

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 iii):

- 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); and
- 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);

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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):

- 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);
- 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 a further aspect, the disclosure provides a protein comprising

- (i) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79,
- 5 (ii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, or
- (iii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and and a second polypeptide chain
10 specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, or
- (iv) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- 15 (v) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- (vi) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain specifically
20 binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- (vii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:105, or

- (viii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:105, or
- (ix) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of 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

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. In a further aspect, the disclosure provides an isolated nucleic acid molecule encoding the first and/or the second polypeptide
10 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, provided herein is a host cell transfected with the expression vector of the
15 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.

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,
20 wherein said first polypeptide chain comprises a first light chain, a first peptide linker, and a first heavy chain and said second polypeptide chain comprises a second light chain, a second peptide linker, and a second heavy chain, 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-
25 terminus of said second heavy chain via said second peptide linker,

and 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 iii):

- 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);
- 5 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); and
- 10 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).

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 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.

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, 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.

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

5 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 cancer.

10 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.

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 iii):
 - 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); and
 - 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).
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 iii):
 - 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 comprising the amino acid sequences of SEQ ID NO:40; and

- 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.
- 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);
 - 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).
- 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 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 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 claim 1 or 3, wherein

- (i) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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); or
- (ii) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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); or
- (iii) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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); or

- (iv) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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); or
- (v) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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); or
- (vi) said first antigen binding unit comprises 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), and said second antigen binding unit comprises 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).

6. The protein of any one of claims 1 to 4, wherein

- (i) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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; or
- (ii) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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; or
- (iii) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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; or
- (iv) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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; or
- (v) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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; or

- (vi) said first antigen binding unit comprises 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, and said second antigen binding unit comprises 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.
7. The protein of any one of claims 1 to 6, wherein
- i) said 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
 - 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.
8. The protein of claim 7, wherein said first and/or second peptide linker comprises 26 to 42 amino acids, 30 to 40 amino acids, 34 to 40 amino acids, or 36 to 39 amino acids.
9. The protein of claims 7 or 8, wherein said first peptide linker and/or second peptide linker is a Gly-Ser linker comprising the amino acid sequence of SEQ ID NO:89, and wherein said first and second peptide linker comprise the same sequence.
10. The protein of any one of claims 7 to 9, wherein
- (i) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:49, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:71; or
 - (ii) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:50, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:71; or

- (iii) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:51, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:71; or
 - (iv) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:49, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:72; or
 - (v) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:50, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:72; or
 - (vi) said first antigen binding unit comprises the amino acid sequence of SEQ ID NO:51, and said second antigen binding unit comprises the amino acid sequence of SEQ ID NO:72.
11. The protein of any one of claims 7 to 10 further comprising a first and a second Fc domain, said first Fc domain covalently linked to said first antigen binding unit, and a said second Fc domain covalently linked to said second antigen binding unit.
12. The protein of claim 11, wherein
- i) said first Fc domain comprises a tyrosine (Y) at position 366 [T366Y], and said 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 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].
13. The protein of claim 12, wherein said first and/or said second Fc domain further comprises an alanine at position 234[L234A] and at position 235 [L235A].

14. The protein of any one of claims 7 to 13, wherein the first light chain constant domain and the second light chain constant domain comprise a human kappa or lambda domain.

15. A protein comprising

- (i) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79,
- (ii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, or
- (iii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:79, or
- (iv) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- (v) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- (vi) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:80, or
- (vii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:105, or
- (viii) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:74 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:105, or

- (ix) a first polypeptide chain specifically binding to DLL3 comprising the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain specifically binding to CD3 comprising the amino acid sequence of SEQ ID NO:105.
16. 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 10.
17. An isolated nucleic acid molecule encoding the first and/or the second polypeptide chain of claim 15.
18. An expression vector comprising the nucleic acid molecule of claim 16 or 17.
19. A host cell transfected with the expression vector of claim 18.
20. A method of manufacturing a protein of any one of claims 1 to 15 comprising
- i) cultivating the host cell of claim 19 under conditions allowing expression of the protein of any one of claims 1 to 15; and,
 - ii) recovering the protein.
21. 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 peptide linker, and a first heavy chain and said second polypeptide chain comprises a second light chain, a second peptide linker, and a second heavy chain, 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, and 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 iii):

- 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); and
- 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).

