ADCC contribute to antitumor activity of SGN-40 (Law CL, Gordon KA, Collier J, et al: Cancer Res 2005; 65:8331-8338). A Recent study suggested that the anti-tumour activity of SGN-40 significantly depends on Fc interactions with the effector cells and that macrophages are the major effectors contributing to its therapeutic activities (Oflazoglu E, et al. Br J Cancer. 2009 Jan 13;100(1):113-7. Epub 2008 Dec 9). Since SGN-40 is a partial agonist and requires CD40L expressed on T cells, SGN-40 may have limited ability to fully boost the anti-tumor immune response.

Accordingly, there remains a need in the art for novel immunotherapeutics that target CD40 and that act as agonist for this target, activate dendritic cells and immune surveillance and which activate ADCC, thereby providing improved anti-cancer properties.

BRIEF SUMMARY

In a first aspect of the present disclosure, there is provided an isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising (i) a heavy chain variable region comprising the VHCDR1, VHCDR2, and VHCDR3 set forth in SEQ ID NOs:3-5; and (ii) a light chain variable region comprising the VLCDR1, the VLCDR2, and the VLCDR3 set forth in SEQ ID NOs:6-8; or a variant of said antibody, or an antigen-binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions.

In a second aspect of the present disclosure, there is provided an isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:9 and a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:10.

In a third aspect of the present disclosure, there is provided an isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:10 and a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:9.

In a fourth aspect of the present disclosure, there is provided a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof as defined herein.

In a fifth aspect of the present disclosure, there is provided a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof as defined herein.

~~One aspect of t~~The present disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising (i) a heavy chain variable region comprising the VHCDR1 region set forth in SEQ ID NO:3, the VHCDR2 region set forth in SEQ ID NO:4, and the VHCDR3 region set forth SEQ ID NO:5; and (ii) a light chain variable region comprising the VLCDR1 region set forth in SEQ ID NO:6, the VLCDR2 region set forth in SEQ ID NO:7, and the VLCDR3 region set forth in SEQ ID NO: 8; or a variant of said antibody, or an antigen-binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions. In one embodiment of the antibodies disclosed herein, the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1. In a further embodiment, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2.

~~Another aspect of t~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:1. In one embodiment ~~of this aspect~~, the isolated antibody, or antigen-binding fragment thereof comprises a light chain variable region which comprises an amino

acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:2. In a further embodiment ~~of this aspect~~, the isolated antibody, or an antigen-binding fragment thereof comprises a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:2.

~~Yet a further aspect of t~~The present disclosure further provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2. In one embodiment ~~of this aspect~~, the isolated antibody, or antigen binding fragment thereof comprises a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:1.

In certain embodiments, the isolated antibodies as disclosed herein are humanized. Illustrative humanized antibody variable regions are set forth in the VH region amino acid sequence of SEQ ID NO:9 and the VL region amino acid sequence of SEQ ID NO:10.

In one embodiment, an isolated antibody disclosed herein may be single chain antibody, a ScFv, a univalent antibody lacking a hinge region, a minibody, a Fab, a Fab' fragment, or a $F(ab')_2$ fragment. In certain embodiments, the antibodies herein are whole antibodies.

In another embodiment, the isolated antibodies as described herein comprise a human IgG constant domain, such as, but not limited to an IgG1 CH1 domain or an IgG1 Fc region.

A further embodiment of the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that competes with the anti-CD40 antibodies described herein for binding to human CD40.

The present~~In one aspect of this~~ disclosure~~, the~~ also provides an isolated antibody, or antigen-binding fragment thereof, that binds CD40, binds with a KD of 0.96 nM or lower. In a further embodiment, the isolated antibody, or antigen-binding fragment thereof, that binds CD40, binds with a Kd of between 1.1 nM and 0.90 nM. In a further embodiment, the isolated antibody, or antigen-binding fragment thereof, that binds CD40, binds with a Kd of about 1.2, 1.1, 1.0, 0.99, 0.98, 0.97, 0.96, 0.95, 0.94, 0.93,

0.92, 0.91, 0.90, 0.85, or about 0.80 nM. In another embodiment, the antibody binds CD40 with a Kd of about 2.5, 2.4, 2.3, 2.2, 2.1, 2.0, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, or 1.3 nM.

