

SUMMARY

The disclosure generally provides binding agents that bind to CLDN18.2, particularly bispecific binding agents that bind to CLDN18.2 and CD3.

The disclosure provides a binding agent comprising a binding domain with specificity for CLDN18.2 and a binding domain with specificity for CD3, wherein the binding agent comprises at least three polypeptide chains, wherein (i) a first polypeptide chain comprises a variable region of a heavy chain (VH) derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)), (ii) a second polypeptide chain comprises a variable region of a VH derived from an immunoglobulin with specificity for CD3 (VH(CD3)) and a variable region of a light chain (VL) derived from an immunoglobulin with specificity for CD3 (VL(CD3)), and (iii) a third polypeptide chain comprises a VL derived from an immunoglobulin with specificity for CLDN18.2 (VL(CLDN18.2)).

In one aspect, the disclosure provides a binding agent comprising two binding domains with specificity for CLDN18.2 and a binding domain with specificity for CD3, wherein the binding agent comprises

(a) a first polypeptide chain which comprises, from N-terminus to C-terminus,

(i) a variable region of a heavy chain derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)),

(ii) a constant region 1 of a heavy chain (CH1) derived from an immunoglobulin,

(iii) a constant region 2 of a heavy chain (CH2) derived from an immunoglobulin, and

(iv) a constant region 3 of a heavy chain (CH3) derived from an immunoglobulin,

(b) a second polypeptide chain which comprises, from N-terminus to C-terminus,

(i) a variable region of a heavy chain derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)),

(ii) a constant region 1 of a heavy chain (CH1) derived from an immunoglobulin,

(iii) a variable region of a heavy chain derived from an immunoglobulin with specificity for CD3 (VH(CD3)) and a variable region of a light chain derived from an immunoglobulin with specificity for CD3 (VL(CD3)), or

a variable region of a light chain derived from an immunoglobulin with specificity for CD3 (VL(CD3)) and a variable region of a heavy chain derived from an immunoglobulin with specificity for CD3 (VH(CD3)),

- (iv) a constant region 2 of a heavy chain (CH2) derived from an immunoglobulin, and
- (v) a constant region 3 of a heavy chain (CH3) derived from an immunoglobulin,
- (c) a third polypeptide chain which comprises, from N-terminus to C-terminus,
 - (i) a variable region of a light chain derived from an immunoglobulin with specificity for CLDN18.2 (VL(CLDN18.2)), and
 - (ii) a constant region of a light chain (CL) derived from an immunoglobulin, and
- (d) a fourth polypeptide chain identical to the third polypeptide chain,

wherein

the VH(CLDN18.2) on the first polypeptide chain and the VL(CLDN18.2) on the third polypeptide chain interact to form a binding domain with specificity for CLDN18.2,

the VH(CLDN18.2) on the second polypeptide chain and the VL(CLDN18.2) on the fourth polypeptide chain interact to form a binding domain with specificity for CLDN18.2, and

the VH(CD3) and the VL(CD3) interact to form a binding domain with specificity for CD3, and wherein

the VH(CD3) comprises a CDR1 comprising the amino acid sequence TYAMN (SEQ ID NO: 43), a CDR2 comprising the amino acid sequence RIRSKANNYATYYADSVKG (SEQ ID NO: 50), and a CDR3 comprising the amino acid sequence HGNFGDSYVSWFAY (SEQ ID NO: 45),

the VL(CD3) comprises a CDR1 comprising the amino acid sequence GSSTGAVTTSNYAN (SEQ ID NO: 46), a CDR2 comprising the amino acid sequence GTNKRAP (SEQ ID NO: 47), and a CDR3 comprising the amino acid sequence ALWYSNHWV (SEQ ID NO: 48),

the VH(CLDN18.2) comprises a CDR1 comprising the amino acid sequence SYWIN (SEQ ID NO: 32), a CDR2 comprising the amino acid sequence NIYPSDSYTNYNQKFQG (SEQ ID NO: 33), and a CDR3 comprising the amino acid sequence SWRGNSFDY (SEQ ID NO: 34), and

the VL(CLDN18.2) comprises a CDR1 comprising the amino acid sequence KSSQSLLNSGNQKNYLT (SEQ ID NO: 35), a CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO: 36), and a CDR3 comprising the amino acid sequence QNDYSYPFT (SEQ ID NO: 37).

