

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, ~~TGF- β~~ , 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, GAPT, 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 .

23. 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.

34. The chimeric protein of claim 34, 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.

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

58. The chimeric protein of claim 74, wherein the antigen-binding domain comprises a fragment of an antibody.

69. The chimeric protein of claim 74, wherein the antigen-binding domain comprises an scFv, a Fab, or a VHH.

710. The chimeric protein of claim 96, wherein the scFv is an scFv from a monoclonal antibody.

811. The chimeric protein of claim 9 or 106~~or 7~~, wherein the scFv is connected to the transmembrane domain by a linker.

~~9~~12. The chimeric protein of any one of claims ~~1-41-3~~, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of an inhibitory polypeptide that binds the negative signal.

~~40~~13. The chimeric protein of claim 129, wherein the inhibitory polypeptide is an inflammatory mediator receptor, an inhibitory cytokine receptor, an immune checkpoint receptor, or a dual activator-checkpoint receptor.

~~44~~14. The chimeric protein of claim 129, wherein the inhibitory polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.1.

~~42~~15. The chimeric protein of any one of claims ~~1-141-11~~, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of an inhibitory polypeptide presented in Table 1 or Table 1.2.

~~43~~16. The chimeric protein of any one of claims ~~1-141-11~~, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.

~~14.—The chimeric protein of any one of claims 1-13, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of a stimulatory polypeptide selected from the stimulatory polypeptides presented in Table 2 or Table 2.1.~~

~~15.—The chimeric protein of claim 14, wherein the stimulatory polypeptide is selected from one or more isoforms of the stimulatory polypeptide.~~

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.

~~16~~18. The chimeric protein of any one of claims ~~1-17~~1-15, wherein the chimeric protein comprises the intracellular domain, or a portion thereof, of two or more different stimulatory polypeptides.

~~17~~19. The chimeric protein of any one of claims ~~1-18~~1-16, 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.

~~18. — The chimeric protein of any one of claims 1-17, wherein the inhibitory polypeptide is capable of forming a dimer and the stimulatory polypeptide is capable of forming a dimer; or wherein the inhibitory polypeptide is capable of forming a trimer and the stimulatory polypeptide is capable of forming a trimer.~~

~~19~~20. The chimeric protein of any one of claims ~~1-19~~1-18, 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.

~~20~~21. The chimeric protein of any one of claims ~~1-20~~1-19, wherein the extracellular domain and the transmembrane domain are connected by a linker.

~~21~~22. The chimeric protein of any one of claims ~~1-21~~1-20, wherein the transmembrane domain and the intracellular domain are connected by a linker.

2223. The chimeric protein of claims 21 or 2220 or 21, wherein the linker is selected from the linkers presented in Table 3.

2324. A modified immune cell engineered to express a chimeric protein of any one of claims 1-23 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 IL-10, TGF- β , 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, MHCI, TIM-3, IL-18, adenosine, and prostaglandin.

2425. The modified immune cell of claim 2423, 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.

2526. The modified immune cell of claim 2524, wherein the immune cell is an NK cell.

26.—The modified immune cell of any one of claims 23-25, wherein the extracellular domain comprises an antigen-binding domain that specifically binds to the negative signal.

27.—The modified immune cell of claim 26, wherein the antigen-binding domain comprises a fragment of an antibody.

28.—The modified immune cell of claim 26, wherein the antigen-binding domain comprises an scFv or a Fab.

29.—The modified immune cell of claim 28, wherein the scFv is an scFv from a monoclonal antibody.

30.—The modified immune cell of claim 28 or 29, wherein the scFv is connected to the transmembrane domain by a linker.