~~In a further aspect, t~~The present disclosure also~~invention~~ provides an isolated antibody, or antigen-binding fragment thereof as described herein, wherein the isolated antibody, or antigen-binding fragment thereof: blocks binding of CD40 to CD40L; is a CD40 agonist; activates antigen presenting cells; stimulates cytokine release from antigen presenting cells; induces tumor cell apoptosis; inhibits tumor cell proliferation; kills tumor cells via induction of effector functions selected from the group consisting of antibody dependent cellular cytotoxicity, complement dependent cytotoxicty, and antibody dependent cellular phagocytosis; stimulates anti-tumor T cell responses; reduces established tumors; inhibits rituximab-resistant tumors; or a combination of any one or more of the aforementioned.

~~Another aspect of t~~The present disclosure also~~invention~~ provides an isolated antibody, or an antigen binding fragment thereof, that binds to CD40, comprising: (i) a heavy chain variable region comprising the VH CDR1, the VHCDR2, and VHCDR3 of any one of the VH regions shown in Figure 16; and (ii) a light chain variable region comprising the VLCDR1, the VLCDR2, and the VLCDR3 region of the corresponding VL region of any one of the VL regions shown in Figure 16; or a variant of said antibody, or an antigen binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions.

~~Yet another aspect of t~~The present disclosure further~~invention~~ provides an isolated antibody, or an antigen binding fragment thereof that binds to CD40, comprising a heavy chain variable region comprising any one of the VH regions shown in Figure 16. In one embodiment such an antibody further comprises a light chain variable region comprising an amino acid sequence having at least 90% identity to the corresponding VL region as shown in Figure 16. In another embodiment, such an antibody or antigen binding fragment thereof further comprises the corresponding light chain variable region as shown in Figure 16.

~~Yet another aspect of t~~The present disclosure also~~invention~~ provides an isolated antibody, or an antigen binding fragment thereof that binds to CD40, comprising a light chain variable region comprising any one of the VL regions shown in Figure 16. In one embodiment such an antibody further comprises a heavy chain variable region comprising an amino acid sequence having at least 90% identity to the corresponding VH region as shown in Figure 16. In another embodiment, such an antibody or antigen binding fragment thereof further comprises the corresponding heavy chain variable region as shown in Figure 16.

The present disclosure also provides isolated polynucleotides encoding the isolated antibodies, or antigen-binding fragments thereof as disclosed herein.

The present disclosure also provides compositions comprising a physiologically acceptable carrier and a therapeutically effective amount of an anti-CD40 antibody or antigen-binding fragment thereof as described herein.

~~Another aspect of t~~The present disclosure also provides a method for treating a patient having a cancer, comprising administering to the patient a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of an anti-CD40 antibody or antigen-binding fragment thereof as described herein, thereby treating the cancer. In certain embodiments, the cancer is associated with aberrant CD40 expression. In further embodiments, the cancer is selected from the group consisting of non-Hodgkin's lymphomas, Hodgkin's lymphoma, chronic lymphocytic leukemias, hairy cell leukemias, acute lymphoblastic leukemias, multiple myeloma, carcinomas of the pancreas, colon, gastric intestine, prostate, bladder, kidney, ovary, cervix, breast, lung, nasopharynx, malignant melanoma and rituximab resistant NHL and leukemias.

~~Another aspect of t~~The present disclosure also provides a method for treating a patient having cancer and/or autoimmune disease, and/or inflammatory disease, comprising administering to the patient a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of an anti-CD40 antibody or antigen-binding fragment thereof as described herein, thereby treating the patient having autoimmune and inflammatory dieseases.

