

Claims

1. A bispecific antigen binding molecule, comprising
 - (a) at least one antigen binding domain capable of specific binding to CD40, and
 - (b) at least one antigen binding domain capable of specific binding to Fibroblast Activation
- 5 Protein (FAP) comprising a heavy chain variable region (V_HFAP) comprising
 - (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (ii) CDR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:11 and SEQ ID NO:12, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:5, and a light chain variable region (V_LFAP) comprising (iv)
 - 10 CDR-L1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:13 and SEQ ID NO:14, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8.
2. The bispecific antigen binding molecule of claim 1, additionally comprising
- 15 (c) a Fc region composed of a first and a second subunit capable of stable association.
3. The bispecific antigen binding molecule of claims 1 or 2, wherein the antigen binding domain capable of specific binding to FAP comprises a heavy chain variable region (V_HFAP) comprising an amino acid sequence that is at least ~~about~~ 90% identical to the amino acid sequence of SEQ ID NO:9, and a light chain variable region (V_LFAP)
- 20 comprising an amino acid sequence that is at least ~~about~~ 90% identical to the amino acid sequence of SEQ ID NO:10.
4. The bispecific antigen binding molecule of any one of claims 1 to 3, wherein the antigen binding domain capable of specific binding to FAP comprises a heavy chain variable region (V_HFAP) comprising an amino acid sequence selected from
- 25 the group consisting of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20, and a light chain variable region (V_LFAP) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26.
- 30 5. The bispecific antigen binding molecule of any one of claims 1 to 4, wherein the antigen binding domain capable of specific binding to FAP comprises
 - (a) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:15 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:21,

(b) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:16 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:21,

(c) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:16 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:22, or

(d) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:19 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:25.

6. The bispecific antigen binding molecule of any one of claims 1 to 5, 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:27, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:28, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:29, and a light chain variable region (V_LCD40) 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:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:32.

7. The bispecific antigen binding molecule of any one of claims 1 to 6, wherein the 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:37, SEQ ID NO:38, SEQ ID NO:39 and SEQ ID NO:40, and

(ii) a light chain variable region (V_LCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, and SEQ ID NO:44.

8. The bispecific antigen binding molecule of any one of claims 1 to 6, wherein the 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:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49 and SEQ ID NO:50, and

(ii) a light chain variable region (V_LCD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, and SEQ ID NO:54.

9. The bispecific antigen binding molecule of any one of claims 1 to 5 or 7, wherein the antigen binding domain capable of specific binding to CD40 comprises

- (a) a VH comprising the amino acid sequence of SEQ ID NO:37 and a VL comprising the amino acid sequence of SEQ ID NO:41, or
- (b) a VH comprising the amino acid sequence of SEQ ID NO:37 and a VL comprising the amino acid sequence of SEQ ID NO:42, or
- 5 (c) a VH comprising the amino acid sequence of SEQ ID NO:37 and a VL comprising the amino acid sequence of SEQ ID NO:43, or
- (d) a VH comprising the amino acid sequence of SEQ ID NO:37 and a VL comprising the amino acid sequence of SEQ ID NO:44, or
- (e) a VH comprising the amino acid sequence of SEQ ID NO:38 and a VL
10 comprising the amino acid sequence of SEQ ID NO:41, or
- (f) a VH comprising the amino acid sequence of SEQ ID NO:38 and a VL comprising the amino acid sequence of SEQ ID NO:42, or
- (g) a VH comprising the amino acid sequence of SEQ ID NO:38 and a VL comprising the amino acid sequence of SEQ ID NO:43, or
- 15 (h) a VH comprising the amino acid sequence of SEQ ID NO:38 and a VL comprising the amino acid sequence of SEQ ID NO:44, or
- (i) a VH comprising the amino acid sequence of SEQ ID NO:39 and a VL comprising the amino acid sequence of SEQ ID NO:41, or
- (j) a VH comprising the amino acid sequence of SEQ ID NO:39 and a VL
20 comprising the amino acid sequence of SEQ ID NO:42, or
- (k) a VH comprising the amino acid sequence of SEQ ID NO:39 and a VL comprising the amino acid sequence of SEQ ID NO:43, or
- (l) a VH comprising the amino acid sequence of SEQ ID NO:39 and a VL comprising the amino acid sequence of SEQ ID NO:44, or
- 25 (m) a VH comprising the amino acid sequence of SEQ ID NO:40 and a VL comprising the amino acid sequence of SEQ ID NO:41, or
- (n) a VH comprising the amino acid sequence of SEQ ID NO:40 and a VL comprising the amino acid sequence of SEQ ID NO:42, or
- (o) a VH comprising the amino acid sequence of SEQ ID NO:40 and a VL
30 comprising the amino acid sequence of SEQ ID NO:43, or
- (p) a VH comprising the amino acid sequence of SEQ ID NO:40 and a VL comprising the amino acid sequence of SEQ ID NO:44.

