

What is claimed is:

1. A polypeptide comprising a first, second, and third copy of the extracellular domain of a human tumor necrosis factor receptor ligand superfamily (TNFSF) protein or a fragment thereof capable of binding a receptor of the TNFSF protein, wherein at least one of the first, second, or third copies of the extracellular domain or a fragment thereof comprises the stalk region of the TNFSF protein.
2. The polypeptide of claim 1, wherein the TNFSF protein is selected from the group consisting of: GITRL, OX40L, 4-1BB ligand, APRIL, BAFF, CD27 ligand, CD30 ligand, CD40 ligand, EDA, EDA-A1, EDA-A2, Fas ligand, LIGHT, lymphotoxin, lymphotoxin beta, lymphotoxin-alpha, TL1A, TNF-alpha, TRAIL, TRANCE, and TWEAK.
3. The polypeptide of claim 1 or claim 2, wherein the TNFSF protein is
 - a) GITRL and the polypeptide comprises SEQ ID NO:5 or SEQ ID NO:66;
 - b) OX40L and the polypeptide comprises SEQ ID NO:44, SEQ ID NO: 69, SEQ ID NO:70, SEQ ID NO:71, or SEQ ID NO:72; or
 - c) CD40L and the polypeptide comprises SEQ ID NO:85, or SEQ ID NO:97.
4. The polypeptide of any one of claims 1-3, wherein the TNFSF protein is
 - a) GITRL and the stalk region comprises LQLETAK (SEQ ID NO:32);
 - b) OX40L and the stalk region is selected from the group consisting of: QVSHRYP (SEQ ID NO:55), ALQVSHRYP (SEQ ID NO:74), SHRYP (SEQ ID NO:75), and HRYP (SEQ ID NO:76); or
 - c) CD40L and the stalk region is selected from the group consisting of: MQKGDQ (SEQ ID NO:98), FEMQKGDQ (SEQ ID NO:99), EMQKGDQ (SEQ ID NO:100), QKGDQ (SEQ ID NO:101), and KGDQ (SEQ ID NO:102).
5. The polypeptide of any one of claims 1-4, which further comprises a non-TNFSF polypeptide.
6. The polypeptide of claim 5, wherein the non-TNFSF polypeptide comprises:
 - (a) a human Fc region;
 - (b) an immunoglobulin heavy chain;
 - (c) a single chain antibody; or

- (d) a Fab.
7. The polypeptide of claim 6, wherein the immunoglobulin heavy chain is associated with an immunoglobulin light chain to form an antigen-binding site.
 8. The polypeptide of any one of claims 1-7, which specifically binds glucocorticoid-induced tumor necrosis factor receptor (GITR).
 9. The polypeptide of claim 8, which comprises SEQ ID NO:7 or SEQ ID NO:9.
 10. The polypeptide of any one of claims 1-9, which activates GITR and/or induces GITR activity.
 11. The polypeptide of any one of claims 1-7, which specifically binds OX40.
 12. The polypeptide of claim 11, which comprises SEQ ID NO:46, SEQ ID NO:48, or SEQ ID NO:81.
 13. The polypeptide of any one of claims 1-7, 11 or 12, which activates OX40 and/or induces OX40 activity.
 14. The polypeptide of any one of claims 1-7, which specifically binds CD40.
 15. The polypeptide of claim 14, which comprises SEQ ID NO:90 or SEQ ID NO:92.
 16. The polypeptide of any one of claims 1-7, 14, or 15, which activates CD40 and/or induces CD40 activity.
 17. A polypeptide encoded by the plasmid deposited with ATCC and assigned designation number PTA-122112.
 18. A homodimeric agent comprising the polypeptide of any one of claims 1-17.
 19. A heterodimeric agent comprising the polypeptide of any one of claims 1-17.

20. A bispecific agent comprising:
 - a) the polypeptide of any one of claims 1-17, and
 - b) an antigen-binding site from an antibody.
21. The bispecific agent of claim 20, wherein the agent is a homodimer or a heterodimer.
22. The bispecific agent of claim 20 or 21, wherein the antigen-binding site specifically binds a tumor antigen.
23. The bispecific agent of claim 20 or 21, wherein the antigen-binding site specifically binds PD-1, PD-L1, CTLA-4, LAG-3, TIGIT, or TIM-3.
24. The polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23, which:
 - (a) increases cell-mediated immunity;
 - (b) increases T-cell activity;
 - (c) increases cytolytic T-cell (CTL) activity;
 - (d) increases natural killer (NK) activity;
 - (e) decreases or inhibits regulatory T-cell (Treg) activity;
 - (f) decreases or inhibits myeloid-derived suppressor cell (MDSC) activity;
 - (g) increases an effective immune response without causing substantial side effects and/or immune-based toxicities; and/or
 - (h) increases an effective immune response without causing cytokine release syndrome (CRS) or a cytokine storm;
25. A cell producing the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23.
26. A pharmaceutical composition comprising the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 and a pharmaceutically acceptable carrier.
27. A polynucleotide comprising a nucleotide sequence that encodes the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23.

28. A polynucleotide comprising a nucleotide sequence selected from the group consisting of: SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:73, and SEQ ID NO:86.
29. A vector comprising the polynucleotide of any one of claim 27 or claim 28.
30. An isolated cell comprising the polynucleotide of claim 27 or claim 28 or the vector of claim 29.
31. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for inducing, activating, promoting, increasing, enhancing, or prolonging an immune response in a subject.
32. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for increasing T-cell activity in a subject.
33. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for increasing cytolytic T-cell (CTL) activity in a subject.
34. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for increasing natural killer (NK) activity in a subject.
35. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for decreasing or inhibiting regulatory T-cell (Treg) activity in a subject.
36. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for decreasing or inhibiting myeloid-derived suppressor cell (MDSC) activity in a subject.

37. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for inhibiting the growth of a tumor in a subject.
38. Use of a therapeutically effective amount of the polypeptide of any one of claims 1-17 or the agent of any one of claims 18-23 in the manufacture of a medicament for treating cancer in a subject.
39. The use of claim 38, wherein the cancer is selected from the group consisting of colorectal cancer, colon cancer, ovarian cancer, pancreatic cancer, lung cancer, liver cancer, breast cancer, kidney cancer, prostate cancer, gastrointestinal cancer, melanoma, cervical cancer, bladder cancer, glioblastoma, head and neck cancer, lymphoma and leukemia.
40. The use of any one of claims 31-39, wherein the medicament further comprises at least one additional therapeutic agent.
41. A plasmid deposited with ATCC and assigned designation number PTA-122112.