

Claims

1. A bispecific antigen binding molecule, comprising
 - (a) four Fab fragments capable of specific binding to a costimulatory TNF receptor family member selected from the group consisting of OX40, 4-1BB and GITR,
 - (b) at least one moiety capable of specific binding to Fibroblast Activation Protein (FAP) comprising an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH), and
 - (c) a Fc domain composed of a first and a second subunit capable of stable association, wherein a first Fab fragment capable of specific binding to a costimulatory TNF receptor family member is fused at the C-terminus of the CH1 domain to the VH domain of a second Fab fragment capable of specific binding to a costimulatory TNF receptor family member and a third Fab fragment capable of specific binding to a costimulatory TNF receptor family member is fused at the C-terminus of the CH1 domain to the VH domain of a fourth Fab fragment capable of specific binding to a costimulatory TNF receptor family member, optionally via a peptide linker.
2. The bispecific antigen binding molecule of claim 1, wherein the costimulatory TNF receptor family member is OX40.
3. The bispecific antigen binding molecule of claims 1 or 2, wherein the Fab fragments capable of specific binding to a costimulatory TNF receptor family member binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.
4. The bispecific antigen binding molecule of any one of claims 1 to 3, wherein each of the four Fab fragments capable of specific binding to OX40 comprises
 - (a) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:2, CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, CDR-H3 comprising the amino acid sequence of SEQ ID NO:6 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:13, CDR-L2 comprising the amino acid sequence of SEQ ID NO:16 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:19,
 - (b) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:2, CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, CDR-H3 comprising the amino acid sequence of SEQ ID NO:7 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:13, CDR-L2 comprising the amino acid sequence of SEQ ID NO:16 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:20,
 - (c) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:2, CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, CDR-H3 comprising the amino acid sequence of SEQ ID NO:8 and a VL domain comprising CDR-L1 comprising the

amino acid sequence of SEQ ID NO:13, CDR-L2 comprising the amino acid sequence of SEQ ID NO:16 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:21,

(d) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:2, CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, CDR-H3 comprising the amino acid sequence of SEQ ID NO:9 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:13, CDR-L2 comprising the amino acid sequence of SEQ ID NO:16 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:22,

(e) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, CDR-H3 comprising the amino acid sequence of SEQ ID NO:10 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:14, CDR-L2 comprising the amino acid sequence of SEQ ID NO:17 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:23,

(f) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, CDR-H3 comprising the amino acid sequence of SEQ ID NO:11 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:14, CDR-L2 comprising the amino acid sequence of SEQ ID NO:17 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:23, or

(g) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, CDR-H2 comprising the amino acid sequence of SEQ ID NO:5, CDR-H3 comprising the amino acid sequence of SEQ ID NO:12 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:15, CDR-L2 comprising the amino acid sequence of SEQ ID NO:18 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:24.

5. The bispecific antigen binding molecule of any one of claims 1 to 4, wherein each of the Fab fragments capable of specific binding to OX40 comprises

- (i) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:25 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:26,
- (ii) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:27 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:28,
- (iii) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:29 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:30,
- (iv) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:31 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:32,
- (v) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:33 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:34,

(vi) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:35 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:36, or

(vii) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:37 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:38.

6. The bispecific antigen binding molecule of any one of claims 1 to 5, wherein the moiety capable of specific binding to FAP comprises

(a) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:40, CDR-H2 comprising the amino acid sequence of SEQ ID NO:42, CDR-H3 comprising the amino acid sequence of SEQ ID NO:44 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:46, CDR-L2 comprising the amino acid sequence of SEQ ID NO:48 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:50, or

(b) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:39, CDR-H2 comprising the amino acid sequence of SEQ ID NO:41, CDR-H3 comprising the amino acid sequence of SEQ ID NO:43 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:45, CDR-L2 comprising the amino acid sequence of SEQ ID NO:47 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:49.

7. The bispecific antigen binding molecule of any one of claims 1 to 6, wherein

(a) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:26 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,

(b) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:26 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,

(c) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:27 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:28 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,

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sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,

- (k) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:35 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:36 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,
- (l) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:35 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:36 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,
- (m) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:37 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:38 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52, or
- (n) the Fab fragments capable of specific binding to OX40 comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:37 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:38 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54.

8. The bispecific antigen binding molecule of claim 1, wherein the costimulatory TNF receptor family member is 4-1BB.

9. The bispecific antigen binding molecule of any one of claims 1 or 8, wherein the Fab fragments capable of specific binding to a costimulatory TNF receptor family member binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:239.

10. The bispecific antigen binding molecule of any one of claims 1 or 8 or 9, wherein each of the four Fab fragments capable of specific binding to 4-1BB comprise

(a) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:249, CDR-H2 comprising the amino acid sequence of SEQ ID NO:251, CDR-H3 comprising the amino acid sequence of SEQ ID NO:253 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:258, CDR-L2 comprising the amino acid

sequence of SEQ ID NO:260 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:262,

(b) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:249, CDR-H2 comprising the amino acid sequence of SEQ ID NO:251, CDR-H3 comprising the amino acid sequence of SEQ ID NO:255 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:258, CDR-L2 comprising the amino acid sequence of SEQ ID NO:260 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:264,

(c) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:249, CDR-H2 comprising the amino acid sequence of SEQ ID NO:251, CDR-H3 comprising the amino acid sequence of SEQ ID NO:256 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:258, CDR-L2 comprising the amino acid sequence of SEQ ID NO:260 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:265,

