and/or at least one self-cleaving sequence, such as a 2A sequence.

32. The expression vector of any one of claims 28 to 31, further comprising a safety switch, for example an inducible suicide switch.

33. A cloning vector comprising the nucleic acid of claim 27.

34. A method of generating an immune cell according to any one of claims 1 to 26, comprising the steps of:
- (a) Providing an immune cell,
 - (b) Introducing into said cell at least one nucleic acid encoding said antigen receptor
 - 5 and at least one nucleic acid encoding said antibody; and
 - (c) Expressing said nucleic acids by said cell.
35. The method of claim 34, wherein step (b) comprises introducing the expression vector of any one of claims 28 to 32 into said cell.
- 10 36. The method of claim 34 or 35, 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 34; and/or introducing into said cell at least one other antibody having a different antigen specificity than the antibody of claim 34.
- 15 37. A pharmaceutical composition comprising
- i) an effective amount of the engineered immune cell of any one of claims 1 to 26 or of the expression vector of any one of claims 28 to 32, and
 - ii) a pharmaceutically acceptable excipient.
- 20 38. The engineered immune cell of any one of claims 1 to 26, the expression vector of any one of claims 28 to 32 or the pharmaceutical composition of claim 37 for use in therapy.
39. The engineered immune cell, the expression vector or the pharmaceutical composition of claim 38, 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.
- 25 40. A method of treating a subject in need thereof comprising:
- 30 (a) Providing the engineered immune cell according to any one of claims 1 to 26;
 - (b) Administering said immune cells to said subject.
41. The method of claim 40, wherein said immune cell are autologous or allogeneic.

42. The method of any one of claims 40 or 41, wherein cells are administered one or more times to said subject.
43. A method of treating a subject in need thereof comprising:
- 5 (a) Providing the expression vector according to any one of claims 28 to 32 or the pharmaceutical composition of claim 37;
- (b) Administering said expression vector or said pharmaceutical composition to said subject.
- 10 44. The method of any one of claims 40 to 43, in combination with one or more therapies selected from the group of antibody therapy, chemotherapy, cytokine therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.
45. The cell or the vector of claim 38 or 39, or the method of any one of claims 40 to 44,
- 15 wherein the condition to be treated is 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
- 20 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-
- 25 Hodgkin's lymphoma, and ovarian cancer; pathogen infection, an autoimmune disorder.
46. A kit for treatment of cancer, pathogen infection, an autoimmune disorder comprising
- the engineered immune cell of any one of claims 1 to 26 or the expression vector of
- 30 any one of claims 28 to 32, and
- written instructions for use.
47. The kit of claim 46, further comprising an inducer of a safety switch, such as an inducible suicide switch.

48. The engineered immune cell of claim 9, wherein the CAR further comprises one or more costimulatory domains, for example CD28, 4-1BB (CD137), ICOS, or OX40 (CD134), or functional fragments thereof, respectively.

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