

The sequence alignment of CLDN3, CLDN4, CLDN6 and CLDN9 shown in Fig. 1B illustrates that there is a high degree of conservation of CLDN6 to other claudin proteins. This high homology of CLDN6 with other claudin proteins, in particular CLDN9 and CLDN4, render it difficult to provide CLDN6 antibodies which have properties such as specificity and affinity suitable for diagnostic purposes. The present inventors found that antibodies directed against a certain epitope located within the C-terminal portion of CLDN6 fulfill the criteria for the diagnostic applicability of antibodies, in particular for detecting and identifying cells expressing CLDN6.

The antibodies of the invention are useful, for example, in diagnosing cancer and/or in determining whether cancer cells express CLDN6. Preferably, a cancer disease or a cancer cell is characterized by surface expression of CLDN6. Cancer cells expressing CLDN6 are suitable targets for therapies targeting CLDN6 such as therapy with antibodies directed against CLDN6. In one embodiment, cancer cells express or aberrantly express CLDN6 while the corresponding normal cells do not express CLDN6 or express CLDN6 at a lower level.

Summary

In one aspect, the present disclosure relates to an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment comprises:

an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or an amino acid substitution variant thereof, wherein the amino acid substitution variant comprises one substitution, wherein the substitution is Ile at position 3 substituted by an uncharged amino acid;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or an amino acid substitution variant thereof, wherein the amino acid substitution variant comprises from one to three substitutions selected from the group consisting of Phe at position 2 substituted by an aromatic amino acid, Gly at

position 4 substituted by an acidic or uncharged polar amino acid, Thr at position 8 substituted by an uncharged amino acid, and a combination thereof; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
an antibody light chain variable region (VL) comprising:

5 a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; and

which binds:

10 (i) to a peptide having the amino acid sequence EYPTKNY (SEQ ID NO: 38),
and/or

(ii) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence EYPTKNY (SEQ ID NO: 38), and/or

15 (iii) to a peptide having the amino acid sequence EYPTKNYV (SEQ ID NO: 29),
and/or

(iv) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence EYPTKNYV (SEQ ID NO: 29), and/or

20 (v) to a peptide having the amino acid sequence AISRGPSEYPTKNYV (SEQ ID NO: 15), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide having the amino acid sequence TSAPAIRGPSEYPT (SEQ ID NO: 14),
and/or

25 (vi) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence AISRGPSEYPTKNYV (SEQ ID NO: 15), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide having the amino acid sequence TSAPAIRGPSEYPT (SEQ ID NO: 14), and/or

(vii) to one or more of the following peptides:

30 PAIRGPSEYPTKNY (SEQ ID NO: 22), AISRGPSEYPTKNYV (SEQ ID NO: 15),
ISRGPSYPTKNYV (SEQ ID NO: 23), SRGPSEYPTKNYV (SEQ ID NO: 24),
RGPSEYPTKNYV (SEQ ID NO: 25), GPSEYPTKNYV (SEQ ID NO: 26), PSEYPTKNYV (SEQ

ID NO: 27), SEYPTKNYV (SEQ ID NO: 28), and EYPTKNYV (SEQ ID NO: 29), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide having the amino acid sequence TSAPAISRGPSYPT (SEQ ID NO: 14).

5 In another aspect, the present disclosure relates to a method for detecting CLDN6 or the quantity of CLDN6 in a sample comprising the steps of:

- (i) contacting a sample with the antibody or antigen-binding fragment as described herein and
- (ii) detecting the formation of a complex or the quantity of a complex between the antibody or the antigen-binding fragment and CLDN6.

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In another aspect, the present disclosure relates to a method for detecting cells that express CLDN6 comprising the steps of:

- (i) contacting a cellular sample with the antibody or antigen-binding fragment as described herein and
- 15 (ii) detecting the formation of a complex between the antibody or the antigen-binding fragment and CLDN6 expressed by cells in said sample.

In another aspect, the present disclosure relates to a method for diagnosis, detection or monitoring of CLDN6-expressing cancer cells comprising the steps of:

- 20 (i) contacting a biological sample with the antibody or antigen-binding fragment as described herein and (ii) detecting the formation of a complex and/or the quantity of a complex between the antibody or the antigen-binding fragment and CLDN6.

