

CLAIMS

What is claimed is:

1. A composition comprising a nucleic acid comprising a sequence encoding a chimeric fusion protein (CFP), wherein the CFP comprises:
 - (a) an extracellular domain comprising an antigen binding domain,
 - (b) a transmembrane domain that specifically integrates within a membrane protein complex of a cell, the cell being characterized as naturally expressing the membrane protein complex; and
 - (c) an intracellular domain; andwherein the cell that is characterized as naturally expressing the membrane protein complex is a NK cell or a B cell.
2. The composition of claim 1, wherein, when the composition comprising the recombinant nucleic acid is contacted to a heterogenous cell population, greater than 50% cells in the heterogenous cell population that naturally express the membrane protein complex expresses the CFP, and less than 10% cells within the heterogenous cell population that lack the membrane protein complex fails to express the CFP.
3. The composition of claim 1 or 2, wherein the transmembrane domain is a transmembrane domain from a protein that multimerizes with a cell surface receptor expressed by natural killer (NK) cells; wherein upon contacting the composition to a heterogenous population of cells comprising NK cells, the CFP expresses on cell surface of NK cells; and optionally, wherein, the transmembrane domain is a transmembrane domain from a protein listed in Table 4, or the transmembrane domain multimerizes with a transmembrane domain from a protein listed in Table 4.
4. The composition of any one of claims 1-3, wherein the transmembrane domain is from a cell surface receptor selected from a group consisting of CD39, CD56, CD57, CD94, CD159a, CD159c, CD314, CD335, CD336, CD337, DAP12, DAP10, NKG2C, NKG2D, NKG2E, Ly49D, Ly49D, NKp46, NKp30 and NKp44; preferably, wherein the transmembrane domain is a transmembrane domain from NKp44; more preferably, wherein the transmembrane domain from NKp44 comprises an amino acid sequence of LVPVFCGLLVAKSLVLSALLV (amino acids 290-310 of SEQ ID NO: 39).
5. The composition of any one of claims 1-4, wherein the CFP further comprises an extracellular domain or fragment thereof from a cell surface receptor selected from a group

- consisting of CD39, CD56, CD57, CD94, CD159a, CD159c, CD314, CD335, CD336, CD337, DAP12, DAP10, NKG2C, NKG2D, NKG2E, Ly49D, Ly49D, NKp46, NKp30 and NKp44; preferably, wherein the extracellular domain or fragment thereof is an extracellular domain or fragment thereof from NKp44; more preferably, the extracellular domain or fragment thereof from NKp44 comprises an amino acid sequence of VPSQPQNSTLRPGPAAPIA (amino acids 271-289 of SEQ ID NO: 39).
6. The composition of any one of claims 1-5, wherein the CFP further comprises an intracellular domain from CD39, CD56, CD57, CD94, CD159a, CD159c, CD314, CD335, CD336, CD337, DAP12, DAP10, NKG2C, NKG2D, NKG2E, Ly49D, Ly49D, NKp46, NKp30 or NKp44; preferably, wherein the intracellular domain is an intracellular domain from NKp44; more preferably, wherein the intracellular domain from NKp44 comprises an amino acid sequence of WWGDIWWKTMMELRSLDTQKATCHLQQVTDLPWTSVSSPVEREILYHTVARTKISDDDDEHTL (amino acids 311-373 of SEQ ID NO: 39).
 7. The composition of any one of claims 1-3, wherein the nucleic acid comprises:
 - (i) a sequence that is at least 90% identical to any one of sequences set forth in Table 5;
 - (ii) a sequence that is at least 90% identical to a sequence set forth in SEQ ID NO: 1, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 270, SEQ ID NO: 272, or SEQ ID NO: 277; or
 - (iii) a sequence that is at least 90% identical to any one of sequences set forth in SEQ ID NO: 251, 255, 257, 260, 262, 264, 265, 267, 269, 271, 273, 274, 275, 276, 278, 279, 280, 282, 283, or 284.
 8. The composition of any one of claims 1-3, wherein the nucleic acid comprises a sequence set forth in SEQ ID NO: 277, or a sequence that is at least 90% identical to SEQ ID NO: 277.
 9. The composition of any one of claims 1-8, wherein the CFP comprises a sequence with at least 90% sequence identity to VPSQPQNSTLRPGPAAPIALVPVFCGLLVAKSLVLSALLVWWGDIWWKTMMELRSLDTQKATCHLQQVTDLPWTSVSSPVEREILYHTVARTKISDDDDEHTL (amino acids 271-373 of SEQ ID NO: 39).
 10. The composition of claim 1 or 2, wherein the transmembrane domain is a transmembrane domain from a protein that multimerizes with a cell surface receptor expressed by B cells;

wherein upon contacting the composition to a heterogenous population of cells comprising B cells, the CFP expresses on cell surface of B cells.

