

Claims

It is claimed:

1. An isolated antibody that specifically binds to B7-H4, comprising
 - (a) a heavy chain variable region (VH) complementarity determining region (CDR) one (CDR1), a VH CDR2 and a VH CDR3 of a VH having an amino acid sequence selected from the group consisting of SEQ ID NO: 23, SEQ ID NO:155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:165, SEQ ID NO:169, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175 and SEQ ID NO: 176; and
 - (b) a light chain variable region (VL) complementarity determining region one (CDR1), a VL CDR2 and a VL CDR3 of a VL having an amino acid sequence selected from the group consisting of SEQ ID NO:27, SEQ ID NO: 139, SEQ ID NO:141, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169 and SEQ ID NO:170.
2. The antibody of claim 1, wherein the antibody comprises a VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 from an antibody comprising
 - (a) the VH having the amino acid sequence of SEQ ID NO:161; and the VL having the amino acid sequence of SEQ ID NO:167;
 - (b) the VH having the amino acid sequence of SEQ ID NO:172; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (c) the VH having the amino acid sequence of SEQ ID NO:155; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (d) the VH having the amino acid sequence of SEQ ID NO:156; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (e) the VH having the amino acid sequence of SEQ ID NO:157; and the VL having the amino acid sequence of SEQ ID NO:141;
 - (f) the VH having the amino acid sequence of SEQ ID NO:155; and the VL having the amino acid sequence of SEQ ID NO:141;
 - (g) the VH having the amino acid sequence of SEQ ID NO:156; and the VL having the amino acid sequence of SEQ ID NO:141;
 - (h) the VH having the amino acid sequence of SEQ ID NO:159; and the VL having the amino acid sequence of SEQ ID NO:27;
 - (i) the VH having the amino acid sequence of SEQ ID NO:161; and the VL having the amino acid sequence of SEQ ID NO:27;

- (j) the VH having the amino acid sequence of SEQ ID NO:163; and the VL having the amino acid sequence of SEQ ID NO:27;
 - (k) the VH having the amino acid sequence of SEQ ID NO:165; and the VL having the amino acid sequence of SEQ ID NO:27;
 - 5 (l) the VH having the amino acid sequence of SEQ ID NO:23; and the VL having the amino acid sequence of SEQ ID NO:167;
 - (m) the VH having the amino acid sequence of SEQ ID NO:171; and the VL having the amino acid sequence of SEQ ID NO:141;
 - 10 (n) the VH having the amino acid sequence of SEQ ID NO:172; and the VL having the amino acid sequence of SEQ ID NO:141;
 - (o) the VH having the amino acid sequence of SEQ ID NO:171; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (p) the VH having the amino acid sequence of SEQ ID NO:173; and the VL having the amino acid sequence of SEQ ID NO:139;
 - 15 (q) the VH having the amino acid sequence of SEQ ID NO:174; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (r) the VH having the amino acid sequence of SEQ ID NO:175; and the VL having the amino acid sequence of SEQ ID NO:139;
 - (s) the VH having the amino acid sequence of SEQ ID NO:161; and the VL having the amino acid sequence of SEQ ID NO:168;
 - 20 (t) the VH having the amino acid sequence of SEQ ID NO:161; and the VL having the amino acid sequence of SEQ ID NO:169;
 - (u) the VH having the amino acid sequence of SEQ ID NO:161; and the VL having the amino acid sequence of SEQ ID NO:170; or
 - 25 (v) the VH having the amino acid sequence of SEQ ID NO:172; and the VL having the amino acid sequence of SEQ ID NO:139.
3. The antibody of claim 1, comprising
- (a) a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;
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- 5 (b) a VH CDR1 having the amino acid sequence of SEQ ID NO: 205; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;
- 10 (c) a VH CDR1 having the amino acid sequence of SEQ ID NO: 206; a VH CDR2 having the amino acid sequence of SEQ ID NO:207, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;
- 15 (d) a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;
- 20 (e) a VH CDR1 having the amino acid sequence of SEQ ID NO: 199; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;
- 25 (f) a VH CDR1 having the amino acid sequence of SEQ ID NO: 200; a VH CDR2 having the amino acid sequence of SEQ ID NO:201, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;
- 30 (g) a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, a VL CDR1 having the amino acid sequence of SEQ ID NO: 152, a VL CDR2 having the amino acid sequence of SEQ ID NO:41 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;
- (h) a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino

acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138; or

(i) a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:130, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138.

