

What is claimed is:

1. A chimeric protein comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain is capable of binding a negative signal, and wherein the intracellular domain comprises an intracellular domain, or a portion thereof, of a stimulatory polypeptide, and the negative signal is selected from the group consisting of TGF- β , IL-10, IL-1, IL-6, PD-L1, PD-L2, B7-1, B7-2, MHCI, HVEM, CD155, CD112, CD111, CD200, B7-H6, HS-GAG, HLA, N-cadherin, E-cadherin, FasL, MHCII, TIM-3, IL-18, adenosine, and prostaglandin,

wherein the stimulatory polypeptide is selected from the group consisting of: DAP10, DAP12, 2B4, CD2, IL-21, CARD11, LAT, LAT2, SLP76, LAX, MyD88, PAG, GAP, SAP, EAT-2, FcRK, FcRI, FcKRIIa, FcKRIIc, FcKRIIIa, LFA-3, SLAM, SLAMF5, SLAMF6, SLAMF7, SLAMF3, CEACAM-3, CD209, CLEC-2, CLEC-7A, CD370, NKp80, NKp65, NKG2C, NKG2D, NKG2E, CD131, TSLP-R, CD116, IL-1R3, IL-1RA, IL-1RL1, IL-1RL2, IL-11RA, IL-17RA, IL-17RB, IL-17RC, IL-17RE, IL-18R1, IL-18RB, IL-22RA1, IL-23R, IL-27RA, IL-3RA, LIF-R, CSF-1R, OSM-RB, CD220, LEP-R, CD79A, CD79B, DNAM-1, CD83, ICOS, ICAM-1, ICAM-2, ICAM-3, KIR2DL4, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, NKp46, NKp44, NKp30, CD7, CD4, CD28, TMIGD2, CD11A, CD18, CD355, CD22, CD3E, CD3G, CD3Z, Lck, ZAP70, TIM-1, TLR1, TLR10, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, CD27, CD70, CD258, CD153, RANK, CD266, CD267, CD268, CD270, CD271, CD269, CD357, TNFRSF19, TNFRSF19L, CD120A, CD120B, TNFRSF25, TNFRSF27, TNFRSF3, OX-40, CD40, CD30, 4-1BB, EDAR, PILRB, FCARI, CD58, CD35, CD46, CD206, HER2, HGFR, CD331, CD332, TNFSF18, CD257, CD256, TWEAK, CD254, CD253, CD333, CD334, CD309, VEGFR-3, EPHA1, EPHB1, CD140a, CD140b, CD160, ICAM-5, SIGLEC-14, SIGLEC-15, SIGLEC-16, TROY, RELT, TRAMP, XEDAR, LTB-R, CD23, CLEC-4E, CLEC-6A, CLEC-10A, CLEC-4D, CLEC-4C, TNFSF1A, OX40L, CD40L, CD178, and 4-1BBL.

2. The chimeric protein of claim 1, wherein the negative signal is TGF- β .

3. The chimeric protein of claim 1 or 2, wherein said chimeric protein is capable of activating an immune cell selected from a natural killer (NK) cell, an NKT cell, an alpha beta T cell, a gamma delta T cell, a regulatory T cell, a neutrophil, a monocyte, a mast cell, an eosinophil, a basophil, a dendritic cell, a B cell, and a macrophage.

4. The chimeric protein of claim 3, wherein said chimeric protein is capable of activating an NK cell.

5. The chimeric protein of any one of claims 1-4, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of a TGF- β receptor polypeptide.

6. The chimeric protein of any one of claims 1-5, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of a TGF- β R1 polypeptide or a TGF- β R2 polypeptide presented in Table 1.1.

7. The chimeric protein of any one of claims 1-4, wherein the extracellular domain comprises an antigen-binding domain that specifically binds to the negative signal.

8. The chimeric protein of claim 7, wherein the antigen-binding domain comprises a fragment of an antibody.

9. The chimeric protein of claim 7, wherein the antigen-binding domain comprises an scFv, a Fab, or a VHH.

10. The chimeric protein of claim 9, wherein the scFv is an scFv from a monoclonal antibody.

11. The chimeric protein of claim 9 or 10, wherein the scFv is connected to the transmembrane domain by a linker.

12. The chimeric protein of any one of claims 1-4, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of an inhibitory polypeptide that binds the negative signal.

