

SUMMARY

The present disclosure is based on a bispecific T cell engaging approach employing multi-specific binding proteins with a binding arm to CD3 on T cells and a binding arm to DLL3 on the cell surface of tumor cells. Through simultaneously binding to T cells and tumor
5 cells, the T cell engagers force formation of a cytolytic synapse between the two cells and so, redirect the T cell activity selectively to the targeted tumor cells.

In one aspect, the disclosure provides a protein comprising a first antigen binding unit specifically binding to DLL3 and a second antigen binding unit specifically binding to CD3, wherein said first antigen binding unit specifically binding to DLL3 is selected from
10 the group consisting of i) to xviii):

- i) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:4 (CDR1), SEQ ID NO:5 (CDR2) and SEQ ID NO:6 (CDR3);
- 15 ii) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:10 (CDR1), SEQ ID NO:11 (CDR2) and SEQ ID NO:12 (CDR3);
- 20 iii) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:16 (CDR1), SEQ ID NO:17 (CDR2) and SEQ ID NO:18 (CDR3);
- 25 iv) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:22 (CDR1), SEQ ID NO:23 (CDR2) and SEQ ID NO:24 (CDR3);

- 5 v) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:28 (CDR1), SEQ ID NO:29 (CDR2) and SEQ ID NO:30 (CDR3);
- 10 vi) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:34 (CDR1), SEQ ID NO:35 (CDR2) and SEQ ID NO:36 (CDR3);
- 15 vii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:133 (CDR1), SEQ ID NO:134 (CDR2) and SEQ ID NO:135 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:136 (CDR1), SEQ ID NO:137 (CDR2) and SEQ ID NO:138 (CDR3);
- 20 viii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:139 (CDR1), SEQ ID NO:140 (CDR2) and SEQ ID NO:141 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:142 (CDR1), SEQ ID NO:143 (CDR2) and SEQ ID NO:144 (CDR3);
- 25 ix) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:145 (CDR1), SEQ ID NO:146 (CDR2) and SEQ ID NO:147 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:148 (CDR1), SEQ ID NO:149 (CDR2) and SEQ ID NO:150 (CDR3);
- 30 x) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:151 (CDR1), SEQ ID NO:152 (CDR2) and SEQ ID NO:153 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:154 (CDR1), SEQ ID NO:155 (CDR2) and SEQ ID NO:156 (CDR3);
- xi) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:157 (CDR1), SEQ ID NO:158 (CDR2) and

SEQ ID NO:159 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:160 (CDR1), SEQ ID NO:161 (CDR2) and SEQ ID NO:162 (CDR3);

5 xii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:163 (CDR1), SEQ ID NO:164 (CDR2) and SEQ ID NO:165 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:166 (CDR1), SEQ ID NO:167 (CDR2) and SEQ ID NO:168 (CDR3);

10 xiii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:169 (CDR1), SEQ ID NO:170 (CDR2) and SEQ ID NO:171 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:172 (CDR1), SEQ ID NO:173 (CDR2) and SEQ ID NO:174 (CDR3);

15 xiv) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:175 (CDR1), SEQ ID NO:176 (CDR2) and SEQ ID NO:177 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:178 (CDR1), SEQ ID NO:179 (CDR2) and SEQ ID NO:180 (CDR3);

20 xv) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:181 (CDR1), SEQ ID NO:182 (CDR2) and SEQ ID NO:183 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:184 (CDR1), SEQ ID NO:185 (CDR2) and SEQ ID NO:186 (CDR3);

25 xvi) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:187 (CDR1), SEQ ID NO:188 (CDR2) and SEQ ID NO:189 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:190 (CDR1), SEQ ID NO:191 (CDR2) and SEQ ID NO:192 (CDR3);

30 xvii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:193 (CDR1), SEQ ID NO:194(CDR2) and SEQ ID NO:195 (CDR3) and heavy chain CDRs comprising the amino acid

sequences of SEQ ID NO:196 (CDR1), SEQ ID NO:197 (CDR2) and SEQ ID NO:198 (CDR3); and

xviii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:199 (CDR1), SEQ ID NO:200 (CDR2) and SEQ ID NO:201 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:202 (CDR1), SEQ ID NO:203 (CDR2) and SEQ ID NO:204 (CDR3).

