

Claims

[Claim 1]

An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

(a) a light chain CDRL1 consisting of an amino acid sequence set forth in SEQ ID NO: 1;

(b) a light chain CDRL2 consisting of an amino acid sequence set forth in SEQ ID NO: 2;

(c) a light chain CDRL3 consisting of an amino acid sequence set forth in SEQ ID NO: 3;

(d) a heavy chain CDRH1 consisting of an amino acid sequence set forth in SEQ ID NO: 4;

(e) a heavy chain CDRH2 consisting of an amino acid sequence set forth in SEQ ID NO: 5; and

(f) a heavy chain CDRH3 consisting of an amino acid sequence set forth in SEQ ID NO: 6.

[Claim 2]

The antibody according to claim 1, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.

[Claim 3]

The antibody according to claim 1 or 2, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by a proline.

[Claim 4]

The antibody according to claim 3, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 140 to 466 in SEQ ID NO: 25.

[Claim 5]

An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

(ai) a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 126 in SEQ ID NO: 23; or

(aai) a light chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 21 to 126 in SEQ ID NO: 23 and having a binding activity to human SIRP α ; and

(bi) a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20 to 139 in SEQ ID NO: 25; or

(bii) a heavy chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 139 in SEQ ID NO: 25 and having a binding activity to human SIRP α ,

wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.

[Claim 6]

The antibody according to claim 5, wherein the heavy chain constant region is the heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.

[Claim 7]

The antibody according to claim 6, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 140 to 466 in SEQ ID NO: 25.

[Claim 8]

———An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

———(a) a light chain CDRL1 consisting of an amino acid sequence set forth in SEQ ID NO: 7;

———(b) a light chain CDRL2 consisting of an amino acid sequence set forth in SEQ ID NO: 8;

———(c) a light chain CDRL3 consisting of an amino acid sequence set forth in SEQ ID NO: 9;

———(d) a heavy chain CDRH1 consisting of an amino acid sequence set forth in SEQ ID NO: 10;

———(e) a heavy chain CDRH2 consisting of an amino acid sequence set forth in SEQ ID NO: 11; and

———(f) a heavy chain CDRH3 consisting of an amino acid sequence set forth in SEQ ID NO: 12.

[Claim 9]

———The antibody according to claim 8, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.

[Claim 10]

———The antibody according to claim 8 or 9, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by lanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.

[Claim 11]

———The antibody according to claim 10, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 139 to 465 in SEQ ID NO: 29.

[Claim 12]

———An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

———(ai) a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 127 in SEQ ID NO: 27; or

———(a_{ii}) a light chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 21 to 127 in SEQ ID NO: 27 and having a binding activity to human SIRP α ; and

———(bi) a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20 to 138 in SEQ ID NO: 29; or

———(b_{ii}) a heavy chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 138 in SEQ ID NO: 29 and having a binding activity to human SIRP α , wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.

[Claim 13]

———The antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47 according to claim 12, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.

[Claim 14]

———The antibody according to claim 13, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 139 to 465 in SEQ ID NO: 29.

[Claim 15]

———An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

———(a) a light chain CDRL1 consisting of an amino acid sequence set forth in SEQ ID NO: 13;

—— (b) a light chain CDRL2 consisting of an amino acid sequence set forth in SEQ ID NO: 14;

—— (c) a light chain CDRL3 consisting of an amino acid sequence set forth in SEQ ID NO: 15;

—— (d) a heavy chain CDRH1 consisting of an amino acid sequence set forth in SEQ ID NO: 16;

—— (e) a heavy chain CDRH2 consisting of an amino acid sequence set forth in SEQ ID NO: 17; and

—— (f) a heavy chain CDRH3 consisting of an amino acid sequence set forth in SEQ ID NO: 18.

[Claim 16]

—— The antibody according to claim 15, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCCP activity.

[Claim 17]

—— The antibody according to claim 15 or 16, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.