25 In one example, the present disclosure relates to an antibody or antigen-binding fragment thereof, which binds:

- (i) to a peptide having the amino acid sequence EYPTKNY (SEQ ID NO: 38), and/or

- (ii) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment
30 thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence EYPTKNY (SEQ ID NO: 38), and/or

(iii) to a peptide having the amino acid sequence EYPTKNYV (SEQ ID NO: 29),
and/or

(iv) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment
thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino
5 acid sequence EYPTKNYV (SEQ ID NO: 29), and/or

(v) to a peptide having the amino acid sequence AISRGPSEYPTKNYV (SEQ ID
NO: 15), wherein the antibody or antigen-binding fragment thereof does not bind to a
peptide having the amino acid sequence TSAPAISRGPSEYPT (SEQ ID NO: 14), and/or

(vi) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment
10 thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino
acid sequence AISRGPSEYPTKNYV (SEQ ID NO: 15), wherein the antibody or antigen-
binding fragment thereof does not bind to a peptide having the amino acid sequence
TSAPAISRGPSEYPT (SEQ ID NO: 14).

15 In examples described herein and in further examples, the present disclosure relates to
a monoclonal antibody or antigen-binding fragment thereof which

(i) binds to a peptide having the amino acid sequence AISRGPSEYPTKNYV
(SEQ ID NO: 15) and/or

(ii) binds to claudin 6 (CLDN6), wherein said antibody or antigen-binding
20 fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having
the amino acid sequence AISRGPSEYPTKNYV (SEQ ID NO: 15).

In examples described herein and in further examples, the present disclosure relates to
an antibody or antigen-binding fragment thereof, which binds to one or more,
25 preferably all, of the following peptides:

PAISRGPSEYPTKNY (SEQ ID NO: 22), AISRGPSEYPTKNYV (SEQ ID NO: 15),
ISRGPSEYPTKNYV (SEQ ID NO: 23), SRGPSEYPTKNYV (SEQ ID NO: 24), RGPSEYPTKNYV
(SEQ ID NO: 25), GPSEYPTKNYV (SEQ ID NO: 26), PSEYPTKNYV (SEQ ID NO: 27),
SEYPTKNYV (SEQ ID NO: 28), and EYPTKNYV (SEQ ID NO: 29), wherein the antibody or
30 antigen-binding fragment thereof does not bind to a peptide having the amino acid
sequence TSAPAISRGPSEYPT (SEQ ID NO: 14).

In one example, the difference in binding affinity to the peptide to which the antibody or antigen binding fragment binds with the lowest affinity and to the peptide to which the antibody or antigen binding fragment binds with the highest affinity is 50% or less, 40% or less, 30% or less, 20% or less, or 10% or less.

Antibodies or antigen-binding fragments described herein preferably do not bind to a peptide comprising the amino acid sequence EYPTK (SEQ ID NO: 59) and/or the amino acid sequence EYPTKN (SEQ ID NO: 60) but not comprising the amino acid sequence EYPTKNY (SEQ ID NO: 38). In other words, an antibody or antigen-binding fragment described herein which binds to a peptide having the amino acid sequence EYPTKNY (SEQ ID NO: 38) and/or a peptide having the amino acid sequence EYPTKNYV (SEQ ID NO: 29) binds to said peptide(s) due to the presence of the second tyrosine which is missing in the amino acid sequence EYPTK (SEQ ID NO: 59) and/or the amino acid sequence EYPTKN (SEQ ID NO: 60). As shown herein, preferred antibodies or antigen-binding fragments do not bind to a peptide comprising the amino acid sequence YPTKNY (SEQ ID NO: 61) and/or EYPTKN (SEQ ID NO: 60) but not comprising the amino acid sequence EYPTKNY (SEQ ID NO: 38) suggesting that the amino acid sequence EYPTKNY (SEQ ID NO: 38) is a sequence that can be considered to be a minimal epitope for binding of these antibodies.

In examples described herein and in further examples, the present disclosure relates to an antibody produced by or obtainable from a hybridoma deposited at the DSMZ (Inhoffenstr. 7B, 38124 Braunschweig, Germany) and having one of the following designations and accession numbers:

1. 58-4B-2, accesssion no. DSM ACC3311, deposited on November 29, 2016;
2. 58-3A, accesssion no. DSM ACC3312, deposited on November 29, 2016; or
3. 58-1B, accesssion no. DSM ACC3313, deposited on November 29, 2016.

Antibodies of the disclosure are designated herein by referring to the designation of the antibody and/or by referring to the clone producing the antibody.

The present disclosure also relates to an antibody which competes for CLDN6 binding with an antibody produced by and obtainable from the above-described hybridomas and/or has the specificity for CLDN6 of an antibody produced by or obtainable from the above-described hybridomas. In these and other example, the present disclosure also relates to an antibody comprising an antigen binding portion or antigen binding site, in particular a variable region, identical or highly homologous to that of the antibodies produced by or obtainable from the above-described hybridomas. It is contemplated that preferred antibodies are those having CDR regions either identical or highly homologous to the CDR regions of antibodies produced by or obtainable from the above-described hybridomas. By "highly homologous" it is contemplated that from 1 to 5, preferably from 1 to 4, such as 1 to 3 or 1 or 2 substitutions may be made in each CDR region. Particularly preferred antibodies are the chimerized and humanized forms of the antibodies produced by or obtainable from the above-described hybridomas.