4. An isolated antibody that specifically binds to B7-H4, comprising a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;

5. The antibody of claim 1, comprising

(a) a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:167;

(b) a VH having the amino acid sequence of SEQ ID NO:172; and a VL having the amino acid sequence of SEQ ID NO:139;

(c) a VH having the amino acid sequence of SEQ ID NO:155; and a VL having the amino acid sequence of SEQ ID NO:139;

(d) a VH having the amino acid sequence of SEQ ID NO:156; and a VL having the amino acid sequence of SEQ ID NO:139;

(e) a VH having the amino acid sequence of SEQ ID NO:157; and a VL having the amino acid sequence of SEQ ID NO:141;

(f) a VH having the amino acid sequence of SEQ ID NO:155; a VL having the amino acid sequence of SEQ ID NO:141;

(g) a VH having the amino acid sequence of SEQ ID NO:156; and a VL having the amino acid sequence of SEQ ID NO:141;

(h) a VH having the amino acid sequence of SEQ ID NO:159; and a VL having the amino acid sequence of SEQ ID NO:27;

(i) a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:27;

- (j) a VH having the amino acid sequence of SEQ ID NO:163; and a VL having the amino acid sequence of SEQ ID NO:27;
- (k) a VH having the amino acid sequence of SEQ ID NO:165; and a VL having the amino acid sequence of SEQ ID NO:27;
- 5 (l) a VH having the amino acid sequence of SEQ ID NO:23; and a VL having the amino acid sequence of SEQ ID NO:167;
- (m) a VH having the amino acid sequence of SEQ ID NO:171; and a VL having the amino acid sequence of SEQ ID NO:141;
- 10 (n) a VH having the amino acid sequence of SEQ ID NO:172; and a VL having the amino acid sequence of SEQ ID NO:141;
- (o) a VH having the amino acid sequence of SEQ ID NO:171; and a VL having the amino acid sequence of SEQ ID NO:139;
- (p) a VH having the amino acid sequence of SEQ ID NO:173; and a VL having the amino acid sequence of SEQ ID NO:139;
- 15 (q) a VH having the amino acid sequence of SEQ ID NO:174; and a VL having the amino acid sequence of SEQ ID NO:139;
- (r) a VH having the amino acid sequence of SEQ ID NO:175; and a VL having the amino acid sequence of SEQ ID NO:139;
- 20 (s) a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:168;
- (t) a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:169;
- (u) a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:170; or
- 25 (v) a VH having the amino acid sequence of SEQ ID NO:172; and a VL having the amino acid sequence of SEQ ID NO:139.
6. An isolated antibody that specifically binds to B7-H4, comprising a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:167.
- 30 7. An isolated antibody that specifically binds to B7-H4, comprising a VH having the amino acid sequence of SEQ ID NO:172; and a VL having the amino acid sequence of SEQ ID NO:139
8. The antibody of any of claims 1 to 7, further comprising a constant region.

