[0001] B7-H4 ANTIBODIES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of U.S. Provisional Application No. 62/550,173, filed August 25, 2017, U.S. Provisional Application No. 62/579,774, filed October 31, 2017, U.S. Provisional Application No. 62/607,810, filed December 19, 2017, and U.S. Provisional Application No. 62/656,789, filed April 12, 2018, which are each hereby incorporated in its entirety by reference.

REFERENCE TO A SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

[0003] The content of the electronically submitted sequence listing (Name: 3986.0090004_SL_ST25.txt; Size: 331,354 bytes; Date of Creation: August 3, 2018) is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field

[0004] The present disclosure relates to antibodies that specifically bind to human B7-H4 compositions comprising such antibodies, and methods of producing and using antibodies that specifically bind to B7-H4.

Description of The Related Art

[0005] B7-H4 (also known as B7x, B7-S1, and VTCN1) is an immune regulatory molecule that shares homology with other B7 family members, include PD-L1. It is a type I transmembrane protein comprised of both IgV and IgC ectodomains. While B7-H4 expression in healthy tissues is relatively limited at the protein level, B7-H4 is expressed in several solid tumors such as gynecological carcinomas of the breast, ovary, and endometrium. Expression of B7-H4 in tumors tends to correlate with poor prognosis. The receptor for B7-H4 is unknown, but it is believed to be expressed on T cells. B7-H4 is believed to directly inhibit T cell activity.

[0006] Given the expression and function of B7-H4, provided herein are antibodies that specifically bind to B7-H4 and the use of these antibodies to modulate B7-H4 activity, including, e.g., in the treatment of cancer.

SUMMARY

[0007] Provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences selected from the group consisting of: SEQ ID NOs:5-10, respectively; SEQ ID NOs:15-20, respectively; SEQ ID NOs:25-30, respectively; SEQ ID NOs:35-40, respectively; SEQ ID NOs:458-463, respectively; SEQ ID NOs:45-50, respectively; SEQ ID NOs:55-60, respectively; SEQ ID NOs:65-70, respectively; SEQ ID NOs:75-80, respectively; SEQ ID NOs:85-90, respectively; SEQ ID NOs:95-100, respectively; SEQ ID NOs:105-110, respectively; SEQ ID NOs:115-120, respectively; SEQ ID NOs:125-130, respectively; SEQ ID NOs:135-140, respectively; SEQ ID NOs:145-150, respectively; SEQ ID NOs:155-160, respectively; SEQ ID NOs:165-170, respectively; SEQ ID NOs:175-180, respectively; SEQ ID NOs:185-190, respectively; and SEQ ID NOs:195-200, respectively.

[0008] In one embodiment, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201.

[0009] In one embodiment, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, or 202.

[0010] In one embodiment, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201.

[0011] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, or 202.

[0012] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences of: SEQ ID NOs:11 and 12, respectively; SEQ ID NOs:21 and 22, respectively; SEQ ID NOs:31 and 32, respectively; SEQ ID NOs:41 and 42, respectively; SEQ ID NOs:464 and 42, respectively, SEQ ID NOs:51 and 52, respectively;

SEQ ID NOs:61 and 62, respectively; SEQ ID NOs:71 and 72, respectively; SEQ ID NOs:81 and 82, respectively; SEQ ID NOs:91 and 92, respectively; SEQ ID NOs:101 and 102, respectively; SEQ ID NOs:111 and 112, respectively; SEQ ID NOs:121 and 122, respectively; SEQ ID NOs:131 and 132, respectively; SEQ ID NOs:141 and 142, respectively; SEQ ID NOs:151 and 152, respectively; SEQ ID NOs:161 and 162, respectively; SEQ ID NOs:171 and 172, respectively; SEQ ID NOs:181 and 182, respectively; SEQ ID NOs:191 and 192, respectively; or SEQ ID NOs:201 and 202, respectively.

[0013] In one embodiment, the antibody or antigen-binding fragment thereof further comprises a heavy chain constant region. In one embodiment, the heavy chain constant region is selected from the group consisting of human immunoglobulins IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

[0014] In one embodiment, the antibody or antigen-binding fragment further comprises a light chain constant region. In one embodiment, the light chain constant region is selected from the group consisting of human immunoglobulins IgGκ and IgGλ light chain constant regions.

[0015] In one embodiment, the antibody or antigen-binding fragment further comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region is a human IgG_1 heavy chain constant region, and wherein the light chain constant region is a human IgGκ light chain constant region.

[0016] In one embodiment, the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:13, 23, 33, 43, 469, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 153, 163, 173, 183, 193, or 203.

[0017] In one embodiment, the antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence of SEQ ID NO:14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, or 204.

[0018] In one embodiment, the antibody or antigen-binding fragment thereof comprises a heavy chain and light chain comprising the amino acid sequences of: SEQ ID NOs:13 and 14, respectively; SEQ ID NOs:23 and 24, respectively; SEQ ID NOs:33 and 34, respectively; SEQ ID NOs:43 and 44, respectively; SEQ ID NOs:469 and 44, respectively; SEQ ID NOs:53 and 54, respectively; SEQ ID NOs:63 and 64, respectively; SEQ ID NOs:73 and 74, respectively; SEQ ID NOs:83 and 84, respectively; SEQ ID NOs:93 and 94, respectively; SEQ ID NOs:103 and 104, respectively; SEQ ID NOs:113 and 114, respectively; SEQ ID NOs:123 and 124, respectively; SEQ ID NOs:133 and 134, respectively; SEQ ID NOs:143 and 144, respectively; SEQ ID NOs:153 and 154, respectively; SEQ ID NOs:163 and 164, respectively; SEQ ID

NOs:173 and 174, respectively; SEQ ID NOs:183 and 184, respectively; SEQ ID NOs:193 and 194, respectively; or SEQ ID NOs:203 and 204, respectively.

[0019] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody or antigen-binding fragment thereof comprises the VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of an antibody selected from the group consisting of 15461, 20500, 20501, 20502, 20502.1, 22208, 15462, 22213, 15465, 20506, 15483, 20513, 22216, 15489, 20516, 15472, 15503, 15495, 15478, 15441, and 20496. In one embodiment, the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

[0020] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:458-463, respectively. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0021] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0022] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain

region comprising the amino acid sequence of SEQ ID NO:72 or (ii) wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

[0023] Also provided herein is an isolated antibody or antigen-binding fragment thereof that binds to the same epitope of human B7-H4 as the antibody or antigen-binding fragment thereof of any one of claims 1-20. In one embodiment, the antibody or antigen-binding fragment thereof binds to the same epitope of human B7-H4 as determined by SPR.

[0024] In one embodiment, the antibody or antigen-binding fragment thereof is a human antibody or antigen-binding fragment thereof. In one embodiment, the antibody or antigen-binding fragment thereof is a murine, humanized, or chimeric antibody or antigen-binding fragment thereof.

[0025] In one embodiment, the antibody or antigen-binding fragment thereof induces T cell proliferation. In one embodiment, the antibody or antigen-binding fragment increases T-cell proliferation by at least 21% as compared to treatment with a control antibody. In one embodiment, the antibody or antigen-binding fragment increases T-cell proliferation by about 5% to about 35% as compared to treatment with a control antibody. In one embodiment, the antibody or antigen-binding fragment thereof induces CD4+ T cell proliferation. In one embodiment, the antibody or antigen-binding fragment thereof increases CD4+ T cell proliferation by at least 9% as compared to treatment with a control antibody. In one embodiment, the antibody or antigen-binding fragment thereof increases CD4+ T cell proliferation by about 5% to about 15% as compared to treatment with a control antibody. In one embodiment, the antibody or antigen-binding fragment thereof induces CD8+ T cell proliferation. In one embodiment, the antibody or antigen-binding fragment thereof increases CD8+ T cell proliferation by at least 11% as compared to treatment with a control antibody. In one embodiment, the antibody or antigen-binding fragment thereof increases CD8+ T cell proliferation by about 5% to about 15% as compared to treatment with a control antibody.

[0026] In one embodiment, the antibody or antigen-binding fragment thereof induces interferon-gamma (IFNγ) production. In one embodiment, the antibody or antigen-binding fragment thereof is capable of increasing production of IFNγ by at least 2 fold, at least 3 fold, at least 4 fold, and at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, about 2 fold to about 10 fold, or about 3 fold to about 10 fold.

[0027] In one embodiment, the antibody or antigen-binding fragment thereof is capable of inducing antibody dependent cell mediated cytotoxicity (ADCC) in a B7-H4-expressing cell. In

one embodiment, the antibody or antigen-binding fragment thereof induces specific lysis in at least 20%, at least 30%, at least 40%, about 20% to about 50%, or about 30% to about 50% of B7-H4 expressing cells.

[0028] In one embodiment, the antibody or antigen-binding fragment thereof inhibits tumor growth in a murine CT26 colorectal carcinoma model, a murine breast carcinoma 4T1 model, or a melanoma cell line B16-moB7-H4/H3 model. In one embodiment, the antibody or antigen-binding fragment thereof reduces tumor growth by at least 25%, at least 30%, at least 40%, at least 45%, or at least 50% as compared to treatment with a control antibody.

[0029] In one embodiment, the induction of T cell proliferation, the induction of CD4+ T cell proliferation, the induction of CD8+ T cell proliferation, the induction of IFNγ production, the ADCC activity, and/or in the inhibition of tumor growth is dose-dependent.

[0030] In one embodiment, the antibody or antigen-binding fragment thereof binds to cynomolgus monkey B7-H4. In one embodiment, the antibody or antigen-binding fragment thereof binds to rat B7-H4. In one embodiment, the antibody or antigen-binding fragment thereof binds to mouse B7-H4. In one embodiment, the antibody or antigen-binding fragment thereof binds to human B7-H4, cynomolgus monkey B7-H4, rat B7-H4 and mouse B7-H4.

[0031] In one embodiment, the antibody or antigen-binding fragment thereof binds to the IgV domain of human B7-H4.

[0032] In one embodiment, the antibody or antigen-binding fragment thereof is afucosylated.

[0033] In one embodiment, the antibody or antigen binding fragment thereof is a full length antibody. In one embodiment, the antibody or antigen binding fragment thereof is an antigen binding fragment. In one embodiment, the antigen binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

[0034] In one embodiment, the antibody or antigen-binding fragment thereof further comprises a detectable label.

[0035] Also provided herein is an isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of an antibody or antigen-biding fragment thereof provided herein. In one embodiment, the nucleic acid molecule encodes the VH of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201 or the heavy chain of SEQ ID NO:13, 23, 33, 43, 469, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 153, 163, 173, 183, 193, or 203. In one embodiment, the nucleic acid

molecule comprises the sequence of SEQ ID NO:213, 223, 233, 243, 470, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 383, 393, or 403. In one embodiment, the nucleic acid molecule comprises (i) the sequence of SEQ ID NO:213, 223, 233, 243, 470, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 383, 393, or 403 and (ii) the sequence of SEQ ID NO:408.

[0036] Also provided herein is an isolated polynucleotide comprising a nucleic acid molecule encoding the light chain variable region or light chain of an antibody or antigen-biding fragment thereof provided herein. In one embodiment, the nucleic acid molecule encodes the VL of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, or 202 or the light chain of SEQ ID NO:14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, or 204. In one embodiment, the nucleic acid molecule comprises the sequence of SEQ ID NO:214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 384, 394, or 404. In one embodiment, the nucleic acid molecule comprises (i) the sequence of SEQ ID NO:214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 384, 394, or 404 and (ii) the sequence of SEQ ID NO:406.

[0037] Also provided herein is an isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of an antibody or antigen-biding fragment provided herein and the light chain variable region or light chain of the antibody or antigen-biding fragment thereof.

[0038] Also provided herein is an isolated vector comprising a polynucleotide provided herein.

[0039] Also provided herein is a host cell comprising a polynucleotide provided herein, a vector provided herein, a first vector comprising one polynucleotide provided herein (e.g., a polynucleotide comprising a variable heavy chain or heavy chain encoding nucleic acid) and a second vector comprising another polynucleotide provided herein (e.g., a polynucleotide comprising variable light chain or light chain encoding nucleic acid). In one embodiment, the host cell is a cell selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture. In one embodiment, the host cell is a CHO cell. In one embodiment, the host cell (e.g., a mammalian host cell, such as a CHO cell) lacks a functional alpha-1 ,6-fucosyltransferase gene (FUT8) gene.

[0040] Also provided herein is a method (e.g., an *in vitro* method) of producing an antibody

or antigen-binding fragment thereof that binds to human B7-H4 comprising culturing a host cell provided herein so that the nucleic acid molecule is expressed and the antibody or antigen-biding fragment thereof is produced.

[0041] Also provided herein is an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4 and is encoded by a polynucleotide provided herein.

[0042] Also provided herein is a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, or a host cell provided herein; and a pharmaceutically acceptable excipient.

[0043] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments provided herein and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

[0044] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments provided herein and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

[0045] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:458-463, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0046] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 458-

463, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0047] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0048] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[0049] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3

and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:72 or (ii) wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

[0050] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:72 or (ii) wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

[0051] In one embodiment, fucosylation is undetectable in the composition.

[0052] Also provided herein is a method for inducing T cell proliferation comprising contacting a T cell with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one embodiment, T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% (e.g., as compared to treatment with a control antibody).

[0053] Also provided herein is a method for inducing CD4+ T cell proliferation comprising contacting a CD4+ T cell with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one embodiment, CD4+ T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% (e.g., as compared to treatment with a control antibody).

[0054] Also provided herein is a method for inducing CD8+ T cell proliferation comprising contacting a CD8+ T cell with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one embodiment, CD8+ T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% (e.g., as compared to treatment with a control antibody).

[0055] Also provided herein is a method for inducing interferon gamma production comprising contacting a T cell with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one embodiment, interferon gamma production is increased by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% (e.g., as compared to treatment with a control antibody).

[0056] Also provided herein is a method for killing a cell expressing B7-H4 comprising contacting the cell with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein.

[0057] Also provided herein is a method for depleting B7-H4-expressing cells from a population of cells comprising contacting the population of cells with an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein.

[0058] In one embodiment, the killing or depletion occurs via ADCC.

[0059] In one embodiment, the contacting is *in vitro*. In one embodiment, the contacting is in a subject.

[0060] Also provided herein is a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein. In one embodiment, the cancer is selected from the group consisting of breast cancer, such as triple negative breast cancer or invasive ductal carcinoma, endometrial carcinoma, ovarian cancer, non-small cell lung cancer, pancreatic cancer, thyroid cancer, kidney cancer and bladder cancer. In one embodiment, the breast cancer is triple negative breast cancer or wherein the non-small cell lung cancer is squamous cell carcinoma. In one embodiment, the non-small cell lung cancer is an adenocarcinoma. In one embodiment, the cancer is selected from the group consisting of head

and neck cancer, small cell lung cancer, gastric cancer, and melanoma. In one embodiment, the ovarian cancer is a serous adenocarcinoma. In one embodiment, the breast cancer is a ductal adenocarcinoma.

[0061] In one embodiment, the cancer is a PD-1 inhibitor inadequate responder and/or PD-L1 inhibitor inadequate responder. In one embodiment, the cancer expresses a low level of PD-L1.

[0062] In one embodiment, the subject is human.

[0063] Also provided herein is a method for detecting B7-H4 in a sample comprising contacting said sample with an antibody or antigen-binding fragment thereof provided herein. In one embodiment, the sample is obtained from a cancer in a human subject.

[0064] Also provided herein is a kit comprising an antibody or antigen-binding fragment thereof provided herein, a polynucleotide provided herein, a vector provided herein, a host cell provided herein, or a pharmaceutical composition provided herein and a) a detection reagent, b) a B7-H4 antigen, c) a notice that reflects approval for use or sale for human administration, or d) a combination thereof.

[0065] Also provided herein is an isolated antibody or antigen-binding fragment, wherein the antibody or antigen-binding fragment thereof inhibits T cell checkpoint blockade activity of B7-H4. In one embodiment, the T cell checkpoint blockade activity is measured by an increase in IL-2 production relative to control cells.

[0066] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments and (ii) a pharmaceutically acceptable excipient, wherein the antibodies or antigen-binding fragments inhibit T cell checkpoint blockade activity of B7-H4. In an embodiment, the T cell checkpoint blockade activity is measured by an increase in IL-2 production relative to control cells.

BRIEF DESCRIPTION OF THE FIGURES

[0067] **Fig. 1A** shows B7-H4 expression in a variety of tumor tissues. (See Example 1.)

[0068] **Fig. 1B** shows B7-H4 prevalence in various tumor types by IHC. (See Example 1.)

[0069] **Fig. 2A** shows the binding of B7-H4 antibodies to HEK293T cells expressing human, cynomolgus monkey, or mouse B7-H4. (See Example 6.)

[0070] **Fig. 2B** shows the binding of B7-H4 antibodies to SK-BR-3 cells and to HEK293T cells expressing mouse, cynomolgus monkey, or rat B7-H4. (See Example 6.)

[0071] **Fig. 3A** shows the effect of B7-H4 antibodies on $CD4^+$, $CD8^+$ or total T cell proliferation. (See Example 7.)

[0072] **Fig. 3B** shows the effect of B7-H4 antibodies on interferon-gamma (IFNγ) production. (See Example 7.)

[0073] **Fig. 3C** shows the effect of B7-H4 antibodies on $CD4^+$, $CD8^+$ or total T cell proliferation and on interferon-gamma (IFNγ) production. (See Example 7.)

[0074] **Fig. 3D** shows the effect of various concentrations of B7-H4 antibodies on interferon-gamma (IFNγ) production. (See Example 7.)

[0075] **Figs. 4A-4D** show the binding of fucosylated and afucosylated antibodies to B7-H4 on SK-BR-3 cells (Fig. 4A) and to HEK293T cells expressing mouse (Fig. 4B), cynomolgus monkey (Fig. 4C), or rat B7-H4 (Fig. 4D). (See Example 9.)

[0076] **Figs. 5A and 5B** show the binding of afucosylated and fucosylated B7-H4 antibodies (respectively) to human Fcγ receptor IIIa (FcγRIIIa) V158 allele. (See Example 10.)

[0077] **Fig. 6A** shows the T cell checkpoint blockade activity of fucosylated and afucosylated B7-H4 antibodies. (See Example 11.)

[0078] **Fig. 6B** shows T cell checkpoint ligand activity of afucosylated B7-H4 antibodies compared to isotype control treated cells as measured by IL-2 production. (See Example 11.)

[0079] **Fig. 7** shows the ADCC activity of fucosylated and afucosylated B7-H4 antibodies against a B7-H4 expressing cell line. (See Example 12.)

[0080] **Fig. 8** shows the ADCC activity of fucosylated and afucosylated B7-H4 antibodies against cells with various B7-H4 expression levels. (See Example 13.)

[0081] **Fig. 9A** shows the *in vivo* anti-tumor efficacy of the B7-H4 antibody 20502. (See Example 14.)

[0082] **Fig. 9B** shows the *in vivo* anti-tumor efficacy of the B7-H4 antibody 22213. (See Example 14.)

[0083] **Fig. 10** shows the *in vivo* anti-tumor efficacy of a murine version of the B7-H4 antibody 20502 in mice implanted with 4T1 (breast carcinoma) and B16 (melanoma) cells. (See Example 14.)

[0084] **Fig. 11** shows the *in vivo* anti-tumor efficacy of afucosylated 20502 in an MX-1 human breast cancer xenograft model. The images show human B7-H4 expression in the MX-1 xenograft tumor (left) and murine B7-H4 expression in the 4T1 tumors (right). (See Example 14.)

[0085] **Figs. 12A-12C** show the *in vivo* anti-tumor efficacy of 20502-msIgG2a-F administered on the same day as an anti-PD-1 antibody. (See Example 15.) * indicates $p < 0.05$; and **** indicates $p < 0.0001$.

[0086] **Fig. 13** shows that treatment with afucosylated 20502 (bottom panels) results in NK cell infiltration (left panels), T-cell infiltration (center panels), and PD-L1 up-regulation (right panels) as compared to treatment with a control antibody (top panels). (See Example 16.)