Accordingly, in examples described herein and in further examples, the present disclosure relates to an antibody selected from the group consisting of:

- (i) an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2),
 - (ii) an antibody which is a chimerized or humanized form of the antibody under (i),
 - (iii) an antibody which competes for CLDN6 binding with an antibody under (i),
 - (iv) an antibody which has the specificity of the antibody under (i),
- and
- (v) an antibody comprising the antigen binding portion or antigen binding site of the antibody under (i), or
- an antigen-binding fragment of the antibody under any one of (i) to (v).

In one example, the antigen binding portion or antigen binding site of the antibody under (i) comprises the variable region of the antibody under (i).

In examples described herein and in further examples, the present disclosure relates to an antibody selected from the group consisting of:

(a) an antibody comprising:

an antibody heavy chain comprising:

- 5 (i) an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, 42, or 44, or a variant thereof,
- (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, 42, or 44, or a variant thereof, or
- 10 (iii) a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 51 or 57, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 52 or 58, or a variant thereof, and
- (b) an antibody which competes for CLDN6 binding with an antibody according to (a)
- 15 and/or has the specificity for CLDN6 of an antibody according to (a),
- or an antigen-binding fragment of said antibody.

In examples described herein and in further examples, the present disclosure relates to an antibody selected from the group consisting of:

20 (a) an antibody comprising:

an antibody light chain comprising:

- (i) an antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, 43, or 45, or a variant thereof,
- (ii) at least one, preferably two, more preferably all three of the CDR sequences of an
- 25 antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, 43, or 45, or a variant thereof, or
- (iii) a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and
- 30 (b) an antibody which competes for CLDN6 binding with an antibody according to (a)
- and/or has the specificity for CLDN6 of an antibody according to (a),

or an antigen-binding fragment of said antibody.

In examples described herein and in further examples, the present disclosure relates to an antibody selected from the group consisting of:

- 5 (a) an antibody comprising:
 - (I) an antibody heavy chain comprising:
 - (i) an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, 42, or 44, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an
10 antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, 42, or 44, or a variant thereof, or
 - (iii) a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 51 or 57, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 52 or 58, or a variant thereof,
15 and/or
 - (II) an antibody light chain comprising:
 - (i) an antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, 43, or 45, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an
20 antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, 43, or 45, or a variant thereof, or
 - (iii) a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and
- 25 (b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a),
or an antigen-binding fragment of said antibody.

In certain preferred examples, the present disclosure relates to an antibody selected
30 from the group consisting of:

- (a) an antibody comprising:

- (I) an antibody heavy chain comprising:
 - (i) an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 40, or a variant thereof, or
 - (iii) a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 51, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 52, or a variant thereof, and
- (II) an antibody light chain comprising:
 - (i) an antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody light chain sequence comprising the sequence according to SEQ ID NO: 41, or a variant thereof, or
 - (iii) a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and
- (b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

- (a) an antibody comprising:
 - (I) an antibody heavy chain comprising:
 - (i) an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 42, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 42, or a variant thereof, or

- (iii) a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 57, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 58, or a variant thereof, and
- (II) an antibody light chain comprising:
 - 5 (i) an antibody light chain sequence comprising the sequence according to SEQ ID NO: 43, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody light chain sequence comprising the sequence according to SEQ ID NO: 43, or a variant thereof, or
 - 10 (iii) a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and
 - (b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a),
 - 15 or an antigen-binding fragment of said antibody.

In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

- (a) an antibody comprising:
 - 20 (I) an antibody heavy chain comprising:
 - (i) an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 44, or a variant thereof,
 - (ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody heavy chain sequence comprising the sequence according to SEQ ID NO: 44, or
 - 25 a variant thereof, or
 - (iii) a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 57, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 58, or a variant thereof, and
 - (II) an antibody light chain comprising:
 - 30 (i) an antibody light chain sequence comprising the sequence according to SEQ ID NO: 45, or a variant thereof,

(ii) at least one, preferably two, more preferably all three of the CDR sequences of an antibody light chain sequence comprising the sequence according to SEQ ID NO: 45, or a variant thereof, or

(iii) a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and preferably further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and/or a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and

(b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

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In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

(a) an antibody comprising an antibody heavy chain comprising a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and an antibody light chain comprising a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof, and

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(b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

20 In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

(a) an antibody comprising an antibody heavy chain comprising a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and further comprising a CDR1 sequence according to SEQ ID NO: 51, or a variant thereof and a CDR2 sequence according to SEQ ID NO: 52, or a variant thereof, and an antibody light chain comprising a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and

