What is claimed is:

1. An isolated polypeptide that binds a glucocorticoid-induced TNFR-related protein (GITR), comprising at least one GITR-binding domain (GITR-BD) comprising a complementarity determining region 1 (CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 106, 109, 112, 117, 120, 125, 131, 138, 143, 148, and 149; a complementarity determining region 2 (CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 107, 110, 113, 115, 118, 121, 123, 128, 130, 132, 134, 136, 137, 139, 141, 144, and 147; and a complementarity determining region 3 (CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 108, 111, 114, 116, 119, 122, 124, 126, 127, 129, 133, 135, 140, 142, 145, 146, and 150.

2. The isolated polypeptide of claim 1, wherein the polypeptide comprises two or more GITR-binding domains (GITR-BDs) that specifically bind GITR.

3. The isolated polypeptide of claim 2, wherein said two or more GITR-binding domains are operably linked via a linker polypeptide.

4. The isolated polypeptide of any one of claims 1-3, wherein each of the GITR-BDs in the plurality of GITR-BDs comprises a complementarity determining region 1 (CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 106, 109, 112,117, 120, 125, 131, 138, 143, 148, and 149; a complementarity determining region 2 (CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 107, 110, 113, 115, 118, 121, 123, 128, 130, 132, 134, 136, 137, 139, 141, 144,and 147; and a complementarity determining region 3 (CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 108, 111, 114, 116, 119, 122, 124, 126, 127, 129, 133, 135, 140, 142, 145, 146, and 150.

5. The isolated polypeptide of claim 4, wherein the polypeptide comprises at least two or at least three copies of the same GITR-BD.

6. The isolated polypeptide of any one of claims 1 to 5, wherein the polypeptide is tetravalent for binding GITR, optionally wherein the polypeptide comprises two copies of a fusion protein that comprises the structure: (GITR-BD)-Linker-(GITRBD)-Linker-Hinge-Fc.

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7. The isolated polypeptide of any one of claims 1 to 5, wherein the polypeptide is hexavalent for binding GITR, optionally wherein the polypeptide comprises two copies of a fusion protein that comprises the structure: (GITR-BD)-Linker-(GITRBD)-Linker-(GITR-BD)-Linker-Hinge-Fc.

8. The isolated polypeptide of any one of claims 1-7, wherein each GITR-BD is a sdAb and comprises a complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 138; a complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 141; and a complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 116, optionally wherein each GITR-BD comprises the amino acid sequence selected from SEQ ID NOs: 50-59 and 6162.

9. The isolated polypeptide of claim 8, wherein the polypeptide comprises the amino acid sequence SEQ ID NO:93.

10. The isolated polypeptide of any one of claims 1 to 9, comprising one or more additional binding domain.

11. The isolated polypeptide of any one of claims 1 to 7 and 10, wherein the GITR-BD comprises a single domain antibody (sdAb).

12. The isolated polypeptide of any one of claims 1 to 7 and 10, wherein the GITR-BD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 19-80, or a sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1980, wherein the GITR-BD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 42-62 and/or wherein the GITR-BD comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 6380.

13. The isolated polypeptide of any one of claims 1 to 12, wherein the polypeptide comprises an immunoglobulin Fc region polypeptide.

14. The isolated polypeptide of any one of claims 1 to 13, wherein the isolated polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 81-105, or an amino acid sequence that is at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 81-105.

15. The isolated polypeptide of any one of claims 10-14, wherein the one or more additional binding domain binds to a target other than GITR, optionally wherein the one or more additional binding domains binds a Tumor Necrosis Factor receptor

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superfamily (TNFRSF), optionally wherein the TNFRSF member is selected from the group consisting of OX40, CD27, herpesvirus entry mediator (HVEM), CD40, lymphotoxin beta receptor (LTBR), ectodysplasin A2 receptor (ED2R), ectodysplasin A receptor (EDAR), TweakR, B cell maturation antigen (BCMA), B cell-activating factor receptor (BAFFR), death receptor 3 (DR3), death receptor 6 (DR6), and CD13.

16. The isolated polypeptide of any one of claims 10 to 14, wherein the one or more additional binding domains binds a non-TNFRSF-member.

17. The isolated polypeptide of any one of claims 10 to 16, wherein the one or more additional binding domain comprises an antibody or antigen-binding fragment thereof, optionally wherein the antibody or antigen-binding fragment thereof is a scFv, a Fab, a single domain antibody (sdAb), a VNAR, or a VHH.

18. An isolated nucleic acid encoding the polypeptide of any one of claims 1-17.

19. A host cell comprising the nucleic acid of claim 18.

20. A pharmaceutical composition comprising the polypeptide of any one of claims 1-17.

21. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating neoplasms.

22. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for modulating immune cells to enhance tumor destruction.

23. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for treating cancer in a subject in need thereof.

24. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for increasing survival of a subject having cancer.

25. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for inhibiting tumor growth in a subject in need thereof.

26. Use of the polypeptide of any one of claims 1-17 or the pharmaceutical composition of claim 20 in the manufacture of a medicament for reducing the frequency of

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intratumoral regulatory T cells (Treg), for inducing activation and proliferation of CD8+ T cells, or for reducing the frequency of Treg cells and inducing activation and proliferation of CD8+ T cells.

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