In one example, the binding agent of the disclosure is a bispecific trimeric binding agent.

In one example, the first polypeptide chain comprises a constant region 1 of a heavy chain (CH1) derived from an immunoglobulin or a functional variant thereof.

5 In one example, the first and the second polypeptide chains comprise a constant region 2 of a heavy chain (CH2) derived from an immunoglobulin or a functional variant thereof and a constant region 3 of a heavy chain (CH3) derived from an immunoglobulin or a functional variant thereof.

10 In one example, the third polypeptide chain comprises a constant region of a light chain (CL) derived from an immunoglobulin or a functional variant thereof.

In one example, the VH and the CH1, CH2 and CH3 on the first polypeptide chain are arranged, from N-terminus to C-terminus, in the order VH(CLDN18.2)-CH1-CH2-CH3.

15 In one example, the VH, the VL, and the CH2 and CH3 on the second polypeptide chain are arranged, from N-terminus to C-terminus, in the order VH(CD3)-VL(CD3)-CH2-CH3, or VL(CD3)-VH(CD3)-CH2-CH3.

(iii) the third polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 78 or a functional variant thereof.

Preferably, in one example, (i) the first polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 73 or a functional variant thereof,

(ii) the second polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 77 or a functional variant thereof, and

(iii) the third polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 78 or a functional variant thereof.

The disclosure also provides a binding agent comprising a binding domain with specificity for CLDN18.2 comprising a variable region of a heavy chain (VH) derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)) and a variable region of a light chain (VL) derived from an immunoglobulin with specificity for CLDN18.2 (VL(CLDN18.2)), wherein the VH(CLDN18.2) comprises a CDR1 comprising the amino acid sequence SYWIN (SEQ ID NO: 32) or a functional variant thereof, a CDR2 comprising the amino acid sequence NIYPSDSYTNYNQKFQG (SEQ ID NO: 33) or a functional variant thereof, and a CDR3 comprising the amino acid sequence SWRGNSFDY (SEQ ID NO: 34) or a functional variant thereof, and the VL(CLDN18.2) comprises a CDR1 comprising the amino acid sequence KSSQSLLNSGNQKNYLT (SEQ ID NO: 35) or a functional variant thereof, a CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO: 36) or a functional variant thereof, and a CDR3 comprising the amino acid sequence QNDYSYPFT (SEQ ID NO: 37) or a functional variant thereof. In one example, the binding agent further comprises a binding domain with specificity for CD3. In one example, the binding domain with specificity for CD3 comprises a VH derived from an immunoglobulin with specificity for CD3 (VH(CD3)) and a VL derived from an immunoglobulin with specificity for CD3 (VL(CD3)), wherein the VH(CD3) comprises CDR1, CDR2 and CDR3 of an amino acid sequence selected from the group consisting of SEQ ID NO: 54, 58 and 61, and the VL(CD3) comprises CDR1, CDR2 and CDR3 of SEQ ID NO: 55.

In one example, the functional variant of the amino acid sequence NIYPSDSYTNYNQKFQG (SEQ ID NO: 33) comprises or retains the amino acid residues QG.

- 5 In one example, the binding agent is in the format of a full-length antibody or an antibody fragment. In one example, the binding domain with specificity for CLDN18.2 is in the format

example, the polypeptide chains of the binding agent and/or the domains on the polypeptide chains of the binding agent interact with one another as described herein. In one example, the first polypeptide chain interacts with the second polypeptide chain and with the third polypeptide chain.

5 The disclosure also provides a binding agent comprising two binding domains with specificity for CLDN18.2 and a binding domain with specificity for CD3, wherein the binding agent comprises at least four polypeptide chains, wherein the first polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 73 or a functional variant thereof, the second
10 polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 76 or a functional variant thereof, the third polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 78 or a functional variant thereof, and the fourth polypeptide chain is identical to the third polypeptide chain. In one example, the polypeptide chains of the binding agent and/or the domains on the polypeptide chains of the binding agent interact with one another as described herein. In one example, the first polypeptide chain interacts
15 with the second polypeptide chain and with the third polypeptide chain, and the second polypeptide chain interacts with the fourth polypeptide chain.

