Claims

[Claim 1]
An antibody or a functional fragment thereof that specifically binds to the amino acid sequence shown in SEQ ID NO: 4 and has internalization ability to be uptaken in cells.

[Claim 2]
The antibody or the functional fragment thereof according to claim 1, wherein the antibody or the functional fragment thereof has competitive inhibitory activity, for binding to the amino acid sequence shown in SEQ ID NO: 4, against at least one antibody selected from the group consisting of the following (1) to (5):
(1) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 53 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 56,
(2) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,
(3) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,
(4) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(5) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SED NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 3]

The antibody or the functional fragment thereof according to claim 1 or 2, wherein the antibody or the functional fragment thereof comprises a CDRL1, a CDRL2 and a CDRL1, and a CDRH1, a CDRH2 and a CDRH3 selected from the group consisting of (1) to (5):

(1) CDRL1 which consists of the amino acid sequence set forth in SEQ ID NO 12, CDRL2 which consists of the amino acid sequence set forth in SEQ ID NO 13, and CDRL3 which consists of the amino acid sequence set forth in SEQ ID NO 14 -- and CDRH1 which consists of the amino acid sequence set forth in SEQ ID NO 17, CDRH2 which consists of the amino acid sequence set forth in SEQ ID NO 18, and CDRH3 which consists of the amino acid sequence set forth in SEQ ID NO 19,

(2) CDRL1 which consists of the amino acid sequence set forth in SEQ ID NO 22, CDRL2 which consists of the amino acid sequence set forth in SEQ ID NO 23, and CDRL3 which consists of the amino acid sequence set forth in SEQ ID NO 24 -- and CDRH1 which consists of the amino acid sequence set forth in SEQ ID NO 27, CDRH2 which consists of the amino acid sequence set forth in SEQ ID NO 28, and CDRH3 which consists of the amino acid sequence set forth in SEQ ID NO 29,

(3) CDRL1 which consists of the amino acid sequence set forth in SEQ ID NO 32, CDRL2 which consists of the amino acid sequence set

forth in SEQ ID NO 33, and CDRL3 which consists of the amino acid sequence set forth in SEQ ID NO 34 -- and CDRH1 which consists of the amino acid sequence set forth in SEQ ID NO 37, CDRH2 which consists of the amino acid sequence set forth in SEQ ID NO 38, and CDRH3 which consists of the amino acid sequence set forth in SEQ ID NO 39,

(4) CDRL1 which consists of the amino acid sequence set forth in SEQ ID NO 42, CDRL2 which consists of the amino acid sequence set forth in SEQ ID NO 43, and CDRL3 which consists of the amino acid sequence set forth in SEQ ID NO 44 -- and CDRH1 which consists of the amino acid sequence set forth in SEQ ID NO 47, CDRH2 which consists of the amino acid sequence set forth in SEQ ID NO 48, and CDRH3 which consists of the amino acid sequence set forth in SEQ ID NO 49, and

(5) CDRL1 which consists of the amino acid sequence set forth in SEQ ID NO 12, CDRL2 which consists of the amino acid sequence set forth in SEQ ID NO 13, and CDRL3 which consists of the amino acid sequence set forth in SEQ ID NO 14 and CDRH1 which consists of the amino acid sequence set forth in SEQ ID NO 17, CDRH2 which consists of the amino acid sequence set forth in SEQ ID NO 60, and CDRH3 which consists of the amino acid sequence set forth in SEQ ID NO 19.

[Claim 4]

The antibody or the functional fragment according to any one of claims 1 to 3, wherein the antibody or the functional fragment is humanized.

[Claim 5]

The antibody or the functional fragment according to any one of claims 1 to 4, wherein the antibody or the functional fragment comprises a heavy chain variable region and a light chain variable region selected from the group consisting of (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 63 and a heavy chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 71;
(2) a light chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 63 and a heavy chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 75;
(3) a light chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 67 and a heavy chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 75; and
(4) a light chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 63 and a heavy chain variable region consisting of the amino acid sequence set forth in SEQ ID NO : 79.

[Claim 6]

The antibody or the functional fragment according to any one of claims 1 to 5, wherein the antibody or the functional fragment comprises a heavy chain and a light chain selected from the group consisting of (1) to (4):

(1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69;

(2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73;

(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73; and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 61 and a heavy chain consisting of the amino acid sequence at positions in 20 to 471 of SEQ ID NO: 77.