In one example, the disclosure provides a multi-specific binding protein comprising a first antigen binding unit specifically binding to DLL3 and a second antigen binding unit specifically binding to CD3, said first antigen binding unit specifically binding to DLL3 selected from the group consisting of i) to xviii):

i) an antigen binding unit comprising light 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 heavy 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 unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:10 (CDR1), SEQ ID NO:11 (CDR2) and SEQ ID NO:12 (CDR3);

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

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

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

In some examples of the binding protein of the disclosure, the first antigen binding unit specifically binding to DLL3 comprises a first light chain variable domain and a first heavy chain variable domain and is selected from the group consisting of i) to xviii):

- 5 i) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:37 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:38;
- ii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequences of SEQ ID NO:39 and heavy chain variable domain
10 comprising the amino acid sequences of SEQ ID NO:40;
- iii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:41 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:42;
- iv) an antigen binding unit comprising a light chain variable domain comprising the
15 amino acid sequence of SEQ ID NO:43 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:44;
- v) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:45 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:46;
- 20 vi) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:47 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:48;
- vii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:205 and heavy chain variable domain
25 comprising the amino acid sequence of SEQ ID NO:206;
- viii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:207 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:208;

In some examples of the binding protein of the disclosure, the second antigen binding unit specifically binding to CD3 is selected from the group consisting of i) to iii):

- 5 i) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:55 (CDR1), SEQ ID NO:56 (CDR2) and SEQ ID NO:57 (CDR3) and 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);
- 10 ii) an antigen binding unit comprising 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) and 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
- iii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:96 (CDR1), SEQ ID NO:97 (CDR2) and SEQ ID NO:98 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:99 (CDR1), SEQ ID NO:100 (CDR2) and SEQ ID NO:101 (CDR3).

15 In some examples of the binding protein of the disclosure, the second antigen binding unit specifically binding to CD3 comprises a second light chain variable domain and a second heavy chain variable domain and is selected from the group consisting of:

- 20 i) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:67 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:68;
- ii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:69 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:70; and
- 25 iii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:102 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:103.

In some examples of the disclosure, the first antigen binding unit specifically binding to DLL3 comprises from its N- to C-terminus: a first light chain variable domain, a first light chain constant domain, a first peptide linker, a first heavy chain variable domain and a first heavy chain constant CH1 domain; and the second antigen binding unit specifically
5 binding to CD3 comprises from its N- to C-terminus: a second light chain variable domain, a second light chain constant domain, a second peptide linker, a second heavy chain

variable domain and a second heavy chain constant CH1 domain. In some examples of the disclosure, the first and/or second peptide linker comprises 26 to 42 amino acids, preferably any one of 30 to 40 amino acids, 34 to 40 amino acids, or 36 to 39 amino acids, more preferably 38 amino acids. In some examples of the disclosure, the first linker and/or
5 second linker is a Gly-Ser linker, preferably comprising the amino acid sequence of SEQ ID NO:89, more preferably said first and second peptide linker comprise the same sequence.

In some examples, the binding protein of the disclosure further comprises a first and a second Fc domain, said first Fc domain covalently linked to said first antigen binding unit,
10 and said second Fc domain covalently linked to said second antigen binding unit.

In some examples of the disclosure,

- i) the first Fc domain comprises a tyrosine (Y) at position 366 [T366Y], and the second Fc domain comprises a threonine (T) at position 407 [Y407T], or
- 15 ii) the first Fc domain comprises a tryptophan (W) at position 366 [T366W], and the second Fc domain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V], or
- iii) the second Fc domain comprises a tyrosine (Y) at position 366 [T366Y], and the first Fc domain comprises a threonine (T) at position 407 [Y407T], or
- 20 iv) the second Fc domain comprises a tryptophan (W) at position 366 [T366W], and the first Fc domain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V],

preferably the first or the second Fc domain further comprises an arginine at position 435 [H435R] and a phenylalanine at position 436 [Y436F]. In some examples, the first and/or second Fc domain further comprises an alanine at position 234[L234A] and at position 235
25 [L235A]. In some examples, the first light chain constant domain and the second light chain constant domain comprise a human kappa or lambda domain.

