

[0007] In addition to its role in modulating T effector (Teff) cell function, ICOS also modulates T regulatory cells (Tregs). ICOS is expressed at high levels on Tregs, and has been implicated in Treg homeostasis and function.

[0008] Upon activation, ICOS, a disulfide-linked homodimer, induces a signal through the PI3K and AKT pathways. Subsequent signaling events result in expression of lineage specific transcription factors (e.g., T-bet, GATA-3) and, in turn, effects on T cell proliferation and survival.

[0009] ICOS ligand (ICOSL; B7-H2; B7RP1; CD275; GL50), also a member of the B7 superfamily, is the only ligand for ICOS and is expressed on the cell surface of B cells, macrophages and dendritic cells. ICOSL functions as a non-covalently linked homodimer on the cell surface in its interaction with ICOS. Human ICOSL, although not mouse ICOSL, has been reported to bind to human CD28 and CTLA-4 (Yao *et al.*, 2011, *Immunity*, 34: 729-740).

SUMMARY

[0010] In some embodiments, an isolated antibody that binds ICOS is provided, wherein the antibody is an agonist of CD4 T cells (such as CD4 T effector (Teff) cells).

[0010a] In one aspect, there is provided an isolated antibody that binds to ICOS, wherein the antibody comprises:

- i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- ii) (a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 63 and 93; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 66, 76, and 86; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 67; or
- iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 12; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 13; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 14; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 15; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 17; or
- iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 43; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 44; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 45; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 46; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 47; or

- v) a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 33 and 173; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 36, 166, and 186; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 37; or
- vi) (a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising an amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 56, 136, 146, and 156; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 57; or
- vii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 36; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 37; or
- viii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 56; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 57; or
- ix) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- x) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 86; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising

[0010b] In some embodiments, an isolated antibody that binds ICOS is provided, wherein the antibody is an agonist of CD4 T cells (such as CD4 Teff cells) and depletes T regulatory (Treg) cells. In some embodiments, an isolated antibody that binds ICOS is provided, wherein the antibody depletes Treg cells, but does not deplete Teff cells. In some embodiments, an isolated antibody that binds ICOS is provided, wherein the antibody induces pAKT signaling on CD4 T cells. In some embodiments, an isolated antibody that binds ICOS is provided, wherein the antibody induces pAKT signaling on CD4 T cells and depletes Treg cells. In some embodiments, an isolated antibody that binds to ICOS is provided, wherein the antibody comprises:

- i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 12; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 13; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 14; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 15; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 17; or
- ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 43; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 44; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 45; (e) LCDR2 comprising the amino

embodiments, the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or (Fab')₂ fragment. In some embodiments, the antibody is a full length antibody.

[0014] In some embodiments, an antibody that binds to ICOS is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 188 and a light chain comprising the amino acid sequence of SEQ ID NO: 189.

[0015] In some embodiments, administration of the antibody to a mammal results in an increase in T effector (Teff) cells in the mammal. In some embodiments, administration of the antibody to a mammal results in activation of T effector (Teff) cells in the mammal. In some embodiments, administration of the antibody to a mammal increases the ratio of Teff cells to Treg cells. In some embodiments, the Teff cells are CD4+ FoxP3- T cells. In some embodiments, the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells. In some embodiments, the Teff cells are CD8+ T cells. In some embodiments, administration of the antibody to a mammal results in a decrease in T regulatory (Treg) cells in the mammal. In some embodiments, the Treg cells are CD4+ FoxP3+ T cells.

[0016] In some aspects, an isolated antibody is provided that binds to human ICOS, wherein the antibody also binds to mouse ICOS and/or rat ICOS. In some embodiments, the isolated antibody binds to human ICOS with an affinity (K_D) of less than 5 nM. In some embodiments, the isolated antibody binds to rat ICOS with an affinity (K_D) of less than 10 nM. In some embodiments, affinity is determined using biolayer interferometry (*see, e.g.*, Abdiche et al., 2008, *Anal Biochem*, 377: 209-217; and ForteBio Octet® system). In some embodiments, the antibody binds to human ICOS, mouse ICOS, and rat ICOS. In some embodiments, the antibody binds to cynomolgus monkey ICOS. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a chimeric antibody or a humanized antibody. In some embodiments, the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or (Fab')₂ fragment. In some embodiments, the antibody is a full length antibody. In some embodiments, administration of the antibody to a mammal results in an increase in T effector (Teff) cells in the mammal. In some embodiments, administration of the antibody to a mammal results in activation of T effector (Teff) cells in the mammal. In some embodiments, the Teff cells are CD4+ FoxP3- T cells. In some embodiments, the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells. In some embodiments, the Teff cells are CD8+ T cells. In some embodiments, administration of the antibody to a mammal results in a decrease in T regulatory (Treg) cells in the mammal. In some embodiments, the Treg cells are CD4+ FoxP3+ T cells. In some embodiments, the mammal is selected from a mouse, rat, cynomolgus monkey, and human.