(d) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:249, CDR-H2 comprising the amino acid sequence of SEQ ID NO:251, CDR-H3 comprising the amino acid sequence of SEQ ID NO:257 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:258, CDR-L2 comprising the amino acid sequence of SEQ ID NO:260 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:266, or

(e) a VH domain comprising CDR-H1 comprising the amino acid sequence of SEQ ID NO:250, CDR-H2 comprising the amino acid sequence of SEQ ID NO:252, CDR-H3 comprising the amino acid sequence of SEQ ID NO:254 and a VL domain comprising CDR-L1 comprising the amino acid sequence of SEQ ID NO:259, CDR-L2 comprising the amino acid sequence of SEQ ID NO:261 and CDR-L3 comprising the amino acid sequence of SEQ ID NO:263.

11. The bispecific antigen binding molecule of any one of claims 1 or 8 to 10, wherein each of the Fab fragments capable of specific binding to 4-1BB comprises

(i) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:267 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:268,

(ii) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:269 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:270,

(iii) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:271 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:272,

- (iv) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:273 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:274, or
- (v) a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:275 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:276.

12. The bispecific antigen binding molecule of any one of claims 1 or 8 to 11, wherein
- (a) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:267 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:268 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,
 - (b) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:267 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:268 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,
 - (c) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:269 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:270 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,
 - (d) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:269 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:270 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,
 - (e) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:271 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:272 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,
 - (f) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:271 and a light chain variable

region comprising an amino acid sequence of SEQ ID NO:272 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,

- (g) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:273 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:274 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52,
- (h) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:273 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:274 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54,
- (i) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:275 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:276 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52, or
- (j) the Fab fragments capable of specific binding to 4-1BB comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:275 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:276 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54.

13. The bispecific antigen binding molecule of claim 1, wherein the costimulatory TNF receptor family member is GITR.

14. The bispecific antigen binding molecule of any one of claims 1 or 13, wherein the Fab fragments capable of specific binding to a costimulatory TNF receptor family member binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:357.

15. The bispecific antigen binding molecule of any one of claims 1 or 13 or 14, wherein each of the four Fab fragments capable of specific binding to GITR comprises a VH domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO:371, a CDR-H2 comprising the amino acid sequence of SEQ ID NO:372 and a CDR-H3 comprising the amino

acid sequence of SEQ ID NO:373, and a VL domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO:374, a CDR-L2 comprising the amino acid sequence of SEQ ID NO:375 and a CDR-L3 comprising the amino acid sequence of SEQ ID NO:376.

16. The bispecific antigen binding molecule of any one of claims 1 or 13 to 15, wherein each of the Fab fragments capable of specific binding to GITR comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:383 and a light chain variable region VL comprising an amino acid sequence of SEQ ID NO:384.

17. The bispecific antigen binding molecule of any one of claims 1 or 13 to 15, wherein

- (a) the Fab fragments capable of specific binding to GITR comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:383 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:384 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52, or
- (b) the Fab fragments capable of specific binding to GITR comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:383 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:384 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54, or
- (c) the Fab fragments capable of specific binding to GITR comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:385 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:386 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:51 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:52, or
- (d) the Fab fragments capable of specific binding to GITR comprise a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:385 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:386 and the moiety capable of specific binding to FAP comprises a heavy chain variable region VH comprising an amino acid sequence of SEQ ID NO:53 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:54.

18. The bispecific antigen binding molecule of any one of claims 1 to 17, wherein in the Fab fragments capable of specific binding to a costimulatory TNF receptor family member in the constant domain CL the amino acid at position 124 is substituted independently by lysine (K), arginine (R) or histidine (H) (numbering according to Kabat EU Index), and in the constant

domain CH1 the amino acids at positions 147 and 213 are substituted independently by glutamic acid (E) or aspartic acid (D) (numbering according to Kabat EU index).

19. The bispecific antigen binding molecule of any one of claims 1 to 18, wherein the bispecific antigen binding molecule is tetravalent for the costimulatory TNF receptor family member and monovalent for FAP.

20. The bispecific antigen binding molecule of any one of claims 1 to 19, wherein the moiety capable of specific binding to FAP comprises a VH and VL domain and wherein the VH domain is connected via a peptide linker to the C-terminus of the first subunit of the Fc domain and the VL domain is connected via a peptide linker to the C-terminus of the second subunit of the Fc domain.

21. The bispecific antigen binding molecule of any one of claims 1 to 20, wherein the Fc domain is of human IgG1 subclass with the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index).

22. A polynucleotide encoding the bispecific antigen binding molecule of any one of claims 1 to 21.

23. A pharmaceutical composition comprising a bispecific antigen binding molecule of any one of claims 1 to 21, and at least one pharmaceutically acceptable excipient.

24. The bispecific antigen binding molecule of any one of claims 1 to 21, or the pharmaceutical composition of claim 23, for use as a medicament.

25. The bispecific antigen binding molecule of any one of claims 1 to 21, or the pharmaceutical composition of claim 23, for use in the treatment of cancer.

26. The bispecific antigen binding molecule of any one of claims 1 to 21, or the pharmaceutical composition of claim 23, for use in the treatment of cancer, wherein the bispecific antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

27. Use of the bispecific antigen binding molecule of any one of claims 1 to 21, or the pharmaceutical composition of claim 23 in the manufacture of a medicament for the treatment of cancer.