CLAIMS

1. A heterologous chimeric protein comprising:

(a) a first extracellular domain of a Type I transmembrane protein at or near the N-terminus,

(b) a second extracellular domain of a Type II transmembrane protein at or near the C-terminus, and

(c) a linker, wherein the linker comprises a hinge-CH2-CH3 Fc domain; wherein:

the first extracellular domain is an immune inhibitory signal, and

the second extracellular domain is an immune stimulatory signal.

2. The heterologous chimeric protein of claim 1, wherein the Type I transmembrane protein is selected from PD-1, TIM-3, CD172a(SIRPα), TIGIT, CD115(CSF1R), BTLA, TMIGD2, and VSIG8, or a variant thereof capable of binding to its ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, and CD70, or a variant thereof capable of binding its receptor.

3. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is PD-1, or a variant thereof capable of binding to a PD-1 ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, and CD70, or a variant thereof capable of binding its receptor.

4. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is TIM-3, or a variant thereof capable of binding to a TIM-3 ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

5. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is CD172a (SIRPα), or a variant thereof capable of binding to a CD172a (SIRPα) ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

6. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is TIGIT, or a variant thereof capable of binding to a TIGIT ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

7. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is CD115 (CSF1R), or a variant thereof capable of binding to a CD115 (CSF1R) ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

8. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is BTLA, or a variant thereof capable of binding to a BTLA ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

9. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is TMIGD2, or a variant thereof capable of binding to a TMIGD2 ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

10. The heterologous chimeric protein of claim 2, wherein the Type I transmembrane protein is VSIG8, or a variant thereof capable of binding to a VSIG8 ligand, and the Type II transmembrane protein is selected from OX40L, CD40L, LIGHT (CD258), 4-1BBL (CD137L), GITRL, TL1A, CD30L, or CD70, or a variant thereof capable of binding its receptor.

11. The heterologous chimeric protein of any one of claims 1 to 10, wherein the linker which comprises the hinge-CH2-CH3 Fc domain is derived from IgG1, preferably derived from human IgG1.

12. The heterologous chimeric protein of any one of claims 1 to 10, wherein the linker which comprises the hinge-CH2-CH3 Fc domain is derived from IgG4, preferably derived from human IgG4.

13. The heterologous chimeric protein of claim 11 or claim 12, wherein the linker comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 71 or SEQ ID NO: 72.

14. The heterologous chimeric protein of any one of claims 1 to 13, wherein the heterologous chimeric protein is produced in a mammalian host cell as a secreted and fully-functional single polypeptide chain.

15. The heterologous chimeric protein of any one of claims 1 to 14, wherein the heterologous chimeric protein is capable of simultaneously binding the ligand/receptor of the first extracellular domain and binding the ligand/receptor of the second extracellular domain.

16. The heterologous chimeric protein of any one of claims 1 to 15, wherein the heterologous chimeric protein is capable of causing activation of antigen presenting cells.

17. The heterologous chimeric protein of any one of claims 1 to 16, wherein the heterologous chimeric protein is capable of enhancing the ability of antigen presenting cells to present antigen.

18. The heterologous chimeric protein of any one of claims 1 to 17, wherein the heterologous chimeric protein is capable of providing a sustained immunomodulatory effect.

19. The heterologous chimeric protein of any one of claims 1 to 18, wherein the heterologous chimeric protein comprises the entire extracellular domain of the Type I transmembrane protein and/or comprises the entire extracellular domain of the Type II transmembrane protein.

20. A pharmaceutical composition comprising the heterologous chimeric protein of any one of claims 1 to 19.

21. Use of the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating a cancer, or an autoimmune disease or disorder.

22. The use of claim 21, wherein one of the extracellular domains is capable of binding its ligand/receptor to

(i) reduce, mask, or eliminate an inhibitory immune signal and/or one of the extracellular domains is capable of binding its ligand/receptor to (ii) increase, simulate, or activate an immune stimulatory signal, optionally, wherein the chimeric protein is capable of both (i) reducing, masking, or eliminating an immune inhibitory signal and (ii) increasing, simulating, or activating an immune stimulatory signal.

23. The use of claim 21 or claim 22, wherein the heterologous chimeric protein (i) is capable of increasing a ratio of effector T cells to regulatory T cells, (ii) is capable of increasing and/or preventing a decrease in a sub-population of cytotoxic T cells; effector memory T cells; central memory T cells; CD8+ stem cell memory effector cells; TH1 effector T-cells; TH2 effector T cells; TH9 effector T cells; TH17 effector T cells; and/or effector T cells secreting IL-2, IL-4 and/or IFN-γ; and/or (iii) leads to a cytokine response in the peripheral blood of an animal that can be used as a means of defining the appropriate dose of the chimeric protein.

24. An expression vector comprising a nucleic acid encoding the heterologous chimeric protein of any one of claims 1 to 19, preferably the expression vector is a mammalian expression vector.

25. A host cell comprising the expression vector of claim 24.

26. The pharmaceutical composition of claim 20 for use in the treatment of a cancer, for use in the treatment of an autoimmune disease or disorder, or for use in the modulation of a patient's immune response.

27. The pharmaceutical composition for use according to claim 26, wherein one of the extracellular domains is capable of binding its ligand/receptor to (i) reduce, mask, or eliminate an inhibitory immune signal and/or one of the extracellular domains is capable of binding its ligand/receptor to (ii) increase, simulate, or activate an immune stimulatory signal, optionally, wherein the chimeric protein is capable of both (i) reducing, masking, or eliminating an immune inhibitory signal and (ii) increasing, simulating, or activating an immune stimulatory signal.

28. The pharmaceutical composition for use according to claim 26 or claim 27, wherein the heterologous chimeric protein (i) is capable of increasing a ratio of effector T cells to regulatory T cells, (ii) is capable of increasing and/or preventing a decrease in a sub-population of cytotoxic T cells; effector memory T cells; central memory T cells; CD8+ stem cell memory effector cells; TH1 effector T-cells; TH2 effector T cells; TH9 effector T cells; TH17 effector T cells; and/or effector T cells secreting IL-2, IL-4 and/or IFN-γ; and/or (iii) leads to a cytokine response in the peripheral blood of an animal that can be used as a means of defining the appropriate dose of the chimeric protein.

29. The heterologous chimeric protein of any one of claims 1 to 19 for use as a medicament.

30. The pharmaceutical composition of claim 20 for use as a medicament.