[0017] In some embodiments, following treatment of lung tumor tissue with an antibody provided herein, the level of a chemokine or cytokine selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 is at least a 2-fold, or at least 3-fold higher than the level of the chemokine following treatment of the lung tumor tissue with a control antibody. In some embodiments, the level is an mRNA level. In some embodiments, the level is a protein level. In some embodiments, a control antibody is an isotype-matched antibody that binds to an unrelated antigen, and which is not expected to have an effect on the chemokine levels. In some embodiments, the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after treatment. In some embodiments, the chemokine is CXCL11. In some embodiments, the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after treatment. In some embodiments, the level of the chemokine is measured 24 hours after treatment. In some embodiments, the lung tumor tissue is human lung tumor tissue.

[0018] In some embodiments, an antibody provided herein increases the level of at least one chemokine and/or cytokine selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal that has been administered the antibody by at least a 2-fold. In some embodiments, the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody. In some embodiments, the level is an mRNA level. In some embodiments, the level is a protein level. In some embodiments, the chemokine is CXCL11. In some embodiments, the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody. In some embodiments, the level of the chemokine is measured 24 hours after administration of the antibody.

[0019] In some aspects, an agonist anti-ICOS antibody is provided, wherein the antibody increases the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal that has been administered the antibody by at least a 2-fold. In some embodiments, an anti-ICOS agonist antibody is provided, wherein the antibody increases the level of at least one chemokine and/or cytokine selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, and CXCL11 in a mammal that has been administered the antibody by at least a 2-fold. In some embodiments, the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody. In some embodiments, the level is an mRNA level. In some embodiments, the level is a protein level. In some embodiments, the chemokine is CXCL11. In some embodiments, the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48

hours after administration of the antibody. In some embodiments, the level of the chemokine is measured 24 hours after administration of the antibody. In some embodiments, the mammal is a human. In some embodiments, the human has cancer. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0020] In some aspects, an antibody that binds to ICOS is provided, wherein the antibody increases the level of the ligand for NKp46 (NKp46-L) on T cells. In some embodiments, the increased level of NKp46-L on T cells is determined using a soluble NKp46 extracellular domain in a flow cytometry assay. In some embodiments, the antibody increases the level of NKp46-L on Treg cells more than the antibody increases the level of NKp46-L on Teff cells. In some embodiments, the antibody increases CD16 shedding on NK cells.

[0021] In some aspects, an isolated nucleic acid encoding an antibody described herein is provided. In some aspects, a vector comprising the nucleic acid is provided. In some aspects, a host cell comprising the vector is provided. In some aspects, a host cell that produces an antibody described herein is provided. In some aspects, a method for making an anti-ICOS antibody is provided, comprising culturing the host cell under conditions suitable for expression of the antibody. In some embodiments, the method comprises recovering the antibody produced by the host cell.

[0022] In some aspects, a pharmaceutical composition is provided, which comprises an anti-ICOS antibody described herein and a pharmaceutically acceptable carrier.

[0023] In some embodiments, methods of treating cancer are provided, comprising administering an effective amount of an anti-ICOS antibody described herein or a pharmaceutical composition described herein. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0024] In some aspects, use of an anti-ICOS antibody described herein or a pharmaceutical composition described herein is provided in the manufacture of a medicament for increasing the number of T effector (Teff) cells in a mammal. In some embodiments, a method of increasing the number of T effector (Teff) cells in a mammal is provided, comprising administering an effective amount of an anti-ICOS

antibody described herein or a pharmaceutical composition described herein. In some embodiments, the method further comprises activating Teff cells. In some aspects, use of an anti-ICOS antibody described herein or a pharmaceutical composition described herein is provided in the manufacture of a medicament for activating T effector (Teff) cells in a mammal. In some embodiments, a method of activating T effector (Teff) cells in a mammal is provided, comprising administering an effective amount of an anti-ICOS antibody described herein or a pharmaceutical composition described herein. In some embodiments, a method of increasing the ratio of Teff cells to Treg cells in a mammal is provided, comprising administering an effective amount of an anti-ICOS antibody described herein or a pharmaceutical composition described herein. In some embodiments, the Teff cells are CD4⁺ FoxP3⁻ T cells. In some embodiments, the Teff cells are CD4⁺ FoxP3⁻ T cells and CD8⁺ T cells. In some embodiments, the Teff cells are CD8⁺ T cells. In some embodiments, the method further comprises decreasing the number of T regulatory (Treg) cells.