[0087] **Fig. 14A** shows that 20502-msIgG2a-F antibody significantly reduces tumor growth in 4T1 breast carcinoma cells in a dose dependent manner. (See Example 17.)

[0088] **Fig. 14B** shows that 20502-msIgG2a-F antibody significantly inhibits tumor growth at 30 mg/kg ($p = 0.0003$), 20 mg/kg ($p = 0.0103$), 10 mg/kg ($p = 0.0419$), 3 mg/kg ($p = 0.0277$), and 1 mg/kg ($p = 0.0333$) as assessed by OneWay ANOVA on Day 30. (See Example 17.)

[0089] **Fig. 15A** shows that 20502-msIgG2a-F antibody significantly reduces growth of B16 expressing B7-H4/H3. (See Example 17.)

[0090] **Fig. 15B** shows that 20502-msIgG2a-F antibody significantly inhibits tumor growth at 30 mg/kg ($p = 0.0085$), 20 mg/kg ($p = 0.0041$), 10 mg/kg ($p = 0.0017$), and 3 mg/kg ($p = 0.0420$) as assessed by OneWay ANOVA on Day 23. (See Example 17.)

DETAILED DESCRIPTION

[0091] Provided herein are antibodies (*e.g.*, monoclonal antibodies) and antigen-binding fragments thereof that specifically bind to B7-H4 (*e.g.*, human B7-H4). The anti-B7-H4 antibodies and antigen-binding fragments thereof can, for example, result in T cell checkpoint blockade activity (e.g., as measured by an increase in interferon-gamma (IFNγ), CD4 T-cell proliferation, CD8 T-cell proliferation, and/or total T-cell proliferation) and/or have antibody-dependent cellular cytotoxicity (ADCC activity).

[0092] Also provided are isolated nucleic acids (polynucleotides), such as complementary DNA (cDNA), encoding such antibodies and antigen-binding fragments thereof. Further provided are vectors (*e.g.*, expression vectors) and cells (*e.g.*, host cells) comprising nucleic acids (polynucleotides) encoding such antibodies and antigen-binding fragments thereof. Also provided are methods of making such antibodies and antigen-binding fragments thereof. In other aspects, provided herein are methods for treating certain conditions, such as cancer. Related compositions (*e.g.*, pharmaceutical compositions), kits, and detection methods are also provided.

1.1 Terminology

[0093] As used herein, the term "B7-H4" refers to mammalian B7-H4 polypeptides including, but not limited to, native B7-H4 polypeptides and isoforms of B7-H4 polypeptides. "B7-H4" encompasses full-length, unprocessed B7-H4 polypeptides as well as forms of B7-H4

polypeptides that result from processing within the cell. As used herein, the term "human B7-H4" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. A “B7-H4 polynucleotide,” “B7-H4 nucleotide,” or “B7-H4 nucleic acid” refer to a polynucleotide encoding B7-H4.

[0094] The term "PD-1" as used herein, refers to mammalian PD-1 polypeptides, including, but not limited to, native PD-1 polypeptides and isoforms of PD-1 polypeptides. PD-1 is also referred to as Programmed death protein 1 or Programmed cell death protein 1. "PD-1" encompasses full-length, unprocessed PD-1 polypeptides as well as forms of PD-1 polypeptides that result from processing in the cell. As used herein, the term "human PD-1" refers to a polypeptide comprising the amino acid sequence of SEQ ID NO:439:

PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL (SEQ ID NO:439) (mature human PD-1 without a signal sequence). A “PD-1 polynucleotide,” “PD-1 nucleotide” or “PD-1 nucleic acid” refers to a polynucleotide encoding PD-1.

[0095] The term “antibody” means an immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term “antibody” encompasses intact polyclonal antibodies, intact monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies, fusion proteins comprising an antibody, and any other modified immunoglobulin molecule so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules such as toxins, radioisotopes, etc.

[0096] The term “antibody fragment” refers to a portion of an intact antibody. An “antigen-binding fragment,” “antigen-binding domain,” or “antigen-binding region,” refers to a portion of

an intact antibody that binds to an antigen. An antigen-binding fragment can contain the antigenic determining regions of an intact antibody (e.g., the complementarity determining regions (CDR)). Examples of antigen-binding fragments of antibodies include, but are not limited to Fab, Fab', F(ab')2, and Fv fragments, linear antibodies, and single chain antibodies. An antigen-binding fragment of an antibody can be derived from any animal species, such as rodents (*e.g.*, mouse, rat, or hamster) and humans or can be artificially produced.

[0097] The terms "anti-B7-H4 antibody," "B7-H4 antibody" and "antibody that binds to B7-H4" refer to an antibody that is capable of binding B7-H4 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting B7-H4. The extent of binding of an anti-B7-H4 antibody to an unrelated, non-B7-H4 protein can be less than about 10% of the binding of the antibody to B7-H4 as measured, e.g., by a radioimmunoassay (RIA).

[0098] The terms "anti-PD-1 antibody," "PD-1 antibody" and "antibody that binds to PD-1" refer to an antibody that is capable of binding PD-1 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting PD-1. The extent of binding of an anti-PD-1 antibody to an unrelated, non-PD-1 protein can be less than about 10% of the binding of the antibody to PD-1 as measured, e.g., by a radioimmunoassay (RIA).

[0099] A "monoclonal" antibody or antigen-binding fragment thereof refers to a homogeneous antibody or antigen-binding fragment population involved in the highly specific recognition and binding of a single antigenic determinant, or epitope. This is in contrast to polyclonal antibodies that typically include different antibodies directed against different antigenic determinants. The term "monoclonal" antibody or antigen-binding fragment thereof encompasses both intact and full-length monoclonal antibodies as well as antibody fragments (such as Fab, Fab', F(ab')2, Fv), single chain (scFv) mutants, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antigen recognition site. Furthermore, “monoclonal" antibody or antigen-binding fragment thereof refers to such antibodies and antigen-binding fragments thereof made in any number of manners including but not limited to by hybridoma, phage selection, recombinant expression, and transgenic animals.

[00100] As used herein, the terms “variable region” or “variable domain” are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are

used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[00101] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody.

[00102] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody.

[00103] The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody or an antigen-binding fragment thereof. In certain aspects, CDRs can be determined according to the Kabat numbering system (see, *e.g.*, Kabat EA & Wu TT (1971) Ann NY Acad Sci 190: 382-391 and Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[00104] Chothia refers instead to the location of the structural loops (Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither

35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software.

Loop	Kabat	AbM	Chothia
L1	L24-L34	L24-L34	L24-L34
L2	L50-L56	L50-L56	L50-L56
L3	L89-L97	L89-L97	L89-L97
H1	H31-H35B	H26-H35B (Kabat Numbering)	H26-H32..34
H1	H31-H35	H26-H35 (Chothia Numbering)	H26-H32
H2	H50-H65	H50-H58	H52-H56
H3	H95-H102	H95-H102	H95-H102

[00105] As used herein, the term "constant region" or "constant domain" are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain. In certain aspects, an antibody or antigen-binding fragment comprises a constant region or portion thereof that is sufficient for antibody-dependent cell-mediated cytotoxicity (ADCC).

[00106] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG_1, IgG_2, IgG_3, and IgG_4. Heavy chain amino acid sequences are well known in the art. In specific embodiments, the heavy chain is a human heavy chain.

[00107] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific

embodiments, the light chain is a human light chain.

[00108] The term "chimeric" antibodies or antigen-binding fragments thereof refers to antibodies or antigen-binding fragments thereof wherein the amino acid sequence is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies or antigen-binding fragments thereof derived from one species of mammals (e.g. mouse, rat, rabbit, etc.) with the desired specificity, affinity, and capability while the constant regions are homologous to the sequences in antibodies or antigen-binding fragments thereof derived from another (usually human) to avoid eliciting an immune response in that species.

[00109] The term "humanized" antibody or antigen-binding fragment thereof refers to forms of non-human (e.g. murine) antibodies or antigen-binding fragments that are specific immunoglobulin chains, chimeric immunoglobulins, or fragments thereof that contain minimal non-human (e.g., murine) sequences. Typically, humanized antibodies or antigen-binding fragments thereof are human immunoglobulins in which residues from the complementary determining region (CDR) are replaced by residues from the CDR of a non-human species (e.g. mouse, rat, rabbit, hamster) that have the desired specificity, affinity, and capability ("CDR grafted") (Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Verhoeyen et al., Science 239:1534-1536 (1988)). In some instances, the Fv framework region (FR) residues of a human immunoglobulin are replaced with the corresponding residues in an antibody or fragment from a non-human species that has the desired specificity, affinity, and capability. The humanized antibody or antigen-binding fragment thereof can be further modified by the substitution of additional residues either in the Fv framework region and/or within the replaced non-human residues to refine and optimize antibody or antigen-binding fragment thereof specificity, affinity, and/or capability. In general, the humanized antibody or antigen-binding fragment thereof will comprise substantially all of at least one, and typically two or three, variable domains containing all or substantially all of the CDR regions that correspond to the non-human immunoglobulin whereas all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody or antigen-binding fragment thereof can also comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Examples of methods used to generate humanized antibodies are described in U.S. Pat. 5,225,539; Roguska et al., Proc. Natl. Acad. Sci., USA, 91(3):969-973 (1994), and Roguska et al., Protein Eng. 9(10):895-904 (1996). In some embodiments, a "humanized antibody" is a resurfaced antibody.

[00110] The term "human" antibody or antigen-binding fragment thereof means an antibody or antigen-binding fragment thereof having an amino acid sequence derived from a human immunoglobulin gene locus, where such antibody or antigen-binding fragment is made using any technique known in the art. This definition of a human antibody or antigen-binding fragment thereof includes intact or full-length antibodies and fragments thereof.

[00111] An "afucosylated" antibody or antigen-binding fragment thereof or an antibody or antigen-binding fragment thereof "lacking fucose" refers to an IgGl or IgG3 isotype antibody or antigen-binding fragment thereof that lacks fucose in its constant region glycosylation. Glycosylation of human IgGl or IgG3 occurs at Asn297 as core fucosylated biantennary complex oligosaccharide glycosylation terminated with up to 2 Gal residues. In some embodiments, an afucosylated antibody lacks fucose at Asn297. These structures are designated as G0, Gl (a 1,6 or a 1,3), or G2 glycan residues, depending on the amount of terminal Gal residues. See, e.g., Raju, T. S., BioProcess Int. 1: 44-53 (2003). CHO type glycosylation of antibody Fc is described, e.g., in Routier, F. FL, Glycoconjugate J. 14: 201-207 (1997).

[00112] Methods of measuring fucose include any methods known in the art. For purposes herein, fucose is detected by the method described in Example 1 of WO2015/017600, which is herein incorporated by reference in its entirety. Briefly, glycan analysis is performed by releasing glycans from the antibody (e.g., by enzymatic release), labeling the glycans with anthranilic acid (2-AA), and then purifying the labeled glycans. Normal phase HPLC with fluorescent detection is used to separate the glycans and measure the relative amount of each glycan in the antibody. The glycans may be positively identified as lacking or including fucose by mass spectrometry. In some embodiments, fucose is undetectable in a composition comprising a plurality of afucosylated antibodies or antigen-binding fragments thereof. In some embodiments, an afucosylated antibody or antigen-binding fragment thereof has enhanced ADCC activity, which may be measured by the assay provided in Example 12 herein. In some embodiments, an afucosylated antibody or antigen-binding fragment thereof has enhanced affinity for Fc gamma RIIIA. In some embodiments, an afucosylated antibody or antigen-binding fragment thereof has enhanced affinity for Fc gamma RIIIA(V158). In some embodiments, an afucosylated antibody or antigen-binding fragment thereof has enhanced affinity for Fc gamma RIIIA(F158). Affinity for Fc gamma RIIIA or its alleles may be measure by the assay provided in Example 10 herein.

[00113] “Binding affinity” generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody or antigen-binding fragment thereof) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used

herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody or antigen-binding fragment thereof and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on}, whereas K_A is calculated from the quotient of k_{on}/k_{off}. k_{on} refers to the association rate constant of, *e.g.*, an antibody or antigen-binding fragment thereof to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody or antigen-binding fragment thereof from an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIAcore® or KinExA.

[00114] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody or antigen-binding fragment thereof can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody or antigen-binding fragment thereof binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (e.g., liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.,* (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody/antigen-binding fragment thereof:antigen crystals can be studied using well known X-ray diffraction techniques and can be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see*, e.g., Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.,*; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.,* (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies can be accomplished using any method known to one of skill in the art. *See*, *e.g.*, Champe M *et al.,* (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning

mutagenesis techniques.

[00115] A B7-H4 antibody that "binds to the same epitope" as a reference B7-H4 antibody refers to an antibody that binds to the same B7-H4 amino acid residues as the reference B7-H4 antibody. The ability of a B7-H4 antibody to bind to the same epitope as a reference B7-4 antibody is determined by a hydrogen/deuterium exchange assay (see Coales et al. Rapid Commun. Mass Spectrom. 2009; 23: 639–647).

[00116] As used herein, the terms "immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" are analogous terms in the context of antibodies or antigen-binding fragments thereof. These terms indicate that the antibody or antigen-binding fragment thereof binds to an epitope via its antigen-binding domain and that the binding entails some complementarity between the antigen binding domain and the epitope. Accordingly, an antibody that "specifically binds" to human B7-H4 (SEQ ID NO:1) may also bind to B7-H4 from other species (e.g., cynomolgous monkey, mouse, and/or rat B7-H4) and/or B7-H4 proteins produced from other human alleles, but the extent of binding to an un-related, non-B7-H4 protein (e.g., other B7 protein family members such as PD-L1) is less than about 10% of the binding of the antibody to B7-H4 as measured, e.g., by a radioimmunoassay (RIA).

[00117] In a specific embodiment, provided herein is an antibody or antigen-binding fragment thereof that binds to human, cynomolgus monkey, mouse, and rat B7-H4.

[00118] An antibody is said to "competitively inhibit" binding of a reference antibody to a given epitope if it preferentially binds to that epitope or an overlapping epitope to the extent that it blocks, to some degree, binding of the reference antibody to the epitope. Competitive inhibition may be determined by any method known in the art, for example, competition ELISA assays. An antibody may be said to competitively inhibit binding of the reference antibody to a given epitope by at least 90%, at least 80%, at least 70%, at least 60%, or at least 50%.

[00119] A polypeptide, antibody, polynucleotide, vector, cell, or composition which is "isolated" is a polypeptide, antibody, polynucleotide, vector, cell, or composition which is in a form not found in nature. Isolated polypeptides, antibodies, polynucleotides, vectors, cell or compositions include those which have been purified to a degree that they are no longer in a form in which they are found in nature. In some embodiments, an antibody, polynucleotide, vector, cell, or composition which is isolated is substantially pure. As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), at least 90% pure, at least 95% pure, at least 98% pure, or at least 99% pure.

[00120] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer can be linear or branched, it can comprise modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention are based upon antibodies, in certain embodiments, the polypeptides can occur as single chains or associated chains.

[00121] “Percent identity” refers to the extent of identity between two sequences (e.g., amino acid sequences or nucleic acid sequences). Percent identity can be determined by aligning two sequences, introducing gaps to maximize identity between the sequences. Alignments can be generated using programs known in the art. For purposes herein, alignment of nucleotide sequences can be performed with the blastn program set at default parameters, and alignment of amino acid sequences can be performed with the blastp program set at default parameters (see National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov).

[00122] As used herein, the term “host cell” can be any type of cell, e.g., a primary cell, a cell in culture, or a cell from a cell line. In specific embodiments, the term “host cell” refers to a cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule, e.g., due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[00123] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. The formulation can be sterile.

[00124] The terms “administer”, “administering”, “administration”, and the like, as used herein, refer to methods that may be used to enable delivery of a drug, e.g., an anti-B7-H4 antibody or antigen-binding fragment thereof to the desired site of biological action (e.g., intravenous administration). Administration techniques that can be employed with the agents

and methods described herein are found in e.g., Goodman and Gilman, The Pharmacological Basis of Therapeutics, current edition, Pergamon; and Remington's, Pharmaceutical Sciences, current edition, Mack Publishing Co., Easton, Pa.

[00125] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) or consecutive administration in any order.

[00126] The combination therapy can provide "synergy," i.e., the effect achieved when the active agents used together is greater than the sum of the effects that result from using the active agents separately. A synergistic effect can be attained when the active agents are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered serially, by alternation, or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect can be attained when the active agents are administered or delivered sequentially, e.g., by different injections in separate syringes. A "synergistic combination" produces an effect that is greater than the sum of the effects of the individual active agents of the combination.

[00127] The combination therapy can provide an "additive" effect, i.e., the effect achieved when the active agents used together is equal to the sum of the effects the result from using the active agents separately.

[00128] As used herein, the terms "subject" and "patient" are used interchangeably. The subject can be an animal. In some embodiments, the subject is a mammal such as a non-human animal (e.g., cow, pig, horse, cat, dog, rat, mouse, monkey or other primate, etc.). In some embodiments, the subject is a cynomolgus monkey. In some embodiments, the subject is a human.

[00129] The term "therapeutically effective amount" refers to an amount of a drug, e.g., an anti-B7-H4 antibody or antigen-binding fragment thereof effective to treat a disease or disorder in a subject. In the case of cancer, the therapeutically effective amount of the drug can reduce the number of cancer cells; reduce the tumor size or burden; inhibit (i.e., slow to some extent and in a certain embodiment, stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and in a certain embodiment, stop) tumor metastasis; inhibit, to some extent, tumor growth; relieve to some extent one or more of the symptoms associated with the cancer; and/or result in a favorable response such as increased progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS), complete response (CR), partial response (PR), or, in some cases, stable disease (SD), a decrease in progressive disease (PD), a reduced time to progression (TTP), or any combination thereof. To the extent the drug can prevent growth and/or

kill existing cancer cells, it can be cytostatic and/or cytotoxic.

[00130] Terms such as "treating" or "treatment" or "to treat" or "alleviating" or "to alleviate" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. In certain embodiments, a subject is successfully "treated" for cancer according to the methods of the present invention if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumor size; inhibition of or an absence of cancer cell infiltration into peripheral organs including, for example, the spread of cancer into soft tissue and bone; inhibition of or an absence of tumor metastasis; inhibition or an absence of tumor growth; relief of one or more symptoms associated with the specific cancer; reduced morbidity and mortality; improvement in quality of life; reduction in tumorigenicity, tumorigenic frequency, or tumorigenic capacity, of a tumor; reduction in the number or frequency of cancer stem cells in a tumor; differentiation of tumorigenic cells to a non-tumorigenic state; increased progression-free survival (PFS), disease-free survival (DFS), or overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), a decrease in progressive disease (PD), a reduced time to progression (TTP), or any combination thereof.

[00131] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals in which a population of cells are characterized by unregulated cell growth. Examples of cancer include, but are not limited to, gynecological cancers (e.g., breast cancer (including triple negative breast cancer, ductal carcinoma), ovarian cancer, and endometrial cancer), non-small cell lung cancer, pancreatic cancer, thyroid cancer, kidney cancer (e.g., renal cell carcinoma), and bladder cancer (e.g., urothelial cell carcinoma). A non-small cell lung cancer can be e.g., an adenocarcinoma. Additional examples of cancer include, e.g., head and neck cancer, small cell lung cancer, gastric cancer, melanoma, cholangiocarcinoma, glioblastoma or glioblastoma multiforme (GBM), and merkel cell carcinoma. In one embodiment, the ovarian cancer is a serous adenocarcinoma. In one embodiment, the breast cancer is a ductal adenocarcinoma. The cancer can be a “cancer that expresses B7-H4” or a “B7-H4 expressing cancer.” Such terms refer to a cancer comprising cells that express B7-H4. The cancer may be a primary tumor or may be advanced or metastatic cancer.

[00132] A “refractory” cancer is one that progresses even though an anti-tumor treatment, such as a chemotherapy, is administered to the cancer patient.

[00133] A “recurrent” cancer is one that has regrown, either at the initial site or at a distant

site, after a response to initial therapy.

[00134] A "relapsed" patient is one who has signs or symptoms of cancer after remission. Optionally, the patient has relapsed after adjuvant or neoadjuvant therapy.

