

expression systems. Furthermore, the presence or absence of undesired side products can be of high importance.

SUMMARY

The present disclosure refers to bispecific antibodies that particularly consist of two chains although they comprise three antigen binding domains. The antibodies of the present disclosure differ in the spatial orientation of the antigen binding domain from classical antibodies in the IgG format.

The present disclosure, in one aspect, provides a bispecific antibody consisting of two fusion polypeptides and comprising two antigen binding domains capable of specific binding to a first target and one antigen binding domain capable of specific binding to a second target, wherein

(a) the first fusion polypeptide comprises a first part of a first antigen binding domain capable of specific binding to the first target, a spacer domain, a second part of a first antigen binding domain capable of specific binding to the first target and a first part of an antigen binding domain capable of specific binding to the second target, wherein

- the spacer domain is a polypeptide and comprises at least 25 amino acid residues,
- the first part of the first antigen binding domain capable of specific binding to the first target is fused either directly or via a first peptide linker to the N-terminus of the spacer domain,
- the second part of the first antigen binding domain capable of specific binding to the first target is fused either directly or via a second peptide linker to the C-terminus of the spacer domain, and
- the first part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target or is fused either directly or via a third peptide linker to the N-terminus of the first part of the first antigen binding domain capable of specific binding to the first target, and

(b) the second fusion polypeptide comprising a first part of a second antigen binding domain capable of specific binding to a first target, a spacer domain, a second part of the second antigen binding domain capable of specific binding to a first target and the second part of an antigen binding domain capable of specific binding to a second target, wherein

- the spacer domain is a polypeptide and comprises at least 25 amino acid residues,

- the first part of the second antigen binding domain capable of specific binding to a first target is fused either directly or via a first peptide linker to the N-terminus of the spacer domain,

- the second part of the second antigen binding domain capable of specific binding to a first target is fused either directly or via a second peptide linker to the C-terminus of the spacer domain, and

- the second part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the second antigen binding domain capable of specific binding to a first target or is fused either directly or via a third peptide linker to the N-terminus of the first part of the second antigen binding domain capable of specific binding to a first target,

wherein the first part and the second part of the antigen binding domain capable of specific binding to the second target are associated with each other to form the antigen binding domain capable of specific binding to the second target and wherein the first part and the second part of the first and second antigen binding domain capable of specific binding to the first target are associated with each other to form a circular fusion polypeptide, and

wherein the spacer domain of the first fusion polypeptide and the spacer domain of the second fusion polypeptide are associated covalently to each other by a disulfide bond and comprise modifications promoting the association of the first and second fusion polypeptide.

In one example, provided is a bispecific antibody as defined herein before, wherein in the first fusion polypeptide the first part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target and wherein in the second fusion polypeptide the second part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target.

In another example, provided is a bispecific antibody as defined herein before, wherein in the first fusion polypeptide the first part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the N-terminus of the first part of the first antigen binding domain capable of specific binding to the first target and wherein in the second fusion polypeptide the second part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the N-

terminus of the first part of the first antigen binding domain capable of specific binding to the first target.

In one example, provided is a bispecific antibody as defined herein before, wherein the third peptide linker connecting the first part or the second part of an antigen binding domain capable of specific binding to a second target comprises at least 15 amino acids. In one example, the third peptide linker connecting the first part of an antigen binding domain capable of specific binding to a second target and the third peptide linker connecting the second part of an antigen binding domain capable of specific binding to a second target are identical. In one example, the third peptide linker comprises 15 to 25 amino acids. In one particular example, the third peptide linker comprises the amino acid sequence of SEQ ID NO:84.

In one example, the disclosure provides a bispecific antibody as defined herein before, wherein the first fusion polypeptide comprises the heavy chain variable domain of the antigen binding domain capable of specific binding to a second target and the second fusion polypeptide comprises the antibody light chain variable domain of the antigen binding domain capable of specific binding to a second target or vice versa. In one particular example, the first part of the antigen binding domain is an antibody heavy chain Fab fragment and the second part of the antigen binding domain is an antibody light chain Fab fragment or vice versa. In one example, the first part of the antigen binding domain and the second part of the antigen binding domain are associated covalently to each other by a disulfide bond.