10. The bispecific antigen binding molecule of any one of claims 1 to 5 or 7 or 9, wherein the antigen binding domain capable of specific binding to CD40 comprises a VH comprising the amino acid sequence of SEQ ID NO:37 and a VL comprising the amino acid sequence of SEQ ID NO:41.

5 11. The bispecific antigen binding molecule of any one of claims 1 to 5 or 8, wherein the antigen binding domain capable of specific binding to CD40 comprises

(a) a VH comprising the amino acid sequence of SEQ ID NO:45 and a VL comprising the amino acid sequence of SEQ ID NO:51, or

10 (b) a VH comprising the amino acid sequence of SEQ ID NO:46 and a VL comprising the amino acid sequence of SEQ ID NO:51, or

(c) a VH comprising the amino acid sequence of SEQ ID NO:47 and a VL comprising the amino acid sequence of SEQ ID NO:51, or

(d) a VH comprising the amino acid sequence of SEQ ID NO:48 and a VL comprising the amino acid sequence of SEQ ID NO:51, or

15 (e) a VH comprising the amino acid sequence of SEQ ID NO:45 and a VL comprising the amino acid sequence of SEQ ID NO:52, or

(f) a VH comprising the amino acid sequence of SEQ ID NO:46 and a VL comprising the amino acid sequence of SEQ ID NO:52, or

20 (g) a VH comprising the amino acid sequence of SEQ ID NO:47 and a VL comprising the amino acid sequence of SEQ ID NO:52, or

(h) a VH comprising the amino acid sequence of SEQ ID NO:48 and a VL comprising the amino acid sequence of SEQ ID NO:52, or

(i) a VH comprising the amino acid sequence of SEQ ID NO:49 and a VL comprising the amino acid sequence of SEQ ID NO:53, or

25 (j) a VH comprising the amino acid sequence of SEQ ID NO:50 and a VL comprising the amino acid sequence of SEQ ID NO:53, or

(k) a VH comprising the amino acid sequence of SEQ ID NO:49 and a VL comprising the amino acid sequence of SEQ ID NO:54, or

30 (l) a VH comprising the amino acid sequence of SEQ ID NO:50 and a VL comprising the amino acid sequence of SEQ ID NO:54.

12. The bispecific antigen binding molecule of any one of claims 1 to 5 or 8 or 11, wherein the antigen binding domain capable of specific binding to CD40 comprises a VH

comprising the amino acid sequence of SEQ ID NO:45 and a VL comprising the amino acid sequence of SEQ ID NO:51 or wherein the antigen binding domain capable of specific binding to CD40 comprises a VH comprising the amino acid sequence of SEQ ID NO:48 and a VL comprising the amino acid sequence of SEQ ID NO:51.

5 13. The bispecific antigen binding molecule of any one of claims 1 to 7, comprising

(i) at least one antigen binding domain capable of specific binding to CD40, comprising a heavy chain variable region (V_HCD40) comprising the amino acid sequence of SEQ ID NO:37 and a light chain variable region (V_LCD40) comprising the amino acid sequence of SEQ ID NO:41, and

10 (ii) at least one antigen binding domain capable of specific binding to FAP, comprising a heavy chain variable region (V_HFAP) comprising an amino acid sequence of SEQ ID NO:15 and a light chain variable region (V_LFAP) comprising an amino acid sequence of SEQ ID NO:21.

15 14. The bispecific antigen binding molecule of any one of claims 2 to 13, wherein the Fc region is an IgG, particularly an IgG1 Fc region or an IgG4 Fc region and wherein the Fc region comprises one or more amino acid substitution that reduces the binding affinity of the antibody to an Fc receptor and/or effector function.

20 15. The bispecific antigen binding molecule of any one of claims 2 to 14, wherein the Fc region is of human IgG1 subclass with the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index).

16. The bispecific antigen binding molecule of any one of claims 1 to 15, wherein the bispecific antigen binding molecule comprises

(a) at least two Fab fragments capable of specific binding to CD40 connected to a Fc region, and

25 (b) one antigen binding domain capable of specific binding to FAP connected to the C-terminus of the Fc region.

17. The bispecific antigen binding molecule of any one of claims 1 to 16, wherein the bispecific antigen binding molecule comprises

30 (a) at least two Fab fragments capable of specific binding to CD40 fused to a Fc region, and

(b) a cross-fab fragment capable of specific binding to FAP fused to the C-terminus of the Fc region.

