

There is hence a need to develop therapeutically efficacious but safe antibody-based biological molecules which can function as TRAIL-receptor agonist molecules. It was thus an object of the present invention to generate TRAIL-receptor agonist molecules having an improved therapeutic profile.

Summary

The present disclosure is based on the concept of combining an antigen binding site that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) with an antigen binding site that binds specifically to cadherin-17 (CDH17) within a single binding molecule. As discussed in more detail below, one advantage of the molecule of the disclosure is that apoptosis is only promoted in cells that present TRAILR2 and CDH17 on their surface.

Hence, the disclosure provides a binding molecule having at least one antigen binding site (a first antigen binding site) that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) and at least one antigen binding site (a second antigen binding site) that binds specifically to cadherin-17 (CDH17).

A first aspect of the disclosure refers to a binding molecule comprising at least one antigen binding site that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) and at least one antigen binding site that binds specifically to cadherin-17 (CDH17).

In a preferred example of the binding molecule of the disclosure, the molecule is bispecific and tetravalent.

In a preferred example of the binding molecule of the disclosure, the at least one antigen binding site that binds specifically to cadherin-17 (CDH17) is an immunoglobulin (Ig) molecule (having the conventional Y shaped structure of a full length antibody with two light and two heavy chains) and the at least one antigen binding site that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) comprises one or more scFv(s).

In a preferred example of the binding molecule of the disclosure, the one or more scFv(s) have a VL-VH orientation from N-to C-terminus.

5 In a preferred example of the binding molecule of the disclosure, the one or more scFv(s) is fused to the C- terminus of the heavy chain of the Ig molecule. For example, one scFv is fused to the C-terminus of one of the heavy chains of the Ig molecule and one scFv is fused to

the C-terminus is fused to the C-terminus of the other heavy chain of the Ig molecule. As such, an scFv specific for TRAILR2 is fused to each of the heavy chains of the Ig molecule, thereby forming a symmetric, bispecific and tetravalent structure.

5 In a preferred example of the binding molecule of the disclosure, the Ig molecule is IgG1KO. In another preferred example of the binding molecule of the disclosure, the Ig molecule is IgG1FcRnmut.

10 In a preferred example of the binding molecule of the disclosure, the one or more scFv(s) is fused to the Ig molecule by a peptide linker, preferably a peptide linker having a length of about 4 to 20 amino acids (e.g., any one of 6, 9, 12, 15 amino acids).

In a preferred example of the binding molecule of the disclosure, the antigen binding site that binds specifically to TRAILR2 (the first antigen binding site) is selected from the group
15 consisting of antigen binding sites (i) to (xiii):

i) an antigen binding site comprising heavy chain complementary determining regions (CDRs) comprising the amino acid sequences of SEQ ID NO.:1 (CDR1), SEQ ID NO.:2 (CDR2) and SEQ ID NO.:3 (CDR3) and light chain CDRs comprising the
20 amino acid sequences of SEQ ID NO.:4 (CDR1), SEQ ID NO.:5 (CDR2) and SEQ ID NO.:6 (CDR3);

ii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:7 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID
25 NO.:10 (CDR1), SEQ ID NO.11 (CDR2) and SEQ ID NO.:12 (CDR3);

iii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:13 (CDR1), SEQ ID NO.:14 (CDR2) and SEQ ID NO.:15 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID
30 NO.:16 (CDR1), SEQ ID NO.17 (CDR2) and SEQ ID NO.:18 (CDR3);

iv) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:19 (CDR1), SEQ ID NO.:20 (CDR2) and SEQ ID NO.:21

xi) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequence of SEQ ID NO.:43 (CDR1), SEQ ID NO.:45 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.50 (CDR2) and SEQ ID NO.:56 (CDR3);

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xii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequence of SEQ ID NO.:43 (CDR1), SEQ ID NO.:46 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.51 (CDR2) and SEQ ID NO.:57 (CDR3); and

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xiii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequence of SEQ ID NO.:43 (CDR1), SEQ ID NO.:47 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.53 (CDR2) and SEQ ID NO.:57 (CDR3).

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In a preferred example of the binding molecule of the disclosure, the antigen binding site that binds specifically to TRAILR2 (the first antigen binding site) is selected from the group consisting of antigen binding sites (i) to (xiv):

20 i) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:82 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:83;

25 ii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:84 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:85;

30 iii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:86 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:87;

iv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:88 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:89;

xiii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:106 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:107; and

5 xiv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:108 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:109.