9. The antibody of claim 8, wherein the constant region is an isotype of IgG1 or IgG2.
10. The antibody of any one of claims 1-9, wherein the antibody is a human IgG2 comprising one or more substitutions selected from the group consisting of A330S, P331S, D265A, C223E, P228E, L368E, C223R, E225R, P228R, and K409R, wherein the numbering is according to human IgG2 wildtype and the EU numbering scheme, and as shown in Figure 1.
11. The antibody of claim 10, wherein the antibody comprises the substitutions C223E, P228E and L368E.
12. The antibody of claim 10 or claim 11, wherein the antibody comprises the substitutions A330S, P331S and D265A.
13. An isolated antibody that specifically binds to B7-H4, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 190, and a light chain having the amino acid sequence of SEQ ID NO: 191.
14. An isolated antibody that specifically binds to B7-H4, comprising a heavy chain having the amino acid sequence of SEQ ID NO:186, and a light chain having the amino acid sequence of SEQ ID NO: 187.
15. An isolated antibody that specifically binds to B7-H4, comprising a heavy chain comprising the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) of the polynucleotide deposited under ATCC Accession No. PTA-126779, and a light chain comprising the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) of the polynucleotide deposited under with ATCC Accession No. PTA-126781.
16. The antibody of claim 1 or claim 2, wherein each of the VH CDR1, the VH CDR2, the VH CDR3, the VL CDR1, the VL CDR2 and the VL CDR3 is defined in accordance with the Kabat definition, the Chothia definition, the AbM definition, or the contact definition of CDR.
17. An isolated first antibody that specifically binds to B7-H4, that competes for binding with B7-H4 with a second antibody comprising
- (a) a VH having the amino acid sequence of SEQ ID NO:8, and a VL having the amino acid sequence of SEQ ID NO:13;
 - (b) a VH having the amino acid sequence of SEQ ID NO:8, and a VL having the amino acid sequence of SEQ ID NO:13;

(c) a VH having the amino acid sequence of SEQ ID NO:39, and a VL having the amino acid sequence of SEQ ID NO:43;

(d) a VH having the amino acid sequence of SEQ ID NO:46, and a VL having the amino acid sequence of SEQ ID NO:49;

5 (e) a VH having the amino acid sequence of SEQ ID NO:52, and a VL having the amino acid sequence of SEQ ID NO:54;

(f) a VH having the amino acid sequence of SEQ ID NO:57, and a VL having the amino acid sequence of SEQ ID NO:60;

10 (g) a VH having the amino acid sequence of SEQ ID NO:16, and a VL having the amino acid sequence of SEQ ID NO:19;

(h) a VH having the amino acid sequence of SEQ ID NO:64, and a VL having the amino acid sequence of SEQ ID NO:67;

(i) a VH having the amino acid sequence of SEQ ID NO:69, and a VL having the amino acid sequence of SEQ ID NO:70;

15 (j) a VH having the amino acid sequence of SEQ ID NO:74, and a VL having the amino acid sequence of SEQ ID NO:77;

(k) a VH having the amino acid sequence of SEQ ID NO:80, and a VL having the amino acid sequence of SEQ ID NO:84;

20 (l) a VH having the amino acid sequence of SEQ ID NO:87, and a VL having the amino acid sequence of SEQ ID NO:90;

(m) a VH having the amino acid sequence of SEQ ID NO:23, and a VL having the amino acid sequence of SEQ ID NO:27;

(n) a VH having the amino acid sequence of SEQ ID NO:94, and a VL having the amino acid sequence of SEQ ID NO:96;

25 (o) a VH having the amino acid sequence of SEQ ID NO:100, and a VL having the amino acid sequence of SEQ ID NO:77; or

(p) a VH having the amino acid sequence of SEQ ID NO:104, and a VL having the amino acid sequence of SEQ ID NO:67;

30 wherein the first antibody has a K_D to human B7-H4 of between about 1 micromolar and 0.1 nanomolar.

18. An isolated antibody that specifically binds to B7-H4, wherein the antibody binds to an epitope on human B7-H4 comprising at least two amino acid residues selected from the group consisting of L44, K45, E46, G47, V48, L49, G50, L51, E64, D66,

M68, T99 and K101 of the B7-H4 extracellular domain having the amino acid sequence of SEQ ID NO: 1.

19. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 1-18 and a pharmaceutically acceptable carrier.

