Claims

1) An isolated agonistic antibody or antigen-binding fragment thereof specifically binding human CD40 of SEQ ID NO: 75, comprising a heavy chain variable region (HCDR) 1 of SEQ ID NO: 5, a HCDR2 of SEQ ID NO: 10, a HCDR3 of SEQ ID NO: 18, a light chain variable region (LCDR) 1 of SEQ ID NO: 32, a LCDR2 of SEQ ID NO: 34 and a LCDR3 of SEQ ID NO: 47.
2) The antibody of claim 1, wherein the antibody binds human CD40 of SEQ ID NO: 75 within human CD40 residues 46-64 and 75-76 of SEQ ID NO: 75.
3) The antibody of claim 1 or 2, wherein the antibody has at least one of the following properties:
    a) binds to human CD40 of SEQ ID NO: 75 with a dissociation constant (K_D) of about $5x10^{-9}$ M or less, when the K_D is measured using ProteOn XPR36 system at 25°C in Dulbecco's phosphate buffered saline containing 0.01% polysorbate 20 (PS-20) and 100 µg/ml bovine serum albumin; or
    b) requires cross-linking for its agonistic activity on B cells and on dendritic cells (DC), wherein agonistic activity on B cells is measured by B cell CD23 surface expression and agonistic activity on DCs is measured by DC CD83 surface expression in the presence of cross-linker anti-human F(ab')2 at 20 µg/ml, when CD23 and CD83 surface expression is measured using flow cytometry.
4) The antibody of claim 3, comprising a heavy chain variable region (VH) of SEQ ID NOs: 62 or 61 and a light chain variable region (VL) of SEQ ID NO: 69.
5) The antibody of claim 3, comprising the VH and the VL of SEQ ID NOs: 62 and 69, respectively.
6) The antibody of claim 3, comprising the VH and the VL of SEQ ID NOs: 61 and 69, respectively.
7) The antibody of claim 3, wherein the antibody comprises a heavy chain framework derived from human IGHV4-39*01 (SEQ ID NO: 73) and a light chain framework derived from human IGLV2-8*01 (SEQ ID NO: 87).
8) The antibody of any of the claims 1-7, wherein the antibody is an IgG1, IgG2, IgG3 or IgG4 isotype.
9) The antibody of claim 5, comprising the heavy chain and the light chain of SEQ ID NOs: 129 and 136, respectively.

10) The antibody of claim 5, comprising the heavy chain and the light chain of SEQ ID NOs: 128 and 136, respectively.
11) The antibody of claim 6, comprising the heavy chain and the light chain of SEQ ID NOs: 127 and 136, respectively.
12) The antibody of any of the claims 1-11, further comprising at least one mutation in an Fc region.
13) The antibody of claim 12, wherein the at least one mutation in the Fc region enhances binding of the antibody to FcγRIIb.
14) The antibody of claim 13, wherein the at least one mutation in the Fc region is a S267E mutation, a S267E/I332E mutation, a S267E/L328F mutation, a G236D/S267E mutation or an E233D/G237D/H268D/P271G/A330R/P238D mutation, residue numbering according to the EU Index.
15) The antibody of claim 13, wherein the at least one mutation in the Fc region is the S267E mutation.
16) The antibody of any of the claims 1-15, wherein the antibody is a multispecific antibody.
17) The antibody of claim 16, wherein the antibody is a bispecific antibody.
18) An immunoconjugate comprising the antibody of any of the claims 1-17 linked to a cytotoxic agent or an imaging agent.
19) A pharmaceutical composition comprising the antibody of any of the claims 1-17 and a pharmaceutically acceptable carrier.
20) A pharmaceutical composition comprising the immunoconjugate of claim 18 and a pharmaceutically acceptable carrier.
21) A polynucleotide encoding the antibody VH of SEQ ID NOs: 62 or 61, the antibody VL of SEQ ID NO: 69 or the antibody VH of SEQ ID NOs: 62 or 61 and the antibody VL of SEQ ID NO: 69.
22) A polynucleotide encoding the antibody heavy chain of SEQ ID NOs: 129, 128 or 127, the antibody light chain of SEQ ID NO: 136 or the antibody heavy chain of SEQ ID NOs: 129, 128 or 127, and the antibody light chain of SEQ ID NO: 136.
23) A polynucleotide comprising the polynucleotide sequence of SEQ ID NOs: 102, 103, 110, 153, 154, 155 or 162.
24) A vector comprising the polynucleotide of claim 21.
25) A vector comprising the polynucleotide of claim 22.