11. The composition of any one of claims 1-2 and 10, wherein the transmembrane domain is a transmembrane domain from a cell surface receptor selected from a group consisting of CD19, CD20, CD21, CD22, CD27, CD28, CD45, CD72, CD79a, CD79b and CD81.
12. The composition of any one of claims 1-2 and 10-11, wherein the extracellular domain is an extracellular domain from CD19, CD20, CD21, CD22, CD27, CD28, CD45, CD72, CD79a, CD79b or CD81, and/or wherein the intracellular domain comprises an intracellular signaling domain from Fc γ R, Fc α R, Fc ϵ R, Fc μ R, CD40, CD3 ζ , Fc γ RIIB, Siglec-G, CD22, CD72, CD152, LAIR1, CD85j, PIR-B or PD-1.
13. A composition comprising a nucleic acid comprising a sequence encoding a chimeric fusion protein (CFP), wherein the CFP comprises (a) an extracellular domain comprising an antigen binding domain, (b) a transmembrane domain operatively linked to the extracellular domain and that specifically integrates within a membrane protein complex of a cell, the cell being characterized as naturally expressing the membrane protein complex and (c) an intracellular domain; wherein, when the composition comprising the recombinant nucleic acid is contacted to a heterogenous cell population, greater than 50% cells in the heterogenous cell population that naturally express the membrane protein complex expresses the CFP, and greater than 10% cells within the heterogenous cell population that lack the membrane protein complex fail to express the CFP.
14. The composition of claim 13, wherein the transmembrane domain is a transmembrane domain from a protein that multimerizes with a cell surface receptor expressed by T cells; wherein upon contacting the composition to a heterogenous population of cells comprising T cells, the CFP expresses on cell surface of T cells.
15. The composition of claim 13, wherein the transmembrane domain is a transmembrane domain from a cell surface receptor comprising the TCR-CD3 complex, selected from a group consisting of CD3, CD4, CD5, CD7, CD8, CD28, CD48, CD3 ϵ , CD3 δ , CD3 γ , CD3 ζ , TCR α chain, TCR β chain, TCR γ chain and TCR δ ; preferably, wherein the transmembrane domain is a transmembrane domain from CD3 ϵ .
16. The composition of claim 13, or 14, wherein the CFP further comprises an intracellular domain that is an intracellular domain from CD3, CD4, CD5, CD7, CD8, CD28, CD48,

- CD3 ϵ , CD3 δ , CD3 γ or CD3 ζ ; preferably, wherein the intracellular domain that is an intracellular domain from CD3 ϵ .
17. The composition of any one of claims 13-15, wherein the CFP further comprises an extracellular domain or fragment thereof from a cell surface receptor selected from a group consisting of CD3, CD4, CD5, CD7, CD8, CD28, CD48, CD3 ϵ , CD3 δ , CD3 γ , CD3 ζ , TCR α chain, TCR β chain, TCR γ chain and TCR δ ; preferably, wherein the extracellular domain or fragment thereof is an extracellular domain or fragment thereof from CD3 ϵ .
 18. The composition of any one of claims 1-16, the antigen binding domain binds to a cancer antigen selected from TROP2, GPC3, HER2, and CD5, optionally, the antigen binding domain comprises an scFv or an sdAb.
 19. The composition of claim 18, wherein the antigen binding domain binds HER2 and comprises a variable heavy chain (VH) comprising a HCDR1 of DTYIH (amino acids 172-176 of SEQ ID NO: 39), a HCDR2 of RIYPTNGYTRYADSVKG (amino acids 191-207 of SEQ ID NO: 39), and a HCDR3 of WGGDGFYAMDY (amino acids 240-250 of SEQ ID NO: 39); and a variable light chain (VL) comprising a LCDR1 of RASQDVNTAVA (amino acids 41-51 of SEQ ID NO: 39), a LCDR2 of SASFLYS (amino acids 67-73 of SEQ ID NO: 39), and a LCDR3 of QQHYTTPPT (amino acids 106-114 of SEQ ID NO: 39).
 20. The composition of claim 19, wherein the VH comprises a sequence with at least 90% sequence identity to
EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNG
YTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYW
GQGTLTVSS (amino acids 142-261 of SEQ ID NO: 39); and wherein the VL comprises a sequence with at least 90% sequence identity to
DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSG
VPSRFGSGRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK (amino acids 18-124 of SEQ ID NO: 39).
 21. The composition of any one of claim 18-20, wherein the CFP comprises a sequence that is at least 90% identical to SEQ ID NO: 39.
 22. The composition of any one of claims 1-21, wherein the nucleic acid is an RNA.
 23. The composition of any one of claims 1-22, further comprising a nucleic acid delivery vehicle, wherein the nucleic acid delivery vehicle is a lipid nanoparticle (LNP) comprising a

cationic lipid, a non-cationic lipid, a neutral lipid, a cholesterol or a polyethylenel glycol (PEG)-lipid.

24. A pharmaceutical composition, comprising the composition of any one of claims 1-22 and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition is formulated for in vivo delivery in a subject in need thereof.
25. Use of the composition of any one of claims 1-23 in the manufacture of a medicament for treating a disease in a subject, wherein the disease is a cancer, an autoimmune disease, a fibrotic disease, or an infectious disease.
26. The composition of any one of claims 1-23 for use in therapy.