[0025] In some aspects, use of an anti-ICOS antibody described herein or a pharmaceutical composition described herein is provided in the manufacture of a medicament for decreasing the number of T regulatory (Treg) cells in a mammal. In some embodiments, a method of decreasing the number of T regulatory (Treg) cells in a mammal is provided, comprising administering an effective amount of an anti-ICOS antibody described herein or a pharmaceutical composition described herein. In some embodiments, the Treg cells are CD4⁺ FoxP3⁺ T cells.

[0026] In some aspects, use of an anti-ICOS antibody described herein is provided in the manufacture of a medicament for increasing the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal. In some embodiments, a method of increasing the level of at least one chemokine and/or cytokine selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal is provided, comprising administering to the mammal an antibody provided herein. In some embodiments, the level of at least one chemokine is increased by at least 2-fold or at least 3-fold. In some embodiments, the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody. In some embodiments, the level is an mRNA level. In some embodiments, the level is a protein level. In some embodiments, the chemokine is CXCL11. In some embodiments, the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody. In some embodiments, the level of the chemokine is measured 24 hours after administration of the antibody. In some embodiments, the mammal is a human. In some embodiments, the human has cancer. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0027] In some embodiments, the mammal is a human.

[0033] In some embodiments, the mammal receives CAR-T therapy in addition to administration of anti-ICOS an antibody described herein.

[0034] In some embodiments, the mammal undergoes surgery and/or radiation therapy in addition to administration of an anti-ICOS antibody described herein, with or without an additional therapeutic agent. In some embodiments, the mammal undergoes radiation therapy in addition to administration of anti-ICOS an antibody described herein, with or without an additional therapeutic agent.

[0035] In some aspects, use of an antibody described herein or a pharmaceutical composition described herein is provided in the manufacture of a medicament for treating cancer in a mammal. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC). In some embodiments, the medicament is for administration with at least one additional therapeutic agent. In some embodiments, the additional therapeutic agent is selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.

[0036] In some embodiments, use of an antibody described herein or a pharmaceutical composition described herein is provided for treating cancer. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0037] In some embodiments, use of an antibody described herein or a pharmaceutical composition described herein and at least one additional therapeutic agent is provided for treating cancer. In some aspects, use of an antibody described herein or a pharmaceutical composition described herein and at least one additional therapeutic agent is provided in the manufacture of a medicament for treating cancer. In some embodiments, the additional therapeutic agent is selected from an anti-PD-1 antibody and an anti-PD-L1 antibody. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0038] In some aspects, an antibody described herein or a pharmaceutical composition described herein is provided for use in treating cancer. In some embodiments, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC). In some embodiments, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] Figure 1A-B. Levels of ICOS mRNA across multiple human tumors. A) Mean intensity and 75% confidence intervals of normalized ICOS mRNA levels across various indications are plotted. Samples with intensities outside of the 75% confidence range are indicated (dot). B) The percentage of each indicated tumor type showing 0, 1+, 2+ or 3+ ICOS staining by immunohistochemistry (IHC).

[0040] Figure 2. Correlation of ICOS expression with T-cell infiltration. ICOS mRNA levels from ~450 HNSCC tumors were compared with a 12 gene T-cell associated chemokine signature score or FoxP3 mRNA levels. Levels of normalized chemokine signature or FoxP3 mRNA for each tumor is plotted on the Y axis, mRNA levels of ICOS are plotted in the X-axis. The Spearman correlation (R) of the association is shown on the graph [Corr(S)]. A correlation of >0.75 (Spearman R) is viewed as cut-off for strong correlation.