[Claim 18]

—— The antibody according to claim 17, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 144 to 470 in SEQ ID NO: 33.

[Claim 19]

—— An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody comprising:

—— (ai) a light chain variable region consisting of an amino acid sequence consisting of amino acid residues 21 to 130 in SEQ ID NO: 31; or

~~—— (aii) a light chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 21 to 130 in SEQ ID NO: 31 and having a binding activity to human SIRP α ; and~~
~~—— (bi) a heavy chain variable region consisting of an amino acid sequence consisting of amino acid residues 20 to 143 in SEQ ID NO: 33; or~~
~~—— (bii) a heavy chain variable region consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 143 in SEQ ID NO: 33 and having a binding activity to human SIRP α ,~~
~~—— wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.~~

[Claim 20]

~~—— The antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47 according to claim 19, wherein the heavy chain constant region is the heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.~~

[Claim 21]

~~—— The antibody according to claim 20, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 144 to 470 in SEQ ID NO: 33.~~

[Claim 22]

The antibody according to any one of claims 1 to 4, which is any of the following (1) to (8):

(1) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 41; and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 37;

(2) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 41 and having a binding activity to human SIRP α ; and a light chain consisting of an amino acid sequence having at least 95% sequence identity with amino acid residues 21 to 234 in SEQ ID NO: 37 and having a binding activity to human SIRP α ;

(3) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 41; and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 39;

(4) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 41 and having a binding activity to human SIRP α ; and a light chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 39 and having a binding activity to human SIRP α ;

(5) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 43; and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 35;

(6) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 43 and having a binding activity to human SIRP α ; and a light chain consisting of an amino acid sequence having at least 95% sequence

identity with the amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 35 and having a binding activity to human SIRP α ;

(7) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 43; and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 37; and

(8) an antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, the antibody consisting of: a heavy chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 20 to 466 in SEQ ID NO: 43 and having a binding activity to human SIRP α ; and a light chain consisting of an amino acid sequence having at least 95% sequence identity with the amino acid sequence consisting of amino acid residues 21 to 234 in SEQ ID NO: 37 and having a binding activity to human SIRP α .

[Claim 23]

The antibody according to claim 22, wherein the ADCC and/or ADCP activity is reduced.

[Claim 24]

~~—An antibody that binds specifically to human SIRP α to inhibit binding of human SIRP α to CD47, wherein the antibody binds to an epitope comprising Gln at position 82, Lys at position 83, Glu at position 84, and Gly at position 85 in human SIRP α set forth in SEQ ID NO: 57.~~

[Claim 25]

~~—The antibody according to claim 24, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and has a mutation that reduces an ADCC and/or ADCP activity.~~

[Claim 26]

~~—The antibody according to claim 24 or 25, wherein a heavy chain constant region is a heavy chain constant region of human IgG4, and phenylalanine at position 234, as numbered~~

~~according to the EU index as in Kabat et al., is substituted by alanine, leucine at position 235 is substituted by alanine, and serine at position 228 is substituted by proline.~~

~~{Claim 27}~~

~~—— The antibody according to claim 26, wherein an amino acid sequence of the heavy chain constant region is an amino acid sequence consisting of amino acid residues 140 to 466 in SEQ ID NO: 25.~~

~~{Claim 28}~~

~~—— The antibody according to any one of claims 1 to 27, which enhances a phagocytic activity of a macrophage.~~

~~{Claim 29}~~

~~—— The antibody according to any one of claims 1 to 28, wherein a lysine residue at the carboxyl terminus of the heavy chain is deleted.~~

~~{Claim 30}~~

~~—— An antigen binding fragment of the antibody according to any one of claims 1 to 29.~~

~~{Claim 31}~~

~~—— The antigen binding fragment of the antibody according to claim 30, wherein the antigen binding fragment is selected from the group consisting of Fab, F(ab')₂, Fab', and scFv.~~