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(b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

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In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

- 5 (a) an antibody comprising an antibody heavy chain comprising a CDR3 sequence according to SEQ ID NO: 53 or a variant thereof and further comprising a CDR1 sequence according to SEQ ID NO: 57, or a variant thereof and a CDR2 sequence according to SEQ ID NO: 58, or a variant thereof, and an antibody light chain comprising a CDR3 sequence according to SEQ ID NO: 56 or a variant thereof and further comprising a CDR1 sequence according to SEQ ID NO: 54, or a variant thereof and a CDR2 sequence according to SEQ ID NO: 55, or a variant thereof, and
- 10 (b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

15 In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

- (a) an antibody comprising a heavy chain variable region (VH) comprising an amino acid sequence represented by SEQ ID NO: 40 or a variant thereof and a light chain variable region (VL) comprising an amino acid sequence represented by SEQ ID NO: 41 or a variant thereof, and
- 20 (b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

25 In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

- (a) an antibody comprising a heavy chain variable region (VH) comprising an amino acid sequence represented by SEQ ID NO: 42 or a variant thereof and a light chain variable region (VL) comprising an amino acid sequence represented by SEQ ID NO: 43 or a variant thereof, and
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(b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

5 In certain preferred examples, the present disclosure relates to an antibody selected from the group consisting of:

(a) an antibody comprising a heavy chain variable region (VH) comprising an amino acid sequence represented by SEQ ID NO: 44 or a variant thereof and a light chain variable region (VL) comprising an amino acid sequence represented by SEQ ID NO: 45 or a
10 variant thereof, and

(b) an antibody which competes for CLDN6 binding with an antibody according to (a) and/or has the specificity for CLDN6 of an antibody according to (a), or an antigen-binding fragment of said antibody.

15 In preferred examples, an antibody of the disclosure comprises an antibody heavy chain comprising a gamma-2a heavy chain constant region, preferably a human gamma-2a heavy chain constant region and/or comprises an antibody light chain comprising a kappa light chain constant region.

20 The antibodies or antigen-binding fragments described herein bind to CLDN6. An antibody or antigen-binding fragment of the disclosure is preferably able to bind to CLDN6 in its native, i.e. naturally occurring or non-denatured state, or in its denatured state. In one example, an antibody or antigen-binding fragment thereof of the disclosure binds to CLDN6 but not to CLDN9 and preferably does not bind to CLDN4 and/or CLDN3. Preferably,
25 an antibody or antigen-binding fragment thereof of the disclosure does not substantially bind to a CLDN protein other than CLDN6. Preferably, an antibody or antigen-binding fragment thereof of the disclosure is specific for CLDN6.

In one example, CLDN6 is cell surface membrane-bound CLDN6. In one example, CLDN6
30 is present on cancer cells, wherein said cancer cells are preferably CLDN6 expressing cancer cells. In one example, said cancer cells are cells from a cancer selected from the

group consisting of ovarian cancer, in particular ovarian adenocarcinoma and ovarian teratocarcinoma, lung cancer, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), in particular squamous cell lung carcinoma and adenocarcinoma, gastric cancer, breast cancer, hepatic cancer, pancreatic cancer, skin cancer, in particular
5 basal cell carcinoma and squamous cell carcinoma, malignant melanoma, head and neck cancer, in particular malignant pleomorphic adenoma, sarcoma, in particular synovial sarcoma and carcinosarcoma, bile duct cancer, cancer of the urinary bladder, in particular transitional cell carcinoma and papillary carcinoma, kidney cancer, in particular renal cell carcinoma including clear cell renal cell carcinoma and papillary
10 renal cell carcinoma, colon cancer, small bowel cancer, including cancer of the ileum, in particular small bowel adenocarcinoma and adenocarcinoma of the ileum, testicular embryonal carcinoma, placental choriocarcinoma, cervical cancer, testicular cancer, in particular testicular seminoma, testicular teratoma and embryonic testicular cancer, uterine cancer, germ cell tumors such as a teratocarcinoma or an embryonal carcinoma,
15 in particular germ cell tumors of the testis, and the metastatic forms thereof.

In one example, an antibody of the disclosure is a chimeric, human or humanized antibody. In one example, an antibody of the disclosure is a monoclonal antibody.

In one example, an antibody of the disclosure is obtainable by a method comprising the
20 step of immunizing an animal with a peptide comprising, preferably consisting of the amino acid sequence of SEQ ID NO: 49, or an immunologically equivalent peptide, or a nucleic acid or host cell expressing said peptide. Preferably said peptide comprises not more than 110, 100, 90, 80, 70, 60, 50, or 40 contiguous amino acids of CLDN6.