Thus, in one example, the first part of the antigen binding domain is an antibody heavy chain Fab fragment (VH-CH1) and the second part of the antigen binding domain is an antibody light chain Fab fragment (VL-Ckappa). In another example, the first part of the antigen binding domain is an antibody light chain Fab fragment and the second part of the antigen binding domain is an antibody heavy chain Fab fragment. In another example, the first part of the antigen binding domain is an antibody cross Fab fragment comprising VH-Ckappa and the second part of the antigen binding domain is an antibody cross Fab fragment comprising VL-CH1. In a further example, the first part of the antigen binding domain is an antibody cross Fab fragment comprising VL-CH1 and the second part of the antigen binding domain is an antibody cross Fab fragment comprising VH-Ckappa.

As described above, the bispecific antibody consists of a first and a second fusion polypeptide, both comprising a spacer domain, the spacer domain of the first fusion polypeptide and the spacer domain of the second fusion polypeptide are associated covalently to each other by a disulfide bond and comprise modifications promoting the association of the first and second fusion polypeptide. The spacer domain comprises at least 25 amino acids.

In one example of the disclosure, the spacer domain comprises an antibody hinge region or a (C-terminal) fragment thereof and an antibody CH2 domain or a (N-terminal) fragment thereof. In another example, the spacer domain comprises an antibody hinge region or a fragment thereof, an antibody CH2 domain, and an antibody CH3 domain or a fragment thereof. Furthermore, the
5 spacer domain of the first fusion polypeptide and the spacer domain of the second fusion polypeptide comprise modifications promoting the association of the first and second fusion polypeptide. In a particular example, the spacer domain of the first fusion polypeptide comprises holes and the spacer domain of the second fusion polypeptide comprises knobs according to the knobs into hole method. In a further example, the disclosure comprises a bispecific antibody,
10 wherein the spacer domain comprises an antibody hinge region or a fragment thereof and an IgG1 Fc domain. Particularly, the IgG1 Fc domain comprises one or more amino acid substitution that reduces binding to an Fc receptor, in particular towards Fcγ receptor. More particularly, the IgG1 Fc domain comprises the amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).

15 In some examples, provided is a bispecific antibody wherein the one antigen binding domain capable of specific binding to a second target is an antigen binding domain capable of specific binding to a tumor associated antigen (TAA). In particular, the tumor associated antigen is Fibroblast Activation Protein (FAP). In one example, provided is a bispecific antibody, wherein the antigen binding domain capable of specific binding to a second target is an antigen
20 binding domain capable of specific binding to Fibroblast Activation Protein (FAP).

In some examples, the antigen binding domain capable of specific binding to FAP comprises

(a) a heavy chain variable region (VHFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2,
25 and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3, and a light chain variable region (VLFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or

(b) a heavy chain variable region (VHFAP) comprising (i) CDR-H1 comprising the amino acid
30 sequence of SEQ ID NO:9, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:11, and a light chain variable region (VLFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:14.

35 More particularly, the antigen binding domain capable of specific binding to FAP comprises

(a) a heavy chain variable region (VHFAP) comprising an amino acid sequence that is at least

about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:7, and a light chain variable region (VLFAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:8, or

- 5 (b) a heavy chain variable region (VHFAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:15, and a light chain variable region (VLFAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:16.

- 10 In some examples, provided is a bispecific antibody wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to a TNF receptor, in particular a costimulatory TNF receptor. Particularly, the costimulatory TNF receptor is OX40. In one example, provided is a bispecific antibody, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding
15 domain capable of specific binding to OX40. Particularly, the bispecific antibody of the disclosure comprises two antigen binding domains capable of specific binding to OX40.

In some examples, the antigen binding domain capable of specific binding to OX40 comprises

- (a) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid
20 sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:22, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:35, or
25 (b) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:21, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi)
30 CDR-L3 comprising the amino acid sequence of SEQ ID NO:34, or
(c) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:23, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence
35 of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:36, or
(d) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid

sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:24, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:37, or

(e) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:25, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:29, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:32, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:38, or

(f) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:26, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:29, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:32, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:38, or

(g) a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:27, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:30, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:39.