22. The protein of claim 21, 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);
- 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
- 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).

23. The protein of claim 22, wherein

- i) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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); or
- ii) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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); or
- iii) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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); or

- iv) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain and heavy chain variable domain 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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); or
- v) 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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); or
- vi) 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); and said second polypeptide chain specifically binding to CD3 comprises a light chain variable domain and a heavy chain variable domain 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).

24. The protein of any one of claims 21 to 23, 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 iii):

- 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;
- 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; and
- 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. The protein of any one of claims 21 to 24, 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.

26. The protein of claims 24 or 25, wherein

- (i) said first polypeptide chain specifically binding to DLL3 comprises 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; and said second polypeptide chain specifically binding to CD3 comprises 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; or

- (ii) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain comprising the amino acid sequences of SEQ ID NO:39 and heavy chain variable domain comprising the amino acid sequences of SEQ ID NO:40; and said second polypeptide chain specifically binding to CD3 comprises 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; or
- (iii) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain comprising the amino acid sequences of SEQ ID NO:41 and heavy chain variable domain comprising the amino acid sequences of SEQ ID NO:42; and said second polypeptide chain specifically binding to CD3 comprises 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; or
- (iv) said first polypeptide chain specifically binding to DLL3 comprises 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; and said second polypeptide chain specifically binding to CD3 comprises 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; or
- (v) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain comprising the amino acid sequences of SEQ ID NO:39 and heavy chain variable domain comprising the amino acid sequences of SEQ ID NO:40; and said second polypeptide chain specifically binding to CD3 comprises 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; or

- (vi) said first polypeptide chain specifically binding to DLL3 comprises a light chain variable domain comprising the amino acid sequences of SEQ ID NO:41 and heavy chain variable domain comprising the amino acid sequences of SEQ ID NO:42; and said second polypeptide chain specifically binding to CD3 comprises 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.

27. The protein of any one of claims 21 to 26, wherein said first and/or second peptide linker comprises 26 to 42 amino acids, 30 to 40 amino acids, 34 to 40 amino acids, or 36 to 39 amino acids.

28. The protein of claim 27, wherein said first peptide linker and/or second peptide linker is a Gly-Ser linker comprising the amino acid sequence of SEQ ID NO:89, and wherein said first and second peptide linker comprise the same sequence.

29. The protein of any one of claims 21 to 28, wherein

- (i) said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:49, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:71; or
- (ii) said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:50, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:71; or
- (iii) said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:51, and said second polypeptide chain unit comprises the amino acid sequence of SEQ ID NO:71; or
- (iv) said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:49, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:72; or

- (v) said first polypeptide chain comprises the amino acid sequence of SEQ ID NO:50, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:72; or
 - (vi) said first polypeptide chain unit comprises the amino acid sequence of SEQ ID NO:51, and said second polypeptide chain comprises the amino acid sequence of SEQ ID NO:72.
30. The protein of any one of claims 21 to 29, 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 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].
31. The protein of claim 30, wherein said first and/or said second heavy chain further comprises an alanine at position 234[L234A] and at position 235 [L235A].
32. The protein of any one of claims 21 to 31, wherein said first light chain and said second light chain comprise a human kappa or lambda domain.
33. The protein of any one of claims 1 to 15 or 21 to 32 for use in medicine.
34. A pharmaceutical composition comprising the protein of any one of claims 1 to 15 or 21 to 32 and a pharmaceutically acceptable carrier.
35. Use of the protein of any one of claims 1 to 15 or 21 to 32 in preparing a pharmaceutical composition for treating cancer.

36. The protein of any one of claims 1 to 15 or 21 to 32 for use in treating cancer.
37. The use of claim 35 or the protein for use of claim 36, wherein the cancer is a DLL3 expressing tumor, SCLC, glioblastoma or a DLL3 expressing neuroendocrine tumor.
38. The use of claim 35 or 37, or the protein for use of claim 36 or 37, 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.
39. The use or protein for use of claim 38, wherein said protein is in combination with an immune checkpoint inhibitor, preferably an anti- PD-1antibody or an anti-PD-L1 antibody.
40. The use or protein for use of claim 39, wherein the anti-PD-1 antibody is selected from the group consisting of PD1-1, PD1-2, PD1-3, PD1-4, and PD1-5.