10 In a preferred example of the binding molecule of the disclosure, the antigen binding site that binds specifically to CDH17 (the second antigen binding site) is selected from the group consisting of antigen binding sites (i) to (iv):

15 i) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:58 (CDR1), SEQ ID NO.:59 (CDR2) and SEQ ID NO.:60 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:61 (CDR1), SEQ ID NO.:62 (CDR2) and SEQ ID NO.:63 (CDR3);

20 ii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:64 (CDR1), SEQ ID NO.:65 (CDR2) and SEQ ID NO.:66 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:67 (CDR1), SEQ ID NO.:68 (CDR2) and SEQ ID NO.:69 (CDR3);

25 iii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:70 (CDR1), SEQ ID NO.:71 (CDR2) and SEQ ID NO.:72 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:73 (CDR1), SEQ ID NO.:74 (CDR2) and SEQ ID NO.:75 (CDR3); and

30 iv) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:76 (CDR1), SEQ ID NO.:77 (CDR2) and SEQ ID NO.:78 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:79 (CDR1), SEQ ID NO.:80 (CDR2) and SEQ ID NO.:81 (CDR3).

In a preferred example of the binding molecule of the disclosure, the antigen binding site that binds specifically to CDH17 (the second antigen binding site) is selected from the group consisting of antigen binding sites (i) to (v):

5 i) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:110 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:111;

10 ii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:112 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:113;

15 iii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:114 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:115;

20 iv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:116 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:117; and,

 v) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:118 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:119.

25 In some examples, the heavy chain CDR3 sequence of SEQ ID NO:272 is used instead of the heavy chain CDR3 sequences of SEQ ID NO:78 in the context of the binding molecules of the present disclosure.

30 In some examples, the binding molecules provided in the various examples below, which are defined by their heavy chain amino acid sequence (e.g. a modified heavy chain with an scFv fused to the C-terminus of an Ig heavy chain) as well as their light chain amino acid sequences, comprise two heavy chains and two light chains, thereby forming a symmetric tetravalent and bispecific structure.

A further aspect of the disclosure refers to a binding molecule having (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 159, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 160, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 161, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 162, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 163, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 164, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 165, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 166, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 167, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 168, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 169, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 170, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 171, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 172, and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 173.

A further aspect of the disclosure refers to a binding molecule having (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 174, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 175, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 176, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 177, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 178, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 179, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 180, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 181, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 182, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 183, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 184, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 185, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 186, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 187, and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 188.

In a further aspect of the disclosure refers to a binding molecule having (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 189, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 190, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 191, or a

heavy chain comprising the amino acid sequence of SEQ ID NO: 192, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 193, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 194, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 195, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 196, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 197, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 198, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 199, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 200, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 201, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 202, and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 203.

A further aspect of the disclosure refers to a binding molecule having (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 204, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 206, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 208, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 209, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 210, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 211, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 212, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 213, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 214, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 215, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 216, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 217; or a heavy chain comprising the amino acid sequence of SEQ ID NO: 271 and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 218.

In a further aspect of the disclosure refers to a binding molecule having (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 145, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 147, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 149, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 151, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 153, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 155, or a

heavy chain comprising the amino acid sequence of SEQ ID NO: 157, or a heavy chain comprising the amino acid

sequence of SEQ ID NO: 219, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 220, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 221, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 222, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 223, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 224, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 225; or a heavy chain comprising the amino acid sequence of SEQ ID NO: 226, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 227, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 228, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 229, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 230, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 231, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 232 and (ii) a light chain comprising the amino acid sequence of SEQ ID NO: 233.

A further aspect of the disclosure refers to an isolated nucleic acid molecule encoding the heavy chain variable domain and/or the light chain variable domain of a binding molecule as defined herein or of an antibody molecule as defined herein.

A further aspect of the disclosure refers to an isolated nucleic acid molecule encoding the heavy chain and/or the light chain of a binding molecule as defined herein.

A further aspect of the disclosure refers to an expression vector comprising a nucleic acid molecule as defined herein.

A further example of the disclosure provides a nucleic acid molecule encoding a binding molecule of the disclosure or an expression vector containing such a nucleic acid molecule.