The disclosure also provides a binding agent comprising two binding domains with specificity for CLDN18.2 and a binding domain with specificity for CD3, wherein the binding agent comprises at least four polypeptide chains, wherein the first polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 73 or a functional variant thereof, the second polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 77 or a functional variant thereof, the third polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 78 or a functional variant thereof, and the fourth polypeptide chain is identical to the third polypeptide chain. In one example, the polypeptide chains of the binding agent and/or the domains on the polypeptide chains of the binding agent interact with one another as described herein. In one example, the first polypeptide chain interacts with the second polypeptide chain and with the third polypeptide chain, and the second polypeptide chain interacts with the fourth polypeptide chain.

In one example, the VH(CLDN18.2), VL(CLDN18.2), VH(CD3) and/or VL(CD3) are humanized.

The disclosure also provides a nucleic acid encoding a polypeptide chain of the binding agent of the disclosure. In another aspect, the disclosure also provides a nucleic acid encoding the binding agent as defined herein. In another aspect, the disclosure also provides a set of nucleic acids together encoding the binding agent as defined herein.

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In another aspect, the disclosure also provides a vector comprising the nucleic acid or the set of nucleic acids as defined herein. In another aspect, the disclosure also provides a set of vectors comprising the set of nucleic acids as defined herein. In one example, each nucleic acid of the set of nucleic acids is contained in a vector of the set of vectors. In one example, the vector or the set of vectors is capable of expressing the binding agent.

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In one example, a nucleic acid is operably linked to any number of regulatory elements (promoters, origin of replication, selectable markers, ribosomal binding sites, inducers, etc.). The vector can be an expression vector and can be extra-chromosomal or integrating vector. In some examples, nucleic acids encoding a polypeptide chain of the binding agent of the disclosure are each contained within a single expression vector. The nucleic acids can be under control of different or the same promoters. In such examples, different vector ratios can be used to drive formation of the binding agent of the disclosure.

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In another aspect, the disclosure also provides a host cell comprising said nucleic acid, set of nucleic acids, vector or set of vectors. In one example, the host cell is a mammalian cell, preferably selected from the group consisting of CHO cells, BHK cells, HeLa cells, COS cells, HEK293 cells, HEK293 T cells and the like. In one example, the host cell is a bacterial cell, a yeast cell, a fungal cell, a plant cell or an insect cell.

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In another aspect, the disclosure also provides a pharmaceutical composition comprising the binding agent as defined herein, the nucleic acid as defined herein, the set of nucleic acids as defined herein, the vector as defined herein, the set of vectors as defined herein or the host cell as defined herein. In one example, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient.

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In another aspect, the disclosure also provides the binding agent as defined herein, the nucleic acid as defined herein, the set of nucleic acids as defined herein, the vector as defined herein, the set of vectors

Claims

1. A binding agent comprising two binding domains with specificity for CLDN18.2 and a binding domain with specificity for CD3,
wherein the binding agent comprises
 - (a) a first polypeptide chain which comprises, from N-terminus to C-terminus,
 - (i) a variable region of a heavy chain derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)),
 - (ii) a constant region 1 of a heavy chain (CH1) derived from an immunoglobulin,
 - (iii) a constant region 2 of a heavy chain (CH2) derived from an immunoglobulin, and
 - (iv) a constant region 3 of a heavy chain (CH3) derived from an immunoglobulin,
 - (b) a second polypeptide chain which comprises, from N-terminus to C-terminus,
 - (i) a variable region of a heavy chain derived from an immunoglobulin with specificity for CLDN18.2 (VH(CLDN18.2)),
 - (ii) a constant region 1 of a heavy chain (CH1) derived from an immunoglobulin,
 - (iii) a variable region of a heavy chain derived from an immunoglobulin with specificity for CD3 (VH(CD3)) and a variable region of a light chain derived from an immunoglobulin with specificity for CD3 (VL(CD3)), or a variable region of a light chain derived from an immunoglobulin with specificity for CD3 (VL(CD3)) and a variable region of a heavy chain derived from an immunoglobulin with specificity for CD3 (VH(CD3)),
 - (iv) a constant region 2 of a heavy chain (CH2) derived from an immunoglobulin, and
 - (v) a constant region 3 of a heavy chain (CH3) derived from an immunoglobulin,
 - (c) a third polypeptide chain which comprises, from N-terminus to C-terminus,
 - (i) a variable region of a light chain derived from an immunoglobulin with specificity for CLDN18.2 (VL(CLDN18.2)), and
 - (ii) a constant region of a light chain (CL) derived from an immunoglobulin,and