[0041] Figure 3. ICOS mRNA expression was compared for ~450 HNSCC tumors using TCGA RNA sequencing data (NCI). Levels of normalized CTLA-4 or PD-1 or PD-L1 mRNA for each tumor is plotted on the Y axis, mRNA levels of ICOS are plotted in the X-axis. The Spearman correlation (R) of the association is shown on the graph [Corr(S)]. ICOS expression levels significantly correlated with expression of checkpoint molecules CTLA-4, PD-1. A weak correlation between ICOS and PD-L1 was observed. A correlation of >0.75 (Spearman R) is viewed as cut-off for strong correlation.

[0042] Figure 4. Representative images of the varying intensities of ICOS staining in human NSCLC tumor.

[0043] Figure 5. Distribution of ICOS cell density from human tumors. ICOS cell density was determined in each of the human tumors, and mean ICOS density from each tumor type is plotted in Y axis [NSCLC (N=100); HNSCC (N=102); Breast cancer, all major subtypes (N=94); triple negative subtype of breast cancer, TNBC (N=95); ovarian cancer (N=94)]. The statistical analysis was performed using ANOVA.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to ICOS, wherein the antibody comprises:
 - i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
 - ii) (a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 63 and 93; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 66, 76, and 86; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 67; or
 - iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 12; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 13; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 14; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 15; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 16; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 17; or
 - iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 43; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 44; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 45; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 46; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 47; or
 - v) (a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 33 and 173; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID

NOs: 36, 166, and 186; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 37; or

- vi) (a) HCDR1 comprising an amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising an amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising an amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising an amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 56, 136, 146, and 156; and (f) LCDR3 comprising an amino acid sequence of SEQ ID NO: 57; or
- vii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 36; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 37; or
- viii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 56; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 57; or
- ix) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or

- x) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 86; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xiii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 64; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 65; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 86; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 67; or
- xiv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 136; and (f) LCDR3

comprising the amino acid sequence of SEQ ID NO: 57; or

- xv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 146; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 57; or
- xvi) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 54; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 55; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 156; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 57; or
- xvii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 166; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 37; or
- xviii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 173; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 36; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 37; or
- xix) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 34; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 35; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 186; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 37.

2. The antibody of claim 1, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

- i) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 10 and the V_L is at

- least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 11; or
- ii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 21; or
- iii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 30 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 31; or
- iv) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 41; or
- v) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 50 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 51; or
- vi) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 60 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61; or
- vii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 60 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 71; or
- viii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 60 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 81; or
- ix) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 90 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61; or

- x) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 90 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 71; or
- xi) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 90 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 81; or
- xii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 120 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 121; or
- xiii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 120 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 131; or
- xiv) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 120 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 141; or
- xv) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 150 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 151; or
- xvi) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 160 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 81; or
- xvii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 170 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61; or
- xviii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 180 and the

V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 181.

3. The antibody of claim 1 or claim 2, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

- i) the V_H comprises the amino acid sequence of SEQ ID NO: 10 and the V_L comprises the amino acid sequence of SEQ ID NO: 11; or
- ii) the V_H comprises the amino acid sequence of SEQ ID NO: 20 and the V_L comprises the amino acid sequence of SEQ ID NO: 21; or
- iii) the V_H comprises the amino acid sequence of SEQ ID NO: 30 and the V_L comprises the amino acid sequence of SEQ ID NO: 31; or
- iv) the V_H comprises the amino acid sequence of SEQ ID NO: 40 and the V_L comprises the amino acid sequence of SEQ ID NO: 41; or
- v) the V_H comprises the amino acid sequence of SEQ ID NO: 50 and the V_L comprises the amino acid sequence of SEQ ID NO: 51; or
- vi) the V_H comprises the amino acid sequence of SEQ ID NO: 60 and the V_L comprises the amino acid sequence of SEQ ID NO: 61; or
- vii) the V_H comprises the amino acid sequence of SEQ ID NO: 60 and the V_L comprises the amino acid sequence of SEQ ID NO: 71; or
- viii) the V_H comprises the amino acid sequence of SEQ ID NO: 60 and the V_L comprises the amino acid sequence of SEQ ID NO: 81; or
- ix) the V_H comprises the amino acid sequence of SEQ ID NO: 90 and the V_L comprises the amino acid sequence of SEQ ID NO: 61; or
- x) the V_H comprises the amino acid sequence of SEQ ID NO: 90 and the V_L comprises the amino acid sequence of SEQ ID NO: 71; or
- xi) the V_H comprises the amino acid sequence of SEQ ID NO: 90 and the V_L comprises the amino acid sequence of SEQ ID NO: 81; or
- xii) the V_H comprises the amino acid sequence of SEQ ID NO: 120 and the V_L comprises the amino acid sequence of SEQ ID NO: 121; or
- xiii) the V_H comprises the amino acid sequence of SEQ ID NO: 120 and the V_L comprises the amino acid sequence of SEQ ID NO: 131; or
- xiv) the V_H comprises the amino acid sequence of SEQ ID NO: 120 and the V_L comprises the amino acid sequence of SEQ ID NO: 141; or
- xv) the V_H comprises the amino acid sequence of SEQ ID NO: 150 and the V_L comprises the amino acid sequence of SEQ ID NO: 151; or