A further aspect of the disclosure refers to a host cell transfected with an expression vector as defined herein.

A further example of the disclosure provides a host cell comprising a nucleic acid molecule of the disclosure in functional association with an expression control sequence. Further provided herein is a host cell comprising an expression vector comprising a nucleic acid molecule encoding a binding molecule as described herein.

A further example of the disclosure provides a method of production of a binding molecule of the invention, comprising

- 5 (a) cultivating the host cell of the disclosure under conditions allowing expression of the molecule; and,
 (b) recovering the molecule.

10 A further aspect of the disclosure refers to a method of manufacturing a binding molecule as defined herein or an antibody as defined herein, comprising

- (a) cultivating the host cell as defined herein under conditions allowing expression of the molecule; and,
 (b) recovering the molecule; and optionally,
 (c) further purifying and/or modifying and/or formulating the molecule.

15 A further aspect of the disclosure refers to a binding molecule as defined herein for use in medicine.

20 A further aspect of the disclosure refers to use of the binding molecule as defined herein for preparing a pharmaceutical composition for treating cancer.

A further aspect of the disclosure refers to a binding molecule as defined herein for use in treating cancer.

25 A further example of the disclosure provides a binding molecule of the disclosure, for use in the therapy of cancer, preferably colorectal cancer (CRC), gastric cancer (GC), pancreatic cancer (PAC), Esophageal cancer or neuroendocrine tumors.

A further example of the disclosure provides a pharmaceutical composition, comprising a binding molecule of the disclosure together with a pharmaceutically acceptable carrier and optionally one or more further active ingredients.

- 5 A further aspect of the disclosure refers to a pharmaceutical composition comprising a binding molecule as defined herein and a pharmaceutically acceptable carrier.

10 A further example of the disclosure provides a method of treatment of cancer comprising administering an effective amount of a binding molecule of the disclosure to a patient in need thereof.

A further aspect of the disclosure refers to antibodies specifically binding to CDH17 comprising (i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:58 (CDR1), SEQ ID NO:59 (CDR2) and SEQ ID NO:60 (CDR3) and light chain CDRs
15 comprising the amino acid sequences of SEQ ID NO:61 (CDR1), SEQ ID NO:62 (CDR2) and SEQ ID NO:63 (CDR3), (ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:64 (CDR1), SEQ ID NO:65 (CDR2) and SEQ ID NO:66 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:67 (CDR1), SEQ ID NO:68 (CDR2) and SEQ ID NO:69 (CDR3), (iii) heavy chain CDRs comprising the amino acid
20 sequences of SEQ ID NO:70 (CDR1), SEQ ID NO:71 (CDR2) and SEQ ID NO:72 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:73 (CDR1), SEQ ID NO:74 (CDR2) and SEQ ID NO:75 (CDR3), or (iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:76 (CDR1), SEQ ID NO:77 (CDR2) and SEQ ID NO:78 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:79
25 (CDR1), SEQ ID NO:80 (CDR2) and SEQ ID NO:81 (CDR3).

Brief description of the figures

Figure 1A and B: Schematic representation of the binding molecule of the invention.

30 An example for a binding molecule of the invention is depicted comprising (i) an Ig molecule specifically binding to CDH17, which comprises two heavy and two light chains, and (ii) two scFv molecules specifically binding to TRAILR2. The N-terminus of an scFv is fused to the C-terminus of each of heavy chains of the Ig molecule, thereby forming a symmetric, bispecific and tetravalent antibody-like molecule.

CLAIMS

1. A binding molecule comprising at least one antigen binding site that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) and at least one antigen binding site that binds specifically to cadherin-17 (CDH17).
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2. The binding molecule of claim 1, wherein the molecule is bispecific and tetravalent.
3. The binding molecule of claims 1 or 2, wherein the at least one antigen binding site that binds specifically to cadherin-17 (CDH17) is an immunoglobulin (Ig) molecule and the at least one antigen binding site that binds specifically to TNF-related apoptosis-inducing ligand receptor 2 (TRAILR2) comprises one or more scFv(s).
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4. The binding molecule of claim 3, wherein the one or more scFv(s) have a VL-VH orientation from N-to C-terminus.
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5. The binding molecule of any one of claims 3 or 4, wherein the one or more scFv(s) is fused to the C- terminus of the heavy chain of the Ig molecule.
- 20 6. The binding molecule of any one of claims 3 to 5, wherein the Ig molecule is IgG.
7. The binding molecule of any one of claims 3 to 6, wherein the one or more scFv(s) is fused to the Ig molecule by a peptide linker, preferably a peptide linker having a length of about 4 to 20 amino acids.
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8. The binding molecule of any one of claims 1 to 7, wherein the antigen binding site that binds specifically to TRAILR2 is selected from the group consisting of antigen binding sites:i) to xiii)
30
 - i) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:1 (CDR1), SEQ ID NO.:2 (CDR2) and SEQ ID NO.:3 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:4 (CDR1), SEQ ID NO.:5 (CDR2) and SEQ ID NO.:6 (CDR3);

