mAbs) or soluble receptors (e.g., Fc-CTLA4). Soluble receptors suffer from a number of deficiencies. While useful for antagonizing interactions between proteins, soluble receptors often lack the ability to agonize such interactions. Antibodies have proven less limited in this regard and examples of both agonistic and antagonistic antibodies are known in the art. Nevertheless, both soluble receptors and antibodies lack important attributes that are critical to function in the IS. Mechanistically, cell surface proteins in the IS can involve the coordinated and often simultaneous interaction of multiple protein targets with a single protein to which they bind. IS interactions occur in close association with the junction of two cells, and a single protein in this structure can interact with both a protein on the same cell (cis) as well as a protein on the associated cell (trans), likely at the same time. Thus, there is a need for improved molecules for modulation of immune responses. Provided are embodiments that meet such needs.

Summary

[0004a] In one aspect, the present invention provides an engineered cell comprising a transmembrane immunomodulatory protein (TIP), the transmembrane immunomodulatory protein comprising:

(i) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from a wild-type IgSF family member, wherein the at least one affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain; and

(ii) a transmembrane domain

[0004b] In another aspect, the present invention provides a pharmaceutical composition comprising the engineered cell disclosed herein and a pharmaceutically acceptable carrier.

[0004c] In yet another aspect, the present invention provides use of an engineered cell disclosed herein for the preparation of a medicament for modulating an immune response in a mammalian subject.

[0004d] In yet another aspect, the present invention provides a pharmaceutical composition disclosed herein for use in modulating an immune response in a mammalian subject.

[0004e] In yet another aspect, the present invention provides a transmembrane immunomodulatory protein (TIP) comprising:

(i) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from a wild-type IgSF family member, wherein the at least one affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain; and

(ii) a transmembrane domain.

[0004f] In yet another aspect, the present invention provides a pharmaceutical composition comprising the transmembrane immunomodulatory protein disclosed herein.

[0004g] In yet another aspect, the present invention provides a recombinant nucleic acid encoding the transmembrane immunomodulatory protein disclosed herein.

[0004h] In yet another aspect, the present invention provides a recombinant expression vector comprising the nucleic acid disclosed herein.

[0004i] In yet another aspect, the present invention provides a recombinant host cell comprising the nucleic acid disclosed herein or the expression vector disclosed herein.

[0004j] In yet another aspect, the present invention provides use of a transmembrane immunomodulatory protein disclosed herein for the preparation of a medicament for modulating an immune response in a mammalian subject.

[0004k] In yet another aspect, the present invention provides a pharmaceutical composition comprising the immunomodulatory protein disclosed herein for use in modulating an immune response in a mammalian subject. Provided herein are transmembrane immunomodulatory proteins (TIP) containing (1) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain containing one or more amino acid substitution(s) in a wild-type IgSF domain, wherein the at least one affinity-modified IgSF domain specifically binds at least one cell surface cognate binding partner of the wild-type IgSF domain and (2) a transmembrane domain.

[0006] In some of any such examples, the at least one cell surface cognate binding partner is expressed on a mammalian cell. In some of any such examples, the mammalian cell is an antigen presenting cell (APC), a tumor cell, or a lymphocyte. In some examples, the lymphocyte is a T-cell. In some of any such examples, the mammalian cell is a mouse, rat, cynomolgus monkey, or human cell.

[0007] In some of any such examples, the at least one affinity modified IgSF domain has increased binding affinity to the at least one cell surface cognate binding partner compared with the reference wild-type IgSF domain. In some of any such examples, specific binding of the transmembrane immunomodulatory protein containing the at least one affinity-modified IgSF domain modulates immunological activity of the mammalian cell compared with the reference transmembrane domain containing the wild-type IgSF domain. In some of any such examples, specific binding of the transmembrane immunomodulatory protein containing the

at least one affinity-modified IgSF domain increases immunological activity of the mammalian cell compared with the reference transmembrane domain containing the wild-type IgSF domain. In some of any such examples, specific binding of the transmembrane immunomodulatory protein attenuates immunological activity of the mammalian cell compared with the reference transmembrane domain containing the wild-type IgSF domain.