In particular, the antigen binding domain capable of specific binding to OX40 comprises a heavy chain variable region (VHOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:22, and a light chain variable region (VLOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:35.

In some examples, the antigen binding domain capable of specific binding to OX40 comprises

(a) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:40 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ ID NO:41, or

(b) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:42 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ

ID NO:43, or

(c) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:44 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ ID NO:45, or

5 (d) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:46 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ ID NO:47, or

(a) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:48 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ

10 ID NO:49, or

(a) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID NO:50 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ ID NO:51, or

(a) a heavy chain variable region (VHOX40) comprising an amino acid sequence of SEQ ID
15 NO:52 and a light chain variable region (VLOX40) comprising an amino acid sequence of SEQ ID NO:53.

In one particular example, the antigen binding domain capable of specific binding to OX40 comprises (a) a heavy chain variable region (VHOX40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of
20 SEQ ID NO:40, and a light chain variable region (VLOX40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:41.

Particularly, the present disclosure provides a bispecific antibody, wherein the bispecific antibody comprises

25 (a) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:54, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:55,

(b) a fusion polypeptide comprising an amino acid sequence that is at least about 95%,
30 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:56, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:57,

(c) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:58, and a
35 fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:59,

(d) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:60, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:61,

5 (e) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:62, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:63,

10 (f) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:64, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:65, or

(g) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:66, and a
15 fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:67.

Furthermore, the present disclosure provides a bispecific antibody, wherein the bispecific antibody comprises

(a) a fusion polypeptide comprising an amino acid sequence that is at least about 95%,
20 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:116, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:117,

(b) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:118, and a
25 fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:119,

(c) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:120, and a
30 fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:121,

(d) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:122, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:123,

35 (e) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:124, and a

fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:125,

(f) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:126, a fusion
5 polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:127, and a light chain that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:128,

(g) a fusion polypeptide comprising an amino acid sequence that is at least about 95%,
10 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:129, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:130,

(h) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:131, and a
15 fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:132, or

(i) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:133, and a fusion
20 polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:134.

In some examples, provided is a bispecific antibody wherein the costimulatory TNF receptor is 4-1BB. In one example, provided is a bispecific antibody, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to 4-1BB. Particularly, the bispecific antibody of the disclosure comprises
25 two antigen binding domains capable of specific binding to 4-1BB.

In some examples, the antigen binding domain capable of specific binding to 4-1BB a heavy chain variable region (VH4-1BB) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:137, and a light
30 chain variable region (VL4-1BB) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:140. In one example, the antigen binding domain capable of specific binding to 4-1BB comprises a heavy chain variable region (VH4-1BB) comprising an amino acid sequence that is at least about 95%, 96%, 97%,
35 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:141, and a light chain variable region (VL4-1BB) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:142.

Particularly, the present disclosure provides a bispecific antibody, wherein the bispecific antibody comprises

(a) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:143, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:144, or

(b) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:145, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:146.

In some examples, provided is a bispecific antibody wherein the costimulatory TNF receptor is CD40. In one example, provided is a bispecific antibody, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to CD40. Particularly, the bispecific antibody of the disclosure comprises two antigen binding domains capable of specific binding to CD40.

In some examples, the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region (VHCD40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:147, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:148, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:149, and a light chain variable region (VLCD40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:150, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:151, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:152. In one example, the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region (VHCD40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:153, and a light chain variable region (VLCD40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:154.

In another example, the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to CD40 comprises

(i) a heavy chain variable region (VHCD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169 and SEQ ID NO:170, and a light chain variable region (VLCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, and SEQ ID NO:174, or

(ii) a heavy chain variable region (VHCD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178,

SEQ ID NO:179 and SEQ ID NO:180, and a light chain variable region (VLCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, and SEQ ID NO:184.

Particularly, the present disclosure provides a bispecific antibody, wherein the bispecific antibody comprises

(a) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:155, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:156,

(b) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:157, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:158,

(c) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:159, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:160,

(d) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:161, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:162,

(e) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:163, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:164, or

(f) a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:165, and a fusion polypeptide comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:166.