25 Antibodies or antigen-binding fragments of the disclosure may be coupled, i.e. covalently or non-covalently linked, to other moieties such as detectable labels.

In a further example, the present disclosure relates to a conjugate comprising an antibody or antigen-binding fragment described herein coupled to at least one
30 detectable label.

The present disclosure also relates to a cell such as a hybridoma producing an antibody as described herein.

Preferred hybridomas are those deposited at the DSMZ (Inhoffenstr. 7B, 38124 Braunschweig, Germany) and having one of the following designations and accession numbers:

1. 58-4B-2, accesssion no. DSM ACC3311, deposited on November 29, 2016;
2. 58-3A, accesssion no. DSM ACC3312, deposited on November 29, 2016; or
3. 58-1B, accesssion no. DSM ACC3313, deposited on November 29, 2016.

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The present disclosure also relates to a peptide comprising, preferably consisting of the amino acid sequence of SEQ ID NO: 49, or an immunologically equivalent peptide. Preferably said peptide comprises not more than 110, 100, 90, 80, 70, 60, 50, or 40 contiguous amino acids of CLDN6.

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The present disclosure also relates to nucleic acids encoding antibodies or parts thereof, e.g. an antibody chain, or antigen-binding fragments, or peptides as described herein. Preferably, a nucleic acid of the disclosure is operatively attached to one or more expression control elements allowing expression in eukaryotic or prokaryotic cells. Control elements ensuring expression in eukaryotic or prokaryotic cells are well known to those skilled in the art.

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A nucleic acid of the disclosure may be comprised in a vector, e.g., a plasmid, cosmid, virus, bacteriophage or another vector used e.g. conventionally in genetic engineering.

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The vector may comprise further genes such as marker genes which allow for the selection of the vector in a suitable host cell and under suitable conditions. Furthermore, the vector may comprise expression control elements allowing proper expression of the coding regions in suitable hosts. Such control elements are known to the artisan and may include a promoter, a splice cassette, and a translation initiation codon.

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Methods for construction of nucleic acid molecules, for construction of vectors comprising nucleic acid molecules, for introduction of vectors into appropriately chosen host cells, or for causing or achieving expression of nucleic acid molecules are well-known in the art.

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A further example of the present disclosure relates to a host cell comprising a nucleic acid or vector as disclosed herein.

10 A further example the present disclosure relates to the detection of CLDN6 or CLDN6-expressing cells or determination of the quantity of CLDN6 or CLDN6-expressing cells using an antibody or antigen-binding fragment of the disclosure. CLDN6 or CLDN6-expressing cells are detected or the quantity of CLDN6 or CLDN6-expressing cells is determined by detecting or determining the amount of a complex between CLDN6 and an antibody or antigen-binding fragment of the disclosure. Formation of a complex
15 indicates the presence of CLDN6 or CLDN6-expressing cells. Such detection or determination of the amount may be carried out in a number of ways, including but not limited to immunodetection using an antibody or antigen-binding fragment of the disclosure. Methods for using antibodies to detect peptides or proteins are well known and include ELISA, competitive binding assays, and the like. In general, such assays use
20 an antibody or antibody fragment that specifically binds the target peptide or protein directly or indirectly bound to a label that provides for detection, e.g. indicator enzymes, radiolabels, fluorophores, or paramagnetic particles. The methods of the disclosure allow quantitative and/or qualitative evaluations, e.g., absolute and/or relative evaluations, of CLDN6 levels or of levels of CLDN6-expressing cells.

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In one example, the present disclosure relates to a method for detecting CLDN6 or determining the quantity of CLDN6 in a sample comprising the steps of:

- (i) contacting a sample with an antibody or antigen-binding fragment of the disclosure or a conjugate of the disclosure and
30 (ii) detecting the formation of a complex or determining the quantity of a complex between the antibody, the antigen-binding fragment or the conjugate and CLDN6.

In one example, the sample is a cellular sample, i.e. a sample comprising cells such as cancer cells. In this example, the complex is preferably formed between the antibody, the antigen-binding fragment or the conjugate and CLDN6 expressed by cells in said sample.

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In one example, the present disclosure relates to a method for determining whether cells express CLDN6 comprising the steps of:

- (i) contacting a cellular sample with an antibody or antigen-binding fragment of the disclosure or a conjugate of the disclosure and
- 10 (ii) detecting the formation of a complex between the antibody, the antigen-binding fragment or the conjugate and CLDN6 expressed by cells in said sample.

In one example, the cells in the sample are cancer cells. The complex is preferably formed between the antibody, the antigen-binding fragment or the conjugate and
15 CLDN6 expressed by cells in said sample.