[00135] "T cell checkpoint blockade activity" refers to blocking or inhibition of a T cell checkpoint activity or response. T cell checkpoint blockade activity can be measured in an artificial antigen presenting cells (aAPC) assay based on changes in IFNγ production. Primary human T cells can be enriched from PBMCs using a T cell enrichment kit (such as an EasySep™ Human T Cell Enrichment Kit or similar kit). Enriched T cells are incubated with beads (e.g., anti-CD3/anti-CD28 beads). After a period of time, the beads are magnetically removed, and T cells are washed and incubated. Next, T cells are washed and incubated along with artificial antigen presenting cells (aAPCs) in the presence of B7-H4 antibody dose titration. aAPCs can be treated with Mitomycin C and then thoroughly washed prior to adding to the T cell co-culture. After co-culture of T cells, aAPCs, and B7-H4 antibodies, plates can be centrifuged, and supernatants can be harvested and assessed for IFNγ production by ELISA. IFNγ production can be plotted vs. antibody concentration, and the EC50 potency can be calculated using nonlinear regression curve fit. Results can be measured as EC50 +/- STD in nM. T cell checkpoint blockade activity by B7-H4 antibodies can be demonstrated by an increase in IFNγ production. "T cell checkpoint blockade activity" can also be measured in an assay using cells that endogenously express B7-H4. Primary human T cells can be enriched from HLA-A2+ donor PBMCs using a T cell isolation kit (e.g., Human Pan T Cell Isolation Kit). MART-I TCR expressing T cells can be generated by first activating enriched Pan T cells with beads (e.g., anti-CD3/anti-CD28 Dynabeads), IL-2 and IL-7 for 48 hours. Activated T cells can then be transduced with MART-I TCR lentiviral particles in the presence of IL-2, IL-7 and polybrene. After transduction, MART-I TCR+ Pan T cells can be expanded over a period of time in the presence of IL-2 and IL-7. To generate HLA-A2 expressing target cell lines, the endogenous B7-H4 expressing cancer cell lines can be transduced with HLA-A2 lentiviral particles for a period of time (*e.g.*, 48 hours). Furthermore, B7-H4 can be knocked-out of the HLA-A2+ cell line. Then, MART-I TCR+ Pan T cells can be co-cultured in the presence of the various target cell lines at a 1:1 E:T ratio, MART-I peptide and a B7-H4 antibody or a human isotype control. After co-incubation, plates can be centrifuged, and supernatants can be harvested and assessed for IL-2 production. IL-2 production can be measured by a standard immunoassay kit (such as an AlphaLISA assay or similar assay).

[00136] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[00137] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided. In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean " includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments

[00138] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both "A and B," "A or B," "A," and "B." Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[00139] As used herein, the terms "about" and "approximately," when used to modify a numeric value or numeric range, indicate that deviations of 5% to 10% above and 5% to 10% below the value or range remain within the intended meaning of the recited value or range.

[00140] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

1.2 Antibodies

[00141] In a specific aspect, provided herein are antibodies (e.g., monoclonal antibodies, such as chimeric, humanized, or human antibodies) and antigen-binding fragments thereof which specifically bind to B7-H4 (*e.g.*, human B7-H4). The amino acid sequences for human, cynomolgus monkey, murine, and rat B7-H4 are known in the art and also provided herein as represented by SEQ ID NOs:1-4, respectively.

Human B7-H4:

MASLGQILFWSIISIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKLSDI
VIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDA

GTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWAS
QVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTES
EIKRRSHLQLLNSKASLCVSSFFAISWALLPLSPYLMLK (SEQ ID NO:1)

Cynomolgus monkey B7-H4:

MASLGQILFWSIISIIFILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKLSD
IVIQWLKEGVIGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDA
GTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWAS
QVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTES
EIKRRSHLQLLNSKASLCVSSFLAISWALLPLAPYLMLK (SEQ ID NO:2)

Murine B7-H4

MASLGQIIFWSIINIIIILAGAIALIIGFGISGKHFITVTTFTSAGNIGEDGTLSCTFEPDIKLNG
IVIQWLKEGIKGLVHEFKEGKDDLSQQHEMFRGRTAVFADQVVVGNASLRLKNVQLTD
AGTYTCYIRTSKGKGNANLEYKTGAFSMPEINVDYNASSESLRCEAPRWFPQPTVAWAS
QVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTD
SEVKRRSQLQLLNSGPSPCVFSSAFVAGWALLSLSCCLMLR (SEQ ID NO:3)

Rat B7-H4

MASLGQIIFWSIINVIIILAGAIVLIIGFGISGKHFITVTTFTSAGNIGEDGTLSCTFEPDIKLN
GIVIQWLKEGIKGLVHEFKEGKDDLSQQHEMFRGRTAVFADQVVVGNASLRLKNVQLT
DAGTYTCYIHTSKGKGNANLEYKTGAFSMPEINVDYNASSESLRCEAPRWFPQPTVAW
ASQVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKV
TDSEVKRRSQLELLNSGPSPCVSSVSAAGWALLSLSCCLMLR (SEQ ID NO:4)

[00142] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof binds to human and cynomolgus monkey B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof binds to human, murine, and rat B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof binds to human, cynomolgus monkey, murine, and rat B7-H4.

[00143] B7-H4 contains an IgC ectodomain (amino acids 153-241 of SEQ ID NO:1) and an IgV domain (amino acids 35-146 of SEQ ID NO:1).

[00144] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to the IgV domain of human B7-H4. Accordingly, provided herein are antibodies and antigen-binding fragments thereof that bind to a polypeptide consisting of amino acids 35-146 of SEQ ID NO:1.

[00145] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2).

Table 1. VH CDR Amino Acid Sequences [1]

Anti-body	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
15461	GSISSSSYYWG (SEQ ID NO:5)	NIYYSGSTYYNPSLKS (SEQ ID NO:6)	AREGSYPNWFDP (SEQ ID NO:7)
20500	GSIKSGSHYWG (SEQ ID NO:15)	NIYYSGSTYYNPSLRS (SEQ ID NO:16)	AREGSYPNWFDP (SEQ ID NO:17)
20501	GSIKSGSHYWG (SEQ ID NO:25)	NIYYSGSTYYNPSLKS (SEQ ID NO:26)	AREGSYPNWLDP (SEQ ID NO:27)
20502	GSIKSGSYYWG (SEQ ID NO:458)	NIYYSGSTYYNPSLRS (SEQ ID NO:459)	AREGSYPNQFDP (SEQ ID NO:460)
20502.1	GSIKSGSYYWG (SEQ ID NO:35)	NIYYSGSTYYNPSLKS (SEQ ID NO:36)	AREGSYPNQFDP (SEQ ID NO:37)
22208	GSIKSGSHYWG (SEQ ID NO:45)	NIYYSGSTYYNPSLKS (SEQ ID NO:46)	AREGSYPNWFDP (SEQ ID NO:47)
15462	GSISSSSYYWG (SEQ ID NO:55)	NIYYSGSTYYNPSLKS (SEQ ID NO:56)	AREGSYTTVLNV (SEQ ID NO:57)
22213	GSIGRGSYYWG (SEQ ID NO:65)	NIYYSGSTYYNPSLKS (SEQ ID NO:66)	AREGSYTTVLNV (SEQ ID NO:67)
15465	GSISSGGYYWS (SEQ ID NO:75)	NIYYSGSTYYNPSLKS (SEQ ID NO:76)	ARESSTISADFDL (SEQ ID NO:77)
20506	GSISHGGYYWS (SEQ ID NO:85)	NIYYSGSTYYNPSLKS (SEQ ID NO:86)	ARESSTISADFDL (SEQ ID NO:87)
15483	GSISSGGYYWS (SEQ ID NO:95)	NIYYSGSTYYNPSLKS (SEQ ID NO:96)	ARGLSTIDEAFDP (SEQ ID NO:97)
20513	GSISDGSYYWS (SEQ ID NO:105)	NIYYSGSTYYNPSLRS (SEQ ID NO:106)	ARGLSTIDEAFDP (SEQ ID NO:107)
22216	GSISDGSYYWS (SEQ ID NO:115)	NIYYSGSTYYNPSLRS (SEQ ID NO:116)	ARGLSTIDEAFDP (SEQ ID NO:117)
15489	GSISSYYWS (SEQ ID NO:125)	YIYSSGSTNYNPSLKS (SEQ ID NO:126)	ARGSGQYAAPDYGMDV (SEQ ID NO:127)
20516	GSIISYYWG (SEQ ID NO:135)	YIYSSGSTSYNPSLKS (SEQ ID NO:136)	ARGSGLYAAPDYGLDV (SEQ ID NO:137)
15472	FTFSSYAMS (SEQ ID NO:145)	TISGSGGSTYYADSVKG (SEQ ID NO:146)	ARGAGHYDLVGRY (SEQ ID NO:147)
15503	FTFSSYAMS (SEQ ID NO:155)	AISGSGGSTYYADSVKG (SEQ ID NO:156)	ARVGFRALNY (SEQ ID NO:157)

15495	GTFSSYAIS (SEQ ID NO:165)	GIIPIFGTASYAQKFQG (SEQ ID NO:166)	ARQQYDGRRYFGL (SEQ ID NO:167)
15478	GTFSSYAIS (SEQ ID NO:175)	GIIPIFGTANYAQKFQG (SEQ ID NO:176)	ARGGPWFDP (SEQ ID NO:177)
15441	FTFSSYAMS (SEQ ID NO:185)	AISGSGGSTSYADSVKG (SEQ ID NO:186)	AKPSLATMLAFDI (SEQ ID NO:187)
20496	GSISSSVYYWS (SEQ ID NO:195)	SILVSGSTYYNPSLKS (SEQ ID NO:196)	ARAVSFLDV (SEQ ID NO:197)

[1]The VH CDRs in Table 1 are determined according to Kabat.

Table 2. VL CDR Amino Acid Sequences [2]

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
15461	RASQSVSSNLA (SEQ ID NO:8)	GASTRAT (SEQ ID NO:9)	QQYHSFPFT (SEQ ID NO:10)
20500	RASQSVSSNLA (SEQ ID NO:18)	GASTRAT (SEQ ID NO:19)	QQYHSFPFT (SEQ ID NO:20)
20501	RASQSVSSNLA (SEQ ID NO:28)	GASTRAT (SEQ ID NO:29)	QQYHSFPFT (SEQ ID NO:30)
20502	RASQSVSSNLA (SEQ ID NO:461)	GASTRAT (SEQ ID NO:462)	QQYHSFPFT (SEQ ID NO:463)
20502.1	RASQSVSSNLA (SEQ ID NO:38)	GASTRAT (SEQ ID NO:39)	QQYHSFPFT (SEQ ID NO:40)
22208	RASQSVSTNLA (SEQ ID NO:48)	DASARVT (SEQ ID NO:49)	QQYHSFPFT (SEQ ID NO:50)
15462	RASQSVSSSYLA (SEQ ID NO:58)	GASSRAT (SEQ ID NO:59)	QQAASYPLT (SEQ ID NO:60)
22213	RASQSVASSHLA (SEQ ID NO:68)	DAVSRAT (SEQ ID NO:69)	QQAASYPLT (SEQ ID NO:70)
15465	RASQGISRWLA (SEQ ID NO:78)	AASSLQS (SEQ ID NO:79)	QQAHTFPYT (SEQ ID NO:80)
20506	RASQGISRWLA (SEQ ID NO:88)	AASSLQS (SEQ ID NO:89)	QQAHTFPYT (SEQ ID NO:90)
15483	RASQSISSWLA (SEQ ID NO:98)	KASSLES (SEQ ID NO:99)	QQDNSYPYT (SEQ ID NO:100)
20513	RASQSISSWLA (SEQ ID NO:108)	KASSLES (SEQ ID NO:109)	QQDNSYPYT (SEQ ID NO:110)
22216	RASKSISSWLA (SEQ ID NO:118)	EASSLHS (SEQ ID NO:119)	QQDNSYPYT (SEQ ID NO:120)

15489	RASQSISSWLA (SEQ ID NO:128)	KASSLES (SEQ ID NO:129)	QQDNSFPFT (SEQ ID NO:130)
20516	RASQSISSWLA (SEQ ID NO:138)	KASSLES (SEQ ID NO:139)	QQDNSFPFT (SEQ ID NO:140)
15472	RASQSISSYLN (SEQ ID NO:148)	AASSLQS (SEQ ID NO:149)	QQLYSLPPT (SEQ ID NO:150)
15503	RASQDISSWLA (SEQ ID NO:158)	AASSLQS (SEQ ID NO:159)	QQATSYPPWT (SEQ ID NO:160)
15495	RASQSVSSNLA (SEQ ID NO:168)	SASTRAT (SEQ ID NO:169)	QQVNVWPPT (SEQ ID NO:170)
15478	RASQSISSWLA (SEQ ID NO:178)	KASSLES (SEQ ID NO:179)	QQYNSYPPFT (SEQ ID NO:180)
15441	RASQSISSWLA (SEQ ID NO:188)	DASSLES (SEQ ID NO:189)	QQSKSYPRT (SEQ ID NO:190)
20496	RASQSISSYLN (SEQ ID NO: 198)	GASSLQS (SEQ ID NO: 199)	QQSYDPPWT (SEQ ID NO: 200)

[00146] [2]The VL CDRs in Table 2 are determined according to Kabat.

[00147] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the VH of an antibody listed in Table 3.

Table 3: Variable Heavy Chain (VH) Amino Acid Sequences

Antibody	VH Amino Acid Sequence (SEQ ID NO)
15461	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYPNWFDPWGQGTLVTVSS (SEQ ID NO: 11)
20500	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLRSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYPNWFDPWGQGTLVTVSS (SEQ ID NO:21)
20501	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYPNWLDPWGQGTLVTVSS (SEQ ID NO:31)
20502	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLRSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYPNQFDPWGQGTLVTVSS (SEQ ID NO:464)
20502.1	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYPNQFDPWGQGILVTVSS (SEQ ID NO:41)
22208	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAVY YCAREGSYPNWFDPWGQGTLVTVSS (SEQ ID NO:51)
15462	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAREGSYTTVLNVWGQGTMVTVSS (SEQ ID NO:61)
22213	QLQLQESGPGLVKPSETLSLTCTVSGGSIGRGSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY

	CAREGSYTTVLNVWGQGTMVTVSS (SEQ ID NO:71)
15465	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARESSTISADFDLWGRGTLVTVSS (SEQ ID NO:81)
20506	QLQLQESGPGLVKPSETLSLTCTASGGSISHGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCARESSTISADFDLWGRGTLVTVSS (SEQ ID NO:91)
15483	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGLSTIDEAFDPWGQGTLVTVSS (SEQ ID NO:101)
20513	QLQLQESGPGLVKPSETLSLTCTVSGGSISDGSYYWSWIRQHPGKGLE WIGNIYYSGSTYYNPSLRSRVTMSVDTSKNQFSLKLSSVTAADTAVY YCARGLSTIDEAFDPWGQGTLVTVSS (SEQ ID NO:111)
22216	QVQLQESGPGLVKPSQTLSLTCTVSGGSISDGSYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLRSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCARGLSTIDEAFDPWGQGTLVTVSS (SEQ ID NO:121)
15489	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWI GYIYSSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RGSGQYAAPDYGMDVWGQGTTVTVSS (SEQ ID NO:131)
20516	QVQLQESGPGLVKPSETLSLTCTVSGGSIISYYWGWIRQPPGKGLEWI GYIYSSGSTSYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RGSGLYAAPDYGLDVWGQGTTVTVSS (SEQ ID NO:141)
15472	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSTISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARGAGHYDLVGRYWGQGTLVTVSS (SEQ ID NO:151)
15503	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARVGFRALNYWGQGTTVTVSS (SEQ ID NO:161)
15495	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGGIIPIFGTASYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCARQQYDGRRYFGLWGRGTLVTVSS (SEQ ID NO:171)
15478	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVY YCARGGPWFDPWGQGTLVTVSS (SEQ ID NO:181)
15441	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSAISGSGGSTSYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKPSLATMLAFDIWGQGTMVTVSS (SEQ ID NO:191)
20496	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSVYYWSWIRQPPGKGLE WIGSILVSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARAVSFLDVWGQGTMVIVSS (SEQ ID NO:201)

[00148] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the VL of an antibody listed in Table 4.

Table 4: Variable Light Chain (VL) Amino Acid Sequences

Antibody	VL Amino Acid Sequence (SEQ ID NO)

15461	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPFT FGGGTKVEIK (SEQ ID NO:12)
20500	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPFT FGGGTKVEIK (SEQ ID NO:22)
20501	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPFT FGGGTKVEIK (SEQ ID NO:32)
20502 and 20502.1	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPFT FGGGTKVEIK (SEQ ID NO:42)
22208	EIVMTQSPATLSVSPGERATLSCRASQSVSTNLAWYQQKPGQAPRLLI YDASARVTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPFT FGGGTKVEIK (SEQ ID NO:52)
15462	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAASYPLT FGGGTKVEIK (SEQ ID NO:62)
22213	EIVLTQSPGTLSLSPGERATLSCRASQSVASSHLAWYQQKPGQAPRLL IYDAVSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAASYPL TFGGGTKVEIK (SEQ ID NO:72)
15465	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHTFPYT FGGGTKVEIK (SEQ ID NO:82)
20506	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHTFPYT FGGGTKVEIK (SEQ ID NO:92)
15483	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYPYT FGGGTKVEIK (SEQ ID NO:102)
20513	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYPYT FGGGTKVEIK (SEQ ID NO:112)
22216	DIQMTQSPSTLSASVGDRVTITCRASKSISSWLAWYQQKPGKAPKLLI YEASSLHSGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYPYT FGGGTKVEIK (SEQ ID NO:122)
15489	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSFPFT FGGGTKVEIK (SEQ ID NO:132)
20516	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSFPFT FGGGTKVEIK (SEQ ID NO:142)
15472	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLYSLPPT FGGGTKVEIK (SEQ ID NO:152)
15503	DIQLTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQATSYPP WTFGGGTKVEIK (SEQ ID NO:162)

15495	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YSASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQVNVWPP TFGGGTKVEIK (SEQ ID NO:172)
15478	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPPF TFGGGTKVEIK (SEQ ID NO:182)
15441	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLI YDASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSKSYPRT FGGGTKVEIK (SEQ ID NO:192)
20496	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYDPPW TFGGGTKVEIK (SEQ ID NO:202)

[00149] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the VH and the VL of an antibody listed in Tables 3 and 4 (i.e., the VH of the antibody listed in Table 3 and the VL of the same antibody listed in Table 4).

[00150] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the VH framework regions of an antibody listed in Table 5.