[Claim 7]

The antibody or the functional fragment thereof according to claim 6, comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

[Claim 8]

The antibody or the functional fragment thereof according to claim 6, comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting

of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 9]

The antibody or the functional fragment thereof according to claim 6, comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 of SEQ ID NO: 73.

[Claim 10]

The antibody or the functional fragment thereof according to claim 6, comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 of SEQ ID NO: 77.

[Claim 11]

The functional fragment of the antibody according to any one of claims 1 to 10, wherein the functional fragment is selected from the group consisting of Fab, F (ab′)2, Fab′ and Fv.

[Claim 12]

A polynucleotide encoding the antibody or the functional fragment thereof according to any one of claims 1 to 11.

[Claim 13]

The polynucleotide of claim 12, comprising a polynucleotide of any one of the group consisting of (1) to (5):

(1) a polynucleotide which encodes a light chain variable region comprising CDRL1 consisting of the amino acid sequence set forth in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence set forth in SEQ ID NO: 13 and CDRL3 consisting of the amino acid sequence set forth in SEQ ID NO 14, and a polynucleotide which encodes a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence set forth in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence set forth in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence set forth in and SEQ ID NO 19;

(2) a polynucleotide which encodes a light chain variable region comprising CDRL1 consisting of the amino acid sequence set forth in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence set forth in SEQ ID NO: 23 and CDRL3 consisting of the amino acid sequence set forth in SEQ ID NO 24, and a polynucleotide which encodes a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence set forth in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence set forth in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence set forth in and SEQ ID NO 29;

(3) a polynucleotide which encodes a light chain variable region comprising CDRL1 consisting of the amino acid sequence set forth in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence set forth in SEQ ID NO: 33 and CDRL3 consisting of the amino acid sequence set forth in SEQ ID NO 34, and a polynucleotide which encodes a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence set forth in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence set forth in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence set forth in and SEQ ID NO 39;

(4) a polynucleotide which encodes a light chain variable region comprising CDRL1 consisting of the amino acid sequence set forth in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence set forth in SEQ ID NO: 43 and CDRL3 consisting of the amino acid sequence set forth in SEQ ID NO 44, and a polynucleotide which encodes a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence set forth in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence set forth in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence set forth in and SEQ ID NO 49; and

(5) a polynucleotide which encodes a light chain variable region comprising CDRL1 consisting of the amino acid sequence set forth in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence set forth in SEQ ID NO: 13 and CDRL3 consisting of the amino acid sequence set forth in SEQ ID NO 14, and a polynucleotide which encodes a heavy chain variable region comprising CDRH1 consisting of the amino acid sequence set forth in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence set forth in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence set forth in and SEQ ID NO 19.

[Claim 14]

The polynucleotide according to claim 12 or 13, comprising a polynucleotide which encodes a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide which encodes a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

[Claim 15]

The polynucleotide according to claim 12 or 13, comprising a polynucleotide which encodes a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide which encodes a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 16]

The polynucleotide according to claim 12 or 13, comprising a polynucleotide which encodes a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a polynucleotide which encodes a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

[Claim 17]

The polynucleotide according to claim 12 or 13, comprising a polynucleotide which encodes a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a polynucleotide which encodes a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 18]

An expression vector comprising the polynucleotide according to any one of claims 12 to 17.

[Claim 19]

A host cell transformed with an expression vector according to claim 18.

[Claim 20]

The host cell according to claim 19, wherein the host cell is a eukaryotic cell.

[Claim 21]

A method for producing an antibody or a functional fragment thereof comprising a step of culturing the host cell according to claim 19 or 20 and a step of collecting the antibody or the functional fragment thereof from the culture obtained in the previous step.

[Claim 22]

The antibody or the functional fragment thereof according to any one of claims 1 to 11, wherein a heavy chain or light chain has undergone 1 or 2 or more modifications selected from the group consisting of glycosylation to an N-linkage, glycosylation to an O-linkage, processing of an N-terminus, processing of a C-terminus, deamidation, isomerization of an aspartic acid, oxidation of a methionine, addition of a methionine residue to an N-terminus, amidation of a proline residue, conversion of an N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and deletion of one or two amino acids at the carboxyl terminus.

[Claim 23]

The antibody or the functional fragment thereof according to claim 22, wherein a heavy chain has undergone deletion of one or two amino acids at the carboxyl terminus.

[Claim 24]

The antibody or the functional fragment thereof according to claim 22, wherein both heavy chains have undergone deletion of one amino acids at the carboxyl terminus.