- xvi) the V_H comprises the amino acid sequence of SEQ ID NO: 160 and the V_L comprises the amino acid sequence of SEQ ID NO: 81; or
 - xvii) the V_H comprises the amino acid sequence of SEQ ID NO: 170 and the V_L comprises the amino acid sequence of SEQ ID NO: 61; or
 - xviii) the V_H comprises the amino acid sequence of SEQ ID NO: 180 and the V_L comprises the amino acid sequence of SEQ ID NO: 181.
4. The antibody of any one of the preceding claims, wherein the antibody is a monoclonal antibody.
 5. The antibody of any one of the preceding claims, wherein the antibody is a chimeric antibody or a humanized antibody.
 6. The antibody of any one of the preceding claims, wherein the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or (Fab')₂ fragment.
 7. The antibody of any one of the preceding claims, wherein the antibody is a full length antibody.
 8. The antibody of claim 7, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 188 and the light chain comprises the amino acid sequence of SEQ ID NO: 189.
 9. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal results in an increase in T effector (Teff) cells in the mammal.
 10. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal results in activation of T effector (Teff) cells in the mammal.
 11. The antibody of claim 9 or claim 10, wherein the Teff cells are CD4+ FoxP3- T cells.
 12. The antibody of claim 9 or claim 10, wherein the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells.
 13. The antibody of claim 9 or claim 10, wherein the Teff cells are CD8+ T cells.
 14. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal results in a decrease in T regulatory (Treg) cells in the mammal.
 15. The antibody of claim 14, wherein the Treg cells are CD4+ FoxP3+ T cells.
 16. An isolated nucleic acid encoding the antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124.
 17. A vector comprising the nucleic acid of claim 16.
 18. A host cell comprising the vector of claim 17.
 19. A host cell that produces the antibody of any one of claims 1 to 15 or 44 to 81 or 111 to 118.

20. A method for making an anti-ICOS antibody, comprising culturing the host cell of claim 19 under conditions suitable for expression of the antibody.
21. The method of claim 20, further comprising recovering the antibody produced by the host cell.
22. A pharmaceutical composition comprising the anti-ICOS antibody of any one of claims 1 to 15 or 50 to 72 and a pharmaceutically acceptable carrier.
23. Use of the anti-ICOS antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 in the manufacture of a medicament for treating cancer in a mammal.
24. The use of claim 23, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC).
25. The use of claim 24, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).
26. Use of the anti-ICOS antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 in the manufacture of a medicament for increasing the number of T effector (Teff) cells in a mammal.
27. The use of claim 26, wherein the use further comprises activating Teff cells.
28. Use of the anti-ICOS antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 in the manufacture of a medicament for activating T effector (Teff) cells in a mammal.
29. The use of any one of claims 26 to 28, wherein the Teff cells are CD4+ FoxP3- T cells.
30. The use of any one of claims 26 to 28, wherein the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells.
31. The use of any one of claims 26 to 28, wherein the Teff cells are CD8+ T cells.
32. The use of any one of claims 26 to 31, wherein the use further comprises decreasing the number of T regulatory (Treg) cells.
33. Use of the anti-ICOS antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 in the manufacture of a medicament for decreasing the number of T regulatory (Treg) cells in a mammal.

34. The use of claim 32 or claim 33, wherein the Treg cells are CD4⁺ FoxP3⁺ T cells.
35. The use of any one of claims 23 to 34, wherein the mammal is a human.
36. The use of any one of claims 23 to 35, wherein the mammal is to be administered at least one additional therapeutic agent.
37. The use of claim 36, wherein the additional therapeutic agent is to be administered concurrently or sequentially with the anti-ICOS antibody.
38. The use of claim 36 or claim 37, wherein the additional therapeutic agent is selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.
39. The use of claim 36 or claim 37, wherein the additional therapeutic agent is a cancer vaccine.
40. The use of claim 39, wherein the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

41. Use of an antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 and at least one additional therapeutic agent in the manufacture of a medicament for treating cancer.

