

CLAIMS

What is claimed is:

1. A heterologous chimeric protein comprising:
 - (a) a first domain comprising a portion of SIRP α (CD172a) that is capable of binding a SIRP α (CD172a) ligand,
 - (b) a second domain comprising
 - a portion of CD40 ligand (CD40L) that is capable of binding a CD40L receptor, or
 - a portion of OX40 ligand (OX40L) that is capable of binding an OX40L receptor, and
 - (c) a linker linking the first domain and the second domain and comprising a hinge-CH2-CH3 Fc domain.
2. The heterologous chimeric protein of claim 1, wherein the first domain comprises substantially all of the extracellular domain of SIRP α (CD172a) and the second domain comprises substantially all of the extracellular domain of CD40L or OX40L.
3. The heterologous chimeric protein of claim 1 or claim 2, wherein the heterologous chimeric protein is capable of inhibiting an immunosuppressive signal.
4. The heterologous chimeric protein of any one of claims 1 to 3, wherein the heterologous chimeric protein is capable of:
 - (a) reducing or eliminating an immune inhibitory signal when the portion of SIRP α (CD172a) is bound to its ligand, and/or
 - (b) increasing or activating an immune stimulatory signal when the portion of CD40L or OX40L is bound to its receptor.
5. The heterologous chimeric protein of any one of claims 1 to 4, wherein the SIRP α (CD172a) ligand is CD47.
6. The heterologous chimeric protein of any one of claims 1 to 5, wherein the CD40L receptor is CD40 or the OX40L receptor is OX40.
7. The heterologous chimeric protein of any one of claims 1 to 6, wherein the heterologous chimeric protein is capable of contemporaneously binding
 - the SIRP α (CD172a) ligand, and
 - the CD40L or OX40L receptor,wherein the SIRP α (CD172a) ligand is CD47, the CD40L receptor is CD40, and the OX40L receptor is OX40.

8. The heterologous chimeric protein of any one of claims 1 to 7, wherein the heterologous chimeric protein is capable of causing activation of antigen presenting cells.
9. The heterologous chimeric protein of any one of claims 1 to 8, wherein the heterologous chimeric protein is capable enhancing the ability of antigen presenting cells to present antigen.
10. The heterologous chimeric protein of any one of claims 1 to 9, wherein the heterologous chimeric protein is capable of providing a sustained immunomodulatory effect.
11. The heterologous chimeric protein of any one of claims 1 to 10, wherein the hinge-CH2-CH3 Fc domain is derived from IgG4 or IgG1.
12. The heterologous chimeric protein of claim 11, wherein the hinge-CH2-CH3 Fc domain is derived from human IgG4 or human IgG1.
13. The heterologous chimeric protein of any one of claims 1 to 12, wherein the chimeric protein is expressed by a mammalian host cell as a secretable and functional single polypeptide chain.
14. The heterologous chimeric protein of any one of claims 1 to 13, wherein the portion of SIRPα (CD172a) comprises the amino acid sequence of SEQ ID NO: 33 or an amino acid sequence having about 98% identity thereto.
15. The heterologous chimeric protein of any one of claims 1 to 14, wherein the portion of CD40L comprises the amino acid sequence of SEQ ID NO: 60 or an amino acid sequence having at least about 98% identity thereto, or the portion of OX40L comprises the amino acid sequence of SEQ ID NO: 56 or an amino acid sequence having at least about 98% identity thereto.
16. The heterologous chimeric protein of any one of claims 1 to 15, wherein the linker comprises an amino acid sequence of SEQ ID NO: 71 or an amino acid sequence having at least about 95% identity thereto or SEQ ID NO: 72 or an amino acid sequence having at least about 95% identity thereto.
17. The heterologous chimeric protein of any one of claims 1 to 16, wherein
 - (a) the first domain comprises the amino acid sequence of SEQ ID NO: 33,
 - (b) the second domain comprises the amino acid sequence of SEQ ID NO: 60, and
 - (c) the linker comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 72.
18. The heterologous chimeric protein of any one of claims 1 to 16, wherein
 - (a) the first domain comprises the amino acid sequence of SEQ ID NO: 33,
 - (b) the second domain comprises the amino acid sequence of SEQ ID NO: 56, and

(c) the linker comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 72.

19. A heterologous chimeric protein comprising:
- (a) a first domain comprising a portion of SIRP α (CD172a) comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 33 and which is capable of binding a SIRP α (CD172a) ligand,
 - (b) a second domain comprising
 - a portion of CD40 ligand (CD40L) comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 60 and which is capable of binding a CD40L receptor, or
 - a portion of OX40 ligand (OX40L) comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 56 and which is capable of binding a OX40L receptor, and
 - (c) a linker linking the first domain and the second domain and comprising a hinge-CH2-CH3 Fc domain.

20. The heterologous chimeric protein of claim 19, wherein the linker comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 72.

21. The heterologous chimeric protein of claim 19 or claim 20, wherein the heterologous fusion protein is capable of contemporaneously binding

- the SIRP α (CD172a) ligands, and
- the CD40L receptor or OX40L receptor,

wherein the SIRP α (CD172a) ligand is CD47, the CD40L receptor is CD40, and the OX40L receptor is OX40.

22. A heterologous chimeric protein comprising:
- (a) a first domain comprising a portion of SIRP α (CD172a) comprising the amino acid sequence of SEQ ID NO: 33 and which is capable of binding a SIRP α (CD172a) ligand,
 - (b) a second domain comprising a portion of CD40 ligand (CD40L) comprising the amino acid sequence of SEQ ID NO: 60 and which is capable of binding a CD40L receptor, and
 - (c) a linker linking the first domain and the second domain and comprising a hinge-CH2-CH3 Fc domain.

23. A heterologous chimeric protein comprising:
- (a) a first domain comprising a portion of SIRP α (CD172a) comprising the amino acid sequence of SEQ ID NO: 33 and which is capable of binding a SIRP α (CD172a) ligand,

- (b) a second domain comprising a portion of OX40 ligand (OX40L) comprising the amino acid sequence of SEQ ID NO: 56 and which is capable of binding a OX40L receptor, and
 - (c) a linker linking the first domain and the second domain and comprising a hinge-CH2-CH3 Fc domain.
24. An expression vector, comprising a nucleic acid encoding the heterologous chimeric protein of any one of claims 1 to 23.
25. A host cell, comprising the expression vector of claim 24.
26. A pharmaceutical composition, comprising a therapeutically effective amount of the heterologous chimeric protein of any one of claims 1 to 23.
27. Use of the heterologous chimeric protein of any one of claims 1 to 23, the expression vector of claim 24, the host cell of claim 25, or the pharmaceutical composition of claim 26, for the manufacture of a medicament for the treatment of cancer.