[Claim 25]

The antibody or the functional fragment thereof according to any one of claims 22 to 24, wherein the proline residue at the carboxyl terminus of a heavy chain is further amidated.

[Claim 26]

The antibody or the functional fragment thereof according to any one of claims 1 to 11 and 22 to 25, wherein the sugar chain modification of the antibody or the functional fragment thereof is modulated to enhance antibody-dependent cellular cytotoxicity.

[Claim 27]

An antibody-drug conjugate, wherein a drug is bound to the antibody or functional fragment thereof according to any one of claims 1 to 11 and 22 to 26.

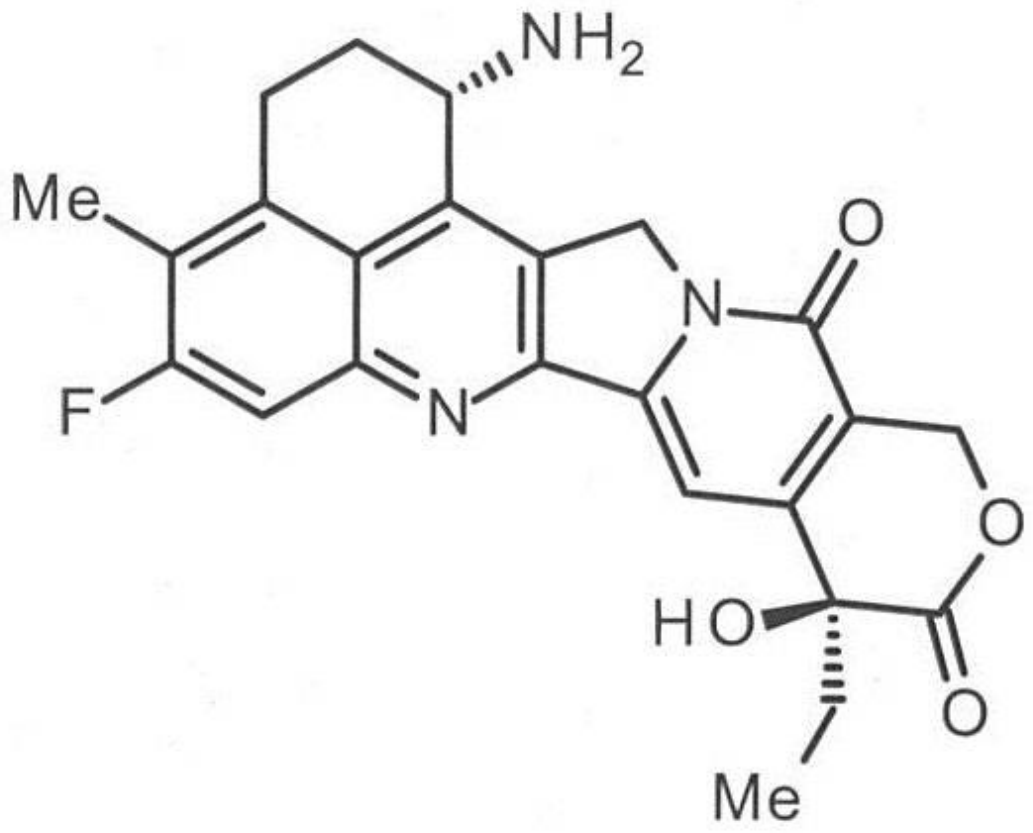
[Claim 28]

The antibody-drug conjugate according to claim 27, wherein the drug is an antitumor compound.

[Claim 29]

The antibody-drug conjugate according to claim 28, wherein the antitumor compound has the following formula:

[Chemical formula 1]



[Claim 30]

The antibody-drug conjugate according to any one of claims 27 to 29, wherein the antibody is conjugated to the drug via a linker having any structure selected from the group consisting of the following formulas (a) to (f):

(a) -(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-;

(b) -(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-;

(c)-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-;

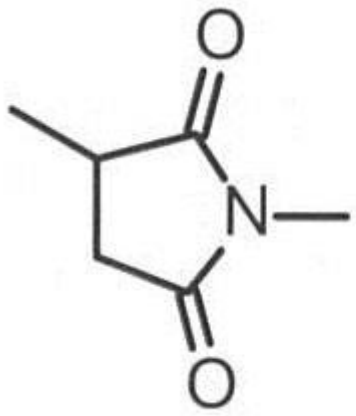
(d)-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-O-CH_2-C(=O)-;