The present disclosure, in another aspect, provides isolated nucleic acid encoding the bispecific antibody of the present disclosure. Provided is also an expression vector comprising the nucleic acid of the present disclosure and furthermore a host cell comprising the isolated nucleic acid or the expression vector of the present disclosure is provided. In another aspect, the disclosure provides a vector or host cell comprising the nucleic acid of the present disclosure. Also included, in another aspect, is a method of producing a bispecific antibody, comprising culturing the host cell of the present disclosure under conditions suitable for the expression of the bispecific antibody. The method may also include the step of isolating the bispecific antibody.

The present disclosure, in another aspect, provides a pharmaceutical composition comprising the bispecific antibody of the present disclosure and at least one pharmaceutically acceptable excipient.

5 The present disclosure, in another aspect, provides the bispecific antibody of the present disclosure, or the pharmaceutical composition of the present disclosure, for use as a medicament. More particularly, provided is also the bispecific antibody of the disclosure for use in treating cancer or infectious diseases. In another aspect, the present disclosure provides the bispecific antibody of the disclosure or the pharmaceutical composition of the disclosure for use in treating cancer or infectious diseases. In particular, the bispecific antibody of the disclosure for use in
10 treating cancer is provided.

In a further aspect, provided is the use of bispecific antibody of the present disclosure, or the pharmaceutical composition of the present disclosure, in the manufacture of a medicament for use

- (i) in stimulating T cell response,
- 15 (ii) in supporting survival of activated T cells,
- (iii) in the treatment of infections,
- (iv) in the treatment of cancer,
- (v) in delaying progression of cancer, or
- (vi) in prolonging the survival of a patient suffering from cancer.

20 The present disclosure also provides a method of treating an individual having cancer or infectious diseases comprising administering to the individual an effective amount of the bispecific antibody of the present disclosure, or the pharmaceutical composition of the present disclosure.

25 The present disclosure also provides the use of the bispecific antibody of the present disclosure, or the pharmaceutical composition of the present disclosure, in the manufacture of a medicament for up-regulating or prolonging cytotoxic T cell activity. Also provided is a method of up-regulating or prolonging cytotoxic T cell activity in an individual having cancer, comprising administering to the individual an effective amount of the bispecific antibody of the present disclosure, or the pharmaceutical composition of the present disclosure. In some
30 examples in accordance with various aspects of the present disclosure the individual is a mammal, particularly a human.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A, 1B, 1C and 1D show examples, how the contorsbodies of the invention can be assembled. In **Figure 1A**, the contorsbody consists of a first fusion polypeptide comprising
5 the first half of a fab capable of specific binding to the first target (heavy chain fab) linked via a peptide linker (black line) to a spacer domain linked via peptide linker (black line) to the second

Claims

1. A bispecific antibody consisting of two fusion polypeptides and comprising two antigen binding domains capable of specific binding to a first target and one antigen binding domain capable of specific binding to a second target comprising

- 5 (a) a first fusion polypeptide comprising a first part of a first antigen binding domain capable of specific binding to the first target, a spacer domain, a second part of a first antigen binding domain capable of specific binding to the first target and a first part of an antigen binding domain capable of specific binding to the second target, wherein
 - 10 - the spacer domain is a polypeptide and comprises at least 25 amino acid residues,
 - the first part of the first antigen binding domain capable of specific binding to the first target is fused either directly or via a first peptide linker to the N-terminus of the spacer domain,
 - the second part of the first antigen binding domain capable of specific binding to the first target is fused either directly or via a second peptide linker to the C-terminus of the spacer domain, and
 - 15 - the first part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target or is fused either directly or via a third peptide linker to the N-terminus of the first part of the first antigen binding domain capable of specific binding to the first target, and
 - 20 (b) a second fusion polypeptide comprising a first part of a second antigen binding domain capable of specific binding to a first target, a spacer domain, a second part of the second antigen binding domain capable of specific binding to a first target and the second part of an antigen binding domain capable of specific binding to a second target, wherein
 - 25 - the spacer domain is a polypeptide and comprises at least 25 amino acid residues,
 - the first part of the second antigen binding domain capable of specific binding to a first target is fused either directly or via a first peptide linker to the N-terminus of the spacer domain,
 - 30 - the second part of the second antigen binding domain capable of specific binding to a first target is fused either directly or via a second peptide linker to the C-terminus of the spacer domain, and