Table 5. VH FR Amino Acid Sequences [4]

Anti-body	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
15461	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:205)	WIRQPPGKGLEWIG (SEQ ID NO:206)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:207)	WGQGTLVTVSS (SEQ ID NO:208)
20500	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:215)	WIRQPPGKGLEWIG (SEQ ID NO:216)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:217)	WGQGTLVTVSS (SEQ ID NO:218)
20501	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:225)	WIRQPPGKGLEWIG (SEQ ID NO:226)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:227)	WGQGTLVTVSS (SEQ ID NO:228)
20502	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:465)	WIRQPPGKGLEWIG (SEQ ID NO:466)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:467)	WGQGTLVTVSS (SEQ ID NO:468)
20502.1	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:235)	WIRQPPGKGLEWIG (SEQ ID NO:236)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:237)	WGQGILVTVSS (SEQ ID NO:238)
22208	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:245)	WIRQPPGKGLEWIG (SEQ ID NO:246)	RVTMSVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:247)	WGQGTLVTVSS (SEQ ID NO:248)
15462	QLQLQESGPGLVKPSETLSLTCTVSG	WIRQPPGKGLEWIG (SEQ ID	RVTISVDTSKNQFSLKLSSVTAADTAVYY	WGQGTMVTVSS (SEQ ID

	(SEQ ID NO:255)	NO:256)	C (SEQ ID NO:257)	NO:258)
22213	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:265)	WIRQPPGKGLEWIG (SEQ ID NO:266)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:267)	WGQGTMVTVSS (SEQ ID NO:268)
15465	QVQLQESGPGLVKPSQTLSLTCTVSG (SEQ ID NO:275)	WIRQHPGKGLEWIG (SEQ ID NO:276)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:277)	WGRGTLVTVSS (SEQ ID NO:278)
20506	QLQLQESGPGLVKPSETLSLTCTASG (SEQ ID NO:285)	WIRQHPGKGLEWIG (SEQ ID NO:286)	RVTMSVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:287)	WGRGTLVTVSS (SEQ ID NO:288)
15483	QVQLQESGPGLVKPSQTLSLTCTVSG (SEQ ID NO:295)	WIRQHPGKGLEWIG (SEQ ID NO:296)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:297)	WGQGTLVTVSS (SEQ ID NO:298)
20513	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:305)	WIRQHPGKGLEWIG (SEQ ID NO:306)	RVTMSVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:307)	WGQGTLVTVSS (SEQ ID NO:308)
22216	QVQLQESGPGLVKPSQTLSLTCTVSG (SEQ ID NO:315)	WIRQHPGKGLEWIG (SEQ ID NO:316)	RVTMSVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:317)	WGQGTLVTVSS (SEQ ID NO:318)
15489	QVQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:325)	WIRQPPGKGLEWIG (SEQ ID NO:326)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:327)	WGQGTTVTVSS (SEQ ID NO:328)
20516	QVQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:335)	WIRQPPGKGLEWIG (SEQ ID NO:336)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:337)	WGQGTTVTVSS (SEQ ID NO:338)
15472	EVQLLESGGGLVQPGGSLRLSCAASG (SEQ ID NO:345)	WVRQAPGKGLEWVS (SEQ ID NO:346)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYC (SEQ ID NO:347)	WGQGTLVTVSS (SEQ ID NO:348)
15503	EVQLLESGGGLVQPGGSLRLSCAASG (SEQ ID NO:355)	WVRQAPGKGLEWVS (SEQ ID NO:356)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYC (SEQ ID NO:357)	WGQGTTVTVSS (SEQ ID NO:358)
15495	QVQLVQSGAEVKKPGSSVKVSCKASG(SEQ ID NO:365)	WVRQAPGQGLEWMG (SEQ ID NO:366)	RVTITADESTSTAYMELSSLRSEDTAVYYC (SEQ ID NO:367)	WGRGTLVTVSS (SEQ ID NO:368)
15478	QVQLVQSGAEVKKPGSSVKVSCKASG (SEQ ID NO:375)	WVRQAPGQGLEWMG (SEQ ID NO:376)	RVTITADESTSTAYMELSSLRSEDTAVYYC (SEQ ID NO:377)	WGQGTLVTVSS (SEQ ID NO:378)
15441	EVQLLESGGGLVQPGGSLRLSCAASG (SEQ ID NO:385)	WVRQAPGKGLEWVS (SEQ ID NO:386)	RFTISRDNSKNTLYLQMNSLRAEDTAVYYC (SEQ ID NO:387)	WGQGTMVTVSS (SEQ ID NO:388)
20496	QLQLQESGPGLVKPSETLSLTCTVSG (SEQ ID NO:395)	WIRQPPGKGLEWIG (SEQ ID NO:396)	RVTISVDTSKNQFSLKLSSVTAADTAVYYC (SEQ ID NO:397)	WGQGTMVIVSS (SEQ ID NO:398)

[4]The VH framework regions described in Table 5 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VH CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00151] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the VL framework regions of an antibody listed in Table 6.

Table 6. VL FR Amino Acid Sequences [3]

Anti-body	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
15461	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO:209)	WYQQKPGQAPRLLIY (SEQ ID NO:210)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID	FGGGTKVEIK (SEQ ID NO:212)
20500	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO:219)	WYQQKPGQAPRLLIY (SEQ ID NO:220)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID NO:221)	FGGGTKVEIK (SEQ ID NO:222)
20501	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO:229)	WYQQKPGQAPRLLIY (SEQ ID NO:230)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID NO:231)	FGGGTKVEIK (SEQ ID NO:232)
20502 and 20502.1	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO:239)	WYQQKPGQAPRLLIY (SEQ ID NO:240)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID NO:241)	FGGGTKVEIK (SEQ ID NO:242)
22208	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO: 249)	WYQQKPGQAPRLLIY (SEQ ID NO:250)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID NO:251)	FGGGTKVEIK (SEQ ID NO:252)
15462	EIVLTQSPGTLSLSPGERATLSC (SEQ ID NO:259)	WYQQKPGQAPRLLIY (SEQ ID NO:260)	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC (SEQ ID NO:261)	FGGGTKVEIK (SEQ ID NO:262)
22213	EIVLTQSPGTLSLSPGERATLSC (SEQ ID NO:269)	WYQQKPGQAPRLLIY (SEQ ID NO:270)	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC (SEQ ID NO:271)	FGGGTKVEIK (SEQ ID NO:272)
15465	DIQMTQSPSSVSASVGDRVTITC (SEQ ID NO:279)	WYQQKPGKAPKLLIY (SEQ ID NO:280)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:281)	FGGGTKVEIK (SEQ ID NO:282)
20506	DIQMTQSPSSVSASVGDRVTITC (SEQ ID NO:289)	WYQQKPGKAPKLLIY (SEQ ID NO:290)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:291)	FGGGTKVEIK (SEQ ID NO:292)

15483	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:299)	WYQQKPGKAPKLLIY (SEQ ID NO:300)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:301)	FGGGTKVEIK (SEQ ID NO:302)
20513	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:309)	WYQQKPGKAPKLLIY (SEQ ID NO:310)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:311)	FGGGTKVEIK (SEQ ID NO:312)
22216	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:319)	WYQQKPGKAPKLLIY (SEQ ID NO:320)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:321)	FGGGTKVEIK (SEQ ID NO:322)
15489	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:329)	WYQQKPGKAPKLLIY (SEQ ID NO:330)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:331)	FGGGTKVEIK (SEQ ID NO:332)
20516	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:339)	WYQQKPGKAPKLLIY (SEQ ID NO:340)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:341)	FGGGTKVEIK (SEQ ID NO:342)
15472	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO:349)	WYQQKPGKAPKLLIY (SEQ ID NO:350)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:351)	FGGGTKVEIK (SEQ ID NO:352)
15503	DIQLTQSPSSVSASVGDRVTITC (SEQ ID NO:359)	WYQQKPGKAPKLLIY (SEQ ID NO:360)	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO:361)	FGGGTKVEIK (SEQ ID NO:362)
15495	EIVMTQSPATLSVSPGERATLSC (SEQ ID NO:369)	WYQQKPGQAPRLLIY (SEQ ID NO:370)	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC (SEQ ID NO:371)	FGGGTKVEIK (SEQ ID NO:372)
15478	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:379)	WYQQKPGKAPKLLIY (SEQ ID NO:380)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:381)	FGGGTKVEIK (SEQ ID NO:382)
15441	DIQMTQSPSTLSASVGDRVTITC (SEQ ID NO:389)	WYQQKPGKAPKLLIY (SEQ ID NO:390)	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC (SEQ ID NO:391)	FGGGTKVEIK (SEQ ID NO:392)

20496	DIQMTQSPSSLSAS VGDRVTITC (SEQ ID NO:399)	WYQQKPGKAP KLLIY (SEQ ID NO:400)	GVPSRFSGSGSGT DFTLTISSLQPEDF ATYYC (SEQ ID NO:401)	FGGGTKVEI K (SEQ ID NO:402)

[3]The VL framework regions described in Table 6 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VL CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00152] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the four VH framework regions and the four VL framework regions of an antibody listed in Tables 5 and 6 (i.e., the four VH framework regions of the antibody listed in Table 5 and the four VL framework regions of the same antibody listed in Table 6.)

[00153] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the heavy chain sequence of an antibody listed in Table 7.

Table 7: Full-length heavy chain amino acid sequences

Antibody	Full-Length Heavy Chain Amino Acid Sequence (SEQ ID NO)
15461	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAREGSYPNWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:13)
20500	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGL EWIGNIYYSGSTYYNPSLRSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAREGSYPNWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:23)
20501	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YYCAREGSYPNWLDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG

	GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:33)
20502	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWGWIRQPPGKGL EWIGNIYYSGSTYYNPSLRSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAREGSYPNQFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:469)
20502.1	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSYYWGWIRQPPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YYCAREGSYPNQFDPWGQGILVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:43)
22208	QLQLQESGPGLVKPSETLSLTCTVSGGSIKSGSHYWGWIRQPPGKGL EWIGNIYYSGSTYYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCAREGSYPNWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:53)
15462	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLE WIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAREGSYTTVLNVWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:63)
22213	QLQLQESGPGLVKPSETLSLTCTVSGGSIGRGSYYWGWIRQPPGKGL

	EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YYCAREGSYTTVLNVWGQGTMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:73)
15465	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YYCARESSTISADFDLWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:83)
20506	QLQLQESGPGLVKPSETLSLTCTASGGSISHGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCARESSTISADFDLWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:93)
15483	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAV YYCARGLSTIDEAFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:103)
20513	QLQLQESGPGLVKPSETLSLTCTVSGGSISDGSYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLRSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCARGLSTIDEAFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW

	QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:113)
22216	QVQLQESGPGLVKPSQTLSLTCTVSGGSISDGSYYWSWIRQHPGKGL EWIGNIYYSGSTYYNPSLRSRVTMSVDTSKNQFSLKLSSVTAADTAV YYCARGLSTIDEAFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:123)
15489	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEW IGYIYSSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARGSGQYAAPDYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:133)
20516	QVQLQESGPGLVKPSETLSLTCTVSGGSIISYYWGWIRQPPGKGLEWI GYIYSSGSTSYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RGSGLYAAPDYGLDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:143)
15472	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSTISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCARGAGHYDLVGRYWGQGTLVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:153)
15503	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCARVGFRALNYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS

	NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:163)
15495	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGGIIPIFGTASYAQKFQGRVTITADESTSTAYMELSSLRSEDTAV YYCARQQYDGRRYFGLWGRGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:173)
15478	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAV YYCARGGPWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK(SEQ ID NO:183)
15441	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVSAISGSGGSTSYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAKPSLATMLAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:193)
20496	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSVYYWSWIRQPPGKGLE WIGSILVSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARAVSFLDVWGQGTMVIVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:203)

[00154] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the light chain sequence of an antibody listed in Table 8.

Table 8: Full-length light chain amino acid sequences

Antibody	Full-Length Light Chain Amino Acid Sequence (SEQ ID NO)
15461	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLL IYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:14)
20500	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLL IYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:24)
20501	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLL IYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:34)
20502 and 20502.1	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLL IYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:44)
22208	EIVMTQSPATLSVSPGERATLSCRASQSVSTNLAWYQQKPGQAPRLL IYDASARVTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYHSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:54)
15462	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLL IYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAASYP LTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:64)
22213	EIVLTQSPGTLSLSPGERATLSCRASQSVASSHLAWYQQKPGQAPRL LIYDAVSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQAASY PLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:74)
15465	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHTFP YTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:84)
20506	DIQMTQSPSSVSASVGDRVTITCRASQGISRWLAWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAHTFP YTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:94)
15483	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYP

	YTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:104)
20513	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYP YTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:114)
22216	DIQMTQSPSTLSASVGDRVTITCRASKSISSWLAWYQQKPGKAPKLL IYEASSLHSGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSYP YTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:124)
15489	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:134)
20516	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQDNSFPF TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:144)
15472	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLYSLPP TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:154)
15503	DIQLTQSPSSVSASVGDRVTITCRASQDISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQATSYPP WTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:164)
15495	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLL IYSASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQVNVWP PTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:174)
15478	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPP FTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:184)
15441	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLL IYDASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQSKSYPR TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:194)

20496	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YGASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYDPPW TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:204)

[00155] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4 and comprises the heavy chain sequence and the light chain sequence of an antibody listed in Tables 7 and 8 (i.e., the heavy chain sequence of the antibody listed in Table 7 and the light chain sequence of the same antibody listed in Table 8).

[00156] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 80% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 80% identical to the VL sequence of the same antibody in Table 4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 85% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 85% identical to the VL sequence of the same antibody in Table 4.

[00157] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 90% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 90% identical to the VL sequence of the same antibody in Table 4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 95% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 95% identical to the VL sequence of the same antibody in Table 4.

[00158] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 96% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 96% identical to the VL sequence of the same antibody in Table 4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 97% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 97% identical to the VL sequence of the same antibody in Table 4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 98% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 98% identical to the VL sequence of the same antibody in Table 4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), and comprises a VH comprising a sequence at least 99% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 99% identical to the VL sequence of the same antibody in Table 4.

[00159] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 80% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 80% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least

85% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 85% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4.

[00160] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 90% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 90% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 95% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 95% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4.

[00161] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 96% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 96% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 97% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 97% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 98% identical to the VH sequence of the same antibody in Table 3

and a VL comprising a sequence at least 98% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 99% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 99% identical to the VL sequence of the same antibody in Table 4, and binds to human, cynomolgus monkey, rat, and/or mouse B7-H4.

[00162] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 80% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 80% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 85% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 85% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells.

[00163] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 90% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 90% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and/or mediates ADCC activity against B7-H4-expressing cells. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in

Table 2), comprises a VH comprising a sequence at least 95% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 95% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells.

[00164] In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 96% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 96% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 97% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 97% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 98% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 98% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells. In certain embodiments, an antibody or antigen-binding fragment thereof described herein binds to human B7-H4, comprises the six CDRs of an antibody listed in Tables 1 and 2 (i.e., the three VH CDRs of the antibody listed in Table 1 and the three VL CDRs of the same antibody listed in Table 2), comprises a VH comprising a sequence at least 99% identical to the VH sequence of the same antibody in Table 3 and a VL comprising a sequence at least 99% identical to the VL sequence of the same antibody in Table 4, increases T cell proliferation, increases IFNγ production, and mediates ADCC activity against B7-H4-expressing cells.

[00165] In certain aspects, an antibody or antigen-binding fragment thereof described herein

may be described by its VL domain alone, or its VH domain alone, or by its 3 VL CDRs alone, or its 3 VH CDRs alone. See, for example, Rader C et al., (1998) PNAS 95: 8910-8915, which is incorporated herein by reference in its entirety, describing the humanization of the mouse anti-αvβ3 antibody by identifying a complementing light chain or heavy chain, respectively, from a human light chain or heavy chain library, resulting in humanized antibody variants having affinities as high or higher than the affinity of the original antibody. See also Clackson T et al., (1991) Nature 352: 624-628, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VL domain (or VH domain) and screening a library for the complementary variable domains. The screen produced 14 new partners for a specific VH domain and 13 new partners for a specific VL domain, which were strong binders, as determined by ELISA. See also Kim SJ & Hong HJ, (2007) J Microbiol 45: 572-577, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VH domain and screening a library (e.g., human VL library) for complementary VL domains; the selected VL domains in turn could be used to guide selection of additional complementary (e.g., human) VH domains.

[00166] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, e.g., Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B et al., (1997) J Mol Biol 273: 927-948; Chothia C et al., (1992) J Mol Biol 227: 799-817; Tramontano A et al., (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34).

[00167] In certain aspects, provided herein are antibodies and antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) and comprise the Chothia VH and

VL CDRs of an antibody listed in Tables 3 and 4. In certain embodiments, antibodies or antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, provided herein are antibodies and antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) and comprise combinations of Kabat CDRs and Chothia CDRs.

[00168] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) The Immunologist 7: 132-136 and Lefranc M-P et al., (1999) Nucleic Acids Res 27: 209-212. According to the IMGT numbering scheme, VH-CDR1 is at positions 26 to 35, VH-CDR2 is at positions 51 to 57, VH-CDR3 is at positions 93 to 102, VL-CDR1 is at positions 27 to 32, VL-CDR2 is at positions 50 to 52, and VL-CDR3 is at positions 89 to 97. In a particular embodiment, provided herein are antibodies and antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) and comprise the IMGT VH and VL CDRs of an antibody listed in Tables 3 and 4, for example, as described in Lefranc M-P (1999) supra and Lefranc M-P et al., (1999) supra).

[00169] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to MacCallum RM et al., (1996) J Mol Biol 262: 732-745. See also, e.g., Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in Antibody Engineering, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In a particular embodiment, provided herein are antibodies or antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) and comprise VH and VL CDRs of an antibody listed in Tables 3 and 4 as determined by the method in MacCallum RM et al.

[00170] In certain aspects, the CDRs of an antibody or antigen-binding fragment thereof can be determined according to the AbM numbering scheme, which refers AbM hypervariable regions which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.). In a particular embodiment, provided herein are antibodies or antigen-binding fragments thereof that specifically bind to B7-H4 (e.g., human B7-H4) and comprise VH and VL CDRs of an antibody listed in Tables 3 and 4 as determined by the AbM numbering scheme.

[00171] In specific aspects, provided herein are antibodies that comprise a heavy chain and a light chain. With respect to the heavy chain, in a specific embodiment, the heavy chain of an

antibody described herein can be an alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In another specific embodiment, the heavy chain of an antibody described can comprise a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In a particular embodiment, an antibody described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a heavy chain wherein the amino acid sequence of the VH domain comprises an amino acid sequence set forth in Table 3 and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region. In a specific embodiment, an antibody described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises a heavy chain wherein the amino acid sequence of the VH domain comprises a sequence set forth in Table 3, and wherein the constant region of the heavy chain comprises the amino acid of a human heavy chain described herein or known in the art. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Patent No. 5,693,780 and Kabat EA et al., (1991) supra.

[00172] With respect to the light chain, in a specific embodiment, the light chain of an antibody described herein is a kappa light chain. The constant region of a human kappa light chain can comprise the following amino acid sequence:

[00173] RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:405).

[00174] The constant region of a human kappa light chain can be encoded by the following nucleotide sequence:

[00175] CGGACCGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAG GCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGC TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAG GGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT (SEQ ID NO:406).

[00176] In another specific embodiment, the light chain of an antibody described herein is a lambda light chain. In yet another specific embodiment, the light chain of an antibody described herein is a human kappa light chain or a human lambda light chain. In a particular embodiment, an antibody described herein, which immunospecifically binds to a B7-H4 polypeptide (e.g., human B7-H4) comprises a light chain wherein the amino acid sequence of the VL domain comprises a sequence set forth in Table 4, and wherein the constant region of the light chain

comprises the amino acid sequence of a human kappa light chain constant region. In another particular embodiment, an antibody described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprises a light chain wherein the amino acid sequence of the VL domain comprises a sequence set forth in Table 4 and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. In a specific embodiment, an antibody described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprises a light chain wherein the amino acid sequence of the VL domain comprises a sequence set forth in Table 4 and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa or lambda light chain constant region. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Patent No. 5,693,780 and Kabat EA et al., (1991) supra.

[00177] In a specific embodiment, an antibody described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprises a VH domain and a VL domain comprising any amino acid sequence described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule. In another specific embodiment, an antibody described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprises a VH domain and a VL domain comprising any amino acid sequence described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. In a particular embodiment, the constant regions comprise the amino acid sequences of the constant regions of a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule.

[00178] The constant region of a human IgG1 heavy chain can comprise the following amino acid sequence:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:407).

[00179] The constant region of a human IgG_1 heavy chain can be encoded by the following nucleotide sequence:

GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCT
GGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC
GGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGAC
ACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC
CAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCC
TCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCC
AACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACC
AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAG
CAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG
CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA. (SEQ ID NO:408)

[00180] Non-limiting examples of human constant regions are described in the art, *e.g.*, *see* Kabat EA *et al.*, (1991) *supra.*

[00181] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody or antigen-binding fragment thereof described herein (*e.g.*, CH2 domain (residues 231-340 of human IgG_1) and/or CH3 domain (residues 341-447 of human IgG_1) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to alter one or more functional properties of the antibody or antigen-binding fragment thereof, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity.

[00182] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, *e.g.*, U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1

domain may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody or antigen-binding fragment thereof.