(e)-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-; and

(f)-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-,

(wherein the antibody is conjugated at the end of -(Succinimid-3-yl-N), the antitumor compound is bound to the carbonyl group of the -$CH_2CH_2CH_2$-C(=O)-moiety of (a), (b), (e), or (f), the CH_2-O-CH_2-C(=O)-moiety of (c), or the CH_2CH_2-O-CH_2-C(=O)- moiety of (d) with the nitrogen atom of an amino group at position 1 as a connecting position, GGFG in the above formulas represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine linked through peptide bonds, and -(Succinimid-3-yl-N)- as represented by the following formula is connected to the antibody at position 3 thereof, and is connected to a methylene group in the linker structure containing this structure on the nitrogen atom at position 1.).

[Chemical formula 2]



[Claim 31]

The antibody-drug conjugate according to any one of claims 27 to 30, wherein the linker is represented by any formula selected from the group consisting of (c), (d) and (e):

(c)-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-;

(d)-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2CH_2-O-CH_2-C(=O)-; and

(e)-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-.

[Claim 32]

The antibody-drug conjugate according to any one of claims 27 to 31, wherein the linker is represented by the following formula (c) or (e):

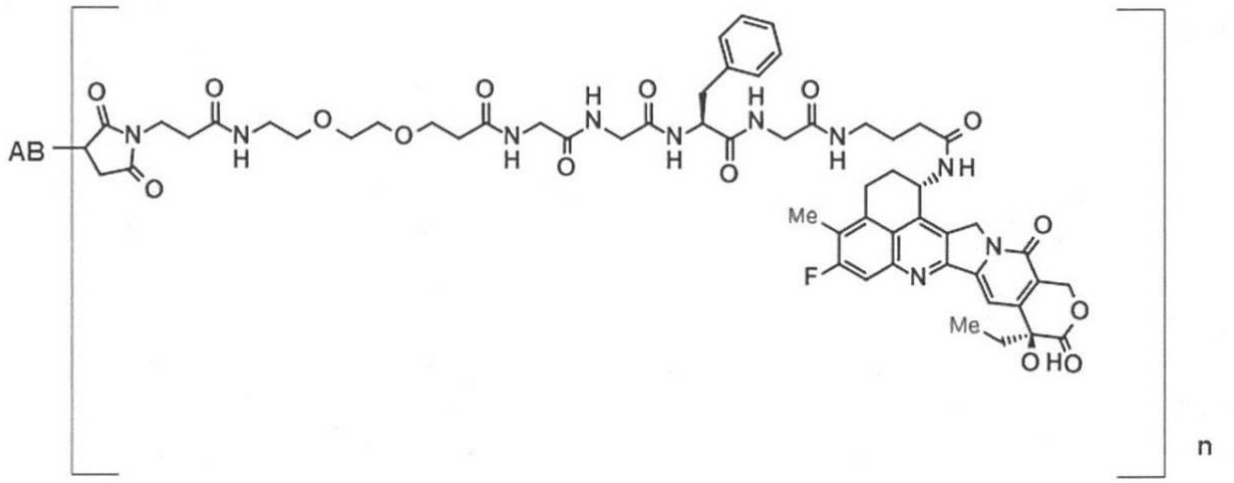
(c)-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-; and

(e)-(Succinimid-3-yl-N)-CH_2CH_2-C(=O)-NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C(=O)-GGFG-NH-$CH_2CH_2CH_2$-C(=O)-.

[Claim 33]

The antibody-drug conjugate according to any one of claims 27 to 32, having the structure shown in the following formula:

[Chemical formula 3]