[0008] In some of any such examples, the wild-type IgSF domain is from an IgSF family member of a family selected from Signal-Regulatory Protein (SIRP) Family, Triggering Receptor Expressed On Myeloid Cells Like (TREML) Family, Carcinoembryonic Antigen-related Cell Adhesion Molecule (CEACAM) Family, Sialic Acid Binding Ig-Like Lectin (SIGLEC) Family, Butyrophilin Family, B7 family, CD28 family, V-set and Immunoglobulin Domain Containing (VSIG) family, V-set transmembrane Domain (VSTM) family, Major Histocompatibility Complex (MHC) family, Signaling lymphocytic activation molecule (SLAM) family, Leukocyte immunoglobulin-like receptor (LIR), Nectin (Nec) family, Nectin-like (NECL) family, Poliovirus receptor related (PVR) family, Natural cytotoxicity triggering receptor (NCR) family, T cell immunoglobulin and mucin (TIM) family or Killer-cell immunoglobulin-like receptors (KIR) family. In some of any such examples, the wild-type IgSF domain is from an IgSF member selected from CD80, CD86, PD-L1, PD-L2, ICOS Ligand, B7-H3, B7-H4, CD28, CTLA4, PD-1, ICOS, BTLA, CD4, CD8-alpha, CD8-beta, LAG3, TIM-3, CEACAM1, TIGIT, PVR, PVRL2, CD226, CD2, CD160, CD200, CD200R or Nkp30. In some of any such examples, the wild-type IgSF domain is a human IgSF member.

[0009] In some of any such examples, the at least one affinity modified IgSF domain has at least 90% sequence identity to a wild-type IgSF domain or a specific binding fragment thereof contained in the sequence of amino acids set forth in any of SEQ ID NOS: 1-54. In some of any such examples, the transmembrane immunomodulatory protein has at least 90% sequence identity to the amino acid sequence selected from any of SEQ ID NOS: 393-419.

[0010] In some of any such examples, the at least one cell surface cognate binding partner is a stimulatory receptor expressed on a T-cell and the at least one affinity-modified IgSF domain has increased binding affinity to the stimulatory receptor compared to the affinity of the wild-type IgSF domain. In some examples, binding of the affinity-modified IgSF domain to the stimulatory receptor increases immunological activity of the T-cell.

[0011] In some of any such examples, provided is a transmembrane immunomodulatory protein (TIP) comprising: an ectodomain, wherein the ectodomain comprises at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain; and a transmembrane domain, wherein: the TIP is expressed on a first T-cell; the affinity-modified IgSF domain specifically binds at least one counter-structure expressed on a mammalian cell; the mammalian cell is an antigen presenting cell (APC), a tumor cell, or a second T-cell; and specific binding of the affinity-modified IgSF domain to a counter-structure modulates immunological activity of the mammalian cell. In some examples, the TIP comprises a first affinity-modified IgSF domain, wherein the counter-structure expressed on the mammalian cell is a stimulatory counter-structure expressed on the second T-cell; and the first affinity-modified IgSF domain specifically binds to the stimulatory counter-structure and increases immunomodulatory activity of the second T-cell.

[0012] In some cases, the stimulatory receptor is CD28, ICOS or CD226. In some of any such examples, the at least one affinity-modified IgSF domain is an affinity modified B7-1 IgSF domain and the stimulatory receptor is CD28. In some of any such examples, the at least one affinity-modified IgSF domain is an affinity modified ICOSL IgSF domain and the stimulatory receptor is ICOS. In some of any such examples, the affinity-modified IgSF domain is an affinity modified ICOSL IgSF domain and the stimulatory receptor is CD28. In some of any such examples, the at least one affinity-modified IgSF domain is an affinity-modified ICOSL IgSF domain that has increased binding affinity to at least one of: ICOS and CD28. In some of any such examples, the affinity modified IgSF domain is an affinity modified ICOSL IgV IgSF domain with increased binding affinity to both ICOS and CD28. In some of any such examples, the affinity-modified IgSF domain does not substantially specifically bind to CTLA-4 or exhibits decreased binding affinity to CTLA-4 compared to the wild-type IgSF domain.