Further examples of the present disclosure relate to methods of diagnosing or classifying diseases by targeting CLDN6 using an antibody or antigen-binding fragment of the disclosure. These methods provide for the selective detection of cells that express
20 CLDN6 thereby differentiating these cells from normal cells not expressing CLDN6 or diseased cells not expressing CLDN6. Diseases characterized by diseased cells expressing CLDN6 are treatable by a therapy targeting CLDN6 such as therapy with therapeutic antibodies directed against CLDN6. Preferred diseases for a therapy or diagnosis are those in which CLDN6 is expressed or aberrantly expressed, in particular cancer diseases,
25 such as those described herein.

In one example the present disclosure relates to methods for diagnosis, detection or monitoring, i.e. determining the regression, progression, course and/or onset, of a cancer disease comprising the detection of CLDN6 or CLDN6-expressing cells and/or
30 determination of the quantity of CLDN6 or CLDN6-expressing cells in a biological sample isolated from a patient using an antibody or antigen-binding fragment of the disclosure.

Such methods may be used to detect whether a subject has a cancer disease or is at (increased) risk of developing a cancer disease or, for instance, whether a treatment regimen is efficient.

- 5 Thus, in one example, the present disclosure relates to a method for diagnosis, detection or monitoring of cancer comprising the steps of:
- (i) contacting a biological sample with an antibody or antigen-binding fragment of the disclosure or a conjugate of the disclosure and
 - (ii) detecting the formation of a complex and/or determining the quantity of a
- 10 complex between the antibody, the antigen-binding fragment or the conjugate and CLDN6.

In one example, the biological sample is a cellular sample, i.e. a sample comprising cells such as cancer cells. In this example, the complex is preferably formed between the

15 antibody, the antigen-binding fragment or the conjugate and CLDN6 expressed by cells in said sample.

The methods of monitoring according to the disclosure preferably comprise a detection of and/or determination of the quantity of CLDN6 or CLDN6-expressing cells in a first

20 sample at a first point in time and in a further sample at a second point in time, wherein the regression, progression, course and/or onset of a tumor disease may be determined by comparing the two samples.

Typically, the level of CLDN6 or level of CLDN6-expressing cells in a biological sample is

25 compared to a reference level, wherein a deviation from said reference level is indicative of the presence and/or stage of a cancer disease in a subject. The reference level may be a level as determined in a control sample (e.g., from a healthy tissue or subject, in particular a patient without a cancer disease) or a median level from healthy subjects. A "deviation" from said reference level designates any significant change, such as an

30 increase by at least 10%, 20%, or 30%, preferably by at least 40% or 50%, or even more.

Preferably, the presence of CLDN6 or CLDN6-expressing cells and/or a quantity of CLDN6 or CLDN6-expressing cells which is increased compared to a reference level, e.g. compared to a patient without a cancer disease, indicates the presence of or risk for (i.e. a potential for a development of) a cancer disease in the patient.

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A quantity of CLDN6 or CLDN6-expressing cells which is decreased compared to a biological sample taken earlier from a patient may indicate a regression, a positive course, e.g. a successful treatment, or a reduced risk for an onset of a cancer disease in a patient.

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A quantity of CLDN6 or CLDN6-expressing cells which is increased compared to a biological sample taken earlier from a patient may indicate a progression, a negative course, e.g. an unsuccessful treatment, recurrence or metastatic behavior, an onset or a risk for an onset of a cancer disease in said patient.

15

In one example, the present disclosure relates to a method for determining whether a cancer is treatable by a cancer therapy targeting CLDN6 comprising the steps of:

- (i) contacting a sample comprising cancer cells with an antibody or antigen-binding fragment of the disclosure or a conjugate of the disclosure and
- 20 (ii) detecting the formation of a complex between the antibody, the antigen-binding fragment or the conjugate and CLDN6.

The complex is preferably formed between the antibody, the antigen-binding fragment or the conjugate and CLDN6 expressed by cancer cells in said sample.

25

Such methods may be used to detect whether a patient is suitable for a therapy involving the targeting of cells expressing CLDN6 such as a therapy using antibodies exerting one or more immune effector functions such as cytotoxic CLDN6 specific antibodies, e.g. antibodies labeled with a cytotoxic substance such as a toxin or a radiolabel or inducing
30 a cell killing mechanism such as CDC or ADCC. Diseases characterized by diseased cells

expressing CLDN6 are treatable by a therapy targeting CLDN6 such as cancer diseases, in particular those described herein.