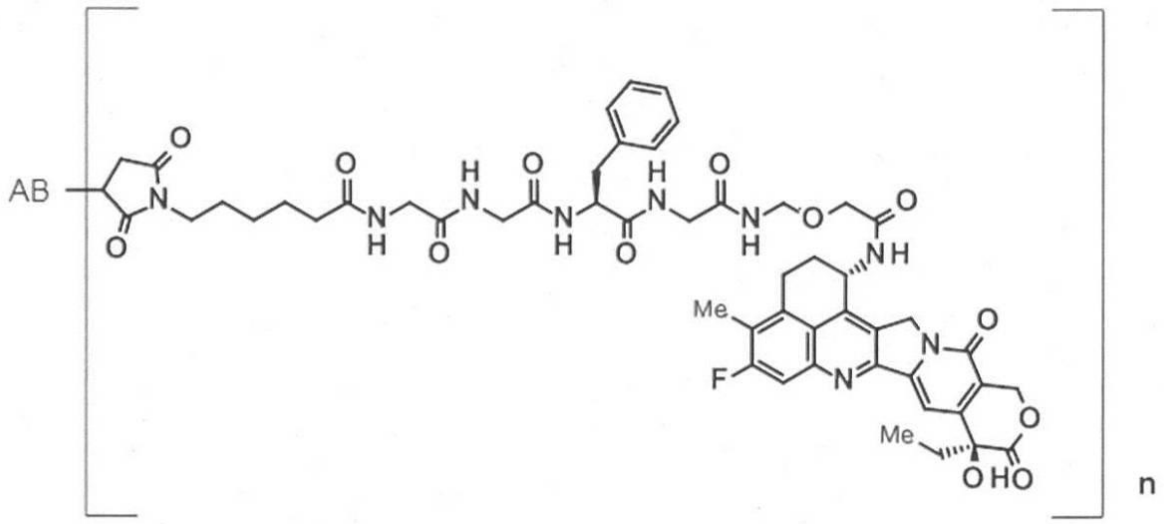


wherein AB represents an antibody or a functional fragment thereof, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

[Claim 34]

The antibody-drug conjugate according to any one of claims 27 to 32, having the structure shown in the following formula:

[Chemical formula 4]



wherein AB represents an antibody or a functional fragment thereof, n represents the average number of units of the drug-linker structure conjugated to the antibody per antibody, and the antibody is connected to the linker via a sulfhydryl group derived from the antibody.

[Claim 35]

The antibody-drug conjugate according to any one of claims 27 to 34, wherein the antibody is an antibody or a functional fragment thereof comprising a heavy chain and a light chain selected from the group consisting of the following (1) to (4):

(1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69;

(2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73 ;

(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO : 73 ; and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO : 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO : 77.

[Claim 36]

The antibody-drug conjugate according to claim 35, wherein the antibody is an antibody or a functional fragment thereof comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

[Claim 37]

The antibody-drug conjugate according to claim 35, wherein the antibody is an antibody or a functional fragment thereof comprising a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

[Claim 38]

The antibody-drug conjugate according to any one of claims 27 to 37, wherein a heavy chain or light chain has undergone 1 or 2 or more modifications selected from the group consisting of glycosylation to an N-linkage, glycosylation to an O-linkage, processing of an N-terminus, processing of a C-terminus, deamidation, isomerization of an aspartic acid, oxidation of a methionine, addition of a methionine residue to an N-terminus, amidation of a proline residue, conversion of an N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and deletion of one or two amino acids at the carboxyl terminus.

[Claim 39]

The antibody-drug conjugate according to any one of claims 27 to 38, wherein the average number of the selected drug-linker structures conjugated per antibody is in the range of 1 to 10.

[Claim 40]

The antibody-drug conjugate according to any one of claims 39, wherein the average number of the selected drug-linker structures conjugated per antibody is in the range of 2 to 8.

[Claim 41]

The antibody-drug conjugate according to claim 40, wherein the average number of the selected drug-linker structures conjugated per antibody is in the range of 5 to 8.

[Claim 42]

The antibody-drug conjugate according to claim 41, wherein the average number of the selected drug-linker structures conjugated per antibody is in the range of 7 to 8.

[Claim 43]

A pharmaceutical composition comprising the antibody-drug conjugate according to any one of claims 27 to 42, a salt thereof, or a hydrate thereof.

[Claim 44]

The pharmaceutical composition according to claim 43, wherein the pharmaceutical composition is characterized to be an antitumor agent.

[Claim 45]

The pharmaceutical composition according to claim 44, wherein the tumor is a tumor expressing CDH6.

[Claim 46]

The pharmaceutical composition according to claim 44 or 45, wherein the tumor is renal cell carcinoma, clear cell renal cell carcinoma, papillary renal cell carcinoma, ovarian cancer, ovary serous adenocarcinoma, thyroid cancer, bile duct cancer, lung cancer, small-cell lung cancer, glioblastoma, mesothelioma, uterine cancer, pancreatic cancer, Wilms' tumor, or neuroblastoma.

[Claim 47]

A method for producing an antibody-drug conjugate comprising a step of reacting with a drug-linker intermediate compound any one of the antibody or the functional fragment thereof selected from the group consisting of claims 1 to 11 and 22 to 26 or an antibody or a functional fragment thereof obtained by the method according to claim 21.