[00183] In some embodiments, one, two, or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of an antibody or antigen-binding fragment thereof described herein (e.g., CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to increase or decrease the affinity of the antibody or antigen-binding fragment thereof for an Fc receptor (e.g., an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region that decrease or increase affinity for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor that can be made to alter the affinity of the antibody or antigen-binding fragment thereof for an Fc receptor are described in, e.g., Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[00184] In a specific embodiment, one, two, or more amino acid mutations (i.e., substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (e.g., decrease or increase) half-life of the antibody or antigen-binding fragment thereof in vivo. See, e.g., International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (e.g., decrease or increase) the half-life of an antibody or antigen-binding fragment thereof in vivo. In some embodiments, one, two or more amino acid mutations (i.e., substitutions, insertions, or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the antibody or antigen-binding fragment thereof in vivo. In other embodiments, one, two or more amino acid mutations (i.e., substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody or antigen-binding fragment thereof in vivo. In a specific embodiment, the antibodies or antigen-binding fragments thereof may have one or more amino acid mutations (e.g., substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat EA et al., (1991) supra). In a specific embodiment,

the constant region of the IgG1 comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Patent No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua WF et al., (2006) J Biol Chem 281: 23514-24). In certain embodiments, an antibody or antigen-binding fragment thereof comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[00185] In a further embodiment, one, two, or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the antibody or antigen-binding fragment thereof. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322, numbered according to the EU index as in Kabat, can be replaced with a different amino acid residue such that the antibody or antigen-binding fragment thereof has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating antibody or antigen-binding fragment thereof thereby increasing tumor localization. See, e.g., U.S. Patent Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In certain embodiments, one or more amino acid substitutions can be introduced into the Fc region to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, e.g., Shields RL et al., (2001) J Biol Chem 276: 6591-604).

[00186] In certain embodiments, one or more amino acids selected from amino acid residues 329, 331, and 322 in the constant region, numbered according to the EU index as in Kabat, can be replaced with a different amino acid residue such that the antibody or antigen-binding fragment thereof has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues within amino acid positions 231 to 238 in the N-terminal region of the CH2 domain are altered to thereby alter the

ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In certain embodiments, the Fc region is modified to increase the ability of the antibody or antigen-binding fragment thereof to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody or antigen-binding fragment thereof for an Fcγ receptor by mutating one or more amino acids (e.g., introducing amino acid substitutions) at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 328, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438, or 439, numbered according to the EU index as in Kabat. This approach is described further in International Publication No. WO 00/42072.

[00187] In certain embodiments, an antibody or antigen-binding fragment thereof described herein comprises the constant domain of an IgG1 with a mutation (e.g., substitution) at position 267, 328, or a combination thereof, numbered according to the EU index as in Kabat. In certain embodiments, an antibody or antigen-binding fragment thereof described herein comprises the constant domain of an IgG1 with a mutation (e.g., substitution) selected from the group consisting of S267E, L328F, and a combination thereof. In certain embodiments, an antibody or antigen-binding fragment thereof described herein comprises the constant domain of an IgG1 with a S267E/L328F mutation (e.g., substitution). In certain embodiments, an antibody or antigen-binding fragment thereof described herein comprising the constant domain of an IgG1 with a S267E/L328F mutation (e.g., substitution) has an increased binding affinity for FcγRIIA, FcγRIIB, or FcγRIIA and FcγRIIB.

[00188] Antibodies with reduced fucose content have been reported to have an increased affinity for Fc receptors, such as, e.g., FcγRIIIA. Accordingly, in certain embodiments, an antibody or antigen-binding fragment thereof described herein has reduced fucose content or lacks fucose (i.e., is "afucosylated"). Such antibodies or antigen-binding fragments thereof can be produced using techniques known to one skilled in the art. For example, they can be expressed in cells deficient or lacking the ability to fucosylate. In a specific example, cell lines with a knockout of both alleles of α1,6-fucosyltransferase can be used to produce antibodies or antigen-binding fragments thereof with reduced fucose content. The Potelligent® system (Lonza) is an example of such a system that can be used to produce antibodies and antigen-binding fragments thereof with reduced fucose content. Alternatively, antibodies or antigen-

binding fragments thereof with reduced fucose content or no fucose content can be produced by, e.g.: (i) culturing cells under conditions which prevent or reduce fucosylation; (ii) posttranslational removal of fucose (e.g., with a fucosidase enzyme); (iii) post-translational addition of the desired carbohydrate, e.g., after recombinant expression of a non-glycosylated glycoprotein; or (iv) purification of the glycoprotein so as to select for antibodies or antigen-binding fragments thereof which are not fucsoylated. See, e.g., Longmore GD & Schachter H (1982) Carbohydr Res 100: 365-92 and Imai-Nishiya H et al., (2007) BMC Biotechnol. 7: 84 for methods for producing antibodies thereof with no fucose content or reduced fucose content. See also Example 8 herein describing the production of afucosylated B7-H4 antibodies.

[00189] In some embodiments, the B7-H4 antibody or antigen-binding fragment thereof has enhanced ADCC activity in vitro compared to fucosylated B7-H4 antibodies or antigen-binding fragments thereof having the same amino acid sequence. In some embodiments, the afucosylated B7-H4 antibodies or antigen-binding fragments thereof cause specific lysis that is at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 60, at least 65, at least 70, or at least 75 percentage points greater than specific lysis with fucosylated B7-H4 antibodies.

[00190] In some embodiments, the B7-H4 antibody or antigen-binding fragment thereof has enhanced affinity for Fc gamma RIIIA compared to fucosylated B7-H4 antibodies or antigen-binding fragments thereof having the same amino acid sequence. In some embodiments, the afucosylated B7-H4 antibodies or antigen-binding fragments thereof bind to Fc gamma RIIIA with at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 7-fold, at least 10-fold, at least 12-fold, at least 15-fold, at least 17-fold, or at least 20-fold greater affinity than fucosylated B7-H4 antibodies or antigen-binding fragments thereof. In some embodiments, affinity for Fc gamma RIIIA is determined using surface plasmon resonance. In some embodiments, Fc gamma RIIIA is selected from Fc gamma RIIIA(V158) and Fc gamma RIIIA(F158). In some embodiments, Fc gamma RIIIA is Fc gamma RIIIA(V158).

[00191] In some embodiments, the presence of fucose can be determined by a method comprising high performance liquid chromatography (HPLC), capillary electrophoresis, or MALDI-TOF mass spectrometry.

[00192] In specific embodiments, an antibody or antigen-binding fragment thereof (i) comprises the CDR sequences of 20502 (e.g., the amino acid sequences of SEQ ID NOs:458-463), the VH and VL sequences of 20502 (the amino acid sequences of SEQ ID NOs:464 and 42, respectively), or the heavy and light chain sequences of 20502 (the amino acid sequences of SEQ

ID NOs:469 and 44, respectively) and (ii) is afucosylated.

[00193] In specific embodiments, a composition comprises antibodies or antigen-binding fragments thereof that (i) comprises the CDR sequences of 20502 (e.g., the amino acid sequences of SEQ ID NOs:458-463), the VH and VL sequences of 20502 (the amino acid sequences of SEQ ID NOs:464 and 42, respectively), or the heavy and light chain sequences of 20502 (the amino acid sequences of SEQ ID NOs:469 and 44, respectively) and (ii) are afucosylated, e.g., wherein at least 95% of the antibodies in the composition are afucosylated or wherein fucosylation is undetectable in the composition.

[00194] In specific embodiments, an antibody or antigen-binding fragment thereof (i) comprises the CDR sequences of 20502.1 (e.g., the amino acid sequences of SEQ ID NOs:35-40), the VH and VL sequences of 20502.1 (the amino acid sequences of SEQ ID NOs:41 and 42, respectively), or the heavy and light chain sequences of 20502.1 (the amino acid sequences of SEQ ID NOs:43 and 44, respectively) and (ii) is afucosylated.

[00195] In specific embodiments, a composition comprises antibodies or antigen-binding fragments thereof that (i) comprises the CDR sequences of 20502.1 (e.g., the amino acid sequences of SEQ ID NOs:35-40), the VH and VL sequences of 20502.1 (the amino acid sequences of SEQ ID NOs:41 and 42, respectively), or the heavy and light chain sequences of 20502.1 (the amino acid sequences of SEQ ID NOs:43 and 44, respectively) and (ii) are afucosylated, e.g., wherein at least 95% of the antibodies in the composition are afucosylated or wherein fucosylation is undetectable in the composition.

[00196] In specific embodiments, an antibody or antigen-binding fragment thereof (i) comprises the CDR sequences of 22213 (e.g., the amino acid sequences of SEQ ID NOs:65-70), the VH and VL sequences of 22213 (the amino acid sequences of SEQ ID NOs:71 and 72, respectively), or the heavy and light chain sequences of 22213 (the amino acid sequences of SEQ ID NOs:73 and 74, respectively) and (ii) is afucosylated.

[00197] In specific embodiments, a composition comprises antibodies or antigen-binding fragments thereof that (i) comprises the CDR sequences of 22213 (e.g., the amino acid sequences of SEQ ID NOs:65-70), the VH and VL sequences of 22213 (the amino acid sequences of SEQ ID NOs:71 and 72, respectively), or the heavy and light chain sequences of 22213 (the amino acid sequences of SEQ ID NOs:73 and 74, respectively) and (ii) are afucosylated, e.g., wherein at least 95% of the antibodies in the composition are afucosylated or wherein fucosylation is undetectable in the composition.

[00198] Engineered glycoforms may be useful for a variety of purposes, including but not

limited to enhancing or reducing effector function. Methods for generating engineered glycoforms in an antibody or antigen-binding fragment thereof described herein include but are not limited to those disclosed, e.g., in Umaña P et al., (1999) Nat Biotechnol 17: 176-180; Davies J et al., (2001) Biotechnol Bioeng 74: 288-294; Shields RL et al., (2002) J Biol Chem 277: 26733-26740; Shinkawa T et al., (2003) J Biol Chem 278: 3466-3473; Niwa R et al., (2004) Clin Cancer Res 1: 6248-6255; Presta LG et al., (2002) Biochem Soc Trans 30: 487-490; Kanda Y et al., (2007) Glycobiology 17: 104-118; U.S. Patent Nos. 6,602,684; 6,946,292; and 7,214,775; U.S. Patent Publication Nos. US 2007/0248600; 2007/0178551; 2008/0060092; and 2006/0253928; International Publication Nos. WO 00/61739; WO 01/292246; WO 02/311140; and WO 02/30954; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb® glycosylation engineering technology (Glycart biotechnology AG, Zurich, Switzerland). See also, e.g., Ferrara C et al., (2006) Biotechnol Bioeng 93: 851-861; International Publication Nos. WO 07/039818; WO 12/130831; WO 99/054342; WO 03/011878; and WO 04/065540.

[00199] In certain embodiments, any of the constant region mutations or modifications described herein can be introduced into one or both heavy chain constant regions of an antibody or antigen-binding fragment thereof described herein having two heavy chain constant regions.

[00200] In another particular embodiment, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a heavy chain and a light chain, wherein (i) the heavy chain comprises a VH domain comprising the VH CDR1, VL CDR2, and VL CDR3 amino acid sequences of an antibody listed in Table 1 (e.g., SEQ ID NOs:458-460, 35-37, or 65-67); (ii) the light chain comprises a VL domain comprising the VL CDR1, VH CDR2, and VH CDR3 amino acid sequences of the same antibody listed in Table 2 (e.g., SEQ ID NOs:461-463, 38-40, or 68-70); (iii); and the heavy chain further comprises a constant heavy chain domain comprising the amino acid sequence of the constant domain of a human IgG1 heavy chain (iv); the light chain further comprises a constant light chain domain comprising the amino acid sequence of the constant domain of a human kappa light chain.

[00201] In another particular embodiment, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a heavy chain and a light chain, wherein (i) the heavy chain comprises a VH domain comprising the amino acid sequence of an antibody listed in Table 3 (e.g., SEQ ID NO:464, 41, or 71); (ii) the light chain comprises a VL domain comprising the amino acid sequence of the same antibody listed in Table 4 (e.g., SEQ ID NO:42 or 73); (iii); and the heavy chain further comprises a

constant heavy chain domain comprising the amino acid sequence of the constant domain of a human IgG1 heavy chain (iv); the light chain further comprises a constant light chain domain comprising the amino acid sequence of the constant domain of a human kappa light chain.

[00202] In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits T cell checkpoint blockade activity. Exemplary methods of measuring T cell checkpoint blockade activity are provided herein in Examples 7 and 11. In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) increases interferon-gamma (IFNγ) production in T cells. Exemplary methods of measuring IFNγ production are provided herein in Examples 7 and 11. In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) increases T cell proliferation. Exemplary methods of measuring T-cell proliferation are provided herein in Example 7. In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) increases CD4+ T cell proliferation. Exemplary methods of measuring CD4+ T-cell proliferation are provided herein in Example 7. In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) increases CD8+ T cell proliferation. Exemplary methods of measuring CD8+ T-cell proliferation are provided herein in Example 7.

[00203] In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity. In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity on cell lines with at least 300,000 cell surface B7-H4 molecules (e.g., SK-BR-3 cells). In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity on cell lines with at least 100,000 cell surface B7-H4 molecules (e.g., HCC 1569 cells). In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity on cell lines with at least 50,000 cell surface B7-H4 molecules (e.g., ZR-75-1 cells). In specific embodiments, an antibody

or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity on cell lines with at least 30,000 cell surface B7-H4 molecules (e.g., MDA-MB-468 cells). In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4) exhibits antibody-dependent cellular cytotoxicity (ADCC) activity on cell lines with at least 15,000 cell surface B7-H4 molecules (e.g., HCC1964 cells). Exemplary methods of measuring ADCC activity are provided herein in Example 13.

[00204] In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises framework regions (e.g., framework regions of the VH domain and/or VL domain) that are human framework regions or derived from human framework regions. Non-limiting examples of human framework regions are described in the art, e.g., see Kabat EA et al., (1991) supra). In certain embodiment, an antibody or antigen-binding fragment thereof described herein comprises framework regions (e.g., framework regions of the VH domain and/or VL domain) that are primate (e.g., non-human primate) framework regions or derived from primate (e.g., non-human primate) framework regions.

[00205] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises one, two, or more VH framework regions (FRs) having the amino acid sequences described herein for an antibody set forth in Table 5, supra (e.g., SEQ ID NOs: 465, 466, 467, and/or 469; SEQ ID NOs:235, 236, 237 and/or 238; or SEQ ID NOs:265, 266, 267, and/or 268). In some embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises one, two, or more VL framework regions (FRs) having the amino acid sequences described herein for an antibody set forth in Table 6, supra (e.g., SEQ ID NOs:239, 240, 241, and/or 242 or SEQ ID NOs:269, 270, 271, and/or 272). In specific embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises one, two, or more VH framework regions having the amino acid sequences described herein for an antibody set forth in Table 5, supra, and one, two, or more VL framework regions having the amino acid sequences described herein for the same antibody set forth in Table 6, supra (e.g., (i) SEQ ID NOs: 465, 466, 467, and/or 469 and SEQ ID NOs:239, 240, 241, and/or 242; (ii) SEQ ID NOs:235, 236, 237 and/or 238 and SEQ ID NOs:239, 240, 241, and/or 242 or (iii) SEQ ID NOs:265, 266, 267, and/or 268 and SEQ ID

NOs:269, 270, 271, and/or 272).

[00206] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises VH framework regions (FRs) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein in Table 5, supra. In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises VL framework regions (FRs) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein Table 6, supra. In some embodiments, an antibody or antigen-binding fragment thereof described herein, which specifically binds to B7-H4 (e.g., human B7-H4), comprises VH framework regions (FRs) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein Table 5, supra, and VL framework regions (FRs) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein Table 6, supra.

[00207] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a VH domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of 20502 or 22213 (e.g., SEQ ID NO:464 or 71), wherein the antibody comprises VH CDRs that are identical to the VH CDRs of 20502 or 22213 (e.g., SEQ ID NOs:458-460 or 65-67).

[00208] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a VL domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of 20502 or 22213 (e.g., SEQ ID NO:42 or 72), wherein the antibody or antigen-binding fragment thereof comprises VL CDRs that are identical to the VL CDRs of 20502 or 22213 (e.g., SEQ ID NO:461-463 or 68-70).

[00209] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises: (i) a VH domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of 20502 or

22213 (e.g., SEQ ID NO:464 or 71),; and (ii) a VL domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of 20502 or 22213 (e.g., SEQ ID NO:42 or 72), wherein the antibody comprises VH CDRs and VL CDRs that are identical to the VH CDRs and VL CDRs of 20502 or 22213 (e.g., SEQ ID NOs:458-463 or SEQ ID NOs:65-70).

[00210] In another aspect, provided herein are antibodies or antigen-binding fragments thereof that bind the same epitope of B7-H4 (e.g., an epitope of human B7-H4) as an antibody or antigen-binding fragment thereof described herein (e.g., 20502 or 22213).

[00211] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a VH domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of 20502.1 or 22213 (e.g., SEQ ID NO:41 or 71), wherein the antibody comprises VH CDRs that are identical to the VH CDRs of 20502.1 or 22213 (e.g., SEQ ID NOs: 35-37 or 65-67).

[00212] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises a VL domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of 20502.1 or 22213 (e.g., SEQ ID NO:42 or 72), wherein the antibody or antigen-binding fragment thereof comprises VL CDRs that are identical to the VL CDRs of 20502.1 or 22213 (e.g., SEQ ID NO:38-40 or 68-70).

[00213] In certain embodiments, an antibody or antigen-binding fragment thereof described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), comprises: (i) a VH domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of 20502.1 or 22213 (e.g., SEQ ID NO:41 or 71),; and (ii) a VL domain having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of 20502.1 or 22213 (e.g., SEQ ID NO:42 or 72), wherein the antibody comprises VH CDRs and VL CDRs that are identical to the VH CDRs and VL CDRs of 20502.1 or 22213 (e.g., SEQ ID NOs:35-40 or SEQ ID NOs:65-70).

[00214] In another aspect, provided herein are antibodies or antigen-binding fragments thereof that bind the same epitope of B7-H4 (e.g., an epitope of human B7-H4) as an antibody or antigen-binding fragment thereof described herein (e.g., 20502.1 or 22213).

[00215] Competition binding assays can be used to determine whether two antibodies bind to overlapping epitopes. Competitive binding can be determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as B7-H4. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli C et al., (1983) Methods Enzymol 9: 242-253); solid phase direct biotin-avidin EIA (see Kirkland TN et al., (1986) J Immunol 137: 3614-9); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow E & Lane D, (1988) Antibodies: A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (see Morel GA et al., (1988) Mol Immunol 25(1): 7-15); solid phase direct biotin-avidin EIA (Cheung RC et al., (1990) Virology 176: 546-52); and direct labeled RIA. (Moldenhauer G et al., (1990) Scand J Immunol 32: 77-82). Typically, such an assay involves the use of purified antigen (e.g., B7-H4 such as human B7-H4) bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition can be measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70%, 70-75% or more. A competition binding assay can be configured in a large number of different formats using either labeled antigen or labeled antibody. In a common version of this assay, the antigen is immobilized on a 96-well plate. The ability of unlabeled antibodies to block the binding of labeled antibodies to the antigen is then measured using radioactive or enzyme labels. For further details see, for example, Wagener C et al., (1983) J Immunol 130: 2308-2315; Wagener C et al., (1984) J Immunol Methods 68: 269-274; Kuroki M et al., (1990) Cancer Res 50: 4872-4879; Kuroki M et al., (1992) Immunol Invest 21: 523-538; Kuroki M et al., (1992) Hybridoma 11: 391-407 and Antibodies: A Laboratory Manual, Ed Harlow E & Lane D editors supra, pp. 386-389.

[00216] In one embodiment, a competition assay is performed using surface plasmon resonance (BIAcore®), e.g., by an 'in tandem approach' such as that described by Abdiche YN et al., (2009) Analytical Biochem 386: 172-180, whereby B7-H4 antigen is immobilized on the chip surface, for example, a CM5 sensor chip and the anti-B7-H4 antibodies are then run over the chip. To determine if an antibody or antigen-binding fragment thereof competes with an anti-B7-H4 antibody described herein, the anti-B7-H4 antibody is first run over the chip surface to

achieve saturation and then the potential, competing antibody is added. Binding of the competing antibody or antigen-binding fragment thereof can then be determined and quantified relative to a non-competing control.

