[0002d] Disclosed herein, in another aspect, is an engineered T cell comprising the expression vector as described herein, wherein the Claudin 18.2-TAC polypeptide as described herein is expressed by the engineered T cell.

[0002e] Disclosed herein, in another aspect, is a pharmaceutical composition comprising the T cell as described herein, and a pharmaceutically acceptable excipient.

[0002f] Disclosed herein, in another aspect, is the use of the pharmaceutical composition of as described herein in the manufacture of a medicament for providing a cancer immunotherapy for treating a Claudin 18.2-expressing cancer in an individual in need thereof, wherein the medicament is to be administered to the individual, wherein an antigen binding antibody fragment of the Claudin 18.2-TAC polypeptide binds to a Claudin 18.2 antigen expressed by the cancer, wherein administration of the T cell results in a reduction in cancer cells in the individual.

[0002g] Disclosed herein, in another aspect, is the pharmaceutical composition as described herein for use as a medicament.

[0003] Disclosed herein, in certain embodiments, are nucleic acids encoding a Claudin 18.2 T cell-antigen coupler (TAC). In some embodiments, the nucleic acid comprises: (a) a first polynucleotide encoding an antigen-binding domain that binds Claudin 18.2; (b) a second polynucleotide encoding an antigen-binding domain that binds a protein associated with a TCR complex; and (c) a third polynucleotide encoding a TCR co-receptor cytosolic domain and transmembrane domain. In some embodiments, the nucleic acid comprises, in order (*e.g.*, from 5’ to 3’): (a) a first polynucleotide encoding an antigen-binding domain that binds Claudin 18.2; (b) a second polynucleotide encoding an antigen-binding domain that binds a protein associated with a TCR complex; and (c) a third polynucleotide encoding a TCR co-receptor cytosolic domain and transmembrane domain. In some embodiments, the antigen-binding domain that binds Claudin 18.2 is a designed ankyrin repeat (DARPin) polypeptide, single chain variable fragment (scFv), single domain antibody, diabody, affibody, adnectin, affilin, phylomer, fynomer, affimer, peptide aptamer, knottin, centyrin, anticalin, or nanobody. In some embodiments, the antigen-binding domain that binds Claudin 18.2 comprises an antigen-binding domain derived from an antibody selected from IMAB362 (claudiximab, zolbetuximab), 43-14A, EPR 19202, and aGC182. In some embodiments, the antigen-binding domain that binds Claudin 18.2 comprises an amino acid sequence having at least 80% sequence identity with the amino acid sequence of the antigen-binding domain(s) of IMAB362 (claudiximab, zolbetuximab), 43-14A, EPR 19202, or aGC182. In some embodiments, the antigen-binding

CLAIMS

WHAT IS CLAIMED IS:

1. A Claudin 18.2 T cell-antigen coupler (TAC) polypeptide, comprising:

(a) an extracellular Claudin 18.2- single antigen binding domain of heavy chain only antibodies (VHH) comprising a CDR1 having the amino acid sequence of SEQ ID NO: 57, a CDR2 having the amino acid sequence of SEQ ID NO: 63, and a CDR3 having the amino acid sequence of SEQ ID NO: 59;

(b) an extracellular CD3 binding domain consisting of an amino acid sequence 100% identical to SEQ ID NO: 36; and

(c) a T cell co-receptor domain polypeptide comprising a CD4 cytosolic domain and a CD4 transmembrane domain and consisting of an amino acid sequence 100% identical to SEQ ID NO: 12;

wherein component (a), component (b), and component (c) are fused directly to each other, or joined by at least one linker.

2. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-binding domain comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 56.

3. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-binding domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 56.

4. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-binding domain comprises the amino acid sequence of SEQ ID NO: 56.

5. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-TAC polypeptide comprises an amino acid sequence having at least 80% sequence identity with the amino acid sequence of SEQ ID NO: 73.

6. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-TAC polypeptide comprises an amino acid sequence having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 73.

7. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-TAC polypeptide comprises an amino acid sequence having the amino acid sequence of SEQ ID NO: 73.

8. The Claudin 18.2-TAC polypeptide of claim 1, wherein component (a) and component (c) are fused to component (b) or wherein component (b) and component (c) are fused to component (a).

9. The Claudin 18.2-TAC polypeptide of claim 1, wherein the Claudin 18.2-TAC does not comprise a co-stimulatory domain or an activation domain.

10. A nucleic acid encoding the Claudin 18.2-TAC polypeptide of claim 1.

11. The nucleic acid of claim 10, wherein the nucleic acid comprises a sequence having at least 80% sequence identity with the nucleic acid sequence of SEQ ID NO: 72.

12. An expression vector comprising the nucleic acid of claim 11.

13. An engineered T cell comprising the expression vector of claim 12, wherein the Claudin 18.2-TAC polypeptide of claim 1 is expressed by the engineered T cell.

14. The T cell of claim 13, wherein the T cell is a γδ T cell.

15. A pharmaceutical composition comprising the T cell of claim 13 or 14, and a pharmaceutically acceptable excipient.

16. Use of the pharmaceutical composition of claim 15 in the manufacture of a medicament for providing a cancer immunotherapy for treating a Claudin 18.2-expressing cancer in an individual in need thereof, wherein the medicament is to be administered to the individual, wherein an antigen binding antibody fragment of the Claudin 18.2-TAC polypeptide binds to a Claudin 18.2 antigen expressed by the cancer, wherein administration of the T cell results in a reduction in cancer cells in the individual.

17. The use of claim 16, wherein the cancer is a solid cancer.

18. The use of claim 16, wherein the cancer is a pancreatic cancer, a gastric cancer, a signet ring cell carcinoma, a mucinous gastric cancer, a gastroesophageal cancer, an esophageal cancer, a digestive system cancer, an ovarian cancer, a mucinous ovarian cancer, a non-small cell lung cancer, or a lung cancer.

19. The pharmaceutical composition of claim 15 for use as a medicament.