In a further aspect, the disclosure provides a protein comprising a first polypeptide chain specifically binding to DLL3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:241, SEQ ID NO; 242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, and SEQ ID NO: 252 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, SEQ ID NO:80 or SEQ ID NO:105.

In preferred examples, the binding protein of the disclosure comprises a first polypeptide chain specifically binding to DLL3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:241, SEQ ID NO; 242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, and SEQ ID NO: 252

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and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, SEQ ID NO:80 or SEQ ID NO:105.

The disclosure also provides an isolated nucleic acid molecule i) encoding a first antigen binding unit and/or a second antigen binding unit of a protein of the disclosure, optionally
5 further encoding a first and/or a second Fc domain, or ii) encoding a first and/or a second polypeptide chain of a protein of the disclosure. In a further aspect, the disclosure provides an isolated nucleic acid molecule encoding the first antigen binding unit and/or the second antigen binding unit of a protein of the disclosure, optionally further encoding a first and/or a second Fc domain. In a further aspect, the disclosure provides an isolated nucleic acid
10 molecule encoding the first and/or the second polypeptide chain of the disclosure. The disclosure also provides expression vectors comprising the nucleic acid molecule of the disclosure, host cells transfected with such expression vectors, and methods of manufacturing a protein of the disclosure. In a further aspect, provided herein is an expression vector comprising the nucleic acid molecule of the disclosure. In a further aspect,
15 provided herein is a host cell transfected with the expression vector of the disclosure. In a further aspect, provided herein is a method of manufacturing a protein of the disclosure comprising i) cultivating the host cell of disclosure under conditions allowing expression of the protein of the disclosure; and, ii) recovering the protein; and optionally iii) further purifying and/or modifying and/or formulating the protein.

20 In a further aspect, provided herein is a protein comprising a first polypeptide chain specifically binding to DLL3 and a second polypeptide chain specifically binding to CD3, wherein said first polypeptide chain comprises a first light chain, a first linker, and a first heavy chain and said second polypeptide chain comprises a second light chain, a second linker, and a second heavy chain, preferably wherein the C-terminus of said first light
25 chain is covalently linked to the N-terminus of said first heavy chain via said first peptide linker and wherein the C-terminus of said second light chain is covalently linked to the N-terminus of said second heavy chain via said second peptide linker.

In a further example of the disclosure, provided herein is a multi-specific binding protein comprising a first polypeptide chain specifically binding to DLL3 and a second polypeptide chain specifically binding to CD3, where the first polypeptide chain comprises a first light chain, a first linker, and a first heavy chain and the second polypeptide chain
5 comprises a second light chain, a second linker, and a second heavy chain, preferably the C-terminus of said first light chain is covalently bound to the N-terminus of said first heavy chain via said first peptide linker and the C-terminus of said second light chain is covalently bound to the N-terminus of said second heavy chain via said second peptide linker.

10 In some examples of the binding protein of the disclosure, the first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain comprising CDR sequences and/or VH/VL sequences as defined for the antigen binding units of DLL3#1, DLL3#2, DLL3#3, DLL3#4, DLL3#5, DLL3#6, DLL3#7, DLL3#8, DLL3#9, DLL3#10, DLL3#11, DLL3#12, DLL3#13, DLL3#14,
15 DLL3#15, DLL3#16, DLL3#17, or DLL3#18 described herein. In some examples, the second polypeptide chain specifically binding to CD3 comprises a light chain variable and heavy chain variable domain comprising CDR sequences and/or VH/VL sequences as defined for the antigen binding units of CD3#1, CD3#2, or CD3#3 described herein.

In a further aspect, the disclosure provides the protein of the disclosure for use in medicine.

20 In a further aspect, the disclosure provides a pharmaceutical composition comprising the protein of the disclosure and a pharmaceutically acceptable carrier.

In a further aspect, the disclosure provides a use of the protein of the disclosure in preparing a pharmaceutical composition for treating cancer.

In a further aspect, the disclosure provides the protein of the disclosure for use in treating
25 cancer.

Further examples, uses and methods involving the binding proteins of the disclosure will become clear from the following detailed description of the disclosure and from the appended claims.

The disclosure provides for novel binding proteins that allow a more efficient treatment of DLL3 expressing cancers, such as SCLC, glioblastoma or a DLL3 expressing neuroendocrine tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Schematic representation of a bispecific binding protein of the invention

Figure 2: Schematic representation of the DLL3 full length protein and DLL3 domain constructs expressed on HEK293 cells for epitope domain mapping. For the DLL3 domain constructs, the transmembrane and the intracellular domains are derived from EpCAM.