[00217] In one embodiment, Fortebio Octet competition binding (e.g., as described in Example 2 below) is used to determine that a B7-H4 antibody or antigen-binding fragment thereof competitively inhibits the binding of another B7-H4 antibody or antigen-binding fragment thereof to B7-H4.

[00218] In another aspect, provided herein are antibodies that competitively inhibit (e.g., in a dose dependent manner) an antibody or antigen-binding fragment thereof described herein (e.g., 20502, 20502.1 or 22213) from binding to B7-H4 (e.g., human B7-H4), as determined using assays known to one of skill in the art or described herein (e.g., ELISA competitive assays, or suspension array or surface plasmon resonance assay).

[00219] In specific aspects, provided herein is an antibody or antigen-binding fragment which competitively inhibits (e.g., in a dose dependent manner) binding to B7-H4 (e.g., human B7-H4), of an antibody comprising a VH domain having the amino acid sequence set forth in SEQ ID NO:464, and a VL domain having the amino acid sequence set for the in SEQ ID NO:42.

[00220] In specific aspects, provided herein is an antibody or antigen-binding fragment which competitively inhibits (e.g., in a dose dependent manner) binding to B7-H4 (e.g., human B7-H4), of an antibody comprising a VH domain having the amino acid sequence set forth in SEQ ID NO:41, and a VL domain having the amino acid sequence set for the in SEQ ID NO:42.

[00221] In specific aspects, provided herein is an antibody or antigen-binding fragment which competitively inhibits (e.g., in a dose dependent manner) binding to B7-H4 (e.g., human B7-H4), of an antibody comprising a VH domain having the amino acid sequence set forth in SEQ ID NO:71, and a VL domain having the amino acid sequence set for the in SEQ ID NO:72.

[00222] In specific aspects, provided herein is an antibody or antigen-binding fragment thereof which competitively inhibits (e.g., in a dose dependent manner) binding to B7-H4 (e.g., human B7-H4), with an antibody comprising (i) a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of the VH CDRs listed in Table 1; and (ii) a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of the CDRs listed in Table 2.

[00223] In specific aspects, provided herein is an antibody or antigen-binding fragment thereof, which immunospecifically binds to the same B7-H4 (e.g., human B7-H4) epitope as that of 20502, 20502.1, or 22213.

[00224] In another specific embodiment, an antibody or antigen-binding fragment thereof described herein, immunospecifically binds to the same B7-H4 (e.g., human B7-H4) epitope as that of an antibody comprising (i) a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of the CDRs listed in Table 1 and (ii) a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of the CDRs listed in Table 2.

[00225] In a specific aspect, an antigen-binding fragment as described herein, which immunospecifically binds to B7-H4 (e.g., human B7-H4), is selected from the group consisting of a Fab, Fab', F(ab')2, and scFv, wherein the Fab, Fab', F(ab')2, or scFv comprises a heavy chain variable region sequence and a light chain variable region sequence of an anti-B7-H4 antibody or antigen-binding fragment thereof as described herein. A Fab, Fab', F(ab')2, or scFv can be produced by any technique known to those of skill in the art, including, but not limited to, those discussed in Section 5.3, infra. In certain embodiments, the Fab, Fab', F(ab')2, or scFv further comprises a moiety that extends the half-life of the antibody in vivo. The moiety is also termed a "half-life extending moiety." Any moiety known to those of skill in the art for extending the half-life of a Fab, Fab', F(ab')2, or scFv in vivo can be used. For example, the half-life extending moiety can include a Fc region, a polymer, an albumin, or an albumin binding protein or compound. The polymer can include a natural or synthetic, optionally substituted straight or branched chain polyalkylene, polyalkenylene, polyoxylalkylene, polysaccharide, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, methoxypolyethylene glycol, lactose, amylose, dextran, glycogen, or derivative thereof. Substituents can include one or more hydroxy, methyl, or methoxy groups. In certain embodiments, the Fab, Fab', F(ab')2, or scFv can be modified by the addition of one or more C-terminal amino acids for attachment of the half-life extending moiety. In certain embodiments the half-life extending moiety is polyethylene glycol or human serum albumin. In certain embodiments, the Fab, Fab', F(ab')2, or scFv is fused to a Fc region.

[00226] An anti-B7-H4 antibody or antigen-binding fragment thereof can be fused or conjugated (e.g., covalently or noncovalently linked) to a detectable label or substance. Examples of detectable labels or substances include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (121In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. Such labeled antibodies or antigen-binding fragments thereof can be used to detect B7-H4 (e.g., human B7-H4) protein. See, e.g., Section 5.5.2, infra.

[00227] Antibody Production

[00228] Antibodies and antigen-binding fragments thereof that immunospecifically bind to B7-H4 (e.g., human B7-H4) can be produced by any method known in the art for the synthesis of antibodies and antigen-binding fragments thereof, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employ, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. See, e.g., Sambrook J et al., (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM et al., Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B et al., (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00229] In a certain aspect, provided herein is a method of making an antibody or antigen-binding fragment which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprising culturing a cell or host cell described herein. In a certain aspect, provided herein is a method of making an antibody or antigen-binding fragment thereof which immunospecifically binds to B7-H4 (e.g., human B7-H4) comprising expressing (e.g., recombinantly expressing) the antibody or antigen-binding fragment thereof using a cell or host cell described herein (e.g., a cell or a host cell comprising polynucleotides encoding an antibody or antigen-binding fragment thereof described herein). In a particular embodiment, the cell is an isolated cell. In a particular embodiment, the exogenous polynucleotides have been introduced into the cell. In a particular embodiment, the method further comprises the step of purifying the antibody or antigen-binding fragment obtained from the cell or host cell.

[00230] Methods for producing polyclonal antibodies are known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM et al., eds., John Wiley and Sons, New York).

[00231] Monoclonal antibodies or antigen-binding fragments thereof can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, yeast-based presentation technologies, or a combination thereof. For example, monoclonal antibodies or antigen-binding fragments thereof can be produced using

hybridoma techniques including those known in the art and taught, for example, in Harlow E & Lane D, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981), or as described in Kohler G & Milstein C (1975) Nature 256: 495. Examples of yeast-based presentation methods that can be employed to select and generate the antibodies described herein include those disclosed in, for example, WO2009/036379A2; WO2010/105256; and WO2012/009568, each of which is herein incorporated by reference in its entirety.

[00232] In specific embodiments, a monoclonal antibody or antigen-binding fragment is an antibody or antigen-binding fragment produced by a clonal cell (e.g., hybridoma or host cell producing a recombinant antibody or antigen-binding fragment), wherein the antibody or antigen-binding fragment immunospecifically binds to B7-H4 (e.g., human B7-H4) as determined, e.g., by ELISA or other antigen-binding assays known in the art or in the Examples provided herein. In particular embodiments, a monoclonal antibody or antigen-binding fragment thereof can be a chimeric or a humanized antibody or antigen-binding fragment thereof. In certain embodiments, a monoclonal antibody or antigen-binding fragment thereof can be a Fab fragment or a F(ab')2 fragment. Monoclonal antibodies or antigen-binding fragments thereof described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495 or can, e.g., be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies and antigen-binding fragments thereof expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM et al., supra).

[00233] Antigen-binding fragments of antibodies described herein can be generated by any technique known to those of skill in the art. For example, Fab and F(ab')2 fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). A Fab fragment corresponds to one of the two identical arms of a tetrameric antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A F(ab')2 fragment contains the two antigen-binding arms of a tetrameric antibody molecule linked by disulfide bonds in the hinge region.

[00234] Further, the antibodies or antigen-binding fragments thereof described herein can also be generated using various phage display and/or yeast-based presentation methods known in the

art. In phage display methods, proteins are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with a scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in E. coli and the E. coli is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13, and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antibody or antigen-binding fragment thereof that binds to a particular antigen can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies or fragments described herein include those disclosed in Brinkman U et al., (1995) J Immunol Methods 182: 41-50; Ames RS et al., (1995) J Immunol Methods 184: 177-186; Kettleborough CA et al., (1994) Eur J Immunol 24: 952-958; Persic L et al., (1997) Gene 187: 9-18; Burton DR & Barbas CF (1994) Advan Immunol 57: 191-280; PCT Application No. PCT/GB91/001134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO 97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743, and 5,969,108.

[00235] A humanized antibody or antigen-binding fragment thereof can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and IgG4.

1.2.1 Polynucleotides

[00236] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding an antibody or antigen-binding fragment thereof described herein or a domain thereof (*e.g.*, a variable light chain region and/or variable heavy chain region) that immunospecifically binds to a B7-H4 (*e.g.*, human B7-H4) antigen, and vectors, *e.g.*, vectors comprising such polynucleotides for recombinant expression in host cells (*e.g.*, *E. coli* and mammalian cells).

[00237] In particular aspects, provided herein are polynucleotides comprising nucleotide sequences encoding antibodies or antigen-binding fragments thereof, which immunospecifically bind to a B7-H4 polypeptide (e.g., human B7-H4) and comprise an amino acid sequence as

described herein, as well as antibodies or antigen-binding fragments that compete with such antibodies or antigen-binding fragments for binding to a B7-H4 polypeptide (e.g., in a dose-dependent manner), or which bind to the same epitope as that of such antibodies or antigen-binding fragments.

[00238] Also provided herein is a polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, and 202. In some embodiments, an antibody or antigen-binding fragment thereof comprising the polypeptide immunospecifically binds to B7-H4.

[00239] Also provided herein is a polynucleotide comprising a nucleotide sequence encoding a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs:13, 14, 23, 24, 33, 34, 43, 469, 44, 53, 54, 63, 64, 73, 74, 83, 84, 93, 94, 103, 104, 113, 114, 123, 124, 133, 134, 143, 144, 153, 154, 163, 164, 173, 174, 183, 184, 193, 194, 203, and 204. In some embodiments, an antibody or antigen-binding fragment thereof comprising the polypeptide immunospecifically binds to B7-H4.

[00240] Also provided herein are polynucleotides comprising a variable heavy chain-encoding nucleotide sequence shown in Table 9, e.g., wherein an antibody or antigen-binding fragment thereof comprising the encoded variable heavy chain binds to B7-H4.

Table 9: Variable heavy chain-encoding polynucleotide sequences

Antibody	Variable Heavy Chain-Encoding Polynucleotide Sequence (SEQ ID NO)
15461	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTA GTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACCCCAATTGGTTTGATCCATGGGGACAGGG TACATTGGTCACCGTCTCCTCA (SEQ ID NO:213)
20500	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAAGAGTGGTA GTCACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAGGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGGGAAGGATCTTACCCCAATTGGTTTGATCCATGGGGACAGGG TACATTGGTCACCGTCTCCTCA (SEQ ID NO:223)

20501	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAAGAGTGGTA GTCACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACCCCAATTGGTTGGATCCATGGGGACAGGG TACATTGGTCACCGTCTCCTCA (SEQ ID NO:233)
20502	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAAAAGTGGTA GTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAGAAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACCCCAATCAGTTTGATCCATGGGGACAGGG TACATTGGTCACCGTCTCCTCA (SEQ ID NO:470)
20502.1	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAAGAGTGGTA GTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACCCCAATCAGTTTGATCCATGGGGACAGGG TATATTGGTCACCGTCTCCTCA (SEQ ID NO:243)
22208	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAAGAGTGGTA GTCACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATGTCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACCCCAATTGGTTTGATCCATGGGGACAGGG TACATTGGTCACCGTCTCCTCA (SEQ ID NO:253)
15462	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTA GTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACACAACCGTGTTAAACGTATGGGGTCAGGG TACAATGGTCACCGTCTCCTCA (SEQ ID NO:263)
22213	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCGGGAGGGGGA GTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGT GGATTGGGAACATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAAGGATCTTACACAACCGTGTTAAACGTATGGGGTCAGGG TACAATGGTCACCGTCTCCTCA (SEQ ID NO:273)

15465	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAG ACCCTGTCCCTCACCTGTACTGTCTCTGGTGGCTCCATCAGCAGTGGTG GTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGT GGATTGGGAACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAATCTAGCACCATATCTGCCGACTTCGACCTATGGGGGAG AGGTACCTTGGTCACCGTCTCCTCA (SEQ ID NO:283)
20506	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGTACTGCCTCTGGTGGCTCCATCAGCCATGGTG GGTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGT GGATTGGGAACATCTATTACAGTGGGAGCACCTACTACAATCCGTCCCT CAAGAGTCGAGTTACCATGTCAGTAGACACGTCTAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGAATCTAGCACCATATCTGCCGACTTCGACCTATGGGGGAG AGGTACCTTGGTCACCGTCTCCTCA (SEQ ID NO:293)
15483	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAG ACCCTGTCCCTCACCTGTACTGTCTCTGGTGGCTCCATCAGCAGTGGTG GTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGT GGATTGGGAACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCT CAAGAGTCGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGGGTTGAGCACCATAGACGAGGCATTCGACCCATGGGGACA GGGTACATTGGTCACCGTCTCCTCA (SEQ ID NO:303)
20513	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCGATGGTA GTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGT GGATTGGGAACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCT CAGGAGTCGAGTTACCATGTCAGTAGACACGTCTAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGGGTTGAGCACCATAGACGAGGCATTCGACCCATGGGGACA GGGTACATTGGTCACCGTCTCCTCA (SEQ ID NO:313)
22216	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAG ACCCTGTCCCTCACCTGTACTGTCTCTGGTGGCTCCATCAGCGATGGTA GTTACTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGT GGATTGGGAACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCT CAGGAGTCGAGTTACCATGTCAGTAGACACGTCTAAGAACCAGTTCTC CCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTG CGCCAGAGGGTTGAGCACCATAGACGAGGCATTCGACCCATGGGGACA GGGTACATTGGTCACCGTCTCCTCA (SEQ ID NO:323)
15489	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACT ACTGGAGCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTG GGTATATCTATAGTAGTGGGAGCACCAACTACAACCCCTCCCTCAAGA GTCGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGA AGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTGCGCCA GAGGCTCTGGACAGTATGCAGCTCCTGATTATGGAATGGACGTATGGG GCCAGGGAACAACTGTCACCGTCTCCTCA (SEQ ID NO:333)

20516	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCATTAGTTACTA CTGGGGGTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGG GTATATCTATTCTAGTGGGAGCACCTCGTACAACCCCTCCCTCAAGAGT CGAGTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAG CTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACTGCGCCAGA GGCTCTGGACTGTATGCAGCTCCTGATTATGGACTTGACGTATGGGGTC AGGGAACAACTGTCACCGTCTCCTCA (SEQ ID NO:343)
15472	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATG CCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCT CAACCATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGA AGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAGGACACGGCGGTGTACTACTGCG CCAGAGGTGCCGGACACTACGACCTCGTCGGACGATACTGGGGACAGG GTACATTGGTCACCGTCTCCTCA (SEQ ID NO:353)
15503	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATG CCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCT CAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGCAGACTCCGTGA AGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAGGACACGGCGGTGTACTACTGCG CCAGAGTGGGATTCAGAGCATTAAACTACTGGGGACAGGGTACAACTG TCACCGTCTCCTCA (SEQ ID NO:363)
15495	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCC TCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATG CTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGG GAGGGATCATCCCTATCTTTGGTACAGCAAGCTACGCACAGAAGTTCC AGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACA TGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCG CAAGACAGCAATACGACGGTAGACGATACTTCGGCCTATGGGGGAGAG GTACCTTGGTCACCGTCTCCTCA (SEQ ID NO:373)
15478	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCC TCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATG CTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGG GAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCC AGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACA TGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCG CCAGAGGTGGGCCTTGGTTTGATCCATGGGGACAGGGTACATTGGTCA CCGTCTCCTCA (SEQ ID NO:383)
15441	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATG CCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCT CAGCTATTAGTGGTAGTGGTGGTAGCACATCCTACGCAGACTCCGTGA AGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATC TGCAAATGAACAGCCTGAGAGCCGAGGACACGGCGGTGTACTACTGCG CCAAGCCTTCTTTGGCAACAATGTTAGCCTTCGATATCTGGGGTCAGGG TACAATGGTCACCGTCTCCTCA (SEQ ID NO:393)

20496	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAG ACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTG TTTACTACTGGAGTTGGATCCGCCAGCCCCCAGGGAAGGGGTTGGAGT GGATTGGGAGTATCCTGGTGAGTGGGAGCACCTACTACAACCCGTCCC TCAAGAGTCGAGTCACCATATCCGTAGACACGTCCAAGAACCAGTTCT CCCTGAAGCTGAGTTCTGTGACCGCCGCAGACACGGCGGTGTACTACT GCGCCAGAGCTGTATCCTTCTTAGACGTATGGGGTCAGGGTACAATGGT CATCGTCTCCTCA (SEQ ID NO:403)

[00241] Also provided herein are polynucleotides comprising a variable light chain-encoding nucleotide sequence shown in Table 10, e.g., wherein an antibody or antigen-binding fragment thereof comprising the encoded variable light chain binds to B7-H4.

Table 10: Variable light chain-encoding polynucleotide sequences

Antibody	Variable Light Chain-Encoding Polynucleotide Sequence (SEQ ID NO)
15461	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAA CTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCAT CTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGG CAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGCAGTACCACTCCTTCCCTTTC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:214)
20500	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAA CTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCAT CTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGG CAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGCAGTACCACTCCTTCCCTTTC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:224)
20501	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAA CTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCAT CTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGG CAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGCAGTACCACTCCTTCCCTTTC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:234)
20502 and 20502.1	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAA CTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCAT CTATGGTGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGG CAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGCAGTACCACTCCTTCCCTTTC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:244)
22208	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGTCCGTTAGCACCAAC TTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATC TATGACGCATCCGCCAGGGTCACTGGTATCCCAGCCAGGTTCAGTGGC

	AGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTCT GAAGATTTTGCAGTTTATTACTGTCAGCAGTACCACTCCTTCCCTTTCA CTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:254)
15462	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAG CTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAG TGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGA GCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGGCCGCCAGTTACCC TCTCACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:264)
22213	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTGCCAGCAGC CACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTC ATCTATGACGCAGTCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGT GGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAG CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGGCCGCCAGTTACCCT CTCACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:274)
15465	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGGTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCAGCAGGCACACACCTTCCCTTAC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:284)
20506	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGGTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCAGCAGGCACACACCTTCCCTTAC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:294)
15483	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATAAAGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGGACAACAGTTACCCTTAC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:304)
20513	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATAAAGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGGACAACAGTTACCCTTAC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:314)
22216	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTAAAAGTATTAGTTCCTGG TTGGCCTGGTATCAGCAGAAACCAGGAAAAGCCCCTAAGCTCCTGATC

	TATGAAGCCTCCTCCTTGCACAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGGACAACAGTTACCCTTAC ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:324)
15489	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATAAAGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGGACAATAGCTTCCCTTTCA CTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:334)
20516	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATAAAGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGGACAATAGCTTCCCTTTCA CTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:344)
15472	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTAT TTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAGCAACTATACAGTCTCCCTCCTA CTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:354)
15503	GACATCCAGTTGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGTCGGGCGAGTCAGGATATTAGCAGCTGGT TAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCT ATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCA GTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTG AAGATTTTGCAACTTATTACTGTCAGCAGGCAACCAGTTACCCTCCTTG GACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:364)
15495	GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAA CTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCAT CTATAGCGCATCCACCAGGGCCACTGGTATCCCAGCCAGGTTCAGTGG CAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGCAGGTCAACGTCTGGCCTCCT ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:374)
15478	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATAAAGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGTACAATAGCTACCCTCCTT TCACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:384)
15441	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGG

	TTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACCATCAGCAGCCTGCAGCCT GATGATTTTGCAACTTATTACTGCCAGCAGTCCAAAAGTTACCCTAGG ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:394)
20496	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTAT TTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAGCAAAGCTACGACCCCCCTTGG ACTTTTGGCGGAGGGACCAAGGTTGAGATCAAA (SEQ ID NO:404)

[00242] Also provided herein are polynucleotides comprising the nucleotide sequence of SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404. Also provided herein are polynucleotides comprising (i) the nucleotide sequence of SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404 and (ii) the nucleotide sequence of SEQ ID NO:408 or 406.