ii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:7 (CDR1), SEQ ID NO.:8 (CDR2) and SEQ ID NO.:9 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:10 (CDR1), SEQ ID NO.11 (CDR2) and SEQ ID NO.:12 (CDR3);

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iii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:13 (CDR1), SEQ ID NO.:14 (CDR2) and SEQ ID NO.:15 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:16 (CDR1), SEQ ID NO.17 (CDR2) and SEQ ID NO.:18 (CDR3);

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iv) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:19 (CDR1), SEQ ID NO.:20 (CDR2) and SEQ ID NO.:21 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:22 (CDR1), SEQ ID NO.23 (CDR2) and SEQ ID NO.:24 (CDR3);

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v) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:25 (CDR1), SEQ ID NO.:26 (CDR2) and SEQ ID NO.:27 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:28 (CDR1), SEQ ID NO.29 (CDR2) and SEQ ID NO.:30 (CDR3);

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vi) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:31 (CDR1), SEQ ID NO.:32 (CDR2) and SEQ ID NO.:33 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:34 (CDR1), SEQ ID NO.35 (CDR2) and SEQ ID NO.:36 (CDR3);

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vii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:37 (CDR1), SEQ ID NO.:38 (CDR2) and SEQ ID NO.:39 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:40 (CDR1), SEQ ID NO.41 (CDR2) and SEQ ID NO.:42 (CDR3);

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viii) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:44 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.50 (CDR2) and SEQ ID NO.:54 (CDR3);

ix) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:45 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.51 (CDR2) and SEQ ID NO.:55 (CDR3);

x) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:45 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.52 (CDR2) and SEQ ID NO.:56 (CDR3);

xi) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:45 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.50 (CDR2) and SEQ ID NO.:56 (CDR3);

xii) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:46 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.51 (CDR2) and SEQ ID NO.:57 (CDR3); and

xiii) an antigen binding site comprising heavy chain CDRs comprising of SEQ ID NO.:43 (CDR1), SEQ ID NO.:47 (CDR2) and SEQ ID NO.:48 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:49 (CDR1), SEQ ID NO.53 (CDR2) and SEQ ID NO.:57 (CDR3).

9. The binding molecule of any one of claims 1 to 8, wherein the antigen binding site that binds specifically to TRAILR2 is selected from the group consisting of antigen binding sites i) to xiv):

i) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:82 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:83;

- ii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:84 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:85;
- 5 iii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:86 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:87;
- 10 iv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:88 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:89;
- 15 v) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:90 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:91;
- 20 vi) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:92 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:93;
- 25 vii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:94 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:95;
- 30 viii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:96 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:97;
- ix) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:98 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:99;

x) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:100 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:101;

5 xi) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:102 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:103;

10 xii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:104 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:105;

15 xiii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:106 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:107; and

xiv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:108 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:109.

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10. The binding molecule of any one of claims 1 to 9, wherein the antigen binding site that binds specifically to CDH17 is selected from the group consisting of antigen binding sites i) to iv):

25 i) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:58 (CDR1), SEQ ID NO.:59 (CDR2) and SEQ ID NO.:60 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:61 (CDR1), SEQ ID NO.62 (CDR2) and SEQ ID NO.:63 (CDR3);

30 ii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:64 (CDR1), SEQ ID NO.:65 (CDR2) and SEQ ID NO.:66 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:67 (CDR1), SEQ ID NO.68 (CDR2) and SEQ ID NO.:69 (CDR3);

iii) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:70 (CDR1), SEQ ID NO.:71 (CDR2) and SEQ ID NO.:72 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:73 (CDR1), SEQ ID NO.74 (CDR2) and SEQ ID NO.:75 (CDR3); and,

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iv) an antigen binding site comprising heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:76 (CDR1), SEQ ID NO.:77 (CDR2) and SEQ ID NO.:78 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO.:79 (CDR1), SEQ ID NO.80 (CDR2) and SEQ ID NO.:81 (CDR3).