[0013] In some of any such examples, the at least one affinity-modified IgSF domain specifically binds to no more than one cell surface cognate binding partner. In some of any such examples, the transmembrane immunomodulatory protein specifically binds to no more than one cell surface cognate binding partner. In some of any such examples, the at least one affinity-modified domain specifically binds to at least two cell surface cognate binding partners.

[0014] In some of any such examples, the first cell surface cognate binding partner is a stimulatory receptor expressed on a T cell; and the second cell surface cognate binding partner is an inhibitory ligand of an inhibitory receptor, wherein the inhibitory receptor is expressed on a T-cell.

[0015] In some of any such examples, binding of the affinity-modified domain to the inhibitory ligand competitively inhibits binding of the inhibitory ligand to the inhibitory receptor. In some examples, the inhibitory receptor is PD-1, CTLA-4, LAG-3, TIGIT, CD96, CD112R, BTLA, CD160 or TIM-3; or the ligand of the inhibitory receptor is PD-L1, PD-L2, B7-1, B7-2, HVEM, MHC class II, PVR, CEACAM-1 or GAL9. In some of any such examples, the affinity modified IgSF domain is an affinity modified B7-1 domain and the stimulatory receptor is CD28. In some of any such examples, the inhibitory ligand is PD-L1 and the inhibitory receptor is PD-1.

[0016] In some of any such examples, the affinity-modified IgSF domain exhibits decreased binding affinity to CTLA-4 compared to the wild-type IgSF domain for CTLA-4. In some of any such examples, the affinity-modified IgSF domain does not substantially specifically bind to CTLA-4. In some of any such examples, the affinity modified IgSF domain is an affinity modified CD155 IgSF domain or an affinity modified CD112 IgSF domain and the stimulatory receptor is CD226. In some of any such examples, the affinity-modified IgSF domain exhibits decreased binding affinity to TIGIT (T-cell immunoreceptor with Ig and ITIM domains) compared to the affinity of the wild-type IgSF domain.

[0017] In some of any such examples, the at least one affinity-modified IgSF domain specifically binds to a cell surface cognate binding partner that is a tumor specific antigen. In some examples, the tumor specific antigen is B7-H6.

[0018] In some of any such examples, the affinity-modified IgSF domain is an affinity modified Nkp30 IgSF domain. In some of any such examples, the at least one affinity-modified IgSF domain is a first affinity-modified IgSF domain and the ectodomain contains a second affinity-modified IgSF domain. In some examples, the first and second affinity-modified IgSF domain are different. In some of any such examples, the first affinity-modified IgSF domain and the second affinity-modified IgSF domain each contain one or more amino acid different substitutions in the same wild-type IgSF domain. In some of any such examples, the first affinity-modified IgSF domain and the second affinity-modified IgSF domain each contain one or more amino acid substitutions in a different wild-type IgSF domain.

[0019] In some of any such examples, the transmembrane immunomodulatory protein further contains an endodomain or cytoplasmic signaling domains. In some examples, the endodomain is the endodomain from the wild-type IgSF member containing the wild-type IgSF domain or is a functionally active portion thereof. In some examples, the transmembrane immunomodulatory protein is a chimeric receptor, wherein the endodomain is not the endodomain from the wild-type IgSF member containing the wild-type IgSF domain. In some of any such examples, the endodomain contains at least one ITAM (immunoreceptor tyrosine-based activation motif)-containing signaling domain. In some of any such examples, the endodomain contains a CD3-zeta signaling domain. In some of any such examples, the endodomain further contains at least one of: a CD28 costimulatory domain, an ICOS signaling domain, an OX40 signaling domain, and a 41BB signaling domain.