(d) a fourth polypeptide chain identical to the third polypeptide chain,

wherein

the VH(CLDN18.2) on the first polypeptide chain and the VL(CLDN18.2) on the third polypeptide chain interact to form a binding domain with specificity for CLDN18.2,

the VH(CLDN18.2) on the second polypeptide chain and the VL(CLDN18.2) on the fourth polypeptide chain interact to form a binding domain with specificity for CLDN18.2, and

the VH(CD3) and the VL(CD3) interact to form a binding domain with specificity for CD3, and wherein

the VH(CD3) comprises a CDR1 comprising the amino acid sequence TYAMN (SEQ ID NO: 43), a CDR2 comprising the amino acid sequence RIRSKANNYATYYADSVKG (SEQ ID NO: 50), and a CDR3 comprising the amino acid sequence HGNFGDSYVSWFAY (SEQ ID NO: 45),

the VL(CD3) comprises a CDR1 comprising the amino acid sequence GSSTGAVTTSNYAN (SEQ ID NO: 46), a CDR2 comprising the amino acid sequence GTNKRAP (SEQ ID NO: 47), and a CDR3 comprising the amino acid sequence ALWYSNHWV (SEQ ID NO: 48),

the VH(CLDN18.2) comprises a CDR1 comprising the amino acid sequence SYWIN (SEQ ID NO: 32), a CDR2 comprising the amino acid sequence NIYPSDSYTNYNQKFQG (SEQ ID NO: 33), and a CDR3 comprising the amino acid sequence SWRGNSFDY (SEQ ID NO: 34), and

the VL(CLDN18.2) comprises a CDR1 comprising the amino acid sequence KSSQSLLNSGNQKNYLT (SEQ ID NO: 35), a CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO: 36), and a CDR3 comprising the amino acid sequence QNDYSPFT (SEQ ID NO: 37).

2. The binding agent of claim 1, wherein:

(a) the CH1 on the first polypeptide chain interacts with the CL on the third polypeptide chain;

(b) the immunoglobulin is IgG1, optionally human IgG1;

(c) the CH2 on the first polypeptide chain interacts with the CH2 on the second polypeptide chain and/or the CH3 on the first polypeptide chain interacts with the CH3 on the second polypeptide chain, and/or

(d) the CH1 on the second polypeptide chain interacts with the CL on the fourth polypeptide chain.

3. The binding agent of claim 1 or 2, wherein
the VH(CD3) comprises or consists of an amino acid sequence represented by SEQ ID NO: 58,
the VL(CD3) comprises or consists of an amino acid sequence represented by SEQ ID NO: 55,
the VH(CLDN18.2) comprises or consists of an amino acid sequence represented by SEQ ID NO: 39, and/or
the VL(CLDN18.2) comprises or consists of an amino acid sequence represented by SEQ ID NO: 42.
4. The binding agent of any one of claims 1 to 3, wherein on the first polypeptide chain the CH1 is connected to the CH2 by a peptide linker which optionally comprises the amino acid sequence EPKSCDKTHTCPPCP (SEQ ID NO: 27).
5. The binding agent of any one of claims 1 to 4, wherein the VH(CD3) or VL(CD3) is connected to the CH2 by a peptide linker.
6. The binding agent of any one of claims 1 to 5, wherein the VH(CD3) or VL(CD3) is connected to the CH1 by a peptide linker.
7. The binding agent of claim 5 or 6, wherein the peptide linker comprises the amino acid sequence $(G_4S)_x$, wherein x is 2, 3, 4, 5 or 6, wherein optionally the peptide linker comprises the amino acid sequence $(G_4S)_2$ (SEQ ID NO: 26).
8. The binding agent of any one of claims 1 to 7, wherein the VH(CD3) and the VL(CD3) are connected to one another by a peptide linker, wherein optionally the peptide linker comprises the amino acid sequence $(GKPGS)_x$, wherein x is 2, 3, 4, 5 or 6, wherein further optionally the peptide linker comprises the amino acid sequence $(GKPGS)_4$ (SEQ ID NO: 11).
9. The binding agent of any one of claims 1 to 8, wherein the CH1 comprises an amino acid sequence comprising an aspartic acid residue at position 208 according to EU numbering.

