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Summary

[0011A] In one aspect, the present invention refers to a method for producing an antibody-drug conjugate, in

which a drug-linker structure represented by the following formula is conjugated to an anti-TROP2 antibody via a thioether bond which is formed at a disulfide bond moiety present in the hinge part of the anti-TROP2 antibody,

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX),

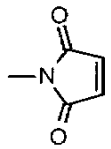
comprising a step of

treating the antibody in a reducing condition and thereafter

reacting the antibody with a compound represented by the following formula:

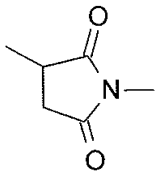
(maleimid-N-yl)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX) wherein,

(maleimid-N-yl)- is a group represented by the following formula:



wherein the nitrogen atom is a connecting position,

-(Succinimid-3-yl-N)- has a structure represented by the following formula:



which 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,

Claims

[Claim 1]

A method for producing an antibody-drug conjugate, in which a drug-linker structure represented by the following formula is conjugated to an anti-TROP2 antibody via a thioether bond which is formed at a disulfide bond moiety present in the hinge part of the anti-TROP2 antibody,

-(Succinimid-3-yl-N)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX),

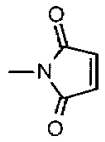
comprising a step of

treating the antibody in a reducing condition and thereafter

reacting the antibody with a compound represented by the following formula:

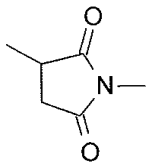
(maleimid-N-yl)-$CH_2CH_2CH_2CH_2CH_2$-C(=O)-GGFG-NH-CH_2-O-CH_2-C(=O)-(NH-DX) wherein,

(maleimid-N-yl)- is a group represented by the following formula:



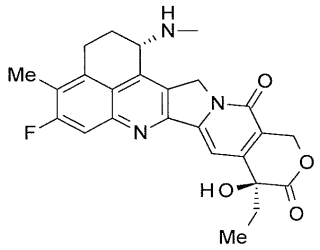
wherein the nitrogen atom is a connecting position,

-(Succinimid-3-yl-N)- has a structure represented by the following formula:



which 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,

-(NH-DX) represents a group represented by the following formula:



wherein the nitrogen atom of the amino group at position 1 is a connecting position, and

-GGFG- represents a tetrapeptide residue of -Gly-Gly-Phe-Gly-.

[Claim 2]

The method according to claim 1, wherein an average number of units of the drug-linker structure conjugated per antibody is in a range of from 2 to 8.

[Claim 3]

The method according to claim 1, wherein an average number of units of the drug-linker structure conjugated per antibody is in a range of from 3 to 8.

[Claim 4]

The method according to any one of claims 1 to 3, wherein the anti-TROP2 antibody comprises CDRH1 consisting of the amino acid sequence of SEQ ID NO: 23, CDRH2 consisting of the amino acid sequence of SEQ ID NO: 24 and CDRH3 consisting of the amino acid sequence of SEQ ID NO: 25 in its heavy chain variable region and CDRL1 consisting of the amino acid sequence of SEQ ID NO: 26, CDRL2 consisting of the amino acid sequence of SEQ ID NO: 27 and CDRL3 consisting of the amino acid sequence of SEQ ID NO: 28 in its light chain variable region.

[Claim 5]

The method according to any one of claims 1 to 3, wherein the anti-TROP2 antibody comprises a heavy chain variable region and a light chain variable region selected from the group;

a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 12 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 18,

a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 14 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 SEQ ID NO: 18,

a heavy chain variable region consisting of the amino acid sequence of positions of 20 to 140 of SEQ ID NO:

14 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 20, and
a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 16 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 22.

[Claim 6]

The method according to any one of claims 1 to 3, wherein the anti-TROP2 antibody comprises a heavy chain and a light chain selected from the group;
a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 12 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18,
a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 14 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18,
a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 14 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 20, and
a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 16 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 22.

[Claim 7]

The method according to claim 5, wherein the anti-TROP2 antibody comprises a heavy chain variable region consisting of the amino acid sequence of positions 20 to 140 of SEQ ID NO: 12 and a light chain variable region consisting of the amino acid sequence of positions 21 to 129 of SEQ ID NO: 18.

[Claim 8]

The method according to claim 6, wherein the anti-TROP2 antibody comprises a heavy chain consisting of the amino acid sequence of positions 20 to 470 of SEQ ID NO: 12 and a light chain consisting of the amino acid sequence of positions 21 to 234 of SEQ ID NO: 18.

[Claim 9]

The method according to claim 6, wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.

[Claim 10]

The method according to claim 8, wherein the anti-TROP2 antibody lacks a lysine residue at the carboxyl terminus of the heavy chain.