CLAIMS

WHAT IS CLAIMED IS:

1. An immune cell comprising a nucleic acid molecule comprising a first polynucleotide encoding a chimeric antigen receptor (CAR) comprising an antibody that specifically recognizes human mesothelin, and a 4-1BB intracellular region, and a second polynucleotide encoding an interleukin 15 (IL-15)or a vector comprising the nucleic acid molecule, optionally wherein the immune cell further comprises a polynucleotide encoding gamma-TCR (γTCR) and a polynucleotide encoding delta-TCR (δTCR), optionally wherein the γTCR is V gamma 9 TCR (Vγ9 TCR) and the δTCR is V delta 2 TCR (Vδ2TCR).

2. An immune cell expressing:

a) a chimeric antigen receptor (CAR) comprising an antibody that specifically recognizes human mesothelin, and a 4-1BB intracellular region; and

b) IL-15; and

c) optionally CCL19.

3. The immune cell of claim 2, wherein the CAR further comprises a CD8 hinge region, a CD8 transmembrane region and a CD3ζ intracellular region.

4. The immune cell of any one of claims 1-3, wherein the immune cell is a T cell, a natural killer (NK) cell, a B cell, an antigen presenting cell, or a granulocyte, optionally a T cell or an NK cell or wherein the immune cell is derived from an induced pluripotent stem cell (iPSC).

5. The immune cell of any one of claims 1-4, wherein the immune cell does not express alpha TCR (αTCR) and/or beta TCR (βTCR), optionally αβTCR.

6. The immune cell of any one of claims 1-5, wherein the immune cell expresses a γδTCR, optionally wherein the γδTCR comprises Vγ9 TCR and Vδ2TCR.

7. A pharmaceutical composition comprising the immune cell of any one of claims 1-6, and a pharmaceutically acceptable additive.

8. Use of the immune cell of any one of claims 1-6 or the pharmaceutical composition of claim 7 in the manufacture of a medicament for treating a mesothelin-expressing cancer, wherein said immune cell or pharmaceutical composition is to be administered to a subject in need thereof, optionally wherein the mesothelin-expressing cancer is a solid tumor, optionally selected from mesothelioma, colorectal cancer, pancreatic cancer, thymic cancer, bile duct cancer, lung

cancer, skin cancer, breast cancer, prostate cancer, urinary bladder cancer, virginal cancer, neck cancer, uterine cancer, liver cancer, kidney cancer, spleen cancer, tracheal cancer, bronchial cancer, stomach cancer, esophageal cancer, gallbladder cancer, testis cancer, ovarian cancer, and bone cancer.

9. The use of claim 8, wherein the use further comprises an additional therapeutic agent or an additional therapeutic regimen to be administered to the subject, optionally wherein the additional therapeutic agent comprises a chemotherapeutic agent, an immunotherapeutic agent, a targeted therapy, radiation therapy, or a combination thereof, optionally wherein the additional therapeutic regimen comprises a first-line therapy, optionally wherein the additional therapeutic regimen comprises surgery.

10. An *in vitro* method of decreasing tumor cell proliferation comprising contacting the tumor cell with the immune cell of any one of claims 1-6, thereby decreasing the tumor cell proliferation.

11. An isolated nucleic acid molecule comprising a first polynucleotide encoding a chimeric antigen receptor (CAR) comprising an antibody that specifically recognizes human mesothelin, and a 4-1BB intracellular region, and a second polynucleotide encoding an interleukin 15 (IL-15), optionally further comprising a third polynucleotide encoding CCL19, optionally wherein the CCL19 comprises SEQ ID NO: 13.

12. The isolated nucleic acid molecule of claim 11, wherein the CAR further comprises a CD8 hinge region, a CD8 transmembrane region and a CD3ζ intracellular region, optionally wherein the CD8 hinge region comprises SEQ ID NO: 26, optionally wherein the CD8 transmembrane region comprises SEQ ID NO: 27.

13. The isolated nucleic acid molecule of claim 11 or 12, wherein the isolated nucleic acid molecule comprises the first polynucleotide encoding a CAR and the second polynucleotide encoding IL-15.

14. The isolated nucleic acid molecule of any one of claims 11-13, wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises three complementarity-determining regions (CDRs) comprising SEQ ID NOs: 16-18, and wherein the VL comprises three CDRs comprising SEQ ID NOs: 19-21.

15. The isolated nucleic acid molecule of any one of claims 11-14, wherein the VH comprises SEQ ID NO: 22 and the VL comprises SEQ ID NO: 23.

16. The isolated nucleic acid molecule of any one of claims 11-15, wherein the antibody comprises a single-chain variable fragment (scFv) format.

17. The isolated nucleic acid molecule of any one of claims 11-16, wherein the antibody comprises SEQ ID NO: 1.

18. The isolated nucleic acid molecule of claims 11-17, wherein the 4-1BB intracellular region comprises SEQ ID NO: 24, optionally wherein the CD3ζ intracellular region comprises SEQ ID NO: 25.

19. The isolated nucleic acid molecule of claim 12, wherein the CAR further comprises a peptide linker of 3 to 10 amino acid residues in length linking the antibody and the CD8 hinge region, optionally wherein the peptide linker comprises SEQ ID NO: 4.

20. The isolated nucleic acid molecule of any one of claims 11-19, wherein the CAR further comprises a signaling peptide, optionally wherein the signaling peptide is located upstream of the antibody that specifically recognizes human mesothelin in the isolated nucleic acid molecule, optionally wherein the signaling peptide comprises SEQ ID NO: 2.

21. The isolated nucleic acid molecule of any one of claims 11-20, wherein the IL-15 comprises a sequence selected from any one of SEQ ID NOs: 8-11 and 28-29.

22. The isolated nucleic acid molecule of any one of claims 11-21, wherein the first polynucleotide encoding the CAR and the second polynucleotide encoding IL-15 are arranged in the nucleic acid molecule from the 5’ terminus to the 3’ terminus as the first polynucleotide encoding the CAR - the second polynucleotide encoding IL-15 or wherein the first polynucleotide encoding the CAR, the second polynucleotide encoding IL-15, and the third polynucleotide encoding CCL19 are arranged in the nucleic acid molecule from the 5’ terminus to the 3’ terminus as the first polynucleotide encoding the CAR - the second polynucleotide encoding IL-15 – the third polynucleotide encoding CCL19.

23. The isolated nucleic acid molecule of any one of claims 11-22, wherein the isolated nucleic acid molecule encodes a polypeptide comprising SEQ ID NO: 14, 15, 31, 34, 35, 36, 37, 38, 39, or 40.

24. A vector comprising the nucleic acid molecule of any one of claims 11-23.

25. A method for producing an immune cell expressing cell surface molecules that specifically recognize human mesothelin, IL-15, and optionally CCL19, the method comprising:

introducing the nucleic acid molecule of any one of claims 11-23 or the vector of claim 24 to an immune cell to induce expression of cell surface molecules that specifically recognize human mesothelin, IL-15, and optionally CCL19 by the immune cell.

26. A kit comprising the nucleic acid molecule of any one of claims 11-23; the vector of claim 24, the immune cell of any one of claims 1-6, or the pharmaceutical composition of claim 7, and instructions of use.

27. The immune cell of any one of claims 1-6 or the pharmaceutical composition of claim 7 for use in medicine.

28. The immune cell of any one of claims 1-6 or the pharmaceutical composition of claim 7 for use in treating a mesothelin-expressing cancer in a subject.