~~31.—The modified immune cell of any one of claims 23–30, wherein the antigen-binding domain specifically binds to a negative signal selected from the group consisting of IL-10, TGF- β , 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, and MHCII.~~

~~32.—The modified immune cell of any one of claims 23–25, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of an inhibitory polypeptide.~~

~~33.—The modified immune cell of claim 32, wherein the inhibitory polypeptide is an inflammatory mediator receptor, an inhibitory cytokine receptor, an immune-checkpoint receptor, or a dual activator-checkpoint receptor.~~

~~34.—The modified immune cell of claim 32, wherein the inhibitory polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.1.~~

~~35.—The modified immune cell of any one of claims 23–34, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of an inhibitory polypeptide presented in Table 1 or Table 1.2.~~

~~36.—The modified immune cell of any one of claims 23–34, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.~~

~~37.—The modified immune cell of any one of claims 23–36, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of a stimulatory polypeptide selected from the stimulatory polypeptides presented in Table 2 or Table 2.1.~~

~~38.—The modified immune cell of any one of claims 23–37, wherein the chimeric protein comprises the intracellular domain, or a portion thereof, of two or more different stimulatory polypeptides.~~

~~39. The modified immune cell of any one of claims 23-38, wherein the extracellular domain and the transmembrane domain are connected with a linker.~~

~~40. The modified immune cell of any one of claims 23-39, wherein the transmembrane domain and the intracellular domain are connected with a linker.~~

~~41. The modified immune cell of claim 39 or 40, wherein the linker is selected from the linkers presented in Table 3.~~

~~42. The modified immune cell of any one of claims 1-41, wherein the immune cell is engineered to further comprise a chimeric antigen receptor (CAR).~~

~~43. The modified immune cell of claim 42, wherein the CAR targets a tumor antigen.~~

~~44. The modified immune cell of any one of claims 1-43, wherein the immune cell is engineered to further comprise a cytokine.~~

~~45. The modified immune cell of claim 44, 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.~~

~~46. The modified immune cell of claim 44, wherein the cytokine is an IL-15 or a fragment or variant thereof.~~

~~47. A chimeric protein comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain binds to TGF- β , and wherein the intracellular domain comprises an intracellular domain, or a portion thereof, of a stimulatory polypeptide.~~

48.—The chimeric protein of claim 47, wherein said chimeric protein is capable of activating an immune cell selected from the group consisting of a natural killer (NK) cell, an NKT cell, a T-cell, and a macrophage.

49.—The chimeric protein of claim 47, wherein said chimeric protein is capable of activating an NK cell.

50.—The chimeric protein of any one of claims 47-49, wherein the extracellular domain comprises an antigen-binding domain that specifically binds TGF- β .

51.—The chimeric protein of claim 49, wherein the antigen-binding domain comprises a fragment of an antibody.

52.—The chimeric protein of claim 49, wherein the antigen-binding domain comprises an scFv or a Fab.

53.—The chimeric protein of claim 52, wherein the scFv is an scFv from a monoclonal antibody.

54.—The chimeric protein of claim 52 or 53, wherein the scFv is connected to the transmembrane domain by a linker.

55.—The chimeric protein of any one of claims 47-49, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of a TGF- β receptor polypeptide.

56.—The chimeric protein of any one of claims 47-49, 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.

~~57.—The chimeric protein of any one of claims 47-56, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of a stimulatory polypeptide selected from the stimulatory polypeptides presented in Table 2 or Table 2.1.~~

~~58.—The chimeric protein of any one of claims 47-57, wherein the intracellular domain comprises, the intracellular domain, or a portion thereof, of two or more different stimulatory polypeptides.~~

~~59.—The chimeric protein of any one of claims 47-58, wherein the stimulatory polypeptide is selected from the group consisting of DAP10, DAP12, 2B4, CD2, LFA1, and IL21.~~

~~60.—The chimeric protein of any one of claims 47-58, wherein the stimulatory polypeptide is not one or more of BMP, IL1, IL2, IL7, IL15, IL21, IL12, IL18, IL19, IFN- γ , TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, CD28, 41BB, OX40, CD3 (CD3zeta), CD40, CD27, IL-12R, IL-7R, CD137, and ICOS.~~

~~61.—The chimeric protein of any one of claims 47-58, wherein the stimulatory polypeptide is not DAP12.~~

~~62.—The chimeric protein of any one of claims 47-61, wherein the extracellular domain further comprises at least a portion of an extracellular domain of the stimulatory polypeptide.~~

~~63.—The chimeric protein of any one of claims 47-61, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.~~

~~64.—The chimeric protein of any one of claims 55-61, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of the TGF- β receptor.~~

65.—The chimeric protein of any one of claims 47–61, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of the stimulatory polypeptide.