[0020] In some of any such examples, the wild-type IgSF domain is from an IgSF member that is an inhibitory receptor containing an ITIM signaling domain. In some examples, the inhibitory receptor is PD-1, CTLA-4, LAG3, TIGIT, TIM-3, or BTLA and the at least one affinity-modified IgSF domain is an affinity-modified IgSF domain of PD-1, CTLA-4, LAG3, TIGIT, TIM-3, or BTLA, respectively. In some of any such examples, the inhibitory receptor is PD-1 and the at least one affinity-modified IgSF domain is an affinity-modified IgSF of PD-1. In some of any such examples, the affinity-modified IgSF domain has increased binding affinity for a trans surface cognate binding partner compared to the wildtype IgSF domain , whereby the increased binding affinity competitively inhibits binding of the trans surface cognate binding partner to the inhibitory receptor.

[0021] In some of any such examples, the transmembrane immunomodulatory protein does not contain an endodomain, ITIM or cytoplasmic signaling domains.

[0022] In some of any such examples, the affinity modified IgSF domain differs by no more than ten amino acid substitutions from the wildtype IgSF domain. In some of any such examples, the affinity modified IgSF domain differs by no more than five amino acid substitutions from the wildtype IgSF domain.

[0023] In some of any such examples, the affinity-modified IgSF domain is or contains an affinity modified IgV domain, affinity modified IgC1 domain or an affinity modified IgC2 domain or is a specific binding fragment thereof containing the one or more amino acid substitutions. In some of any such examples, the ectodomain further contains one or more non-affinity modified IgSF domains.

[0024] In some of any such examples, the one or more non-affinity modified IgSF domains is from a wild-type IgSF member containing the wild-type IgSF domain. In some of any such examples, the transmembrane domain is the native transmembrane domain from the corresponding wild-type IgSF member. In some of any such examples, the transmembrane domain is not the native transmembrane domain from the corresponding wild-type IgSF member. In some examples, the transmembrane protein is a transmembrane protein derived from CD8.

[0025] Also disclosed is a recombinant nucleic acid encoding any of the transmembrane immunomodulatory proteins summarized above.

[0026] Also disclosed is a recombinant expression vector containing any of the nucleic acids summarized above.

[0027] Also disclosed is a recombinant expression vector containing a nucleic acid encoding any of the transmembrane immunomodulatory proteins summarized above.

[0028] Also disclosed is a recombinant host cell containing any of the expression vectors summarized above.

[0029] Also disclosed is a recombinant host cell containing a nucleic acid described above. In some of any such examples, the host cell is a mammalian host cell. In some of any such examples, the mammalian host cell is a human host cell.

[0030] Also disclosed is an engineered cell containing any of the transmembrane immunomodulatory proteins described above. In some of any such examples, the cell is an immune cell. In some of any such examples, the cell is a lymphocyte. In some examples, the lymphocyte is a T cell, a B cell or an NK cell. In some of any such examples, the cell is a T cell. In some of any such examples, the T cells is CD4+ or CD8+. In some of any such examples, the cell is an antigen presenting cell.

[0031] In some of any such examples, the engineered cell further contains a chimeric antigen receptor (CAR) or an engineered T-cell receptor (TCR).

[0032] Also disclosed is a pharmaceutical composition containing any of the cells described above and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical composition is sterile.

[0033] In some examples, provided herein is a method of modulating an immune response in a mammalian subject, involving administering a cell according to any one of the examples described above or a pharmaceutical composition according to any one of the examples described above to the subject. In some of any such examples, modulating the immune response treats a disease or disorder in the subject. In some of any such examples, the modulated immune response is increased. In some examples, the disease or disorder is a tumor. In some of any such examples, the disease or disorder is a cancer. In some of any such examples, the disease or disorder is melanoma, lung cancer, bladder cancer, or a hematological malignancy.