- the second part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the second antigen binding domain capable of specific binding to a first target or is fused either directly or via a third peptide linker to the N-terminus of the first part of the second antigen binding domain capable of specific binding to a first target,

and wherein the first part and the second part of the antigen binding domain capable of specific binding to the second target are associated with each other to form the antigen binding domain capable of specific binding to the second target and wherein the first part and the second part of the first and second antigen binding domain capable of specific binding to the first target are associated with each other to form a circular fusion polypeptide, and

wherein the spacer domain of the first fusion polypeptide and the spacer domain of the second fusion polypeptide are associated covalently to each other by a disulfide bond and comprise modifications promoting the association of the first and second fusion polypeptide.

2. The bispecific antibody of claim 1, wherein in the first fusion polypeptide the first part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target and wherein in the second fusion polypeptide the second part of an antigen binding domain capable of specific binding to a second target is fused either directly or via a third peptide linker to the C-terminus of the second part of the first antigen binding domain capable of specific binding to the first target.
3. The bispecific antibody of claims 1 or 2, wherein the third peptide linker connecting the first part or the second part of an antigen binding domain capable of specific binding to a second target comprises at least 15 amino acids.
4. The bispecific antibody of any one of claims 1 to 3, wherein the first fusion polypeptide comprises the heavy chain variable domain of the antigen binding domain capable of specific binding to a second target and the second fusion polypeptide comprises the antibody light chain variable domain of the antigen binding domain capable of specific binding to a second target or vice versa.
5. The bispecific antibody of any one of claims 1 to 4, wherein in both the first fusion polypeptide and the second fusion polypeptide the first part of the antigen binding domain capable of specific binding to the first target is an antibody heavy chain Fab fragment and

the second part of the antigen binding domain capable of specific binding to the first target is an antibody light chain Fab fragment.

6. The bispecific antibody of any one of claims 1 to 5, wherein the spacer domain comprises an antibody hinge region or a fragment thereof, an antibody CH2 domain, and an antibody CH3 domain or a fragment thereof.
7. The bispecific antibody of any one of claims 1 to 6, wherein the spacer domain comprises an antibody hinge region or a fragment thereof and an IgG1 Fc domain.
8. The bispecific antibody of any one of claims 1 to 7, wherein the spacer domain of the first fusion polypeptide comprises holes and the spacer domain of the second fusion polypeptide comprises knobs according to the knobs into hole method.
9. The bispecific antibody of any one of claims 1 to 8, wherein the IgG1 Fc domain comprises amino acid substitutions L234A, L235A and P329G (numbering according to Kabat EU index).
10. The bispecific antibody of any one of claims 1 to 9, wherein the antigen binding domain capable of specific binding to a second target is an antigen binding domain capable of specific binding to a tumor associated antigen.
11. The bispecific antibody of any one of claims 1 to 10, wherein the antigen binding domain capable of specific binding to a second target is an antigen binding domain capable of specific binding to Fibroblast Activation Protein (FAP).
12. The bispecific antibody of any one of claims 1 to 11, wherein the antigen binding domain capable of specific binding to FAP comprises
 - (a) a heavy chain variable region (V_HFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:1, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:2, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:3, and a light chain variable region (V_LFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:4, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:5, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:6, or
 - (b) a heavy chain variable region (V_HFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:9, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:11, and a light chain variable region (V_LFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:14.

13. The bispecific antibody of any one of claims 1 to 12, wherein the antigen binding domain capable of specific binding to FAP comprises
- (a) a heavy chain variable region (V_H FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:7, and a light chain variable region (V_L FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:8, or
- (b) a heavy chain variable region (V_H FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:15, and a light chain variable region (V_L FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:16.
14. The bispecific antibody of any one of claims 1 to 13, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to OX40.
15. The bispecific antibody of any one of claims 1 to 14, wherein the antigen binding domain capable of specific binding to OX40 comprises
- (a) a heavy chain variable region (V_H OX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:22, and a light chain variable region (V_L OX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:35, or
- (b) a heavy chain variable region (V_H OX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:21, and a light chain variable region (V_L OX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:34, or
- (c) a heavy chain variable region (V_H OX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:23, and a light chain variable region (V_L OX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:36, or
- (d) a heavy chain variable region (V_H OX40) comprising (i) CDR-H1 comprising the amino