42. The use of claim 41, wherein the additional therapeutic agent is selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.

43. The use of claim 41, wherein the additional therapeutic agent is a cancer vaccine.

44. The use of claim 43, wherein the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

45. The use of any one of claims 41 to 44, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC).

46. The use of claim 45, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

47. An antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 or the pharmaceutical composition of claim 22 for use in treating cancer.

48. The antibody of claim 47, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC).

49. The antibody of claim 48, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

50. An isolated antibody that binds to human ICOS, wherein the antibody also binds to mouse ICOS and/or rat ICOS.
51. The isolated antibody of claim 50, wherein the antibody binds to human ICOS with an affinity (K_D) of less than 5 nM.
52. The isolated antibody of claim 50 or claim 51, wherein the antibody binds to rat ICOS with an affinity (K_D) of less than 10 nM.
53. The isolated antibody of claim 51 or claim 52, wherein affinity is determined using biolayer interferometry.
54. The isolated antibody of any one of claims 50 to 53, wherein the antibody binds to human ICOS, mouse ICOS, and rat ICOS.
55. The isolated antibody of any one of claims 50 to 54, wherein the antibody binds to cynomolgus monkey ICOS.
56. The isolated antibody of any one of claims 50 to 55, wherein the antibody is a monoclonal antibody.
57. The isolated antibody of any one of claims 50 to 56, wherein the antibody is a chimeric antibody or a humanized antibody.
58. The isolated antibody of any one of claims 50 to 57, wherein the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or (Fab')₂ fragment.
59. The isolated antibody of any one of claims 50 to 57, wherein the antibody is a full length antibody.
60. The isolated antibody of any one of claims 50 to 59, wherein administration of the antibody to a mammal results in an increase in T effector (Teff) cells in the mammal.
61. The isolated antibody of any one of claims 50 to 60, wherein administration of the antibody to a mammal results in activation of T effector (Teff) cells in the mammal.
62. The isolated antibody of claim 60 or claim 61, wherein the Teff cells are CD4+ FoxP3- T cells.
63. The isolated antibody of claim 60 or claim 61, wherein the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells.
64. The isolated antibody of claim 60 or claim 61, wherein the Teff cells are CD8+ T cells.
65. The isolated antibody of any one of claims 50 to 64, wherein administration of the antibody to a mammal results in a decrease in T regulatory (Treg) cells in the mammal.
66. The isolated antibody of claim 65, wherein the Treg cells are CD4+ FoxP3+ T cells.

67. The isolated antibody of any one of claims 60 to 66, wherein the mammal is selected from a mouse, rat, cynomolgus monkey, and human.

68. The antibody of any one of claims 1 to 15 or 50 to 67, wherein following treatment of lung tumor tissue with the antibody, the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 is at least a 2-fold, or at least 3-fold higher than the level of the chemokine following treatment of the lung tumor tissue with a control antibody.

69. The antibody of claim 68, wherein the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after treatment.

70. The antibody of claim 68, wherein at least one chemokine is CXCL11.

71. The antibody of claim 70, wherein the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after treatment.

72. The antibody of claim 71, wherein the level of the chemokine is measured 24 hours after treatment.

73. The antibody of any one of claims 68 to 72, wherein the lung tumor tissue is human lung tumor tissue.

74. The antibody of any one of claims 1 to 15 or 50 to 73, wherein the antibody increases the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal that has been administered the antibody by at least a 2-fold.

75. The antibody of claim 74, wherein the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody.

76. The antibody of claim 74, wherein at least one chemokine is CXCL11.

77. The antibody of claim 76, wherein the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody.

78. The antibody of claim 76, wherein the level of the chemokine is measured 24 hours after administration of the antibody.

79. An agonist anti-ICOS antibody that increases the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal that has been administered the antibody by at least a 2-fold.