20. An isolated polynucleotide encoding: (i) a heavy chain of the antibody of any one of claims 1 to 16; or (ii) a light chain of the antibody of any one of claims 1 to 16.

21. A vector comprising the polynucleotide of claim 20.

22. An isolated host cell that recombinantly produces the antibody of any one of claims 1 to 16.

23. Use of the pharmaceutical composition of claim 19 in the manufacture of a medicament for the treatment of ~~A method of treating~~ a condition associated with cells expressing B7-H4 in a subject, wherein an effective amount of the medicament is to be administered ~~comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 19.~~

24. ~~The method use~~ of claim 23, wherein the condition is cancer.

25. ~~The method use~~ of claim 24, wherein the cancer is breast cancer, ovarian cancer, bladder cancer, cancer of the uterus or cancer of the bile duct.

26. A bispecific antibody that specifically binds to both B7-H4 and CD3, comprising a first heavy chain and a first light chain, and a second heavy chain and a second light chain, wherein the first heavy chain and the first light chain form a first arm which comprises a first antigen binding domain that binds to B7-H4, and the second heavy chain and the second light chain form a second arm which comprises a second antigen binding domain that binds to CD3, wherein

(a) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO: 21, a VH CDR3 having the amino acid sequence of SEQ ID NO: 160, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO: 25 and a VL CDR3 having the amino acid sequence of SEQ ID NO: 153;

(b) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 205; a VH CDR2 having the amino acid sequence of SEQ ID NO: 21, a VH CDR3 having the amino acid sequence of SEQ ID NO: 160, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID

NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;

5 (c) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 206; a VH CDR2 having the amino acid sequence of SEQ ID NO:207, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;

10 (d) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;

15 (e) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 200; a VH CDR2 having the amino acid sequence of SEQ ID NO:201, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;

20 (f) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 199; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138;

25 (g) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 152, a VL CDR2 having the amino acid sequence of SEQ ID NO:41 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153;

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(h) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, and the first light chain comprises a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138; or

(i) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:130, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138.

27. The bispecific antibody of claim 26, wherein

(a) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161, and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:167;

(b) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:172, and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;

(c) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:155; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;

(d) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:156; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;

(e) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:157; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:141;

(f) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:155; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:141;

- (g) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:156; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:141;
- 5 (h) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:159; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:27;
- (i) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:27;
- 10 (j) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:163; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:27;
- (k) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:165; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:27;
- 15 (l) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:23; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:167;
- (m) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:171; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:141;
- 20 (n) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:172; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:141;
- 25 (o) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:171; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;
- (p) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:173; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;
- 30 (q) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:174; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;

- (r) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:175; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139;
- 5 (s) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161; and a VL having the amino acid sequence of SEQ ID NO:168;
- (t) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:169;
- 10 (u) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:170; or
- (v) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:172; and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139.
- 15 28. The bispecific antibody of claim 26 or claim 27, wherein
- (a) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:105, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34;
- 20 (b) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 202, a VH CDR2 having the amino acid sequence of SEQ ID NO:105, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34;
- 25 (c) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 203, a VH CDR2 having the amino acid sequence of SEQ ID NO:204, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34;
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(d) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:105, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:116;

(e) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:109, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 111, a VL CDR2 having the amino acid sequence of SEQ ID NO:112 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34; or

(f) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:29, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 32, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34.

29. The bispecific antibody of any of claims 26 or 27, wherein

(a) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 106, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO: 108;

(b) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 115, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO: 117;

(c) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 110, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO: 113; or

(d) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 31, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO: 35.

30. The bispecific antibody of claim 26, wherein

(a) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 20; a VH CDR2 having the amino acid sequence of SEQ ID NO:21, a VH CDR3 having the amino acid sequence of SEQ ID NO:160, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 166, a VL CDR2 having the amino acid sequence of SEQ ID NO:25 and a VL CDR3 having the amino acid sequence of SEQ ID NO:153; and

(b) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:105, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34.