[00243] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 80%, 85%, or 90% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00244] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 95% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00245] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92,

101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 96% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00246] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 97% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00247] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 98% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00248] Also provided herein are polynucleotides comprising a nucleotide sequence that encodes SEQ ID NO:11, 12, 21, 22, 31, 32, 41, 464, 42, 51, 52, 61, 62, 71, 72, 81, 82, 91, 92, 101, 102, 111, 112, 121, 122, 131, 132, 141, 142, 151, 152, 161, 162, 171, 172, 181, 182, 191, 192, 201, or 202 and is at least about 99% identical to SEQ ID NO:213, 214, 223, 224, 233, 234, 243, 470, 244, 253, 254, 263, 264, 273, 274, 283, 284, 293, 294, 303, 304, 313, 314, 323, 324, 333, 334, 343, 344, 353, 354, 363, 364, 373, 374, 383, 384, 393, 394, 403, or 404, respectively.

[00249] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding the light chain or heavy chain of an antibody or an antigen-binding fragment described herein. The polynucleotides can comprise nucleotide sequences encoding a heavy chain comprising the VH FRs and CDRs of antibodies described herein (*see*, *e.g.*, Tables 1 and 5). The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VL FRs and CDRs of antibodies described herein (*see*, *e.g.*, Tables 2 and 6).

[00250] In specific embodiments, a polynucleotide described herein encodes a VH domain comprising the amino acid sequence set forth in SEQ ID NO:464. In specific embodiments, a polynucleotide described herein encodes a VL domain comprising the amino acid sequence set forth in SEQ ID NO:42.

[00251] In specific embodiments, a polynucleotide described herein encodes a VH domain

comprising the amino acid sequence set forth in SEQ ID NO:41. In specific embodiments, a polynucleotide described herein encodes a VL domain comprising the amino acid sequence set forth in SEQ ID NO:42.

[00252] In specific embodiments, a polynucleotide described herein encodes a VH domain comprising the amino acid sequence set forth in SEQ ID NO:71. In specific embodiments, a polynucleotide described herein encodes a VL domain comprising the amino acid sequence set forth in SEQ ID NO:72.

[00253] In particular embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-B7-H4 antibody comprising three VH chain CDRs, e.g., containing VH CDR1, VH CDR2, VH VL CDR3 of any one of antibodies described herein (e.g., see Table 1). In specific embodiments, provided herein are polynucleotides comprising three VL chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Table 2). In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-B7-H4 antibody comprising three VH chain CDRs, *e.g.*, containing VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies described herein (*e.g.*, see Table 1) and three VL chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Table 2).

[00254] In particular embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-B7-H4 antibody or an antigen-binding fragment thereof or a fragment thereof comprising a VH domain, e.g., containing FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, comprising an amino acid sequence described herein (e.g., see Tables 1 and 5, e.g., the VH CDRs and VH FRs of a particular antibody identified by name in the tables). In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-B7-H4 antibody or antigen-binding fragment thereof or a fragment thereof comprising a VL domain, e.g., containing FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, comprising an amino acid sequence described herein (e.g., see Tables 2 and 6, e.g., the VL CDRs and VL FRs of a particular antibody identified by name in the Tables).

[00255] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a heavy chain variable region comprising an amino acid sequence described herein (e.g., SEQ ID NO:464, 41, or 71), wherein an antibody containing the heavy chain variable region immunospecifically binds to B7-H4 (e.g., human B7-H4). In a certain embodiment, a polynucleotide described herein comprises a heavy chain variable region-encoding sequence provided herein (e.g., the variable region-encoding portion of SEQ ID

NO:470, 243, or 273), wherein an antibody containing the heavy chain variable region immunospecifically binds to B7-H4 (e.g., human B7-H4).

[00256] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a light chain variable region comprising an amino acid sequence described herein (e.g., SEQ ID NO:42 or 72), wherein an antibody containing the light chain variable region immunospecifically binds to B7-H4 (e.g., human B7-H4). In a certain embodiment, a polynucleotide described herein comprises a light chain variable region-encoding sequence provided herein (e.g., the variable region-encoding portion of SEQ ID NO:244 or 274), wherein an antibody containing the heavy chain variable region immunospecifically binds to B7-H4 (e.g., human B7-H4).

[00257] In a particular embodiment, a polynucleotide or combination of polynucleotides provided herein comprises a nucleotide sequence or combination of nucleotide sequences encoding an antibody or antigen-binding fragment thereof that immunospecifically binds to B7-H4 (e.g., human B7-H4), wherein the antibody or antigen-binding fragment thereof comprises a heavy chain, wherein the heavy chain comprises a heavy chain variable domain comprising an amino acid sequence set forth in Table 3 (e.g., SEQ ID NO:464, 41, or 71) and a constant region comprising the amino acid sequence of a human gamma (γ) heavy chain constant region.

[00258] In a particular embodiment, a polynucleotide or combination of polynucleotides provided herein comprises a nucleotide sequence or combination of nucleotide sequences encoding an antibody or antigen-binding fragment thereof that immunospecifically binds to B7-H4 (e.g., human B7-H4), wherein the antibody or antigen-binding fragment thereof comprises a light chain, wherein the light chain comprises a light chain variable domain comprising an amino acid sequence set forth in Table 4 (e.g., SEQ ID NO:42 or 72) and a constant region comprising the amino acid sequence of a human lambda light chain constant region.

[00259] In a particular embodiment, a polynucleotide or combination of polynucleotides provided herein comprises a nucleotide sequence or combination of nucleotide sequences encoding an antibody or antigen-binding fragment thereof that immunospecifically binds to B7-H4 (e.g., human B7-H4), wherein the antibody or antigen-binding fragment thereof comprises (i) a heavy chain, wherein heavy chain comprises a heavy chain variable domain comprising an amino acid sequence set forth in Table 3 (e.g., SEQ ID NO:464, 41, or 71) and a constant region comprising the amino acid sequence of a human gamma (γ) heavy chain constant region and (ii) a light chain, wherein light chain comprises a light chain variable domain comprising an amino acid sequence set forth in Table 4 (e.g., SEQ ID NO:42 or 72) and a constant region comprising

the amino acid sequence of a human lambda light chain constant region.

[00260] In one embodiment, a combination of polynucleotides provided herein comprises a polynucleotide comprising the nucleotide sequence of SEQ ID NO:470 and a polynucleotide comprising the nucleotide sequence of SEQ ID NO:244.

[00261] In one embodiment, a combination of polynucleotides provided herein comprises a polynucleotide comprising the nucleotide sequence of SEQ ID NO:243 and a polynucleotide comprising the nucleotide sequence of SEQ ID NO:244.

[00262] In one embodiment, a combination of polynucleotides provided herein comprises a polynucleotide comprising the nucleotide sequence of SEQ ID NO:273 and a polynucleotide comprising the nucleotide sequence of SEQ ID NO:274.

[00263] In a specific embodiment, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-B7-H4 antibody or antigen-binding fragment thereof or a domain thereof, designated herein, see, e.g., Tables 1-8.

[00264] Also provided herein are polynucleotides encoding an anti-B7-H4 antibody or antigen-binding fragment thereof described herein or a domain thereof that are optimized, e.g., by codon/RNA optimization, replacement with heterologous signal sequences, and elimination of mRNA instability elements. Methods to generate optimized nucleic acids encoding an anti-B7-H4 antibody or antigen-binding fragment thereof or a domain thereof (e.g., heavy chain, light chain, VH domain, or VL domain) for recombinant expression by introducing codon changes (e.g., a codon change that encodes the same amino acid due to the degeneracy of the genetic code) and/or eliminating inhibitory regions in the mRNA can be carried out by adapting the optimization methods described in, e.g., U.S. Patent Nos. 5,965,726; 6,174,666; 6,291,664; 6,414,132; and 6,794,498, accordingly.

[00265] A polynucleotide encoding an antibody or antigen-binding fragment thereof described herein or a domain thereof can be generated from nucleic acid from a suitable source (e.g., a hybridoma) using methods well known in the art (e.g., PCR and other molecular cloning methods). For example, PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of a known sequence can be performed using genomic DNA obtained from hybridoma cells producing the antibody of interest. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the light chain and/or heavy chain of an antibody or antigen-binding fragment thereof. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the variable light chain region and/or the variable heavy chain region of an antibody or antigen-binding fragment thereof. The amplified

nucleic acids can be cloned into vectors for expression in host cells and for further cloning, for example, to generate chimeric and humanized antibodies or antigen-binding fragments thereof.

[00266] Polynucleotides provided herein can be, e.g., in the form of RNA or in the form of DNA. DNA includes cDNA, genomic DNA, and synthetic DNA, and DNA can be double-stranded or single-stranded. If single stranded, DNA can be the coding strand or non-coding (anti-sense) strand. In certain embodiments, the polynucleotide is a cDNA or a DNA lacking one more endogenous introns. In certain embodiments, a polynucleotide is a non-naturally occurring polynucleotide. In certain embodiments, a polynucleotide is recombinantly produced. In certain embodiments, the polynucleotides are isolated. In certain embodiments, the polynucleotides are substantially pure. In certain embodiments, a polynucleotide is purified from natural components.

1.2.2 Cells and Vectors

[00267] In certain aspects, provided herein are vectors (*e.g.*, expression vectors) comprising polynucleotides comprising nucleotide sequences encoding anti-B7-H4 antibodies and antigen-binding fragments thereof or a domain thereof for recombinant expression in host cells, preferably in mammalian cells. Also provided herein are cells, e.g. host cells, comprising such vectors for recombinantly expressing anti-B7-H4 antibodies or antigen-binding fragments thereof described herein (*e.g.*, human or humanized antibodies or antigen-binding fragments thereof). In a particular aspect, provided herein are methods for producing an antibody or antigen-binding fragments thereof described herein, comprising expressing such antibody or antigen-binding fragment thereof in a host cell.

[00268] In certain embodiments, recombinant expression of an antibody or antigen-binding fragment thereof or domain thereof described herein (e.g., a heavy or light chain described herein) that specifically binds to B7-H4 (e.g., human B7-H4) involves construction of an expression vector containing a polynucleotide that encodes the antibody or antigen-binding fragment thereof or domain thereof. Once a polynucleotide encoding an antibody or antigen-binding fragment thereof or domain thereof (e.g., heavy or light chain variable domain) described herein has been obtained, the vector for the production of the antibody or antigen-binding fragment thereof can be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody or antigen-binding fragment thereof or domain thereof (e.g., light chain or heavy chain)

encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody or antigen-binding fragment thereof or domain thereof (e.g., light chain or heavy chain) coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Also provided are replicable vectors comprising a nucleotide sequence encoding an antibody or antigen-binding fragment thereof described herein, a heavy or light chain, a heavy or light chain variable domain, or a heavy or light chain CDR, operably linked to a promoter. Such vectors can, for example, include the nucleotide sequence encoding the constant region of the antibody or antigen-binding fragment thereof (see, e.g., International Publication Nos. WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464), and variable domains of the antibody or antigen-binding fragment thereof can be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[00269] An expression vector can be transferred to a cell (e.g., host cell) by conventional techniques and the resulting cells can then be cultured by conventional techniques to produce an antibody or antigen-binding fragment thereof described herein (*e.g.*, an antibody or antigen-binding fragment thereof comprising the six CDRs, the VH, the VL, the VH and the VL, the heavy chain, the light chain, or the heavy and the light chain of 20502, 20502.1, or 22213) or a domain thereof (*e.g.*, the VH, the VL, the VH and the VL, the heavy chain, or the light chain of 20502, 20502.1, or 22213). Thus, provided herein are host cells containing a polynucleotide encoding an antibody or antigen-binding fragment thereof described herein (*e.g.*, an antibody or antigen-binding fragment thereof comprising the six CDRs, the VH, the VL, the VH and the VL, the heavy chain, the light chain, or the heavy and the light chain of 20502, 20502.1, or 22213) or a domain thereof (*e.g.*, the VH, the VL, the VH and the VL, the heavy chain, or the light chain of 20502, 20502.1, or 22213), operably linked to a promoter for expression of such sequences in the host cell. In certain embodiments, for the expression of double-chained antibodies or antigen-binding fragments thereof, vectors encoding both the heavy and light chains, individually, can be co-expressed in the host cell for expression of the entire immunoglobulin, as detailed below. In certain embodiments, a host cell contains a vector comprising a polynucleotide encoding both the heavy chain and light chain of an antibody described herein (*e.g.*, the heavy and the light chain of 20502, 20502.1, or 22213), or a domain thereof (*e.g.*, the VH and the VL of 20502, 20502.1, or 22213). In specific embodiments, a host cell contains two different vectors, a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an

antibody or antigen-binding fragment thereof described herein, and a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody described herein (*e.g.*, an antibody comprising the six CDRs of 20502, 20502.1, or 22213), or a domain thereof. In other embodiments, a first host cell comprises a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an antibody or antigen-binding fragment thereof described herein , and a second host cell comprises a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody or antigen-binding fragment thereof described herein (*e.g.*, an antibody or antigen-binding fragment thereof comprising the six CDRs of 20502, 20502.1, or 22213). In specific embodiments, a heavy chain/heavy chain variable region expressed by a first cell associated with a light chain/light chain variable region of a second cell to form an anti-B7-H4 antibody or antigen-binding fragment thereof described herein (*e.g.*, antibody or antigen-binding fragment thereof comprising the six CDRs of 20502, 20502.1, or 22213). In certain embodiments, provided herein is a population of host cells comprising such first host cell and such second host cell.

[00270] In a particular embodiment, provided herein is a population of vectors comprising a first vector comprising a polynucleotide encoding a light chain/light chain variable region of an anti-B7-H4 antibody or antigen-binding fragment thereof described herein, and a second vector comprising a polynucleotide encoding a heavy chain/heavy chain variable region of an anti-B7-H4 antibody or antigen-binding fragment thereof described herein (e.g., antibody or antigen-binding fragment thereof comprising the CDRs of 20502, 20502.1, or 22213). Alternatively, a single vector can be used which encodes, and is capable of expressing, both heavy and light chain polypeptides.

[00271] A variety of host-expression vector systems can be utilized to express antibodies and antigen-binding fragments thereof described herein (e.g., an antibody or antigen-binding fragment thereof comprising the CDRs of 20502, 20502.1, or 22213) (see, e.g., U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also represent cells which can, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody or antigen-binding fragment thereof described herein in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli and B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces Pichia) transformed with recombinant yeast

expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems (e.g.,green algae such as Chlamydomonas reinhardtii) infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS (e.g., COS1 or COS), CHO, BHK, MDCK, HEK 293, NS0, PER.C6, VERO, CRL7O3O, HsS78Bst, HeLa, and NIH 3T3, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20 and BMT10 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). In a specific embodiment, cells for expressing antibodies and antigen-binding fragments thereof described herein (e.g., an antibody or antigen-binding fragment thereof comprising the CDRs of 20502, 20502.1, or 22213) are CHO cells, for example CHO cells from the CHO GS System™ (Lonza). In a particular embodiment, cells for expressing antibodies described herein are human cells, e.g., human cell lines. In a specific embodiment, a mammalian expression vector is pOptiVEC™ or pcDNA3.3. In a particular embodiment, bacterial cells such as Escherichia coli, or eukaryotic cells (e.g., mammalian cells), especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary (CHO) cells in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking MK & Hofstetter H (1986) Gene 45: 101-105; and Cockett MI et al., (1990) Biotechnology 8: 662-667). In certain embodiments, antibodies or antigen-binding fragments thereof described herein are produced by CHO cells or NS0 cells.

[00272] In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products can contribute to the function of the protein. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product can be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, Hela, MDCK, HEK 293, NIH 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O, COS (e.g., COS1 or COS), PER.C6, VERO,

HsS78Bst, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20, BMT10 and HsS78Bst cells. In certain embodiments, anti-B7-H4 antibodies described herein (e.g., an antibody or antigen-binding fragment thereof comprising the CDRs of 20502, 20502.1, or 22213) are produced in mammalian cells, such as CHO cells.

[00273] In certain embodiments, anti-B7-H4 antibodies described herein (e.g., an antibody or antigen-binding fragment thereof comprising the CDRs of 20502, 20502.1, or 22213) are produced in Potelligent® CHOK1SV cells.

[00274] In some embodiments, host cells are provided that comprise nucleic acid encoding a B7-H4 antibody or antigen-binding fragment thereof described herein, wherein the host cell lacks a functional alpha- 1 ,6-fucosyltransferase gene (FUT8) gene. In some embodiments, the host cell is a CHO cell.

[00275] Once an antibody or antigen-binding fragment thereof described herein has been produced by recombinant expression, it can be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies or antigen-binding fragments thereof described herein can be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[00276] In specific embodiments, an antibody or antigen-binding fragment thereof described herein is isolated or purified. Generally, an isolated antibody or antigen-binding fragment thereof is one that is substantially free of other antibodies or antigen-binding fragments thereof with different antigenic specificities than the isolated antibody or antigen-binding fragment thereof. For example, in a particular embodiment, a preparation of an antibody or antigen-binding fragment thereof described herein is substantially free of cellular material and/or chemical precursors.

1.3 Pharmaceutical Compositions

[00277] Provided herein are compositions comprising an antibody or antigen-binding fragment thereof described herein having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed.

[00278] In various embodiments, compositions comprising an anti-B7-H4 antibody or antigen-binding fragment thereof are provided in formulations with a pharmaceutically acceptable carrier (see, e.g., Gennaro, Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus, 20th ed. (2003); Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippencott Williams and Wilkins (2004); Kibbe et al., Handbook of Pharmaceutical Excipients, 3rd ed., Pharmaceutical Press (2000)).

[00279] Pharmaceutical compositions described herein can be useful in blocking the inhibitory activity of B7-H4 against T cells and/or in ADCC-dependent depletion of B7-H4 expressing cells. Pharmaceutical compositions described herein can be useful in treating a condition such as cancer. Examples of cancer that can be treated in accordance with the methods described herein include, but are not limited to, breast cancer (e.g., triple negative breast cancer, ductal carcinoma), endometrial carcinoma, ovarian cancer, and non-small cell lung cancer (e.g., squamous cell carcinoma), pancreatic cancer, thyroid cancer, kidney cancer (e.g., renal cell carcinoma), and bladder cancer (e.g., urothelial cell carcinoma). A non-small cell lung cancer can be, e.g., an adenocarcinoma. Additional examples of cancer that can be treated in accordance with the methods described herein include, but are not limited to, head and neck cancer, small cell lung cancer, gastric cancer, melanoma, and cholangiocarcinoma. In one embodiment, the ovarian cancer is a serous adenocarcinoma. In one embodiment, the breast cancer is a ductal adenocarcinoma.

[00280] The pharmaceutical compositions described herein are in one embodiment for use as a medicament. The pharmaceutical compositions described herein are in one embodiment for use as a diagnostic, e.g., to detect the presence of B7-H4 in a sample obtained from a patient (e.g., a human patient).

[00281] The compositions to be used for in vivo administration can be sterile. This is readily accomplished by filtration through, e.g., sterile filtration membranes.

[00282] In some embodiments, pharmaceutical compositions are provided, wherein the pharmaceutical composition comprises anti-B7-H4 antibodies or antigen-binding fragments thereof described herein and a pharmaceutically acceptable carrier. In some embodiments, pharmaceutical compositions are provided, wherein the pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments thereof described herein and a pharmaceutically acceptable carrier. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 80% of the antibodies in the composition are afucosylated. In specific embodiments, such

pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 85% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 90% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 95% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 96% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 97% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 98% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments e.g., wherein at least 99% of the antibodies in the composition are afucosylated. In specific embodiments, such pharmaceutical composition comprises afucosylated anti-B7-H4 antibodies or antigen-binding fragments wherein fucose is undetectable in the composition.