80. The antibody of claim 79, wherein the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody.

81. The antibody of claim 79, wherein at least one chemokine is CXCL11.
82. The antibody of claim 81, wherein the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody.
83. The antibody of claim 81, wherein the level of the chemokine is measured 24 hours after administration of the antibody.
84. The antibody of any one of claims 74 to 83, wherein the mammal is a human.
85. The antibody of claim 84, wherein the human has cancer.
86. The antibody of claim 85, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC).
87. The antibody of claim 86, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).
88. Use of an antibody of any one of claims 1 to 15 or 50 to 87 or 117 to 124 in the manufacture of a medicament for increasing the level of at least one chemokine and/or cytokine mRNA selected from GZMa, GZMb, CSF2, IL2, CXCL9, CXCL10, CXCL11, and CXCL13 in a mammal.
89. The use of claim 88, wherein the level of the chemokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours after administration of the antibody.
90. The use of claim 88, wherein at least one chemokine is CXCL11.
91. The use of claim 90, wherein the level of the chemokine is measured 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody.
92. The use of claim 90, wherein the level of the chemokine is measured 24 hours after administration of the antibody.
93. The use of any one of claims 88 to 92, wherein the mammal is a human.
94. The use of claim 93, wherein the human has cancer.
95. The use of claim 94, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), and triple negative breast cancer (TNBC).

96. The use of claim 94, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).
97. The use of any one of claims 23 to 27, wherein Teff cells are activated following administration of the anti-ICOS antibody.
98. The use of any one of claims 23 to 27 and 97, wherein the number of Teff cells is increased following administration of the anti-ICOS antibody.
99. The use of claim 97 or claim 98, wherein the Teff cells are CD4+ FoxP3- T cells.
100. The use of any one of claims 97 to 99, wherein the Teff cells are CD4+ FoxP3- T cells and CD8+ T cells.
101. The use of any one of claims 97 to 100, wherein the Teff cells are CD8+ T cells.
102. The use of any one of claims 23 to 27 and 97 to 101, wherein the number of T regulatory (Treg) cells is decreased following administration of the anti-ICOS antibody.
103. The use of claim 102, wherein the Treg cells are CD4+ FoxP3+ T cells.
104. The use of any one of claims 97 to 103, wherein the mammal is a human.
105. The use of any one of claims 97 to 104, wherein the mammal is administered at least one additional therapeutic agent.
106. The use of claim 105, wherein the additional therapeutic agent is administered concurrently or sequentially with the anti-ICOS antibody.
107. The use of claim 106, wherein the additional therapeutic agent is a PD-1 therapy.
108. The use of any one of claims 105 to 107, wherein the additional therapeutic agent is selected from an anti-PD-1 antibody and an anti-PD-L1 antibody.
109. The use of claim 105 or claim 106, wherein the additional therapeutic agent is a cancer vaccine.
110. The use of claim 109, wherein the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.
111. The use of any one of claims 23 to 27 and 97 to 110, wherein a sample of the cancer has been determined to express ICOS.
112. The use of claim 111, wherein the sample shows 1+, 2+, or 3+ staining of ICOS by immunohistochemistry (IHC).

113. The use of any one of claims 23 to 27 and 97 to 112, wherein the sample has been determined to have a low level of PD-L1.
114. The use of any one of claims 23 to 27 and 97 to 113, wherein the sample has been determined to be PD-L1-negative.
115. The use of any one of claims 23 to 27 and 97 to 112, wherein the sample has been determined to have an elevated level of PD-L1.
116. The use of any one of claims 113 to 115, wherein PD-L1 levels are determined using IHC.
117. An antibody that binds to ICOS, wherein the antibody increases the level of the ligand for NKp46 (NKp46-L) on T cells.
118. The antibody of claim 117, wherein the increased level of NKp46-L on T cells is determined using a soluble NKp46 extracellular domain in a flow cytometry assay.
119. The antibody of claim 117 or claim 118, wherein the antibody increases the level of NKp46-L on Treg cells more than the antibody increases the level of NKp46-L on Teff cells.
120. The antibody of any one of claims 117 to 119, wherein the antibody increases CD16 shedding on NK cells.
121. The antibody of any one of claims 1 to 15 or 50 to 87, wherein the antibody increases the level of the ligand for NKp46 (NKp46-L) on T cells.
122. The antibody of claim 121, wherein the increased level of NKp46-L on T cells is determined using a soluble NKp46 extracellular domain in a flow cytometry assay.
123. The antibody of claim 121 or claim 122, wherein the antibody increases the level of NKp46-L on Treg cells more than the antibody increases the level of NKp46-L on Teff cells.
124. The antibody of any one of claims 121 to 123, wherein the antibody increases CD16 shedding on NK cells.