Figure 3A: DLL3 epitope domain mapping of seven exemplary DLL3/CD3 binding proteins. Exemplary DLL3/CD3 binding proteins recognizing the membrane proximal peptide, EGF4, EGF1 and DSL domains of DLL3. The y-axis depicts counts, the x-axis depicts PE-A (phycoerythrin signal area).

Figure 3B: DLL3 epitope domain mapping of six exemplary DLL3/CD3 binding proteins. Exemplary DLL3/CD3 binding proteins recognizing the EGF1, EGF3, EGF4 or EGF6 of DLL3. The y-axis depicts counts, the x-axis depicts PE-A (phycoerythrin signal).

Figure 3C: DLL3 epitope domain mapping of six exemplary DLL3/CD3 binding proteins. Exemplary DLL3/CD3 binding proteins recognizing the DSL domains or neither DSL, EGF, nor membrane proximal peptide of DLL3. The y-axis depicts counts, the x-axis depicts PE-A (phycoerythrin signal).

Figure 4: Binding of seven exemplary DLL3/CD3 binding proteins to cell lines expressing human and cyno DLL3. The y-axis depicts counts, the x-axis depicts PE-A (phycoerythrin signal area).

Figure 5: Binding of seven exemplary DLL3/CD3 binding proteins to cell lines expressing human DLL1 and DLL4, no binding to human DLL1 and DLL4 detected. The y-axis depicts counts, the x-axis depicts PE-A (phycoerythrin signal area).

Figure 6A: Binding of seven exemplary DLL3/CD3 binding proteins to SCLC cell lines and human T cells by flow cytometry analysis.

Figure 6 B: Binding of exemplary DLL3/CD3 binding proteins (directed to a peptide that is neither the DSL nor the EGF1-6 nor the membrane proximal peptide) to SHP77 cells.

CLAIMS

1. A protein comprising a first antigen binding unit specifically binding to DLL3 and a second antigen binding unit specifically binding to CD3, wherein said first antigen binding unit specifically binding to DLL3 is selected from the group consisting of i) to xviii):
- 5
- i) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:4 (CDR1), SEQ ID NO:5 (CDR2) and SEQ ID NO:6 (CDR3);
- 10
- ii) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:10 (CDR1), SEQ ID NO:11 (CDR2) and SEQ ID NO:12 (CDR3);
- 15
- iii) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:16 (CDR1), SEQ ID NO:17 (CDR2) and SEQ ID NO:18 (CDR3);
- 20
- iv) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:22 (CDR1), SEQ ID NO:23 (CDR2) and SEQ ID NO:24 (CDR3);
- 25
- v) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:28 (CDR1), SEQ ID NO:29 (CDR2) and SEQ ID NO:30 (CDR3);
- 30
- vi) an antigen binding unit comprising light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:34 (CDR1), SEQ ID NO:35 (CDR2) and SEQ ID NO:36 (CDR3);

5 vii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:133 (CDR1), SEQ ID NO:134 (CDR2) and SEQ ID NO:135 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:136 (CDR1), SEQ ID NO:137 (CDR2) and SEQ ID NO:138 (CDR3);

10 viii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:139 (CDR1), SEQ ID NO:140 (CDR2) and SEQ ID NO:141 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:142 (CDR1), SEQ ID NO:143 (CDR2) and SEQ ID NO:144 (CDR3);

15 ix) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:145 (CDR1), SEQ ID NO:146 (CDR2) and SEQ ID NO:147 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:148 (CDR1), SEQ ID NO:149 (CDR2) and SEQ ID NO:150 (CDR3);

20 x) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:151 (CDR1), SEQ ID NO:152 (CDR2) and SEQ ID NO:153 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:154 (CDR1), SEQ ID NO:155 (CDR2) and SEQ ID NO:156 (CDR3);

25 xi) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:157 (CDR1), SEQ ID NO:158 (CDR2) and SEQ ID NO:159 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:160 (CDR1), SEQ ID NO:161 (CDR2) and SEQ ID NO:162 (CDR3);