[0034] In some of any such examples, the modulated immune response is decreased. In some of any such examples, the disease or disorder is an inflammatory disease or condition. In some of any such examples, the disease or condition is Crohn's disease, ulcerative colitis, multiple sclerosis, asthma, rheumatoid arthritis, or psoriasis.

[0035] In some of any such examples, the subject is human. In some of any such examples, the cell is autologous to the subject. In some of any such examples, the cell is allogenic to the subject.

Brief Description of the Drawings

[0036] **Fig. 1A** depicts results of a competition binding assay for binding of biotinylated recombinant CD28 Fc fusion protein (rCD28.Fc) to immobilized CD80 variant A91G ECD-Fc fusion molecule in the presence of unlabeled recombinant human PD-L1-his, human CTLA-4-his or human-PD-L2-Fc fusion protein.

[0037] **FIG. 1B** depicts results of a competition binding assay for binding of biotinulated recombinant human PD-L1-his monomeric protein to immobilized CD80 variant A91G ECD-Fc fusion molecule in the presence of unlabeled recombinant human rCD28.Fc, human CTLA-4.Fc or human PD-L2.Fc

[0038] **FIG. 2** depicts impedance results reflecting cytotoxic killing activity of cells engineered with an anti-CD19 chimeric antigen receptor (CAR) alone or with an exemplary transmembrane immunomodulatory TIP (CD80-TIP or ICOSL-TIP) or the corresponding CD80 or ICOSL wild-type transmembrane protein following co-culture with target antigen-expressing cells. Impedance was assessed using the Acea Real-Time Cell Analyzer (RTCA), which

CLAIMS

WHAT IS CLAIMED:

1. An engineered cell comprising a transmembrane immunomodulatory protein (TIP), the transmembrane immunomodulatory protein comprising:

(i) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from a wild-type IgSF family member, wherein the at least one affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain; and

(ii) a transmembrane domain.

2. The engineered cell of claim 1, wherein the at least one affinity modified IgSF domain has increased binding affinity to the at least one cell surface cognate binding partner compared to the binding affinity of the wild-type IgSF domain to the at least one cell surface cognate binding partner.

3. The engineered cell of claim 1 or 2, wherein the wild-type IgSF domain is from an IgSF family member of a family selected from Signal-Regulatory Protein (SIRP) Family, Triggering Receptor Expressed On Myeloid Cells Like (TREML) Family, Carcinoembryonic Antigen-related Cell Adhesion Molecule (CEACAM) Family, Sialic Acid Binding Ig-Like Lectin (SIGLEC) Family, Butyrophilin Family, B7 family, CD28 family, V-set and Immunoglobulin Domain Containing (VSIG) family, V-set transmembrane Domain (VSTM) family, Major Histocompatibility Complex (MHC) family, Signaling lymphocytic activation molecule (SLAM) family, Leukocyte immunoglobulin-like receptor (LIR), Nectin (Nec) family, Nectin-like (NECL) family, Poliovirus receptor related (PVR) family, Natural cytotoxicity triggering receptor (NCR) family, T cell immunoglobulin and mucin (TIM) family or Killer-cell immunoglobulin-like receptors (KIR) family.

4. The engineered cell of any of claims 1-3, wherein the wild-type IgSF domain is from an IgSF member selected from CD80, CD86, PD-L1, PD-L2, ICOS Ligand, B7-H3, B7-

H4, CD28, CTLA4, PD-1, ICOS, BTLA, CD4, CD8-alpha, CD8-beta, LAG3, TIM-3, CEACAM1, TIGIT, PVR, PVRL2, CD226, CD2, CD160, CD200, CD200R or Nkp30.

5. The engineered cell of any of claims 1-4, wherein the wild-type IgSF domain is an IgSF domain of CD80.

6. The engineered cell of any of claims 1-4, wherein the at least one cell surface cognate binding partner is a stimulatory receptor expressed on a T cell and the at least one affinity-modified IgSF domain has increased binding affinity to the stimulatory receptor compared to the affinity of the wild-type IgSF domain to the stimulatory receptor.