5 In one example of any of the above examples, the sample, cellular sample or biological sample is from a patient having a cancer disease, being suspected of having or falling ill with a cancer disease or having a potential for a cancer disease. In one example, the sample, cellular sample or biological sample is from a tissue or organ wherein the cells when the tissue or organ is free of cancer do not substantially express CLDN6. Preferably said tissue is a tissue other than placenta tissue. Preferably, said tissue has already been
10 diagnosed as being affected by a cancer disease, e.g. by visual inspection or culture testing of cells of said tissue or organ. In this example, the presence of CLDN6 or CLDN6-expressing cells and/or a quantity of CLDN6 or CLDN6-expressing cells which is increased compared to a reference level, e.g. compared to a patient without a tumor disease, may indicate that a patient is suitable for a therapy involving the targeting of cells expressing
15 CLDN6.

In one example, the disclosure provides compositions, e.g., diagnostic compositions, or kits, comprising an antibody or antigen-binding fragment or a combination of antibodies and/or or antigen-binding fragments described herein. Such diagnostic compositions or
20 test kits are useful in the methods of the disclosure such as the methods for diagnosis, detection or monitoring of the disclosure. These kits may optionally comprise a detectable label, e.g. indicator enzymes, radiolabels, fluorophores, or paramagnetic particles. Kits may include informative pamphlets, for example, pamphlets informing on how to use reagents to practice a method disclosed herein.

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Other features and advantages of the instant disclosure will be apparent from the following detailed description and claims.

Detailed description of the invention

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Although the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodologies, protocols and reagents

described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all technical and scientific terms used herein have the
5 same meanings as commonly understood by one of ordinary skill in the art.

In the following, the elements of the present invention will be described. These elements are listed with specific embodiments, however, it should be understood that they may be combined in any manner and in any number to create additional
10 embodiments. The variously described examples and preferred embodiments should not be construed to limit the present invention to only the explicitly described embodiments. This description should be understood to support and encompass embodiments which combine the explicitly described embodiments with any number of

Claims

1. An antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment comprises:

an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or an amino acid substitution variant thereof, wherein the amino acid substitution variant comprises one substitution, wherein the substitution is Ile at position 3 substituted by an uncharged amino acid;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or an amino acid substitution variant thereof, wherein the amino acid substitution variant comprises from one to three substitutions selected from the group consisting of Phe at position 2 substituted by an aromatic amino acid, Gly at position 4 substituted by an acidic or uncharged polar amino acid, Thr at position 8 substituted by an uncharged amino acid, and a combination thereof; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; and which

binds:

(i) to a peptide having the amino acid sequence EYPTKNY (SEQ ID NO: 38), and/or

(ii) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence EYPTKNY (SEQ ID NO: 38), and/or

(iii) to a peptide having the amino acid sequence EYPTKNYV (SEQ ID NO: 29), and/or

(iv) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence EYPTKNYV (SEQ ID NO: 29), and/or

(v) to a peptide having the amino acid sequence AISRGPSEYPTKNYV (SEQ ID NO: 15), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide

having the amino acid sequence TSAPAIRGPSEYPT (SEQ ID NO: 14), and/or

(vi) to claudin 6 (CLDN6), wherein said antibody or antigen-binding fragment thereof binds to CLDN6 by binding at least to an epitope within CLDN6 having the amino acid sequence AISRGPSYPTKNYV (SEQ ID NO: 15), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide having the amino acid sequence TSAPAIRGPSEYPT (SEQ ID NO: 14), and/or

(vii) to one or more of the following peptides:

PAISRGPSYPTKNY (SEQ ID NO: 22), AISRGPSYPTKNYV (SEQ ID NO: 15), ISRGPSYPTKNYV (SEQ ID NO: 23), SRGPSYPTKNYV (SEQ ID NO: 24), RGPSYPTKNYV (SEQ ID NO: 25), GPSYPTKNYV (SEQ ID NO: 26), PSYPTKNYV (SEQ ID NO: 27), SYPTKNYV (SEQ ID NO: 28), and EYPTKNYV (SEQ ID NO: 29), wherein the antibody or antigen-binding fragment thereof does not bind to a peptide having the amino acid sequence TSAPAIRGPSEYPT (SEQ ID NO: 14).

2. A method for detecting CLDN6 or the quantity of CLDN6 in a sample comprising the steps of:
 - (i) contacting a sample with the antibody or antigen-binding fragment of claim 1 and
 - (ii) detecting the formation of a complex or the quantity of a complex between the antibody or the antigen-binding fragment and CLDN6.
3. A method for detecting cells that express CLDN6 comprising the steps of:
 - (i) contacting a cellular sample with the antibody or antigen-binding fragment of claim 1 and
 - (ii) detecting the formation of a complex between the antibody or the antigen-binding fragment and CLDN6 expressed by cells in said sample.
4. A method for diagnosis, detection or monitoring of CLDN6-expressing cancer cells comprising the steps of:
 - (i) contacting a biological sample with the antibody or antigen-binding fragment of claim 1 and