- acid sequence of SEQ ID NO:17, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:19, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:24, and a light chain variable region (V_LOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:28, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:37, or
- (e) a heavy chain variable region (V_HOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:25, and a light chain variable region (V_LOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:29, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:32, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:38, or
- (f) a heavy chain variable region (V_HOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:26, and a light chain variable region (V_LOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:29, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:32, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:38, or
- (g) a heavy chain variable region (V_HOX40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:18, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:27, and a light chain variable region (V_LOX40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:30, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:33, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:39.
16. The bispecific antibody of any one of claims 1 to 15, wherein the antigen binding domain capable of specific binding to OX40 comprises
- (a) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:40 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:41, or
- (b) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:42 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:43, or
- (c) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:44 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:45, or
- (d) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:46 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:47, or

- (e) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:48 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:49, or
- (f) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:50 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:51, or
- (g) a heavy chain variable region (V_HOX40) comprising an amino acid sequence of SEQ ID NO:52 and a light chain variable region (V_LOX40) comprising an amino acid sequence of SEQ ID NO:53.
17. The bispecific antibody of any one of claims 1 to 15, wherein the antigen binding domain capable of specific binding to OX40 comprises
- (a) a heavy chain variable region (V_HOX40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:40, and a light chain variable region (V_LOX40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:41.
18. The bispecific antibody of any one of claims 1 to 13, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to 4-1BB.
19. The bispecific antibody of any one of claims 1 to 13 or 18, wherein the antigen binding domain capable of specific binding to 4-1BB comprises a heavy chain variable region (V_H4-1BB) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:135, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:136, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:137, and a light chain variable region (V_L4-1BB) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:138, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:139, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:140.
20. The bispecific antibody of any one of claims 1 to 13 or 18 or 19, wherein the antigen binding domain capable of specific binding to 4-1BB comprises a heavy chain variable region (V_H4-1BB) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:141, and a light chain variable region (V_L4-1BB) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:142.

21. The bispecific antibody of any one of claims 1 to 13, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to CD40.
22. The bispecific antibody of any one of claims 1 to 13 or 21, wherein the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region (V_HCD40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:147, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:148, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:149, and a light chain variable region (V_LCD40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:150, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:151, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:152.
23. The bispecific antibody of any one of claims 1 to 13 or 21 or 22, wherein the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region (V_HCD40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:153, and a light chain variable region (V_LCD40) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:154.
24. The bispecific antibody of any one of claims 1 to 13 or 21 or 22, wherein the antigen binding domain capable of specific binding to a first target is an antigen binding domain capable of specific binding to CD40 comprises
(i) a heavy chain variable region (V_HCD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169 and SEQ ID NO:170, and a light chain variable region (V_LCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, and SEQ ID NO:174, or
(ii) a heavy chain variable region (V_HCD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179 and SEQ ID NO:180, and a light chain variable region (V_LCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, and SEQ ID NO:184.
25. Isolated nucleic acid encoding the bispecific antibody of any one of claims 1 to 24.

26. A vector or host cell comprising the nucleic acid of claim 25.
27. A method of producing a bispecific antibody culturing the host cell of claim 26 under conditions suitable for the expression of the bispecific antibody.
28. A pharmaceutical composition comprising the bispecific antibody of any one of claims 1 to 24 and a pharmaceutically acceptable excipient.
29. The bispecific antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 28 for use as medicament.
30. The bispecific antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 28 for use in treating cancer or infectious diseases.
31. Use of the bispecific antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for use
(i) in stimulating T cell response,
(ii) in supporting survival of activated T cells,
(iii) in the treatment of infections,
(iv) in the treatment of cancer,
(v) in delaying progression of cancer, or
(vi) in prolonging the survival of a patient suffering from cancer.
32. The pharmaceutical composition of claim 28, the bispecific antibody or the pharmaceutical composition for use of claim 29 or 30, or the use of claim 31, further comprising an additional therapeutic agent.