66.—The chimeric protein of any one of claims 47–65, where the transmembrane domain and the stimulatory polypeptide are respectively selected from the group consisting of: DAP12 and DAP12; TGF- β R2 and DAP12; 2B4 and 2B4; TGF- β R2 and 2B4; LFA1 and LFA1; TGF- β R2 and LFA1; CD2 and CD2; TGF- β R2 and CD2; CD28 and CD28+CD3zeta; and CD28H and CD28H+CD3zeta.

67.—The chimeric protein of any one of claims 47–66, wherein the extracellular domain and transmembrane domain are connected by a linker.

68.—The chimeric protein of any one of claims 47–66, wherein the transmembrane domain and intracellular domain are connected by a linker.

69.—The chimeric protein of claim 67 or 68, wherein the linker is selected from the linkers presented in Table 3.

70.—A modified immune cell engineered to express a chimeric protein comprising an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain binds to TGF- β , and wherein the intracellular domain comprises an intracellular domain, or a portion thereof, of a stimulatory polypeptide.

71.—The modified immune cell of claim 70, 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.

72.—The modified immune cell of claim 71, wherein the immune cell is an NK cell.

73. — The modified immune cell of claim 72, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of a stimulatory polypeptide that promotes activation of an NK cell.

74. — The modified immune cell of any one of claims 70-73, wherein binding of the extracellular domain to TGF- β activates the immune cell.

75. — The modified immune cell of any one of claims 70-74, wherein the extracellular domain comprises an antigen-binding domain that specifically binds TGF- β .

76. — The modified immune cell of claim 75, wherein the antigen-binding domain comprises a fragment of an antibody.

77. — The modified immune cell of claim 75, wherein the antigen-binding domain comprises an scFv or a Fab.

78. — The modified immune cell of claim 75, wherein the scFv is an scFv from a monoclonal antibody.

79. — The modified immune cell of any one of claims 70-73, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of a TGF- β receptor (TGF- β R) polypeptide.

80. — The modified immune cell of claim 79, 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.

81. — The modified immune cell of any one of claims 70-80, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of a stimulatory polypeptide selected from the stimulatory polypeptides presented in Table 2 or Table 2.1.

~~82.—The modified immune cell of any one of claims 70-81, wherein the intracellular domain comprises the intracellular domain, or a portion thereof, of two or more different stimulatory polypeptides.~~

~~83.—The modified immune cell of any one of claims 70-82, wherein the stimulatory polypeptide is DAP10, DAP12, 2B4, CD2, LFA1, or IL21.~~

~~84.—The modified immune cell of any one of claims 70-82, wherein the stimulatory polypeptide is not one or more of BMP, IL1, IL2, IL7, IL15, IL21, IL12, IL18, IL19, IFN- γ , TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, CD28, 4-1BB, OX40, CD3 (CD3 ζ), CD40, CD27, IL-12R, IL-7R, CD137, and ICOS.~~

~~85.—The modified immune cell of any one of claims 70-82, wherein the stimulatory polypeptide is not DAP12.~~

~~86.—The modified immune cell of any one of claims 70-85, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.~~

~~87.—The modified immune cell of any one of claims 70-85, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of the TGF- β receptor (TGF- β R).~~

~~88.—The modified immune cell of any one of claims 70-85, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of the stimulatory polypeptide.~~

~~89.—The modified immune cell of any one of claims 70-88, where the transmembrane domain and the stimulatory polypeptide are respectively selected from the group consisting of: DAP12 and DAP12; TGF- β R2 and DAP12; 2B4 and 2B4; TGF- β R2 and 2B4; LFA1 and~~

~~LFA1; TGF- β R2 and LFA1; CD2 and CD2; TGF- β R2 and CD2; CD28 and CD28+CD3zeta; and CD28H and CD28H+CD3zeta.~~

~~90.—The modified immune cell of any one of claims 70-89, wherein the immune cell is engineered to further comprise a chimeric antigen receptor (CAR).~~

~~91.—The modified immune cell of claim 90, wherein the CAR targets a tumor antigen.~~

~~9227.~~ The modified immune cell of any one of claims ~~24-2670-90~~, wherein the immune cell is engineered to further comprise a cytokine.