- (ii) detecting the formation of a complex and/or the quantity of a complex between the antibody or the antigen-binding fragment and CLDN6.
5. The method of claim 2, wherein the antibody or antigen-binding fragment thereof comprises: an antibody heavy chain variable region (VH) comprising:
- a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or the amino acid sequence set forth in SEQ ID NO: 57;
 - a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or the amino acid sequence set forth in SEQ ID NO: 58; and
 - a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
- an antibody light chain variable region (VL) comprising:
- a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 - a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 - a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.
6. The method of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
- an antibody heavy chain variable region (VH) comprising:
- a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51;
 - a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52; and
 - a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
- an antibody light chain variable region (VL) comprising:
- a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 - a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 - a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; or
- an antibody heavy chain variable region (VH) comprising:
- a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 57;
 - a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 58; and
 - a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
- an antibody light chain variable region (VL) comprising:
- a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 - a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.

7. The method of claim 2, wherein the antibody or antigen-binding fragment thereof comprises:
(i) an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2), or (ii) an antibody which is a chimerized or humanized form of the antibody under (i), or an antigen-binding fragment of the antibody of (i) or (ii).
8. The method of claim 2, wherein the antibody or antigen-binding fragment thereof comprises an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2).
9. The method of claim 3, wherein the antibody or antigen-binding fragment thereof comprises:
an antibody heavy chain variable region (VH) comprising:
 a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or the amino acid sequence set forth in SEQ ID NO: 57;
 a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or the amino acid sequence set forth in SEQ ID NO: 58; and
 a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
an antibody light chain variable region (VL) comprising:
 a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.
10. The method of claim 3, wherein the antibody or antigen-binding fragment thereof comprises:
an antibody heavy chain variable region (VH) comprising:
 a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51;
 a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52; and
 a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; or
 an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 57;
 a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 58; and
 a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.

- 11.** The method of claim 3, wherein the antibody or antigen-binding fragment thereof comprises:

(i) an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2), or (ii) an antibody which is a chimerized or humanized form of the antibody under (i), or an antigen-binding fragment of the antibody of (i) or (ii).

- 12.** The method of claim 3, wherein the antibody or antigen-binding fragment thereof comprises an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2).

- 13.** The method of claim 4, wherein the antibody or antigen-binding fragment thereof comprises: an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or the amino acid sequence set forth in SEQ ID NO: 57;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or the amino acid sequence set forth in SEQ ID NO: 58; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.

14. The method of claim 4, wherein the antibody or antigen-binding fragment thereof comprises:
 an antibody heavy chain variable region (VH) comprising:
 a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51;
 a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52; and
 a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
 an antibody light chain variable region (VL) comprising:
 a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; **or**
 an antibody heavy chain variable region (VH) comprising:
 a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 57;
 a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 58; and
 a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and
 an antibody light chain variable region (VL) comprising:
 a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;
 a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and
 a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.
15. The method of claim 4, wherein the antibody or antigen-binding fragment thereof comprises:
 (i) an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2), or (ii) an antibody which is a chimerized or humanized form of the antibody under (i), or an antigen-binding fragment of the antibody of (i) or (ii).
16. The method of claim 4, wherein the antibody or antigen-binding fragment thereof comprises an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2).
17. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51 or the amino acid sequence set forth in SEQ ID NO: 57;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52 or the amino acid sequence set forth in SEQ ID NO: 58; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.

- 18.** The antibody or antigen-binding fragment of claim **1**, wherein the antibody or antigen-binding fragment thereof comprises:

an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 51;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 52; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56; or

an antibody heavy chain variable region (VH) comprising:

a VHCDR1 having the amino acid sequence set forth in SEQ ID NO: 57;

a VHCDR2 having the amino acid sequence set forth in SEQ ID NO: 58; and

a VHCDR3 having the amino acid sequence set forth in SEQ ID NO: 53; and

an antibody light chain variable region (VL) comprising:

a VLCDR1 having the amino acid sequence set forth in SEQ ID NO: 54;

a VLCDR2 having the amino acid sequence set forth in SEQ ID NO: 55; and

a VLCDR3 having the amino acid sequence set forth in SEQ ID NO: 56.

- 19.** The antibody or antigen-binding fragment of claim **1**, wherein the antibody or antigen-binding fragment thereof comprises:

(i) an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2), or (ii) an antibody which is a chimerized or humanized form of the antibody under (i), or an antigen-binding fragment of the antibody of (i) or (ii).

- 20.** The antibody or antigen-binding fragment of claim **1**, wherein the antibody or antigen-binding fragment thereof comprises an antibody produced by or obtainable from a clone deposited under the accession no. DSM ACC3313 (58-1B), DSM ACC3312 (58-3A) or DSM ACC3311 (58-4B-2).