30 xii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:163 (CDR1), SEQ ID NO:164 (CDR2) and SEQ ID NO:165 (CDR3) and heavy chain CDRs comprising the amino acid

sequences of SEQ ID NO:166 (CDR1), SEQ ID NO:167 (CDR2) and SEQ ID NO:168 (CDR3);

xiii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:169 (CDR1), SEQ ID NO:170 (CDR2) and SEQ ID NO:171 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:172 (CDR1), SEQ ID NO:173 (CDR2) and SEQ ID NO:174 (CDR3);

xiv) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:175 (CDR1), SEQ ID NO:176 (CDR2) and SEQ ID NO:177 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:178 (CDR1), SEQ ID NO:179 (CDR2) and SEQ ID NO:180 (CDR3);

xv) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:181 (CDR1), SEQ ID NO:182 (CDR2) and SEQ ID NO:183 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:184 (CDR1), SEQ ID NO:185 (CDR2) and SEQ ID NO:186 (CDR3);

xvi) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:187 (CDR1), SEQ ID NO:188 (CDR2) and SEQ ID NO:189 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:190 (CDR1), SEQ ID NO:191 (CDR2) and SEQ ID NO:192 (CDR3);

xvii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:193 (CDR1), SEQ ID NO:194(CDR2) and SEQ ID NO:195 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:196 (CDR1), SEQ ID NO:197 (CDR2) and SEQ ID NO:198 (CDR3); and

xviii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:199 (CDR1), SEQ ID NO:200 (CDR2) and SEQ ID NO:201 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:202 (CDR1), SEQ ID NO:203 (CDR2) and SEQ ID NO:204 (CDR3)..

2. The protein of claim 1, wherein said first antigen binding unit specifically binding to DLL3 comprises a first light chain variable domain and a first heavy chain variable domain and is selected from the group consisting of i) to xviii):

- 5 i) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:37 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:38;
- ii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequences of SEQ ID NO:39 and heavy chain variable domain
10 comprising the amino acid sequences of SEQ ID NO:40;
- iii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:41 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:42;
- iv) an antigen binding unit comprising a light chain variable domain comprising
15 the amino acid sequence of SEQ ID NO:43 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:44;
- v) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:45 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:46;
- vi) an antigen binding unit comprising a light chain variable domain comprising
20 the amino acid sequence of SEQ ID NO:47 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:48;
- vii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:205 and heavy chain variable domain
25 comprising the amino acid sequence of SEQ ID NO:206;
- viii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:207 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:208;
- ix) an antigen binding unit comprising a light chain variable domain comprising
30 the amino acid sequence of SEQ ID NO:209 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:210;

- x) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:211 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:212;
- xi) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:213 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:214;
- xii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:215 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:216;
- xiii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:217 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:218;
- xiv) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:219 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:220;
- xv) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:221 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:222;
- xvi) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:223 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:224;
- xvii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:225 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:226; and
- xviii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:227 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:228.

3. The protein of claims 1 or 2, wherein said second antigen binding unit specifically binding to CD3 is selected from the group consisting of i)-iii):

- i) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:55 (CDR1), SEQ ID NO:56 (CDR2) and SEQ ID NO:57 (CDR3) and 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);
- 5 ii) an antigen binding unit comprising 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) and 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
- 10 iii) an antigen binding unit comprising light chain CDRs comprising the amino acid sequences of SEQ ID NO:96 (CDR1), SEQ ID NO:97 (CDR2) and SEQ ID NO:98 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:99 (CDR1), SEQ ID NO:100 (CDR2) and SEQ ID NO:101 (CDR3).
- 15 4. The protein of any one of claims 1 to 3, wherein said second antigen binding unit specifically binding to CD3 comprises a second light chain variable domain and a second heavy chain variable domain selected from the group consisting of i) to iii):
- i) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:67 and a heavy chain variable domain
- 20 comprising the amino acid sequence of SEQ ID NO:68;
- ii) an antigen binding unit comprising a light chain variable domain comprising the amino acid sequence of SEQ ID NO:69 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:70; and
- iii) an antigen binding unit comprising a light chain variable domain comprising the
- 25 amino acid sequence of SEQ ID NO:102 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:103.
5. The protein of any one of claims 1 to 4, wherein
- i) said first antigen binding unit specifically binding to DLL3 comprises from its N-
- 30 to C-terminus a first light chain variable domain, a first light chain constant domain, a first peptide linker, a first heavy chain variable domain and a first heavy chain constant CH1 domain; and

- ii) said second antigen binding unit specifically binding to CD3 comprises from its N- to C-terminus a second light chain variable domain, a second light chain constant domain, a second peptide linker, a second heavy chain variable domain and a second heavy chain constant CH1 domain.