~~9328.~~ The modified immune cell of claim ~~2792~~, 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.

~~9429.~~ The modified immune cell of claim ~~2893~~, wherein the cytokine is an IL-15 or a fragment or variant thereof.

~~95.—A protein comprising an extracellular domain and a transmembrane domain, wherein the extracellular domain is capable of binding a negative signal, and wherein the protein lacks a fully functional intracellular domain, and the negative signal is selected from the group consisting of IL-10, TGF- β , 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.~~

~~96.—The protein of claim 95, wherein the protein lacks an intracellular domain.~~

~~97.—The protein of claim 95 or 96, wherein the extracellular domain comprises an antigen-binding domain that specifically binds to the negative signal.~~

~~98.—The protein of claim 97, wherein the antigen-binding domain comprises a fragment of an antibody.~~

~~99.—The protein of claim 97, wherein the antigen-binding domain comprises an scFv or a Fab.~~

~~100.—The protein of claim 99, wherein the scFv is an scFv from a monoclonal antibody.~~

~~101.—The protein of claim 99 or 100, wherein the scFv is connected to the transmembrane domain by a linker.~~

~~102.—The protein of any one of claims 95-97, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of an inhibitory polypeptide that binds to the negative signal.~~

~~103.—The protein of claim 102, wherein the inhibitory polypeptide is an inflammatory mediator receptor, an inhibitory cytokine receptor, an immune checkpoint receptor, or a dual activator-checkpoint receptor.~~

~~104.—The protein of claim 102, wherein the inhibitory polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.1.~~

~~105.—The protein of any one of claims 95-97, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of an inhibitory polypeptide presented in Table 1 or Table 1.2.~~

~~106.—The protein of any one of claims 95-97, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.~~

~~107.—The protein of any one of claims 95–106, wherein the extracellular domain and the transmembrane domain are connected by a linker.~~

~~108.—The protein of claim 107, wherein the linker is selected from the linkers presented in Table 3.~~

~~109.—The protein of any of claims 95–108, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a different polypeptide than the extracellular domain.~~

~~110.—The protein of claim 109, wherein the different polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.2; or the stimulatory polypeptides presented in Table 2 or Table 2.2.~~

~~111.—A modified cell engineered to express a protein comprising an extracellular domain and a transmembrane domain, wherein the extracellular domain is capable of binding a negative signal, and wherein the chimeric protein lacks a fully functional intracellular domain, and the negative signal is selected from the group consisting of IL-10, TGF- β , 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, MHCI, TIM-3, IL-18, adenosine, and prostaglandin.~~

~~112.—The modified cell of claim 111, wherein the cell is selected from the group consisting of an artificial cell, an immune cell, a fibrocyte, a mesenchymal stem cell, an induced neural stem cell, an induced pluripotent stem cell (iPSC)-derived cell, and an erythrocyte.~~

~~113.—The modified cell of claim 112, wherein the immune cell is selected from the group consisting of a T cell, a natural killer (NK) cell, an NKT cell, a type 1 innate lymphoid cell (ILC1), an intraepithelial type 1 innate lymphoid cell (ieILC1), a type 2 innate lymphoid cell (ILC2), a type 3 innate lymphoid cell (ILC3), a lymphoid tissue inducer cell (LTi), a monocyte, a macrophage, a dendritic cell (DC), a platelet, a marrow-infiltrating lymphocyte (MIL), and a B cell.~~

~~114.—The modified cell of claim 113, wherein the immune cell is an NK cell.~~

~~115.—The modified cell of any one of claims 111–114, wherein the chimeric protein lacks an intracellular domain.~~