~~Another aspect of t~~The present disclosure also provides a method for ameliorating the symptoms in a patient having cancer, and/or autoimmune disease and/or inflammatory disease, comprising administering to the patient a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of an anti-CD40 antibody or antigen-binding fragment thereof as described herein, thereby ameliorating the symptoms in the patient having cancer, and/or autoimmune and/or inflammatory dieseases.

~~Another aspect of t~~The present disclosure also provides isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:11. In one embodiment, the isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:11 and comprises a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:22 or a light chain comprising the amino acid sequence set forth in SEQ ID NO:22. In certain embodiments, an isolated antibody described herein comprises the light chain as set forth in SEQ ID NO:22 and comprises a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:11.

~~A further aspect of t~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:13. In one embodiment, the antibody comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:13 and a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:24. In one embodiment, the light chain comprises the amino acid sequence set forth in SEQ ID NO:24.

~~A further aspect of t~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40,

comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:24. In one embodiment, the antibody comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:24 and a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:13.

In certain embodiment~~aspect~~s, the isolated antibody, or antigen-binding fragment thereof, that binds CD40 comprises a heavy chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:17. In one embodiment, the isolated antibody that binds CD40 comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:17 and a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:28. In one embodiment, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:28.

~~Another aspect of the~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:28. In one embodiment, the isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:28 and a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:17.

~~Another aspect of the~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:19. In one embodiment, the isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprises a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:19 and a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:30. In one particular

embodiment, the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:30.

~~Yet a further aspect of t~~The present disclosure further provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:30. In one embodiment, the isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprises a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:30 and a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:19.

~~Another aspect of t~~The present disclosure also provides an isolated antibody, or an antigen-binding fragment thereof, that binds to human CD40, comprising a heavy chain variable region that comprises heavy chain variable region CDRs and a light chain variable region that comprises corresponding light chain variable region CDRs, wherein the CDRs are as shown in Figure 16.

BRIEF DESCRIPTION OF THE SEQUENCES

SEQ ID NO:1 is the amino acid sequence of the VH region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:2 is the amino acid sequence of the VL region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:3 is the amino acid sequence of the VHCDR1 region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:4 is the amino acid sequence of the VHCDR2 region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:5 is the amino acid sequence of the VHCDR3 region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:6 is the amino acid sequence of the VLCDR1 region of the R-8 rabbit anti-CD40 antibody.

SEQ ID NO:7 is the amino acid sequence of the VLCDR2 region of the R-8 rabbit anti-CD40 antibody.

CLAIMS

What is claimed is:

1. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising (i) a heavy chain variable region comprising the VHCDR1 region set forth in SEQ ID NO:3, the VHCDR2 region set forth in SEQ ID NO:4, and the VHCDR3 region set forth SEQ ID NO:5; and (ii) a light chain variable region comprising the VLCDR1 region set forth in SEQ ID NO:6, the VLCDR2 region set forth in SEQ ID NO:7, and the VLCDR3 region set forth in SEQ ID NO: 8;

or a variant of said antibody, or an antigen-binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions.

2. The isolated antibody, or antigen-binding fragment thereof, of claim 1 wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1.

3. The isolated antibody, or antigen-binding fragment thereof, of claim 1 wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2.

4. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:1.

5. The isolated antibody, or antigen-binding fragment thereof, of claim 4 comprising a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:2.

6. The isolated antibody, or an antigen-binding fragment thereof, of claim 4 comprising a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:2.

7. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:2.

8. The isolated antibody, or antigen binding fragment thereof, of claim 7 comprising a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:1.

9. The isolated antibody of claim 1, wherein the antibody is humanized.

10. The isolated antibody of claim 9, wherein the VH region comprises the amino acid sequence set forth in SEQ ID NO:9 and the VL region comprises the amino acid sequence set forth in SEQ ID NO:10.

11. The isolated antibody of claim 1 wherein the antibody is selected from the group consisting of a single chain antibody, a ScFv, a univalent antibody lacking a hinge region, and a minibody.