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- 6. The protein of claim 5, wherein said first and/or second peptide linker comprises 26 to 42 amino acids, preferably any one of 30 to 40 amino acids, 34 to 40 amino acids, or 36 to 39 amino acids, more preferably 38 amino acids.

- 10 7. The protein of claims 5 or 6, wherein said first linker and/or second linker is a Gly-Ser linker, preferably comprising the amino acid sequence of SEQ ID NO:89, more preferably said first and second peptide linker comprise the same sequence.

- 8. The protein of any one of claims 5 to 7 further comprising a first and a second Fc domain, said first Fc domain covalently linked to said first antigen binding unit, and a
15 said second Fc domain covalently linked to said second antigen binding unit.

- 9. The protein of claim 8, wherein

- i) said first Fc domain comprises a tyrosine (Y) at position 366 [T366Y], and said
20 second Fc domain comprises a threonine (T) at position 407 [Y407T], or

- ii) said first Fc domain comprises a tryptophan (W) at position 366 [T366W], and said second Fc domain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V], or

- iii) said second Fc domain comprises a tyrosine (Y) at position 366 [T366Y], and
25 said first Fc domain comprises a threonine (T) at position 407 [Y407T], or

- iv) said second Fc domain comprises a tryptophan (W) at position 366 [T366W], and said first Fc domain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V],

- preferably wherein said first or said second Fc domain further comprises an arginine at
30 position 435 [H435R] and a phenylalanine at position 436 [Y436F].

10. The protein of claim 9, wherein said first and/or said second Fc domain further comprises an alanine at position 234[L234A] and at position 235 [L235A].
11. The protein of any one of claims 5 to 10, wherein the first light chain constant domain and the second light chain constant domain comprise a human kappa or lambda domain.
12. A protein comprising a first polypeptide chain specifically binding to DLL3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:241, SEQ ID NO: 242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, and SEQ ID NO: 252 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, SEQ ID NO:80 or SEQ ID NO:105.
13. An isolated nucleic acid molecule encoding the first antigen binding unit and/or the second antigen binding unit of a protein of any one of claims 1 to 5, optionally further encoding a first and/or a second Fc domain.
14. An isolated nucleic acid molecule encoding the first and/or the second polypeptide chain of claim 12.
15. An expression vector comprising the nucleic acid molecule of claim 13 or 14.
16. A host cell transfected with the expression vector of claim 15.
17. A method of manufacturing a protein of any one of claims 1 to 12 comprising
- i) cultivating the host cell of claim 16 under conditions allowing expression of the protein of any one of claims 1 to 12; and,
 - ii) recovering the protein; and optionally
 - iii) further purifying and/or modifying and/or formulating the protein.

18. A protein comprising a first polypeptide chain specifically binding to DLL3 and a second polypeptide chain specifically binding to CD3, wherein said first polypeptide chain comprises a first light chain, a first linker, and a first heavy chain and said second polypeptide chain comprises a second light chain, a second linker, and a second heavy chain, preferably wherein the C-terminus of said first light chain is covalently linked to the N-terminus of said first heavy chain via said first peptide linker and wherein the C-terminus of said second light chain is covalently linked to the N-terminus of said second heavy chain via said second peptide linker.
19. The protein of claim 18, wherein said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain comprising CDR sequences selected from the group consisting of i) to xviii):
- i) light 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 a heavy 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) light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:10 (CDR1), SEQ ID NO:11 (CDR2) and SEQ ID NO:12 (CDR3);
 - iii) light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:16 (CDR1), SEQ ID NO:17 (CDR2) and SEQ ID NO:18 (CDR3);
 - iv) light 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 heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:22 (CDR1), SEQ ID NO:23 (CDR2) and SEQ ID NO:24 (CDR3);
 - v) light 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 heavy