13. The chimeric protein of claim 12, wherein the inhibitory polypeptide is an inflammatory mediator receptor, an inhibitory cytokine receptor, an immune checkpoint receptor, or a dual activator-checkpoint receptor.

14. The chimeric protein of claim 12, wherein the inhibitory polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.1.

15. The chimeric protein of any one of claims 1-14, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of an inhibitory polypeptide presented in Table 1 or Table 1.2.

16. The chimeric protein of any one of claims 1-14, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.

17. The chimeric protein of any one of claims 1-16, wherein the intracellular domain, or a portion thereof, is from a stimulatory polypeptide selected from the group consisting of DAP10, DAP12, 2B4, CD2, LFA1, and IL21.

18. The chimeric protein of any one of claims 1-17, wherein the chimeric protein comprises the intracellular domain, or a portion thereof, of two or more different stimulatory polypeptides.

19. The chimeric protein of any one of claims 1-18, wherein:
the inhibitory polypeptide is a type I receptor, and the stimulatory polypeptide is a type I receptor;

the inhibitory polypeptide is a type I receptor, and the stimulatory polypeptide is a type III receptor;

the inhibitory polypeptide is a type II receptor, and the stimulatory polypeptide is a type II receptor;

the inhibitory polypeptide is a type I receptor, and the stimulatory polypeptide is not associated with the plasma membrane; or

the inhibitory polypeptide is a type I receptor, the stimulatory polypeptide is a type II receptor, and the transmembrane domain, or portion thereof, is from a type I receptor.

20. The chimeric protein of any one of claims 1-19, wherein a combination of the extracellular domain, or a portion thereof, of an inhibitory polypeptide and the intracellular domain, or a portion thereof, of a stimulatory polypeptide is selected from the combinations presented in any one of Tables 6-14.

21. The chimeric protein of any one of claims 1-20, wherein the extracellular domain and the transmembrane domain are connected by a linker.

22. The chimeric protein of any one of claims 1-21, wherein the transmembrane domain and the intracellular domain are connected by a linker.

23. The chimeric protein of claims 21 or 22, wherein the linker is selected from the linkers presented in Table 3.

24. A modified immune cell engineered to express a chimeric protein of any one of claims 1-23.

25. The modified immune cell of claim 24, wherein the immune cell is selected from the group consisting of a natural killer (NK) cell, an NKT cell, a T-cell, and a macrophage.

26. The modified immune cell of claim 25, wherein the immune cell is an NK cell.

27. The modified immune cell of any one of claims 24-26, wherein the immune cell is engineered to further comprise a cytokine.

28. The modified immune cell of claim 27, wherein the cytokine can be selected from the group consisting of a chemokine, an interferon, an interleukin, a lymphokine, a tumor necrosis factor, or a variant or combination thereof.

29. The modified immune cell of claim 28, wherein the cytokine is an IL-15 or a fragment or variant thereof.

30. A polynucleotide comprising a nucleic acid sequence encoding a chimeric protein of any one of claims 1-23.

31. A pharmaceutical composition comprising the modified immune cell of any one of claims 24-29, and a pharmaceutically acceptable excipient.

32. Use of a composition comprising the modified immune cell of any one of claims 24-29 in the manufacture of a medicament for treating a subject in need of an altered immune response.

33. Use of a composition comprising the modified immune cell of any one of claims 24-29 in the manufacture of a medicament for treating a disease or pathological condition in a subject.

34. Use of a composition comprising the modified immune cell of any one of claims 24-29 in the manufacture of a medicament for treating a cancer in a subject.

35. A method of generating a modified immune cell, the method comprising:
(a) introducing a nucleic acid encoding the chimeric protein of any one of claims 1-23, into an immune cell;

(b) culturing the immune cell under conditions allowing the expression of the protein in or on the immune cell; and

(c) recovering the immune cell from the culture,
thereby generating the modified immune cell.

36. A modified immune cell obtained by the method of claim 35.

37. A kit comprising a chimeric protein and/or a nucleic acid encoding the chimeric protein, wherein the chimeric protein is the chimeric protein of any one of claims 1-23.