7. The engineered cell of claim 6, wherein the stimulatory receptor is CD28, ICOS or CD226.

8. The engineered cell of claim 7, wherein:

the at least one affinity-modified IgSF domain is an affinity-modified CD80 IgSF domain and the stimulatory receptor is CD28; or

the at least one affinity-modified IgSF domain is an affinity-modified ICOSL IgSF domain and the stimulatory receptor is ICOS or CD28.

9. The engineered cell of any of claims 1-8, wherein the at least one affinity-modified IgSF domain is a first affinity-modified IgSF domain and the ectodomain comprises a second affinity-modified IgSF domain, wherein the first and second affinity-modified IgSF domains are different.

10. The engineered cell of any of claims 1-9, wherein the transmembrane immunomodulatory protein further comprises an endodomain.

11. The engineered cell of claim 10, wherein:

the endodomain is the endodomain from the wild-type IgSF member comprising the wild-type IgSF domain or is a functionally active portion thereof; or

the transmembrane immunomodulatory protein is a chimeric receptor, wherein the endodomain is not the endodomain from the wild-type IgSF member comprising the wild-type IgSF domain.

12. The engineered cell of claim 10 or claim 11, wherein the endodomain comprises at least one ITAM (immunoreceptor tyrosine-based activation motif)-containing signaling domain, optionally wherein the endodomain comprises a CD3-zeta signaling domain.

13. The engineered cell of claim 12, wherein the endodomain further comprises at least one of: a CD28 costimulatory domain, an ICOS signaling domain, an OX40 signaling domain, and a 41BB signaling domain.

14. The engineered cell of any of claims 1-4 and 9-13, wherein the wild-type IgSF domain is from a wild-type IgSF member that is an inhibitory receptor comprising an ITIM signaling domain.

15. The engineered cell of claim 14, wherein the transmembrane immunomodulatory protein does not comprise an endodomain comprising an ITIM signaling domain of the wild-type IgSF member.

16. The engineered cell of any of claims 1-15, wherein:

the transmembrane domain is the wild-type transmembrane domain from the corresponding wild-type IgSF member; or the transmembrane domain is not the wild-type transmembrane domain from the corresponding wild-type IgSF member.

17. The engineered cell of any of claims 1-16, wherein the affinity-modified IgSF domain comprises no more than ten amino acid substitutions from the wild-type IgSF domain.

18. The engineered cell of any of claims 1-17, wherein the affinity-modified IgSF domain is or comprises an affinity-modified IgV domain or is a specific binding fragment thereof, an affinity modified IgC1 domain or is a specific-binding fragment therof, or an affinity

modified IgC2 domain or is a specific binding fragment thereof, wherein the specific binding fragment thereof comprises the one or more amino acid substitution(s).

19. The engineered cell of any of claims 1-18, wherein the cell is an immune cell.

20. The engineered cell of claim 19, wherein the cell is a lymphocyte or is an antigen presenting cell, optionally wherein the lymphocyte is a T cell.

21. The engineered cell of any of claims 1-20, wherein the cell further comprises a chimeric antigen receptor (CAR) or an engineered T-cell receptor (TCR).

22. A pharmaceutical composition comprising the engineered cell of any of claims 1-21 and a pharmaceutically acceptable carrier.

23. Use of an engineered cell of any of claims 1-21 for the preparation of a medicament for modulating an immune response in a mammalian subject.

24. A pharmaceutical composition of claim 22 for use in modulating an immune response in a mammalian subject.

25. The use of claim 23 or the pharmaceutical composition of claim 24, wherein modulating the immune response treats a disease or disorder in the subject.