chain CDRs comprising the amino acid sequences of SEQ ID NO:28 (CDR1),
SEQ ID NO:29 (CDR2) and SEQ ID NO:30 (CDR3);

vi) light 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 heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:34 (CDR1),
SEQ ID NO:35 (CDR2) and SEQ ID NO:36 (CDR3)

vii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:133
(CDR1), SEQ ID NO:134 (CDR2) and SEQ ID NO:135 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:136
(CDR1), SEQ ID NO:137 (CDR2) and SEQ ID NO:138 (CDR3);

viii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:139
(CDR1), SEQ ID NO:140 (CDR2) and SEQ ID NO:141 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:142
(CDR1), SEQ ID NO:143 (CDR2) and SEQ ID NO:144 (CDR3);

ix) light chain CDRs comprising the amino acid sequences of SEQ ID NO:145
(CDR1), SEQ ID NO:146 (CDR2) and SEQ ID NO:147 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:148
(CDR1), SEQ ID NO:149 (CDR2) and SEQ ID NO:150 (CDR3);

x) light chain CDRs comprising the amino acid sequences of SEQ ID NO:151
(CDR1), SEQ ID NO:152 (CDR2) and SEQ ID NO:153 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:154
(CDR1), SEQ ID NO:155 (CDR2) and SEQ ID NO:156 (CDR3);

xi) light chain CDRs comprising the amino acid sequences of SEQ ID NO:157
(CDR1), SEQ ID NO:158 (CDR2) and SEQ ID NO:159 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:160
(CDR1), SEQ ID NO:161 (CDR2) and SEQ ID NO:162 (CDR3);

xii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:163
(CDR1), SEQ ID NO:164 (CDR2) and SEQ ID NO:165 (CDR3) and heavy
chain CDRs comprising the amino acid sequences of SEQ ID NO:166
(CDR1), SEQ ID NO:167 (CDR2) and SEQ ID NO:168 (CDR3);

- xiii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:169 (CDR1), SEQ ID NO:170 (CDR2) and SEQ ID NO:171 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:172 (CDR1), SEQ ID NO:173 (CDR2) and SEQ ID NO:174 (CDR3);
- 5 light chain CDRs comprising the amino acid sequences of SEQ ID NO:175 (CDR1), SEQ ID NO:176 (CDR2) and SEQ ID NO:177 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:178 (CDR1), SEQ ID NO:179 (CDR2) and SEQ ID NO:180 (CDR3);
- xiv) light chain CDRs comprising the amino acid sequences of SEQ ID NO:181 (CDR1), SEQ ID NO:182 (CDR2) and SEQ ID NO:183 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:184 (CDR1), SEQ ID NO:185 (CDR2) and SEQ ID NO:186 (CDR3);
- 10
- xv) light chain CDRs comprising the amino acid sequences of SEQ ID NO:187 (CDR1), SEQ ID NO:188 (CDR2) and SEQ ID NO:189 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:190 (CDR1), SEQ ID NO:191 (CDR2) and SEQ ID NO:192 (CDR3);
- 15
- xvi) light chain CDRs comprising the amino acid sequences of SEQ ID NO:193 (CDR1), SEQ ID NO:194(CDR2) and SEQ ID NO:195 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:196 (CDR1), SEQ ID NO:197 (CDR2) and SEQ ID NO:198 (CDR3); and
- 20
- xvii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:199 (CDR1), SEQ ID NO:200 (CDR2) and SEQ ID NO:201 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:202 (CDR1), SEQ ID NO:203 (CDR2) and SEQ ID NO:204 (CDR3).

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20. The protein of claim 18 or 19, wherein said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and heavy chain variable domain comprising CDR sequences selected from the group consisting of i) to iii):

- i) light chain CDRs comprising the amino acid sequences of SEQ ID NO:55 (CDR1), SEQ ID NO:56 (CDR2) and SEQ ID NO:57 (CDR3) and 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);
- 30