10. The binding agent of any one of claims 1 to 9, wherein the CH1 on the first polypeptide chain comprises an amino acid sequence comprising an aspartic acid residue at position 208 according to EU numbering and the CH1 on the second polypeptide chain comprises an amino acid sequence comprising an asparagine residue at position 208 according to EU numbering.
11. The binding agent of any one of claims 1 to 10, which does not substantially bind to human FcγRI, IIa, IIb, and/or IIIa.
12. The binding agent of any one of claims 1 to 11, wherein
- a) the CH2 on the first and/or the second polypeptide chain comprises an amino acid sequence comprising one or more of the following: a proline residue at position 233, a valine residue at position 234, an alanine residue at position 235, a deletion at position 236, a lysine residue at position 267 and a glutamic acid residue at position 295 according to EU numbering, wherein optionally the CH2s on the first and the second polypeptide chain comprise an amino acid sequence comprising a proline residue at position 233, a valine residue at position 234, an alanine residue at position 235, a deletion at position 236 and a lysine residue at position 267 according to EU numbering and wherein the CH2 on the first polypeptide chain further comprises a glutamic acid residue at position 295 according to EU numbering and the CH2 on the second polypeptide chain further comprises a glutamine residue at position 295 according to EU numbering; and/or
 - b) the CH3 on the first and/or the second polypeptide chain comprises an amino acid sequence comprising one or more of the following: a glutamine residue at position 357, a lysine residue at position 364, an aspartic acid residue at position 368, a serine residue at position 370, an aspartic acid residue at position 384, a glutamic acid residue at position 418 and an aspartic acid residue at position 421 according to EU numbering, wherein optionally the CH3 on the first polypeptide chain comprises an amino acid sequence comprising a glutamic acid residue at position 357, a serine residue at position 364, an aspartic acid residue at position 368, a serine residue at position 370, an aspartic acid residue at position 384, a glutamic acid residue at position 418 and an aspartic acid residue at position 421 according to EU numbering and the CH3 on the second polypeptide chain comprises an amino acid sequence comprising a glutamine residue at position 357, a lysine residue at position 364, a leucine residue at position 368, a lysine residue at position 370, an asparagine residue at

position 384, a glutamine residue at position 418 and an asparagine residue at position 421 according to EU numbering.

13. The binding agent of any one of claims 1 to 12, wherein
 - (a) the first polypeptide chain comprises an amino acid sequence represented by SEQ ID NO: 28;
 - (b) the second polypeptide chain comprises an amino acid sequence represented by SEQ ID NO: 30; and/or
 - (c) the third and fourth polypeptide chains comprise an amino acid sequence represented by SEQ ID NO: 31.
14. The binding agent of any one of claims 1 to 13, wherein the VH(CLDN18.2), VL(CLDN18.2), VH(CD3) and/or VL(CD3) are humanized.
15. A binding agent comprising two binding domains with specificity for CLDN18.2 and a binding domain with specificity for CD3,
 - wherein the binding agent comprises four polypeptide chains, wherein
 - (i) the first polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 73,
 - (ii) the second polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 74,
 - (iii) the third polypeptide chain comprises or consists of an amino acid sequence represented by SEQ ID NO: 78, and
 - (iv) the fourth polypeptide chain is identical to the third polypeptide chain, wherein the first polypeptide chain interacts with the second polypeptide chain and with the third polypeptide chain, and the second polypeptide chain interacts with the fourth polypeptide chain.
16. The binding agent of any one of claims 1 to 15, wherein CD3 is expressed on the surface of T cells, wherein optionally binding of the binding agent to CD3 on T cells results in proliferation and/or activation of the T cells.
17. The binding agent of any one of claims 1 to 16, wherein CLDN18.2 is expressed in cancer cells, wherein optionally
 - (a) CLDN18.2 is expressed on the surface of the cancer cells; and/or