26. The use or pharmaceutical composition of claim 25, wherein the modulated immune response is increased.

27. The use or pharmaceutical composition of claim 26, wherein the disease or disorder is a tumor or a cancer.

28. The use or pharmaceutical composition of claim 25, wherein the modulated immune response is decreased.

29. The use or pharmaceutical composition of claim 28, wherein the disease or condition is an autoimmune disease or an inflammatory disease.

30. The use or pharmaceutical composition of any of claims 23-29, wherein the cell is autologous to the subject.

31. A transmembrane immunomodulatory protein (TIP) comprising:

(i) an ectodomain comprising at least one non-immunoglobulin affinity-modified immunoglobulin superfamily (IgSF) domain comprising one or more amino acid substitution(s) in a wild-type IgSF domain from a wild-type IgSF family member, wherein the at least one affinity-modified IgSF domain specifically binds to at least one cell surface cognate binding partner of the wild-type IgSF domain; and

(ii) a transmembrane domain.

32. The transmembrane immunomodulatory protein of claim 31, wherein the at least one affinity-modified IgSF domain has increased binding affinity to the at least one cell surface cognate binding partner compared with the binding affinity of the wild-type IgSF domain to the at least one cell surface cognate binding partner.

33. The transmembrane protein of claim 31 or 32, wherein the wild-type IgSF domain is from an IgSF family member of a family selected from Signal-Regulatory Protein (SIRP) Family, Triggering Receptor Expressed On Myeloid Cells Like (TREML) Family, Carcinoembryonic Antigen-related Cell Adhesion Molecule (CEACAM) Family, Sialic Acid Binding Ig-Like Lectin (SIGLEC) Family, Butyrophilin Family, B7 family, CD28 family, V-set and Immunoglobulin Domain Containing (VSIG) family, V-set transmembrane Domain (VSTM) family, Major Histocompatibility Complex (MHC) family, Signaling lymphocytic activation molecule (SLAM) family, Leukocyte immunoglobulin-like receptor (LIR), Nectin (Nec) family, Nectin-like (NECL) family, Poliovirus receptor related (PVR) family, Natural cytotoxicity triggering receptor (NCR) family, T cell immunoglobulin and mucin (TIM) family or Killer-cell immunoglobulin-like receptors (KIR) family.

34. The transmembrane immunomodulatory protein of any of claims 31-33, wherein the wild-type IgSF domain is from an IgSF member selected from CD80, CD86, PD-L1, PD-L2, ICOS Ligand, B7-H3, B7-H4, CD28, CTLA4, PD-1, ICOS, BTLA, CD4, CD8-alpha, CD8-beta, LAG3, TIM-3, CEACAM1, TIGIT, PVR, PVRL2, CD226, CD2, CD160, CD200, CD200R or Nkp30.

35. The transmembrane immunomodulatory protein of any of claims 31-34, wherein the transmembrane immunomodulatory protein further comprises an endodomain.

36. The transmembrane immunomodulatory protein of claim 35, wherein:

the endodomain is an endodomain from a wild-type IgSF member comprising the wild-type IgSF domain or is a functionally active portion thereof; or

the transmembrane immunomodulatory protein is a chimeric receptor, wherein the endodomain is not an endodomain from a wild-type IgSF-containing protein comprising the wild-type IgSF domain.

37. A pharmaceutical composition comprising the transmembrane immunomodulatory protein of any of claims 31-36.

38. A recombinant nucleic acid encoding the transmembrane immunomodulatory protein of any of claims 31-36.

39. A recombinant expression vector comprising the nucleic acid of claim 38.

40. A recombinant host cell comprising the nucleic acid of claim 38 or the expression vector of claim 39.

41. Use of a transmembrane immunomodulatory protein of any of claims 31-36 for the preparation of a medicament for modulating an immune response in a mammalian subject.

42. A pharmaceutical composition comprising the immunomodulatory protein of any of claims 31-36 for use in modulating an immune response in a mammalian subject.

43. The use of claim 41 or the pharmaceutical composition of claim 42, wherein modulating the immune response treats a disease or disorder in the subject.