

CLAIMS

What is claimed is:

1. An immune cell, comprising:
 - a. a first engineered receptor, the first engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a first ligand binding domain capable of specifically binding a first ligand; and
 - b. a second engineered receptor, the second engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a second ligand binding domain capable of specifically binding a second ligand,wherein binding of the first ligand binding domain to the first ligand activates or promotes activation of the immune cell by the first receptor,
wherein binding of the second ligand binding domain to the second ligand inhibits activation of the immune cell by the first receptor, and
wherein the second ligand binding domain comprises CDRs selected from SEQ ID NOs: 41-52.
2. The immune cell of claim 1, comprising:
 - a. a first engineered receptor, the first engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a first ligand binding domain capable of specifically binding an epidermal growth factor receptor (EGFR) ligand; and
 - b. a second engineered receptor, the second engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a second ligand binding domain capable of specifically binding an human leukocyte antigen A*02 (HLA-A*02) allele,wherein binding of the first ligand binding domain to the EGFR ligand activates or promotes activation of the immune cell by the first receptor,

wherein binding of the second ligand binding domain to the HLA-A*02 allele inhibits activation of the immune cell by the first receptor, and

wherein the first ligand binding domain comprises a sequence of SEQ ID NO: 391, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 118, or a sequence having at least 90%, at least 95% or at least 99% identity thereto.

3. The immune cell of claim 1 or claim 2, wherein the first ligand binding domain comprises CDRs selected from SEQ ID NOs: 131-166.

4. The immune cell of any one of claims 1-3, wherein the second ligand binding domain comprises any one of SEQ ID NOs: 53-64 or a sequence having at least 90%, at least 95%, or at least 99% identity thereto.

5. The immune cell of any one of claims 1-4, wherein the second engineered receptor comprises an intracellular domain isolated or derived from LILRB1.

6. The immune cell of claim 1, comprising:

- a. a first engineered receptor, the first engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a first ligand binding domain capable of specifically binding a mesothelin (MSLN) ligand; and
- b. a second engineered receptor, the second engineered receptor comprising a transmembrane region and an extracellular region, the extracellular region comprising a second ligand binding domain capable of specifically binding human leukocyte antigen A*02 (HLA-A*02) allele,

wherein binding of the first ligand binding domain to the MSLN ligand activates or promotes activation of the immune cell by the first receptor,

wherein binding of the second ligand binding domain to the HLA-A*02 allele inhibits activation of the immune cell by the first receptor, and

wherein the first ligand binding domain comprises a sequence of SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 90 or SEQ ID NO: 92, or a sequence having at least 90%, at least 95% or at least 99% identity thereto.

7. The immune cell of claim 6, wherein the second ligand binding domain comprises any one of SEQ ID NOs: 53-64, or a sequence having at least 90%, at least 95%, or at least 99% identity thereto.
8. The immune cell of any one of claim 6 or claim 7, wherein the second engineered receptor comprises an intracellular domain isolated or derived from LILRB1.
9. The immune cell of any one of claims 1-8, wherein the second ligand binding domain comprises a single chain Fv antibody fragment (scFv) or a b chain variable domain (V β).
10. The immune cell of any one of claims 1-8, wherein the first ligand binding domain comprises an scFv or a V β domain.
11. A pharmaceutical composition, comprising a plurality of the immune cells of any one of claims 1-10.
12. Use of a plurality of the immune cells of any one of claims 1-5, 9 and 10, or the pharmaceutical composition of claim 11 in the manufacture of a medicament for treating an EGFR+ cancer with an adoptive cell therapy in a subject.
13. The use of claim 12, wherein cells of the cancer express an EGFR ligand.
14. The use of claim 12 or claim 13, wherein cells of the cancer do not express an HLA-A*02 allele due to loss of heterozygosity or loss of Y chromosome.
15. The use of any one of claims 12-14, wherein non-target cells express both the EGFR ligand and the HLA-A*02 allele.

16. Use of a plurality of the immune cells of any one of claims 6-8 in the manufacture of a medicament for treating an MSLN+ cancer with an adoptive cell therapy in a subject.
17. The use of claim 16, wherein cells of the cancer express a MSLN ligand.
18. The use of claim 16 or claim 17, wherein cells of the cancer do not express an HLA-A*02 allele due to loss of heterozygosity or loss of Y chromosome.
19. The use of claim any one of claims 16-18, wherein non-target cells express both the EGFR ligand and the HLA-A*02 allele.