~~{Claim 32}~~

~~—— A pharmaceutical composition comprising the antibody according to any one of claims 1 to 29 or the antigen binding fragment of the antibody according to claim 30 or 31 as an active ingredient.~~

~~{Claim 33}~~

~~—— The pharmaceutical composition according to claim 32, wherein the pharmaceutical composition is an anti-tumor agent.~~

~~{Claim 34}~~

~~—— The pharmaceutical composition according to claim 33, further comprising an immune checkpoint inhibitor and/or an antibody drug that specifically responds to a cancer antigen to have the ADCC and/or ADCP activity as an active ingredient of the anti-tumor agent.~~

~~{Claim 35}~~

~~—— A pharmaceutical composition used in combination with an immune checkpoint inhibitor and/or an antibody drug that specifically responds to a cancer antigen to have the ADCC and/or ADCP activity, wherein the pharmaceutical composition comprises the antibody according to any one of claims 1 to 29 or the antigen binding fragment of the antibody according to claim 30 or 31 as an active ingredient.~~

~~{Claim 36}~~

~~—— The pharmaceutical composition according to claim 34 or 35, wherein the immune checkpoint inhibitor is an inhibitor of binding of PD-L1 to PD-1 or a CTLA4 inhibitor.~~

~~{Claim 37}~~

~~—— The pharmaceutical composition according to claim 34 or 35, wherein the antibody drug that specifically responds to a cancer antigen to have the ADCC and/or ADCP activity is selected from the group consisting of an anti-CD20 antibody, an anti-HER2 antibody, and an anti-EGFR antibody.~~

~~{Claim 38}~~

~~—— The pharmaceutical composition according to any one of claims 33 to 37, wherein the tumor is one type or two or more types of tumors selected from the group consisting of carcinoma, sarcoma, lymphoma, leukemia, myeloma, germinoma, brain tumor, carcinoid, neuroblastoma, retinoblastoma, and nephroblastoma.~~

~~{Claim 39}~~

~~—— The pharmaceutical composition according to claim 38, wherein the tumor is one type or two or more types of tumors selected from the group consisting of kidney cancer, melanoma, squamous cell cancer, basal cell cancer, conjunctival cancer, oral cancer, laryngeal cancer, pharyngeal cancer, thyroid cancer, lung cancer, breast cancer, esophageal cancer, gastric cancer, duodenal cancer, small intestinal cancer, colon cancer, rectal cancer, appendix cancer, anal cancer, liver cancer, gallbladder cancer, biliary cancer, pancreatic cancer, adrenal cancer, bladder cancer, prostate cancer, uterine cancer, vaginal cancer, liposarcoma, angiosarcoma, chondrosarcoma, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, undifferentiated pleomorphic sarcoma, myxofibrosarcoma, malignant peripheral neurilemmoma, retroperitoneal sarcoma, synoviosarcoma, uterine sarcoma, gastrointestinal~~

~~stromal tumor, leiomyosarcoma, epithelioid sarcoma, B-cell lymphoma, NK/T-cell lymphoma, Hodgkin's lymphoma, myeloid leukemia, lymphatic leukemia, myeloproliferative disease, myelodysplastic syndrome, multiple myeloma, testicular cancer, ovarian cancer, neuroglioma, and meningioma.~~

~~[Claim 40]~~

~~—— A polynucleotide consisting of nucleotide sequences encoding amino acid sequences of a heavy chain and a light chain of the antibody according to any one of claims 1 to 29.~~

~~[Claim 41]~~

~~—— A vector comprising the polynucleotide according to claim 40.~~

~~[Claim 42]~~

~~—— A host cell comprising the polynucleotide according to claim 40 or the vector according to claim 41.~~

~~[Claim 43]~~

~~—— A method for producing the antibody according to any one of claims 1 to 29, comprising culturing the host cell according to claim 42 and purifying an antibody from the culture.~~

~~[Claim 44]~~

~~—— An antibody produced by the method according to claim 43.~~