(b) the binding agent binds to an extracellular portion of CLDN18.2.

18. The binding agent of any one of claims 1 to 17, wherein the binding agent induces T cell-mediated cytotoxicity against cancer cells expressing CLDN18.2.

19. The binding agent of claim 17 or 18, wherein the cancer cells are from a cancer selected from the group consisting of gastric cancer, esophageal cancer, pancreatic cancer, lung cancer such as non small cell lung cancer (NSCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, colorectal cancer, hepatic cancer, head-neck cancer, cancer of the gallbladder and the metastasis thereof, a Krukenberg tumor, peritoneal metastasis and/or lymph node metastasis.

20. A nucleic acid encoding the binding agent of any one of claims 1 to 19.

21. A set of nucleic acids together encoding the binding agent of any one of claims 1 to 19.

22. A vector comprising the nucleic acid of claim 20 or the set of nucleic acids of claim 21.

23. A set of vectors comprising the set of nucleic acids of claim 21.

24. The vector of claim 22 or the set of vectors of claim 23, which is capable of expressing the binding agent.

25. A host cell comprising the nucleic acid of claim 20, the set of nucleic acids of claim 21, the vector of claim 22 or 24, or the set of vectors of claim 23 or 24.

26. A pharmaceutical composition comprising the binding agent of any one of claims 1 to 19, the nucleic acid of claim 20, the set of nucleic acids of claim 21, the vector of claim 22 or 24, the set of vectors of claim 23 or 24, or the host cell of claim 25.

27. The binding agent of any one of claims 1 to 19, the nucleic acid of claim 20, the set of nucleic acids of claim 21, the vector of claim 22 or 24, the set of vectors of claim 23 or 24, the host cell of claim 25 or the pharmaceutical composition of claim 26 for use in therapy.

28. The binding agent of any one of claims 1 to 19, the nucleic acid of claim 20 the set of nucleic acids of claim 21, the vector of claim 22 or 24, the set of vectors of claim 23 or 24, the host cell of claim 25 or the pharmaceutical composition of claim 26 for use in treating or preventing cancer involving cancer cells expressing CLDN18.2, wherein optionally the cancer is selected from the group consisting of gastric cancer, esophageal cancer, cancer of the gastroesophageal junction (GEJ), pancreatic cancer, lung cancer such as non small cell lung cancer (NSCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, colorectal cancer, hepatic cancer, head-neck cancer, cancer of the gallbladder and the metastasis thereof, a Krukenberg tumor, peritoneal metastasis and/or lymph node metastasis.

29. Use of the binding agent of any one of claims 1 to 19, the nucleic acid of claim 20, the set of nucleic acids of claim 21, the vector of claim 22 or 24, the set of vectors of claim 23 or 24, the host cell of claim 25 or the pharmaceutical composition of claim 26 for the preparation of a medicament for treating or preventing cancer involving cancer cells expressing CLDN18.2, wherein optionally the cancer is selected from the group consisting of gastric cancer, esophageal cancer, cancer of the gastroesophageal junction (GEJ), pancreatic cancer, lung cancer such as non small cell lung cancer (NSCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, colorectal cancer, hepatic cancer, head-neck cancer, cancer of the gallbladder and the metastasis thereof, a Krukenberg tumor, peritoneal metastasis and/or lymph node metastasis.

30. A method for producing the binding agent of any one of claims 1 to 19, optionally comprising transfecting a host cell with the nucleic acid of claim 20, the set of nucleic acids of claim 21, the vector of claim 22 or 24, or the set of vectors of claim 23 or 24.