31. The bispecific antibody of claim 26, wherein

(a) the first heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 5; a VH CDR2 having the amino acid sequence of SEQ ID NO:6, a VH CDR3 having the amino acid sequence of SEQ ID NO:7, and the first light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 9, a VL CDR2 having the amino acid sequence of SEQ ID NO:10 and a VL CDR3 having the amino acid sequence of SEQ ID NO:138; and

(b) the second heavy chain comprises a VH CDR1 having the amino acid sequence of SEQ ID NO: 28, a VH CDR2 having the amino acid sequence of SEQ ID NO:105, a VH CDR3 having the amino acid sequence of SEQ ID NO:30, and the second light chain comprises a VL CDR1 having the amino acid sequence of SEQ ID NO: 107, a VL CDR2 having the amino acid sequence of SEQ ID NO:33 and a VL CDR3 having the amino acid sequence of SEQ ID NO:34.

32. The bispecific antibody of claim 26, wherein

(a) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:161, and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:167; and

(b) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 106, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO:108.

33. The bispecific antibody of claim 26, wherein

(c) the first heavy chain comprises a VH having the amino acid sequence of SEQ ID NO:172, and the first light chain comprises a VL having the amino acid sequence of SEQ ID NO:139; and

(d) the second heavy chain comprises a VH having the amino acid sequence of SEQ ID NO: 106, and the second light chain comprises a VL having the amino acid sequence of SEQ ID NO:108.

34. The bispecific antibody of any one of claims 26 to 33, further comprising a constant region.

35. The bispecific antibody of claim 34, wherein the constant region is an IgG1.

36. The bispecific antibody of claim 34, wherein the constant region is human IgG2 comprising one or more substitutions selected from the group consisting of A330S, P331S, D265A, C223E, P228E, L368E, C223R, E225R, P228R, and K409R, wherein the numbering is according to human IgG2 wildtype and the EU numbering scheme, and as shown in Figure 1.

37. The bispecific antibody of any one of claims 26 to 34 and 36, wherein the first arm further comprises human IgG2 Δ A constant region with substitutions D265A, C223E, P228E, and L368E, the second arm further comprises a human IgG2 Δ A constant region with substitutions D265A, C223R, E225R, P228R, and K409R, wherein the numbering is according to the human wildtype IgG2 and EU numbering schemes, and as shown in Figure 1.

38. A bispecific antibody that specifically binds to both B7-H4 and CD3, comprising a first heavy chain and a first light chain, and a second heavy chain and a second light chain, wherein the first heavy chain and the first light chain form a first antibody arm which comprises a first antigen binding domain that binds to B7-H4, and the second heavy chain and the second light chain form a second antigen binding domain that binds to CD3, wherein

(a) the first heavy chain having the amino acid sequence of SEQ ID NO: 190; and the first light chain having the amino acid sequence of SEQ ID NO: 191; and

(b) the second heavy chain having the amino acid sequence of SEQ ID NO:188, and the second light chain having the amino acid sequence of SEQ ID NO: 189.

39. A bispecific antibody that specifically binds to both B7-H4 and CD3, comprising a first heavy chain and a first light chain, and a second heavy chain and a second light chain, wherein the first heavy chain and the first light chain form a first antibody arm

which comprises a first antigen binding domain that binds to B7-H4, and the second heavy chain and the second light chain forms a second antigen binding domain that binds to CD3, wherein

(a) the first heavy chain having the amino acid sequence of SEQ ID NO: 186; and the first light chain having the amino acid sequence of SEQ ID NO: 187; and

(b) the second heavy chain having the amino acid sequence of SEQ ID NO:188, and the second light chain having the amino acid sequence of SEQ ID NO:189.