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11. The binding molecule of any one of claims 1 to 10, wherein the antigen binding site binding site that binds specifically to CDH17 is selected from the group consisting of antigen binding sites i) to v):

15 i) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:110 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:111;

20 ii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:112 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:113;

25 iii) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:114 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:115;

iv) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:116 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:117; and,

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v) an antigen binding site comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO.:118 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO.:119.

ID NO. 195, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 196, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 197, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 198, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 199, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 200, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 201, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 202, and (ii) a light chain comprising the amino acid sequence of SEQ ID NO. 203.

15. A binding molecule comprising (i) a heavy chain comprising the amino acid sequence of SEQ ID NO. 204, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 205, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 206, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 207, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 208, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 209, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 210, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 211, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 212, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 213, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 214, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 215, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 216, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 217; and (ii) a light chain comprising the amino acid sequence of SEQ ID NO. 218.

16. A binding molecule comprising (i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 145, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 147, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 149, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 151, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 153, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 155, or a heavy chain comprising the amino acid sequence of SEQ ID NO: 157, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 219, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 220, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 221, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 222, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 223, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 224, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 225, or a

heavy chain comprising the amino acid sequence of SEQ ID NO. 226, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 227, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 228, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 229, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 230, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 231, or a heavy chain comprising the amino acid sequence of SEQ ID NO. 232; and (ii) a light chain comprising the amino acid sequence of SEQ ID NO. 233.

17. An antibody molecule binding specifically to CDH17 comprising (i) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:58 (CDR1), SEQ ID NO:59 (CDR2) and SEQ ID NO:60 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:61 (CDR1), SEQ ID NO:62 (CDR2) and SEQ ID NO:63 (CDR3), (ii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:64 (CDR1), SEQ ID NO:65 (CDR2) and SEQ ID NO:66 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:67 (CDR1), SEQ ID NO:68 (CDR2) and SEQ ID NO:69 (CDR3), (iii) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO.:70 (CDR1), SEQ ID NO:71 (CDR2) and SEQ ID NO:72 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:73 (CDR1), SEQ ID NO:74 (CDR2) and SEQ ID NO:75 (CDR3), or (iv) heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:76 (CDR1), SEQ ID NO:77 (CDR2) and SEQ ID NO:78 (CDR3) and light chain CDRs comprising the amino acid sequences of SEQ ID NO:79 (CDR1), SEQ ID NO:80 (CDR2) and SEQ ID NO:81 (CDR3).

18. The antibody molecule of claim 17 comprising (i) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:110 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:111, (ii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:112 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:113, (iii) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:114 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:115, (iv) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:116 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:117, or (v) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:118 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO:119.

19. An isolated nucleic acid molecule encoding the heavy chain variable domain and/or the light chain variable domain of a binding molecule of any one of claims 8 to 11 or of an antibody molecule of any one of claims 17 or 18.

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20. An isolated nucleic acid molecule encoding the heavy chain and/or the light chain of a binding molecule of any one of claims 12 to 16.

21. An expression vector comprising a nucleic acid molecule of claim 19 or 20.

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22. A host cell transfected with an expression vector of claim 21.

23. A method of manufacturing a binding molecule of any one of claims 8 to 16 or an antibody molecule of claims 17 or 18 comprising

- 15 (a) cultivating the host cell of claim 22 under conditions allowing expression of the molecule; and,
(b) recovering the molecule; and optionally
c) further purifying and/or modifying and/or formulating the molecule.

20 24. The binding molecule of any one of claims 1 to 16 for use in medicine.

25. A pharmaceutical composition comprising a binding molecule of any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

25 26. Use of the binding molecule of any one of claims 1 to 16 for preparing a pharmaceutical composition for treating cancer.

27. The binding molecule of any one of claims 1 to 16 for use in treating cancer.

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28. The use of claim 26 or the binding molecule for use of claim 27, wherein the cancer is colorectal cancer (CRC), gastric cancer (GC), pancreatic cancer (PAC), esophageal cancer or a neuroendocrine tumor.