26) A vector comprising the polynucleotide of claim 23.
27) A host cell comprising the vector of claim 24.
28) A host cell comprising the vector of claim 25.
29) A host cell comprising the vector of claim 26.
30) A method of producing an agonistic antibody specifically binding human CD40, comprising culturing the host cell of claim 27, 28 or 29 in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.
31) Use of an isolated antibody of any of the claims 1-17 in the manufacture of a medicament for the treatment of cancer.
32) The use of claim 31, wherein the cancer is a solid tumor or a hematological malignancy.
33) The use of claim 32, wherein the solid tumor is a bladder cancer, a renal cancer, a lung cancer, a non-small cell lung cancer, a pancreatic cancer, an ovarian cancer, a breast cancer or a head and neck cancer.
34) The use of any of the claims 31-33, wherein the medicament is to be administered in combination with a second therapeutic agent.
35) The use of claim 34, wherein the second therapeutic agent is a chemotherapeutic agent, a standard of care drug for treatment of a solid tumor or a hematological malignancy, or an immune checkpoint modulator.
36) The use of claim 34 or 35, wherein the second therapeutic agent is to be administered simultaneously, sequentially or separately.
37) An anti-idiotypic antibody binding to the antibody of claim 4, 5 or 6.
38) A kit comprising the antibody of claim 4, 5 or 6.
39) The kit of claim 38, further comprising reagents for detecting the antibody and instructions of use.
40) The antibody of any of the claims 1-17 or the pharmaceutical composition of claim 19 or 20 for use in therapy.
41) An isolated agonistic antibody or antigen-binding fragment thereof specifically binding human CD40 of SEQ ID NO: 75, wherein the antibody has at least one of the following properties:
    a) binds to human CD40 of SEQ ID NO: 75 with a dissociation constant (K_D) of about $5x10^{-9}$ M or less, when the K_D is measured using ProteOn XPR36 system at

25°C in Dulbecco's phosphate buffered saline containing 0.01% polysorbate 20 (PS-20) and 100 µg/ml bovine serum albumin; or

b) requires cross-linking for its agonistic activity on B cells and on dendritic cells (DC), wherein agonistic activity on B cells is measured by B cell CD23 surface expression and agonistic activity on DCs is measured by DC CD83 surface expression in the presence of cross-linker anti-human F(ab')2 at 20 µg/ml, when CD23 and CD83 surface expression is measured using flow cytometry.

42) The antibody of claim 41, comprising

a) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 1, 8, 22, 28, 38 and 42, respectively, the VH and the VL of SEQ ID NOs: 48 and 63, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 114 and 130, respectively;

b) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 2, 7, 25, 26, 39 and 44, respectively, the VH and the VL of SEQ ID NOs: 49 and 64, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 115 and 131, respectively;

c) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 2, 7, 24, 26, 39 and 44, respectively, the VH and the VL of SEQ ID NOs: 50 and 64, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 116 and 131, respectively;

d) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 2, 7, 23, 26, 39 and 44, respectively, the VH and the VL of SEQ ID NOs: 51 and 64, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 117 and 131, respectively;

e) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 3, 13, 17, 27, 33 and 43, respectively; the VH and the VL of SEQ ID NOs: 52 and 65, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 118 and 132, respectively;

f) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 6, 19, 27, 33 and 43, respectively; the VH and the VL of SEQ ID NOs: 53 and 65, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 119 and 132, respectively;

g) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 6, 20, 27, 33 and 43, respectively; the VH and the VL of SEQ ID NOs: 54 and 65, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 120 and 132, respectively;

h) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 2, 7, 14, 27, 33 and 43, respectively; the VH and the VL of SEQ ID NOs: 55 and 65, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 121 and 132, respectively;

i) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 6, 21, 27, 33 and 43, respectively; the VH and the VL of SEQ ID NOs: 56 and 65, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 122 and 132, respectively;

j) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 9, 15, 30, 36 and 41, respectively, the VH and the VL of SEQ ID NOs: 57 and 66, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 123 and 133, respectively;

k) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 11, 16, 29, 37 and 40, respectively, the VH and the VL of SEQ ID NOs: 58 and 67, respectively; or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 124 and 134, respectively;

l) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 12, 15, 30, 35 and 46, respectively, the VH and the VL of SEQ ID NOs: 59 and 68, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 125 and 135, respectively.

m) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 9, 15, 30, 36 and 41, respectively, the VH and the VL of SEQ ID NOs: 57 and 70, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 123 and 137, respectively;

n) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 9, 15, 31, 36 and 41, respectively, the VH and the VL of SEQ ID NOs: 57 and 71, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 123 and 138, respectively;

o) the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 4, 9, 15, 31, 36 and 41, respectively, the VH and the VL of SEQ ID NOs: 57 and 72, respectively, and/or the heavy chain (HC) and the light chain (LC) of SEQ ID NOs: 123 and 139, respectively.

43) The antibody of any of the claims 41-42, wherein the antibody is an IgG1, IgG2, IgG3 or IgG4 isotype.

44) The antibody of claim 43, further comprising at least one mutation in an Fc region.

45) The antibody of claim 44, wherein the at least one mutation in the Fc region enhances binding of the antibody to FcγRIIb.

46) The antibody of claim 45, wherein the at least one mutation in the Fc region is a S267E mutation, a S267E/I332E mutation, a S267E/L328F mutation, a G236D/S267E mutation or a E233D/G237D/H268D/P271G/A330R/P238D mutation, residue numbering according to the EU Index.

47) The antibody of any of the claims 41-46, wherein the antibody is a multispecific antibody.

48) The antibody of claim 47, wherein the antibody is a bispecific antibody.

49) An immunoconjugate comprising the antibody of any of the claims 41-48 linked to a cytotoxic agent or an imaging agent.

50) A pharmaceutical composition comprising the antibody of any of the claims 41-48 and a pharmaceutically acceptable carrier.

51) A pharmaceutical composition comprising the immunoconjugate of claim 49 and a pharmaceutically acceptable carrier.

52) A polynucleotide encoding the antibody VH of SEQ ID NOs: 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58 or 59, the antibody VL of SEQ ID NOs: 63, 64, 65, 66, 67, 68, 70, 71 or 72, or the antibody VH of SEQ ID NOs: 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58 or 59 and the antibody VL of SEQ ID NOs: 63, 64, 65, 66, 67, 68, 70, 71 or 72.

53) A vector comprising the polynucleotide of claim 52.

54) A host cell comprising the vector of claim 53.

55) A method of producing an agonistic antibody specifically binding human CD40, comprising culturing the host cell of claim 54 in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.

56) Use of an isolated antibody of any of the claims 41-48 in the manufacture of a medicament for the treatment of cancer.

57) The use of claim 56, wherein the cancer is a solid tumor or a hematological malignancy.

58) The use of claim 57, wherein the solid tumor is a bladder cancer, a renal cancer, a lung cancer, a non-small cell lung cancer, a pancreatic cancer, an ovarian cancer, a breast cancer or a head and neck cancer.

59) The use of any of the claims 56-58, wherein the medicament is to be administered in combination with a second therapeutic agent.

60) The use of claim 59, wherein the second therapeutic agent is a chemotherapeutic agent, a standard of care drug for treatment of a solid tumor or a hematological malignancy, or an immune checkpoint modulator.

61) The use of claim 59 or 60, wherein the second therapeutic agent is to be administered simultaneously, sequentially or separately.

62) An anti-idiotypic antibody binding to the antibody of claim 42.

63) A kit comprising the antibody of claim 42.

64) The kit of claim 63, further comprising reagents for detecting the antibody and instructions of use.

65) The antibody of any of the claims 41-48 or the pharmaceutical composition of claim 49 or 50 for use in therapy.