

Claims

What is claimed is:

1. A multispecific chimeric receptor comprising a polypeptide chain comprising:
 - (a) an extracellular domain comprising a first NKG2D domain, a second NKG2D domain, and a second antigen binding domain;
 - (b) a transmembrane domain; and
 - (c) an intracellular signaling domain;wherein the first NKG2D domain is derived from extracellular domain of NKG2D, wherein the first NKG2D domain is a reverse NKG2D, wherein the second NKG2D domain is derived from extracellular domain of NKG2D, and wherein the second NKG2D is a forward NKG2D domain having the amino acid sequence in the same order as the wildtype NKG2D domain.
2. The multispecific chimeric receptor of claim 1, wherein the extracellular domain comprises from the N-terminus to the C-terminus: the second antigen binding domain, the first NKG2D domain and the second NKG2D domain.
3. The multispecific chimeric receptor of claim 1, wherein the second antigen binding domain is fused to the first NKG2D domain via a peptide linker.
4. The multispecific chimeric receptor of claim 1, wherein the second antigen binding domain is an antibody fragment.
5. The multispecific chimeric receptor of claim 4, wherein the antibody fragment specifically binds to an antigen selected from the group consisting of CD19, CD20, CD22, CD33, CD38, BCMA, CS1, ROR1, GPC3, CD123, CD138, c-Met, EGFR, EGFRvIII, HER2, HER3, GD-2, NY-ESO-1, MAGE A3, and glycolipid F77.
6. The multispecific chimeric receptor of claim 1, wherein the second antigen binding domain is a ligand or a ligand binding domain.
7. The multispecific chimeric receptor of claim 6, wherein the ligand or ligand binding domain is derived from a molecule selected from the group consisting of NKG2A, NKG2C, NKG2F, IL-3, IL-13, LLT1, AICL, DNAM-1, and Nkp80.
8. The multispecific chimeric receptor of claim 7, wherein the second antigen binding domain is an IL-3 domain.
9. The multispecific chimeric receptor of any one of claims 1-8, wherein each of the first NKG2D domain and the second NKG2D domain comprises the amino acid sequence of SEQ ID NO: 7 or 8.
10. The multispecific chimeric receptor of claim 1, wherein the transmembrane domain is derived from a molecule selected from the group consisting of CD8 α , CD4, CD28, 4-1BB, CD80, CD86, CD152 and PD1.
11. The multispecific chimeric receptor of claim 1, wherein the intracellular signaling domain comprises a primary intracellular signaling domain of an immune effector cell.

12. The multispecific chimeric receptor of claim 1, wherein the intracellular signaling domain comprises a co-stimulatory signaling domain.
13. The multispecific chimeric receptor of claim 12, wherein the co-stimulatory signaling domain is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD30, ICOS, CD40, CD3, LFA-1, CD2, CD7, LIGHT, NKG2C, B7-H3, Ligands of CD83 and combinations thereof.
14. A multispecific chimeric receptor comprising an amino acid sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-17.
15. An isolated nucleic acid comprising a nucleic acid sequence encoding the multispecific chimeric receptor of any one of claims 1-14.
16. An isolated nucleic acid comprising a nucleic acid sequence comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 21-22.
17. An engineered immune effector cell, comprising the multispecific chimeric receptor of any one of claims 1-14, or the isolated nucleic acid of claim 15 or 16.
18. A pharmaceutical composition, comprising the engineered immune effector cell of claim 17, and a pharmaceutically acceptable carrier.
19. Use of the pharmaceutical composition of claim 18 in the manufacture of a medicament for the treatment of a cancer, wherein the cancer comprises multiple myeloma, acute lymphoblastic leukemia, chronic lymphocytic leukemia.