18. The bispecific antigen binding molecule of claim 17, wherein the VH-Ckappa chain of the cross-fab fragment capable of specific binding to FAP is fused to the C-terminus of the Fc region.

19. The bispecific antigen binding molecule of claim 1, comprising

5 (a) two light chains, each comprising the amino acid sequence of SEQ ID NO:62, one light chain comprising the amino acid sequence of SEQ ID NO:61, a first heavy chain comprising the amino acid sequence of SEQ ID NO:63, and a second heavy chain comprising the amino acid sequence of SEQ ID NO:64, or

10 (b) two light chains, each comprising the amino acid sequence of SEQ ID NO:66, one light chain comprising the amino acid sequence of SEQ ID NO:65, a first heavy chain comprising the amino acid sequence of SEQ ID NO:67, and a second heavy chain comprising the amino acid sequence of SEQ ID NO:68.

15 20. The bispecific antigen binding molecule of claim 1, comprising two light chains, each comprising the amino acid sequence of SEQ ID NO:62, one light chain comprising the amino acid sequence of SEQ ID NO:61, a first heavy chain comprising the amino acid sequence of SEQ ID NO:63, and a second heavy chain comprising the amino acid sequence of SEQ ID NO:64.

20 ~~19~~21. The bispecific antigen binding molecule of any one of claims 1 to 18, wherein the bispecific antigen binding molecule comprises four Fab fragments capable of specific binding to CD40.

25 ~~20~~22. An antibody that specifically binds to FAP, wherein said antibody comprises a heavy chain variable region (V_HFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (ii) CDR-H2 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:11 and SEQ ID NO:12, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:5, and a light chain variable region (V_LFAP) comprising (iv) CDR-L1 comprising the amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:13 and SEQ ID NO:14, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8.

30 ~~21~~23. The antibody of claim ~~20~~22, wherein said antibody comprises
(a) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:15 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:21,
(b) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID

NO:16 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:21,

(c) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:16 and a light chain variable region (V_LFAP) comprising the amino acid sequence of

5 SEQ ID NO:22, or

(d) a heavy chain variable region (V_HFAP) comprising the amino acid sequence of SEQ ID NO:19 and a light chain variable region (V_LFAP) comprising the amino acid sequence of SEQ ID NO:25.

10 2224. Isolated nucleic acid encoding the bispecific antigen binding molecule of any one of claims 1 to 19-21 or the antibody of claims 20-22 or 21-23.

2325. An expression vector comprising the isolated nucleic acid of claim 2224.

2426. A host cell comprising isolated nucleic acid of claim 22-24 or the expression vector of claim 2325.

15 2527. A method of producing a bispecific antigen binding molecule, comprising culturing the host cell of claim 24-26 under conditions suitable for the expression of the bispecific antigen binding molecule, and isolating the bispecific antigen binding molecule.

2628. A pharmaceutical composition comprising the bispecific antigen binding molecule of any one of claims 1 to 19-21 or the antibody of claims 20-22 or 21-23 and a pharmaceutically acceptable carrier.

20 2729. The pharmaceutical composition of claim 24628, further comprising an additional therapeutic agent.

2830. The bispecific antigen binding molecule of any one of claims 1 to 1921, or the pharmaceutical composition of claim 2628, for use as a medicament.

25 2931. The bispecific antigen binding molecule of any one of claims 1 to 1921, or the pharmaceutical composition of claim 2428, for use

(i) in inducing immune stimulation by CD40 expressing antigen-presenting cells (APCs),

(ii) in stimulating tumor-specific T cell response,

(iii) in causing apoptosis of tumor cells,

(iv) in the treatment of cancer,

30 (v) in delaying progression of cancer,

(vi) in prolonging the survival of a patient suffering from cancer, or

(vii) in the treatment of infections.

~~3032~~. The bispecific antigen binding molecule of any one of claims 1 to ~~1921~~, or the pharmaceutical composition of claim ~~2628~~, for use in the treatment of cancer.

5 ~~3133~~. The bispecific antigen binding molecule according to any one of claims 1 to ~~1921~~ or the pharmaceutical composition according to claim ~~2628~~ for use in the treatment of cancer, wherein the bispecific antigen binding molecule or pharmaceutical composition is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

10 ~~3234~~. The bispecific antigen binding molecule according to any one of claims 1 to ~~1921~~ or the pharmaceutical composition according to claim ~~2628~~ for use in the treatment of cancer, wherein the bispecific antigen binding molecule is to be administered in combination with an agent blocking PD-L1/PD-1 interaction.

~~3335~~. Use of the bispecific antigen binding molecule of any one of claims 1 to ~~1921~~, or the pharmaceutical composition of claim ~~2628~~, in the manufacture of a medicament for the treatment of cancer.