- ii) 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) and 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
- 5 iii) light chain CDRs comprising the amino acid sequences of SEQ ID NO:96 (CDR1), SEQ ID NO:97 (CDR2) and SEQ ID NO:98 (CDR3) and heavy chain CDRs comprising the amino acid sequences of SEQ ID NO:99 (CDR1), SEQ ID NO:100 (CDR2) and SEQ ID NO:101 (CDR3).
- 10 21. The protein of any one of claims 18 to 20, wherein said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and a heavy chain variable domain selected from the group consisting of i) to xviii):
- 15 i) a light chain variable domain comprising the amino acid sequences of SEQ ID NO:37 and heavy chain variable domain comprising the amino acid sequences of SEQ ID NO:38;
- 20 ii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:39 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:40;
- 20 iii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:41 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:42;
- 25 iv) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:43 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:44;
- 25 v) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:45 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:46;
- 30 vi) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:47 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:48;

- vii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:205 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:206;
- 5 viii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:207 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:208 ;
- ix) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:209 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:210;
- 10 x) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:211 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:212;
- xi) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:213 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:214 ;
- 15 xii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:215 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:216;
- xiii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:217 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:218;
- 20 xiv) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:219 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:220;
- xv) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:221 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:222 ;
- 25 xvi) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:223 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:224;
- 30

- xvii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:225 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:226; and
- xviii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:227 and heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:228.

22. The protein of any one of claims 19 to 22, wherein said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain selected from the group consisting of i)-iii):

- i) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:67 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:68;
- ii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:69 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:70; and
- iii) a light chain variable domain comprising the amino acid sequence of SEQ ID NO:102 and a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:103.

23. The protein of any one of claims 18 to 22, wherein said first and/or second peptide linker comprises 26 to 42 amino acids, preferably any one of 30 to 40 amino acids, 34 to 40 amino acids, or 36 to 39 amino acids, more preferably 38 amino acids.

24. The protein of claim 23, wherein said first linker and/or second linker is a Gly-Ser linker, preferably comprising the amino acid sequence of SEQ ID NO:89, more preferably said first and second peptide linker comprise the same sequence.

25. The protein of any one of claims 18 to 24, wherein

i) said first heavy chain comprises a tyrosine (Y) at position 366 [T366Y], and said second heavy chain comprises a threonine (T) at position 407 [Y407T], or

ii) said first heavy chain comprises a tryptophan (W) at position 366 [T366W], and said second heavy chain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V], or
iii) said second heavy chain comprises a tyrosine (Y) at position 366 [T366Y], and said
5 first heavy chain comprises a threonine (T) at position 407 [Y407T], or
iv) said second heavy chain comprises a tryptophan (W) at position 366 [T366W], and said first heavy chain comprises a serine (S) at position 366 [T366S], an alanine (A) at position 368 [L368A] and a valine (V) at position 407 [Y407V],
preferably wherein said first or said second heavy chain further comprises an arginine
10 at position 435 [H435R] and a phenylalanine at position 436 [Y436F].

26. The protein of claim 25, wherein said first and/or said second heavy chain further comprises an alanine at position 234[L234A] and at position 235 [L235A].

15 27. The protein of any one of claims 18 to 26, wherein said first light chain and said second light chain comprise a human kappa or lambda domain.

28. The protein of any one of claims 1 to 12 or 18 to 27 for use in medicine.

20 29. A pharmaceutical composition comprising the protein of any one of claims 1 to 12 or 18 to 27 and a pharmaceutically acceptable carrier.

30. Use of the protein of any one of claims 1 to 12 or 18 to 27 in preparing a pharmaceutical composition for treating cancer.

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31. The protein of any one of claims 1 to 12 or 18 to 27 for use in treating cancer.

32. The use of claim 30 or the protein for use of claim 31, wherein the cancer is a DLL3 expressing tumor, preferably wherein the cancer is SCLC, glioblastoma or a DLL3
30 expressing neuroendocrine tumor.

33. The use of claim 30 or 32, or the protein for use of claim 31 or 32, wherein said protein is used in combination with a chemotherapeutic agent, a therapeutically active

compound that inhibits angiogenesis, a signal transduction pathway inhibitor, an EGFR inhibitor, an immune modulator, an immune checkpoint inhibitor, or a hormonal therapy agent.

5 34. The use or protein for use of claim 33, wherein said protein is in combination with an immune checkpoint inhibitor, preferably an anti- PD-1antibody or an anti-PD-L1 antibody.

10 35. The use or protein for use of claim 34, wherein the anti-PD-1 antibody is selected from the group consisting of PD1-1, PD1-2, PD1-3, PD1-4, and PD1-5.