40. A bispecific antibody that specifically binds to B7-H4 and CD3, comprising a first heavy chain and a first light chain, and a second heavy chain and a second light chain, wherein the first heavy chain and the first light chain form a first antibody arm which comprises a first antigen binding domain that binds to B7-H4, and the second heavy chain and the second light chain form a second antigen binding domain that binds to CD3, wherein

(a) the first heavy chain comprises the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) deposited under ATCC Accession No. PTA-126779, and the first light chain comprises the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) deposited under ATCC Accession No. PTA-126781; and

(b) the second heavy chain comprises the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) deposited under ATCC Accession No. PTA-126780, and the second light chain comprises the amino acid sequence of the full-length polypeptide encoded by the open reading frame (ORF) deposited under ATCC Accession No. PTA-126782.

41. A bispecific antibody that specifically binds to both B7-H4 and CD3, wherein the antibody binds to an epitope on human B7-H4 comprising at least two amino acid residue from the group consisting of L44, K45, E46, G47, V48, L49, G50, L51, S63, E64, D66, M68, T99 and K101 of the B7-H4 amino acid sequence of SEQ ID NO: 1.

42. An isolated polynucleotide molecule encoding (i) a heavy chain of the antibody of any one of claims 26 to 40 or (i) a light chain of the antibody of any one of claims 26 to 40.

43. A vector comprising the polynucleotide molecule of claim 42.

44. A host cell comprising the polynucleotide molecule of claim 42 or the vector of claim 43.

45. The bispecific antibody of any one of claims 26 to 40 for use as a medicament.
46. The bispecific antibody of claim 45, wherein the medicament is for use in treatment of cancer.

5 47. ~~Use of A method of treating cancer in a subject in need comprising administering to the subject~~ the bispecific antibody of any one of claims 26 to 40 in the manufacture of a medicament for the treatment of cancer in a subject, wherein the medicament is to be administered to a subject in need thereof.

48. A pharmaceutical composition comprising the bispecific antibody of any one of claims 26 to 40.

10 49. ~~A method of treating a condition associated with malignant cells expressing B7-H4 in a subject comprising administering to the subject in need thereof a therapeutically effective amount~~ Use of the pharmaceutical composition of claim 48 in the manufacture of a medicament for the treatment of a condition associated with malignant cells expressing B7-H4 in a subject, wherein a therapeutically effective amount of the medicament is to be administered to the subject in need thereof.

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50. The ~~method~~ use of claim 49, wherein the condition is a cancer.

51. The ~~method~~ use of claim 50, wherein the cancer is breast cancer, ovarian cancer, cancer of the uterus, bladder cancer or cancer of the bile duct.

20 52. ~~A method of inhibiting tumor growth or progression in a subject who has malignant cells expressing B7-H4, comprising administering to the subject in need thereof a therapeutically effective amount~~ Use of the pharmaceutical composition of claim 48 in the manufacture of a medicament for the inhibition of tumor growth or progression of malignant cells expressing B7-H4, wherein a therapeutically effective amount of the medicament is to be administered to the subject in need thereof.

25 53. ~~A method of inducing tumor regression in a subject who has malignant cells expressing B7-H4, comprising administering to the subject in need thereof an effective amount~~ Use of the pharmaceutical composition of claim 48 in the manufacture of a medicament for inducing tumor regression in a subject who has malignant cells expressing B7-H4, wherein an effective amount is to be administered to the subject in need thereof.

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54. The pharmaceutical composition of claim 19 for use in the treatment of a condition associated with cells expressing B7-H4 in a subject.

55. The bispecific antibody of any one of claims 26 to 40 for use in the treatment of cancer.

56. The pharmaceutical composition of claim 48 for use in the treatment of a condition associated with malignant cells expressing B7-H4 in a subject.

5 57. The pharmaceutical composition of claim 48 for use in the inhibition of tumor growth or progression of malignant cells expressing B7-H4 in a subject.

58. The pharmaceutical composition of claim 48 for use in inducing tumor regression in a subject who has malignant cells expressing B7-H4.