12. The isolated antibody of claim 1 wherein the antibody is a Fab or a Fab' fragment.

13. The isolated antibody of claim 1 wherein the antibody is a $F(ab')_2$ fragment.

14. The isolated antibody of claim 1 wherein the antibody is a whole antibody.

15. The isolated antibody of claim 1 comprising a human IgG constant domain.

16. The isolated antibody of claim 15 wherein the IgG constant domain comprises an IgG1 CH1 domain.

17. The isolated antibody of claim 15 wherein the IgG constant domain comprises an IgG1 Fc region.

18. An isolated antibody, or an antigen-binding fragment thereof, that competes with the antibody of claim 1 for binding to CD40.

19. An isolated antibody, or antigen-binding fragment thereof, that binds CD40 with a KD of 0.96 nM or lower.

20. An isolated antibody, or antigen-binding fragment thereof of any one of claims 1 – 19, wherein the isolated antibody, or antigen-binding fragment thereof:

a. blocks binding of CD40 to CD40L;
b. is a CD40 agonist;
c. activates antigen presenting cells;
d. stimulates cytokine release from antigen presenting cells;
e. induces tumor cell apoptosis;
f. Inhibits tumor cell proliferation;
g. kills tumor cells via induction of effector functions selected from the group consisting of antibody dependent cellular cytotoxicity, complement dependent cytotoxicty, and antibody dependent cellular phagocytosis;

h. stimulates anti-tumor T cell responses;
i. reduces established tumors;
j. inhibits rituximab-resistant tumors; or
k. a combination of any one or more of a. - j.

21. An isolated antibody, or antigen-binding fragment thereof, wherein the isolated antibody, or antigen-binding fragment thereof:

a. blocks binding of CD40 to CD40L;
b. is a CD40 agonist;
c. activates antigen presenting cells;
d. stimulates cytokine release from antigen presenting cells;
e. induces tumor cell apoptosis;
f. Inhibits tumor cell proliferation;
g. kills tumor cells via induction of effector functions selected from the group consisting of antibody dependent cellular cytotoxicity, complement dependent cytotoxicty, and antibody dependent cellular phagocytosis;
h. stimulates anti-tumor T cell responses;
i. reduces established tumors;
j. inhibits rituximab-resistant tumors; or
k. a combination of any one or more of a. - j.

22. An isolated polynucleotide encoding the isolated antibody, or antigen-binding fragment thereof, according to any one of claims 1, 10, 18, 19 and 21.

23. An expression vector comprising the isolated polynucleotide of claim 22.

24. An isolated host cell comprising the vector of claim 23.

25. A composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof according to any one of claims 1, 10, 18, 19 and 21.

26. A method for treating or ameliorating the symptoms in a patient having a cancer, comprising administering to the patient the composition of claim 25, thereby treating or ameliorating the symptoms in the patient having the cancer.

27. The method of claim 26 wherein the cancer is selected from the group consisting of non-Hodgkin's lymphomas, Hodgkin's lymphoma, chronic lymphocytic leukemias, hairy cell leukemias, acute lymphoblastic leukemias, multiple myeloma, carcinomas of the bladder, kidney ovary, cervix, breast, lung, nasopharynx, malignant melanoma and rituximab resistant NHL and leukemias.

28. A method for ameliorating symptoms in a patient having an autoimmune disease comprising administering to the patient the composition of claim 25, thereby ameliorating symptoms in the patient having the autoimmune disease.

29. A method for ameliorating symptoms in a patient having an inflammatory disease comprising administering to the patient the composition of claim 25, thereby ameliorating symptoms in the patient having the inflammatory disease.

30. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising (i) a heavy chain variable region comprising the VHCDR1, VHCDR2, and VHCDR3 of any one of the VH regions shown in Figure 16; and (ii) a light chain variable region comprising the VLCDR1, the VLCDR2, and the VLCDR3 region of the corresponding VL region of any one of the antibodies shown in Figure 16;

or a variant of said antibody, or an antigen-binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions.

31. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a heavy chain variable region comprising any one of the VH regions shown in Figure 16.

32. The isolated antibody, or antigen-binding fragment thereof, of claim 31, further comprising a light chain variable region comprising an amino acid sequence having at least 90% identity to the corresponding VL region as shown in Figure 16.

33. The isolated antibody, or antigen-binding fragment thereof, of claim 31, further comprising the corresponding light chain variable region as shown in Figure 16.

34. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a light chain variable region comprising any one of the VL regions shown in Figure 16.

35. The isolated antibody, or antigen-binding fragment thereof, of claim 34, further comprising a heavy chain variable region comprising an amino acid sequence having at least 90% identity to the corresponding VH region as shown in Figure 16.

36. The isolated antibody, or antigen-binding fragment thereof, of claim 34, further comprising the corresponding heavy chain variable region as shown in Figure 16.

CLAIMS

What is claimed is:

1. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising (i) a heavy chain variable region comprising the VHCDR1, VHCDR2, and VHCDR3 set forth in SEQ ID NOs:3-5; and (ii) a light chain variable region comprising the VLCDR1, the VLCDR2, and the VLCDR3 set forth in SEQ ID NOs:6-8;

or a variant of said antibody, or an antigen-binding fragment thereof, comprising heavy and light chain variable regions identical to the heavy and light chain variable regions of (i) and (ii) except for up to 8 amino acid substitutions in said CDR regions.

2. The isolated antibody, or an antigen-binding fragment thereof, of claim 1 comprising (i) a heavy chain variable region comprising the VHCDR1, VHCDR2, and VHCDR3 set forth in SEQ ID NOs:3-5; and (ii) a light chain variable region comprising the VLCDR1, the VLCDR2, and the VLCDR3 set forth in SEQ ID NOs:6-8.

3. The isolated antibody, or antigen-binding fragment thereof, of claim 1 wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:9.

4. The isolated antibody, or antigen-binding fragment thereof, of claim 1 wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:10.

5. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO:9 and a light chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:10.

6. The isolated antibody, or an antigen-binding fragment thereof, of claim 5 comprising a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:10.

7. An isolated antibody, or an antigen-binding fragment thereof, that binds to CD40, comprising a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO:10 and a heavy chain variable region which comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in SEQ ID NO:9.

8. The isolated antibody of claim 1, wherein the antibody is humanized.

9. The isolated antibody, or antigen-binding fragment thereof, of claim 1 that binds CD40 with a KD of 0.96 nM or lower.

10. The isolated antibody, or antigen-binding fragment thereof of claim 9, wherein the isolated antibody, or antigen-binding fragment thereof:
a) blocks binding of CD40 to CD40L;
b) is a CD40 agonist;
c) activates antigen presenting cells;
d) stimulates cytokine release from antigen presenting cells;
e) induces tumor cell apoptosis;
f) inhibits tumor cell proliferation;
g) kills tumor cells via induction of effector functions selected from the group consisting of antibody dependent cellular cytotoxicity, complement dependent cytotoxicty, and antibody dependent cellular phagocytosis;
h) stimulates anti-tumor T cell responses;
i) reduces established tumors;
j) inhibits rituximab-resistant tumors and other CD40 expressing tumors; or

k) a combination of any one or more of a)-j).

11. A composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof according to claim 1.

12. A composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the isolated antibody or antigen-binding fragment thereof according to claim 6.

13. The isolated antibody of claim 1 wherein the antibody is selected from the group consisting of a single chain antibody, a ScFv, a univalent antibody lacking a hinge region, and a minibody.

14. The isolated antibody of claim 1 wherein the antibody is a Fab or a Fab' fragment.

15. The isolated antibody of claim 1 wherein the antibody is a whole antibody.

16. The isolated antibody of claim 1 wherein the isolated antibody comprises an IgG1 Fc region.