~~116.—The modified cell of any one of claims 111–115, wherein the extracellular domain comprises an antigen-binding domain that specifically binds to the negative signal.~~

~~117.—The modified cell of claim 116, wherein the antigen-binding domain comprises a fragment of an antibody.~~

~~118.—The modified cell of claim 116, wherein the antigen-binding domain comprises an scFv or a Fab.~~

~~119.—The modified cell of claim 118, wherein the scFv is an scFv from a monoclonal antibody.~~

~~120.—The modified cell of any one of claims 111–115, wherein the extracellular domain comprises the extracellular domain, or a portion thereof, of an inhibitory polypeptide that binds to the negative signal.~~

~~121.—The modified cell of claim 120, wherein the inhibitory polypeptide is an inflammatory mediator receptor, an inhibitory cytokine receptor, an immune checkpoint receptor, or a dual activator-checkpoint receptor.~~

~~122.—The modified cell of claim 120, wherein the inhibitory polypeptide is selected from the inhibitory polypeptides presented in Table 1 or Table 1.1.~~

~~123.—The modified cell of any one of claims 111–122, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of an inhibitory polypeptide presented in Table 1 or Table 1.2.~~

~~124.—The modified cell of any one of claims 111–122, wherein the transmembrane domain comprises the transmembrane domain, or a portion thereof, of a stimulatory polypeptide presented in Table 2 or Table 2.2.~~

~~125.—The modified cell of any one of claims 111–124, wherein the extracellular domain and the transmembrane domain are connected by a linker.~~

~~126.—The modified cell of claim 125, wherein the linker is selected from the linkers presented in Table 3.~~

~~127.—The modified immune cell of claim 113 or 114, wherein the immune cell is engineered to further comprise a chimeric antigen receptor (CAR).~~

~~128.—The modified immune cell of claim 127, wherein the CAR targets a tumor antigen.~~

~~129.—The modified immune cell of any one of claims 113, 114, 127, and 128, wherein the immune cell is engineered to further comprise a cytokine.~~

~~130.—The modified immune cell of claim 129, 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.~~

~~131.—The modified immune cell of claim 129, wherein the cytokine is an IL-15 or a fragment or variant thereof.~~

~~132.—A modified cell engineered to express a protein comprising a dominant negative isoform of a protein, wherein the dominant negative isoform of the protein competes with a wild-type isoform of the protein for binding a negative signal, wherein the negative signal is selected from the group consisting of IL-10, TGF- β , 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.

133.—The modified cell of claim 132, wherein the cell is selected from the group consisting of an artificial cell, an immune cell, a fibrocyte, a mesenchymal stem cell, an induced neural stem cell, an induced pluripotent stem cell (iPSC)-derived cell, and an erythrocyte.

134.—The modified cell of claim 133, wherein the immune cell is selected from the group consisting of a T cell, a natural killer (NK) cell, an NKT cell, a type 1 innate lymphoid cell (ILC1), an intraepithelial type 1 innate lymphoid cell (ieILC1), a type 2 innate lymphoid cell (ILC2), a type 3 innate lymphoid cell (ILC3), a lymphoid tissue inducer cell (LTi), a monocyte, a macrophage, a dendritic cell (DC), a platelet, a marrow-infiltrating lymphocyte (MIL), and a B cell.

135.—The modified cell of claim 134, wherein the immune cell is an NK cell.

136.—The modified cell of claim 132, wherein the dominant negative isoform of the protein is a dominant negative isoform of an inhibitory polypeptide selected from Table 1.

137.—The modified cell of claim 132, wherein the dominant negative isoform of the protein is a dominant negative isoform of TGF- β 1.

138.—The modified cell of claim 137, wherein the dominant negative isoform of TGF- β 1 is selected from the dominant negative isoforms of TGF- β 1 presented in Table 4.

139.—The modified cell of claim 132, wherein the dominant negative isoform of the protein is a dominant negative isoform of TGF- β 2.

140.—The modified cell of claim 139, wherein the dominant negative isoform of TGF- β 2 is selected from the dominant negative isoforms of TGF- β 2 presented in Table 5.

