

What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that binds glucocorticoid-induced tumor necrosis factor receptor (GITR), wherein the antibody or antigen-binding fragment exhibits one or more properties selected from the group consisting of:

(a) the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 28, 34, and 40; and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 10;

(b) the antibody or antigen-binding fragment thereof comprises an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 28, 34, and 40; and an LCVR amino acid sequence of SEQ ID NO: 10;

(c) the antibody comprises a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 38, and 44; and a light chain amino acid sequence of SEQ ID NO: 20; and

(d) the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs within an HCVR amino acid sequence of SEQ ID NO: 2 modified with N101D, N101E, N101S, or N101T mutation; and three light chain CDRs within an LCVR amino acid sequence of SEQ ID NO: 10.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof exhibits one or more properties selected from the group consisting of:

(a) binds monomeric human GITR at 25°C with a K_D of less than about 12 nM as measured by surface plasmon resonance;

(b) binds monomeric human GITR at 25°C with a $t_{1/2}$ of greater than about 2 minutes;

(c) binds dimeric human GITR at 25°C with a K_D of less than about 1 nM as measured by surface plasmon resonance; and

(d) binds dimeric human GITR at 25°C with a $t_{1/2}$ of greater than about 5 minutes.

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof exhibits one or more properties selected from the group consisting of:
- (a) has a truncation rate in human or mouse serum of less than 0.5% per day; and
 - (b) has an in vivo truncation rate in mouse of about 0%.
4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof exhibits one or more properties selected from the group consisting of:
- (a) binds cell-surface human and cynomolgus monkey GITR with an EC_{50} of less than about 4 nM;
 - (b) enhances Fc-mediated NFAT activity in Jurkat/NFAT-Luc/hFcγR3a and/or Jurkat/NFAT-Luc/MfFcγR3a Effector Cells with an EC_{50} of less than about 40 pM;
 - (c) mediates ADCC against human primary T-cells in the presence of human primary NK cells with an EC_{50} of less than about 20 pM;
 - (d) mediates ADCP by at least about 5-fold in Jurkat T-cells engineered to express human or cynomolgus monkey GITR relative to non-GITR expressing Jurkat T-cells;
 - (e) enhances anti-CD3-mediated primary CD4+ T-cell proliferation;
 - (f) induces anti-tumor immunity by preferentially depleting intratumoral T_{regs} in an FcγR-dependent manner; and
 - (g) blocks human monomeric GITR binding to human GITR ligand with an IC_{50} of less than about 7 nM.
5. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising an HCVR having the amino acid sequence of SEQ ID NO: 22.
6. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising an HCVR having the amino acid sequence of SEQ ID NO: 28.
7. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising an HCVR having the amino acid sequence of SEQ ID NO: 34.

8. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising an HCVR having the amino acid sequence of SEQ ID NO: 40.
9. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 comprising an LCVR having the amino acid sequence of SEQ ID NO: 10.
10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16.
11. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 30, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16.
12. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 36, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16.
13. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 42, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16.

14. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 22, and an LCVR comprising an amino acid sequence of SEQ ID NO: 10.
15. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 28, and an LCVR comprising an amino acid sequence of SEQ ID NO: 10.
16. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 34, and an LCVR comprising an amino acid sequence of SEQ ID NO: 10.
17. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 40, and an LCVR comprising an amino acid sequence of SEQ ID NO: 10.
18. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 26.
19. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 32.
20. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 38.
21. The isolated antibody or antigen-binding fragment thereof of claim 1 comprising a heavy chain and a light chain, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 44.
22. The isolated antibody or antigen-binding fragment thereof of any one of claims 18-21 comprising a heavy chain and a light chain, wherein the light chain comprises an amino acid sequence of SEQ ID NO: 20.
23. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an HCVR of an antibody as set forth in any one of claims 1-22.

24. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a heavy chain of an antibody as set forth in any one of claims 1-22.
25. A vector comprising the polynucleotide sequence of claim 23 or 24.
26. An isolated host cell expressing the vector of claim 25.
27. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any of claims 1-22 and a pharmaceutically acceptable carrier or diluent.
28. The pharmaceutical composition of claim 27 for use in a method for treating cancer in a subject.
29. The antibody or antigen-binding fragment thereof of any of claims 1-22 for use in a method of modulating anti-tumor immune response in a subject.
30. The antibody or antigen-binding fragment thereof for use according to claim 29, wherein the method further comprises administering an antibody or antigen-binding fragment thereof that binds to a second T-cell activating receptor, wherein the T-cell activating receptor is CD28, OX40, CD137, CD27, or HVEM.
31. The antibody or antigen-binding fragment thereof for use according to claim 29, wherein the method further comprises administering an antibody or antigen-binding fragment thereof that binds to a T-cell inhibitory receptor, wherein the T-cell inhibitory receptor is CTLA-4, PD-1, TIM-3, BTLA, VISTA, or LAG-3.
32. The antibody or antigen-binding fragment thereof for use according to claim 31, wherein the T-cell inhibitory receptor is PD1 and the antibody that binds to a T-cell receptor is cemiplimab.
33. The antibody or antigen-binding fragment thereof for use according to claim 29, wherein the method further comprises administering radiation therapy to said subject.
34. The antibody or antigen-binding fragment thereof for use according to claim 29, wherein the method further comprises administering one or more chemotherapeutic agent.
35. The antibody or antigen-binding fragment thereof for use according to claim 29, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell

carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

36. A method for treating cancer, the method comprising administering the pharmaceutical composition of claim 27 to a subject in need thereof.
37. A method for modulating anti-tumor immune response, the method comprising administering an antibody or antigen-binding fragment thereof of any of claims 1-22 to a subject in need thereof.
38. The method of claim 37, further comprising administering an antibody or antigen-binding fragment thereof that binds to a second T-cell activating receptor to the subject, wherein the T-cell activating receptor is CD28, OX40, CD137, CD27, or HVEM.
39. The method of claim 37, further comprising administering an antibody or antigen-binding fragment thereof that binds to a T-cell inhibitory receptor, wherein the T-cell inhibitory receptor is CTLA-4, PD-1, TIM-3, BTLA, VISTA, or LAG-3.
40. The method of claim 39, wherein the T-cell inhibitory receptor is PD1 and the antibody that binds to a T-cell receptor is cemiplimab.
41. The method of claim 37, further comprising administering radiation therapy to the subject.
42. The method of claim 37, further comprising administering one or more chemotherapeutic agents to the subject.
43. The method of claim 36, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC),

cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

44. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, excluding an antibody comprising the HCVR of SEQ ID NO: 2 and the LCVR of SEQ ID NO: 10.

45. A method for treating cancer comprising administering, to a subject in need thereof,

(i) an anti-GITR antibody or antigen-binding fragment thereof comprising a HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and LCDR3 comprising an amino acid sequence of SEQ ID NO: 16; and

(ii) cemiplimab.

46. The method of claim 45, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

47. Use of an anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of

SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16, in the manufacture of a medicament for use in a method of treating cancer in a subject in need thereof, the method comprising administering to the subject the anti-GITR antibody or antigen-binding fragment thereof and cemiplimab.

48. The use of claim 47, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.

49. An antibody or antigen-binding fragment thereof for use in a method of treating cancer in a subject in need thereof, the method comprising administering to the subject:

(i) an anti-GITR antibody or antigen-binding fragment thereof comprising an HCDR1 comprising an amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising an amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising an amino acid sequence of SEQ ID NO: 24, an LCDR1 comprising an amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising an amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising an amino acid sequence of SEQ ID NO: 16; and

(ii) cemiplimab.

50. The antibody or antigen-binding fragment thereof of claim 49, wherein the cancer is selected from the group consisting of squamous cell skin cancer, cutaneous squamous cell carcinoma (CSCC), myeloma, lung cancer, melanoma, head and neck squamous cell carcinoma (SCCHN), small cell lung cancer, non-small cell lung cancer (NSCLC), cervical cancer, e.g. cervical squamous cell carcinoma (cervical SCC), breast cancer, and renal cell carcinoma (RCC), adenocarcinoma, colorectal cancer (CRC), pancreatic carcinoma, head and neck cancer, prostate cancer, glioblastoma multiforme, malignant

gliomas, osteosarcoma, colorectal cancer, gastric cancer (*e.g.*, gastric cancer with MET amplification), malignant mesothelioma, multiple myeloma, ovarian cancer, synovial sarcoma, thyroid cancer, breast cancer, including triple negative breast cancer, testicular cancer, esophageal cancer, uterine cancer, endometrial cancer, liver cancer, immune checkpoint blockade (ICB) naïve cancer, and ICB experienced cancer.