~~141.—The modified immune cell of claim 134 or 135, wherein the immune cell is engineered to further comprise a chimeric antigen receptor (CAR).~~

~~142.—The modified immune cell of claim 141, wherein the CAR targets a tumor antigen.~~

~~143.—The modified immune cell of any one of claims 134, 135, 141, and 142, wherein the immune cell is engineered to further comprise a cytokine.~~

~~144.—The modified immune cell of claim 143, 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.~~

~~145.—The modified immune cell of claim 143, wherein the cytokine is an IL-15 or a fragment or variant thereof.~~

~~146.—A modified cell engineered to express at least two proteins selected from the group consisting of:~~

~~(a) 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;~~

~~(b) a protein comprising a dominant negative isoform of a protein, wherein the dominant negative isoform of the protein competes with a wild-type isoform of the protein for binding a negative signal that prevents the activation of an immune response; and~~

~~(c) a protein comprising an extracellular domain and a transmembrane domain, wherein the extracellular domain is capable of binding a negative signal, and wherein the protein lacks a fully functional intracellular domain;~~

~~wherein the negative signal is selected from the group consisting of IL-10, TGF- β , 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.~~

~~147. The modified cell of claim 146, wherein the cell is selected from the group consisting of an artificial cell, an immune cell, a fibrocyte, a mesenchymal stem cell, an induced neural stem cell, an induced pluripotent stem cell (iPSC)-derived cell, and an erythrocyte.~~

~~148. The modified cell of claim 147, wherein the immune cell is selected from the group consisting of a T cell, a natural killer (NK) cell, an NKT cell, a type 1 innate lymphoid cell (ILC1), an intraepithelial type 1 innate lymphoid cell (ieILC1), a type 2 innate lymphoid cell (ILC2), a type 3 innate lymphoid cell (ILC3), a lymphoid tissue inducer cell (LTi), a monocyte, a macrophage, a dendritic cell (DC), a platelet, a marrow-infiltrating lymphocyte (MIL), and a B cell.~~

~~149. The modified cell of claim 148, wherein the immune cell is an NK cell.~~

~~150~~30. A polynucleotide comprising a nucleic acid sequence encoding a chimeric protein of any one of claims ~~1-23~~1-22 or ~~47-69~~, or a protein of any one of claims ~~95-110~~.

~~151~~31. A pharmaceutical composition comprising the modified immune cell of any one of claims ~~24-2923-46, 70-94, or 112-149~~, and a pharmaceutically acceptable excipient.

~~152~~32. A method of treating a subject in need of an altered immune response, the method comprising administering to the subject an effective amount Use of a composition comprising the modified immune cell of any one of claims ~~24-2923-46, 70-94, or 112-149~~ in the manufacture of a medicament for treating a subject in need of an altered immune response, thereby treating the subject in need of the altered immune response.

~~153~~33. A method of treating a disease or pathological condition in a subject, comprising administering to the subject an effective amount Use of a composition comprising the modified immune cell of any one of claims ~~24-2923-46, 70-94, or 112-149~~ in the manufacture of a medicament for treating a disease or pathological condition in a subject, thereby treating the disease or pathological condition in the subject.

~~15434. A method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount Use~~ of a composition comprising the modified immune cell of any one of claims ~~24-29~~23-46, 70-94, or 112-149 ~~in the manufacture of a medicament for treating a cancer in a subject, thereby treating the cancer in the subject.~~

~~15535. A method of generating a~~ the modified immune cell ~~of any one of the preceding claims,~~ the method comprising:

(a) introducing a nucleic acid encoding the chimeric protein of any one of claims ~~1-23~~1-22 or 47-69, or a protein of any one of claims 95-110, 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.

~~15636. A~~ modified immune cell obtained by the method of claim ~~35~~155.

~~15737. 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~~1-22 or 47-69.

~~158.— A kit comprising an engineered protein and/or a nucleic acid encoding the engineered protein, wherein the engineered protein is the engineered protein of any one of claims 95-110.~~