[00283] In some embodiments, a pharmaceutical composition comprises (i) an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising (a) the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:458-463, respectively, (b) a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42, or (c) a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44, and (ii) a pharmaceutically acceptable excipient.

[00284] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:458-463, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the

antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[00285] In some embodiments, a pharmaceutical composition comprises (i) an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising (a) the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively, (b) a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42, or (c) a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44, and (ii) a pharmaceutically acceptable excipient.

[00286] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

[00287] In some embodiments, a pharmaceutical composition comprises (i) an isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising (a) the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively, (b) a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid

sequence of SEQ ID NO:72, or (c) a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74, and (ii) a pharmaceutically acceptable excipient.

[00288] Also provided herein is a pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% , or at least 99% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated. In one embodiment, (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:72 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

1.4 Uses and Methods

1.4.1 Therapeutic Uses and Methods

[00289] In one aspect, presented herein are methods for modulating one or more immune functions in a subject, comprising administering to a subject in need thereof an anti-B7-H4 antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition thereof as described above and herein.

[00290] In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) to increase the proliferation of T cells, CD4+ T cells, or CD8+ T cells in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) to increase interferon-gamma (IFNγ) production in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) to block the inhibitory activity of B7-H4 against T cells in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) to deplete B7-H4 expressing cancer cells in the

patient. In another embodiment, the anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to achieve two or more of the above effects.

[00291] In a certain embodiment, provided herein are methods of treating a cancer, e.g., a B7-H4 expressing cancer. The method of treating cancer can comprise administering an anti-B7-H4 antibody or antigen-binding fragment thereof provided herein or a pharmaceutical composition comprising an anti-B7-H4 antibody or antigen-binding fragment thereof provided herein to a patient (e.g., a human patient) in need thereof.

[00292] In a certain embodiment, provided herein are methods of treating a cancer selected from the group consisting of: breast cancer (e.g., triple negative breast cancer, ductal carcinoma), endometrial carcinoma, ovarian cancer, non-small cell lung cancer (e.g., squamous cell carcinoma), pancreatic cancer, thyroid cancer, kidney cancer (e.g., renal cell carcinoma), and bladder cancer (e.g., urothelial cell carcinoma). In a certain embodiment, provided herein are methods of treating a non-small cell lung cancer that is an adenocarcinoma. In a certain embodiment, provided herein are methods of treating a cancer selected from the group consisting of: head and neck cancer, small cell lung cancer, gastric cancer, melanoma, and cholangiocarcinoma. In one embodiment, the ovarian cancer is a serous adenocarcinoma. In one embodiment, the breast cancer is a ductal adenocarcinoma. In some embodiments, such methods comprise administering an anti-B7-H4 antibody or antigen-binding fragment thereof provided herein or a pharmaceutical composition comprising an anti-B7-H4 antibody or antigen-binding fragment thereof provided herein to a patient (e.g., a human patient) in need thereof. In some embodiments, the cancer is a B7-H4 expressing cancer.

[00293] In a certain embodiment, provided herein is a method of treating a cancer that is a PD-1/PD-L1 inhibitor inadequate responder. A cancer that is a PD-1/PD-L1 inhibitor inadequate responder, may have previously responded to a PD-1/PD-L1 inhibitor, but may have become less responsive to the PD-1/PD-L1 inhibitor, or the cancer may have never responded to the PD-1/PD-L1 inhibitor. Inadequate response to a PD-1/PD-L1 inhibitor means that aspects of the cancer that would be expected to improve following a standard dose of the PD-1/PD-L1 inhibitor do not improve, and/or improvement only occurs if greater than a standard dose is administered. In some embodiments, a subject with a cancer that is a PD-1/PD-L1 inhibitor inadequate responder has experienced, or is experiencing, an inadequate response to the PD-1/PD-L1 inhibitor after receiving a standard dose for at least two weeks, at least three weeks, at least four weeks, at least six weeks, or at least twelve weeks. A “standard” dose is determined by a medical professional, and may depend on the subject’s age, weight, healthy history, severity of

disease, the frequency of dosing, etc. In some embodiments, subject with a cancer that is a PD-1/PD-L1 inhibitor inadequate responder has experienced, or is experiencing, an inadequate response to an anti-PD-1 antibody and/or an anti-PD-L1 antibody. In some embodiments, a subject with cancer that is a PD-1/PD-L1 inhibitor inadequate responder has experienced, or is experiencing, an inadequate response to AMP-224. In some embodiments, a subject with cancer that is a PD-1/PD-L1 inhibitor inadequate responder has experienced, or is experiencing, an inadequate response to a PD-1/PD-L1 inhibitor selected from nivolumab, pembrolizumab, and atezolizumab.

[00294] In a certain embodiment, provided herein is a method of treating a cancer that expresses a low level of PD-L1. In some embodiments, a cancer that expresses a "low level of PD-L1," or expresses "PD-L1 at a low level," denotes that the level of PD-L1 is under the level of expression for a cancer that is indicated for treatment with a PD-1 or PD-L1 antagonist in which patients are selected for treatment based on PD-L1 expression levels. In some embodiments, a "low level of PD-L1" is one in which less than 1% of the cells in the tumor have membrane staining. In some embodiments, a "low level" in regard to PD-L1 is less than 1% staining, for example, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1% or 0% of the cells of the tumor are stained. In some embodiments, PD-L1 expression levels can be measured by chromogenic IHC or immunofluorescence IHC (Aqua scoring). In certain embodiments, PD-L1 staining of 5% or less (including tumor and/or immune cells) can indicate that a sample expresses a "low level of PD-L1." In certain embodiments, PD-L1 staining of 10% or less (including tumor and/or immune cells) can indicate that a sample expresses a "low level of PD-L1." Unless indicated otherwise herein, a 5% threshold is used herein (i.e., 5% or less indicates a “low level of PD-L1”).

[00295] In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) diagnosed with cancer to increase the proliferation of T cells, CD4+ T cells, or CD8+ T cells in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) diagnosed with cancer to increase interferon-gamma (IFNγ) production in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) diagnosed with cancer to block the inhibitory activity of B7-H4 against T cells in the patient. In another embodiment, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient (e.g., a human patient) diagnosed with cancer to deplete B7-H4 expressing cancer cells in the

patient.

[00296] In further embodiments, an anti-B7-H4 antibody or antigen-binding fragment thereof, or pharmaceutical composition, is administered to a patient as provided above, and further in combination with an additional therapeutic agent, e.g., a chemotherapeutic agent or an immune stimulating agent, such as a T cell checkpoint inhibitor.

[00297] In an exemplary embodiment, the additional therapeutic agent is a PD-1 antagonist, such as an antagonistic PD-1 antibody. Suitable PD-1 antibodies include, for example, OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). Suitable PD-1 antibodies also include, for example, camrelizumab (SHR-1210), tislelizumab (BGB-A317), or spartalizumab (NPVPDR001, NVS240118, PDR001). The additional therapeutic agent may also include pidilizumab (CT-011). A recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224, can also be used to antagonize the PD-1 receptor.

[00298] In another exemplary embodiment, the additional therapeutic agent is a PD-L1 antagonist, such as an antagonistic PD-L1 antibody. Suitable PD-L1 antibodies include, for example, TECENTRIQ (atezolizumab), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), MSB0010718C (WO2013/79174) or rHigM12B7.

[00299] In yet another exemplary embodiment, the additional therapeutic agent is a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, TRX-518 (WO06/105021, WO09/009116), MK-4166 (WO11/028683), or a GITR antibody disclosed in WO2015/031667. In another embodiment, the additional therapeutic agent is a GITR antibody disclosed in WO2017/015623. In a particular embodiment, the GITR antibody is selected from: a) an antibody comprising a GITR binding domain (GITR-BD) comprising a CDR1 comprising the sequence of SEQ ID NO:411, a CDR2 comprising the sequence of SEQ ID NO:412, and a CDR3 comprising the sequence of SEQ ID NO:413; b) an antibody comprising a GITR-BD comprising the sequence of SEQ ID NO:414; c) a tetravalent molecule comprising two copies of a polypeptide having the structure (GITR-BD)-Linker-(GITR-BD)-Linker-Hinge-Fc, wherein (i) the GITR-BD comprises a CDR1 comprising the sequence of SEQ ID NO:411, a CDR2 comprising the sequence of SEQ ID NO:412, and a CDR3 comprising the sequence of SEQ ID NO:413, (ii) the Linker is a polypeptide, (iii) the Hinge is a polypeptide derived from an immunoglobulin hinge region, and (iv) the Fc is an immunoglobulin Fc polypeptide; d) a tetravalent molecule comprising two copies of a polypeptide having the structure (GITR-BD)-Linker-(GITR-BD)-Linker-Hinge-Fc, wherein (i) the GITR-BD comprises the amino acid

sequence of SEQ ID NO:414, (ii) the Linker is a polypeptide, (iii) the Hinge is a polypeptide derived from an immunoglobulin hinge region, and (iv) the Fc is an immunoglobulin Fc polypeptide; and e) a tetravalent molecule comprising two copies of a polypeptide comprising the sequence of SEQ ID NO: 415. In any of the above embodiments of a tetravalent molecule, a Hinge may comprise the sequence of SEQ ID NO:416, 417 or 418. In any of the above embodiments of a tetravalent molecule, a Linker may comprise an amino acid sequence selected from GG, GGG, and SEQ ID NOs:419-425. In certain embodiments, the Hinge comprises SEQ ID NO:417 and the Linker comprises any one of SEQ ID NOs:419-423.

[00300] In yet another exemplary embodiment, the additional therapeutic agent is a CD80 extracellular domain (CD80 ECD), e.g., SEQ ID NO:426; or a CD80 ECD fusion molecule comprising CD80 ECD and a fusion partner, as disclosed in WO2017/079117. In certain embodiments, the CD80 ECD fusion molecule is a CD80 ECD-Fc fusion protein. In a specific embodiment, the CD80 ECD-Fc fusion protein comprises the sequence of SEQ ID NO:427 or 428.

[00301] In yet another examplary embodiment, the additional therapeutic agent is an anti-CSF1R anitbody disclosed in US8,182,813, US8,206,715, US8,263,079, US8,513,199 or US9,221,910. In a particular embodiment, the anti-CSF1R antibody is selected from: a) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO:429 and a light chain comprising the sequence of SEQ ID NO:430; b) an antibody comprising a heavy chain comprising a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the sequence of SEQ ID NO:431, an HC CDR2 comprising the sequence of SEQ ID NO:432, and an HC CDR3 comprising the sequence of SEQ ID NO:433, and a light chain comprising a light chain (LC) CDR1 comprising the sequence of SEQ ID NO:434, a LC CDR2 comprising the sequence of SEQ ID NO:435, and a LC CDR3 comprising the sequence of SEQ ID NO:436; and c) an antibody comprising a heavy chain comprising the sequence of SEQ ID NO:437 and a light chain comprising the sequence of SEQ ID NO:438.

[00302] Usually, the patient is a human but non-human mammals including transgenic mammals can also be treated.

[00303] In some embodiments, the present invention relates to an antibody or antigen-binding fragment thereof or pharmaceutical composition provided herein for use as a medicament. In some aspects, the present invention relates to an antibody or antigen-binding fragment thereof or pharmaceutical composition provided herein, for use in a method for the treatment of cancer. In some aspects, the present invention relates to an antibody or antigen-binding fragment thereof or

pharmaceutical composition provided herein, for use in a method for the treatment of cancer in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof or pharmaceutical composition provided herein.

1.4.1.1 Routes of Administration & Dosage

[00304] An antibody or antigen-binding fragment thereof or composition described herein can be delivered to a subject by a variety of routes, such as parenteral, subcutaneous, intravenous, intradermal, transdermal, intranasal, intratumoral, and administration to a tumor draining lymph node. In one embodiment, the antibody or antigen-binding fragment thereof or composition is administered by an intravenous route.

[00305] The amount of an antibody or antigen-binding fragment thereof or composition which will be effective in the treatment of a condition will depend on the nature of the disease. The precise dose to be employed in a composition will also depend on the route of administration, and the seriousness of the disease.

1.4.2 Detection & Diagnostic Uses

[00306] An anti-B7-H4 antibody or antigen-binding fragment thereof described herein (see, e.g., Section 5.2) can be used to assay B7-H4 protein levels in a biological sample using classical methods known to those of skill in the art, including immunoassays, such as the enzyme linked immunosorbent assay (ELISA), immunoprecipitation, or Western blotting. Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (121In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. Such labels can be used to label an antibody or antigen-binding fragment thereof described herein. Alternatively, a second antibody or antigen-binding fragment thereof that recognizes an anti-B7-H4 antibody or antigen-binding fragment thereof described herein can be labeled and used in combination with an anti-B7-H4 antibody or antigen-binding fragment thereof to detect B7-H4 protein levels.

[00307] Assaying for the expression level of B7-H4 protein is intended to include qualitatively or quantitatively measuring or estimating the level of a B7-H4 protein in a first biological sample either directly (e.g., by determining or estimating absolute protein level) or relatively (e.g., by comparing to the disease associated protein level in a second biological sample). B7-H4 polypeptide expression level in the first biological sample can be measured or estimated and compared to a standard B7-H4 protein level, the standard being taken from a second biological

sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once the "standard" B7-H4 polypeptide level is known, it can be used repeatedly as a standard for comparison.

[00308] As used herein, the term "biological sample" refers to any biological sample obtained from a subject, cell line, tissue, or other source of cells potentially expressing B7-H4. Methods for obtaining tissue biopsies and body fluids from animals (e.g., humans) are well known in the art. Biological samples include peripheral mononuclear blood cells. A biological sample may also be a blood sample, in which circulating tumor cells (or "CTCs") may express B7-H4 and be detected.

[00309] An anti-B7-H4 antibody described herein can be used for prognostic, diagnostic, monitoring and screening applications, including in vitro and in vivo applications well known and standard to the skilled artisan and based on the present description. Prognostic, diagnostic, monitoring and screening assays and kits for in vitro assessment and evaluation of immune system status and/or immune response may be utilized to predict, diagnose and monitor to evaluate patient samples including those known to have or suspected of having an immune system-dysfunction or cancer. This type of prognostic and diagnostic monitoring and assessment is already in practice utilizing antibodies against the HER2 protein in breast cancer (HercepTestTM, Dako) where the assay is also used to evaluate patients for antibody therapy using Herceptin®. In vivo applications include directed cell therapy and immune system modulation and radio imaging of immune responses.

[00310] Anti-B7-H4 antibodies and antigen-binding fragments thereof described herein can carry a detectable or functional label. When fluorescence labels are used, currently available microscopy and fluorescence-activated cell sorter analysis (FACS) or combination of both methods procedures known in the art may be utilized to identify and to quantitate the specific binding members. Anti-B7-H4 antibodies or antigen-binding fragments thereof described herein can carry a fluorescence label. Exemplary fluorescence labels include, for example, reactive and conjugated probes, e.g., Aminocoumarin, Fluorescein and Texas red, Alexa Fluor dyes, Cy dyes and DyLight dyes. An anti-B7-H4 antibody can carry a radioactive label, such as the isotopes 3H, 14C, 32P, 35S, 36Cl, 51Cr, 57Co, 58Co, 59Fe, 67Cu, 90Y, 99Tc, 111In, 117Lu, 121I, 124I, 125I, 131I, 198Au, 211At, 213Bi, 225Ac and 186Re. When radioactive labels are used, currently available counting procedures known in the art may be utilized to identify and quantitate the specific binding of anti-B7-H4 antibody or antigen-binding fragment to B7-H4

(e.g., human B7-H4). In the instance where the label is an enzyme, detection may be accomplished by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques as known in the art. This can be achieved by contacting a sample or a control sample with an anti-B7-H4 antibody or antigen-binding fragment thereof under conditions that allow for the formation of a complex between the antibody or antigen-binding fragment thereof and B7-H4. Any complexes formed between the antibody or antigen-binding fragment thereof and B7-H4 are detected and compared in the sample and the control. In light of the specific binding of the antibodies or antigen-binding fragments thereof described herein for B7-H4, the antibodies or antigen-binding fragments thereof can be used to specifically detect B7-H4 expression on the surface of cells. The antibodies or antigen-binding fragments thereof described herein can also be used to purify B7-H4 via immunoaffinity purification.

[00311] Also included herein is an assay system which may be prepared in the form of a test kit for the quantitative analysis of the extent of the presence of, for instance, B7-H4. The system or test kit may comprise a labeled component, e.g., a labeled antibody or antigen-binding fragment, and one or more additional immunochemical reagents. See, e.g., Section 5.6 below for more on kits.

[00312] In some aspects, methods for in vitro detecting B7-H4 in a sample, comprising contacting said sample with an antibody or antigen-binding fragment thereof, are provided herein. In some aspects, provided herein is the use of an antibody or antigen-binding fragment thereof provided herein, for in vitro detecting B7-H4 in a sample. In one aspect, provided herein is an antibody or antigen-binding fragment thereof or pharmaceutical composition provided herein for use in the detection of B7-H4 in a subject or a sample obtained from a subject. In one aspect, provided herein is an antibody or antigen-binding fragment thereof or pharmaceutical composition provided herein for use as a diagnostic. In one preferred embodiment, the antibody comprises a detectable label. In one preferred embodiment, B7-H4 is human B7-H4. In one preferred embodiment, the subject is a human.

1.5 Kits

[00313] Provided herein are kits comprising one or more antibodies or antigen-binding fragments thereof described herein or conjugates thereof. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more

of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies or antigen-binding fragments thereof provided herein. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00314] Also provided herein are kits that can be used in diagnostic methods. In one embodiment, a kit comprises an antibody or antigen-binding fragment thereof described herein, preferably a purified antibody or antigen-binding fragment thereof, in one or more containers. In a specific embodiment, kits described herein contain a substantially isolated B7-H4 antigen (e.g., human B7-H4) that can be used as a control. In another specific embodiment, the kits described herein further comprise a control antibody or antigen-binding fragment thereof which does not react with a B7-H4 antigen. In another specific embodiment, kits described herein contain one or more elements for detecting the binding of an antibody or antigen-binding fragment thereof to a B7-H4 antigen (e.g., the antibody or antigen-binding fragment thereof can be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody or antigen-binding fragment thereof which recognizes the first antibody or antigen-binding fragment thereof can be conjugated to a detectable substrate). In specific embodiments, a kit provided herein can include a recombinantly produced or chemically synthesized B7-H4 antigen. The B7-H4 antigen provided in the kit can also be attached to a solid support. In a more specific embodiment, the detecting means of the above described kit includes a solid support to which a B7-H4 antigen is attached. Such a kit can also include a non-attached reporter-labeled anti-human antibody or antigen-binding fragment thereof or anti-mouse/rat antibody or antigen-binding fragment thereof. In this embodiment, binding of the antibody or antigen-binding fragment thereof to the B7-H4 antigen can be detected by binding of the said reporter-labeled antibody or antigen-binding fragment thereof.

[00315] The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

[00316] The examples in this Section (*i.e.*, Section 6) are offered by way of illustration, and not by way of limitation.

Example 1: Assessment of prevalence of B7-H4 expression in multiple indications

[00317] The B7-H4 mouse monoclonal antibody A57.1 (ATCC Catalog No. PTA-5180) was used to detect the presence of B7-H4 on archival samples, a mixture of whole sections, and tumor microarrays. The samples were treated with the primary antibody and detected using a polymer detection system attached to DAB (Ventana Medical Systems).

[00318] B7-H4 was readily detected in the membrane and the cytosol in tumor tissues harvested from a variety of cancer patients, including invasive ductal carcinoma, triple negative breast cancer, ovarian cancer, non-small cell lung cancer and endometrial cancer. (Fig. 1). Moreover, frequency of expression was also high in the indications listed in Table 11.

Table 11: B7-H4 detection in tumors

Tumor Type	#Total	#Positive	Percent Positive
Triple Negative Breast Cancer	74	58	78%
Invasive Ductal Carcinoma	51	38	74.50%
Endometrial Carcinoma	77	54	70%
Ovarian Cancer	141	85	60%
Non-Small Cell Lung Cancer (Squamous)	47	19	40%

[00319] B7-H4 is expressed in other cancers, such as kidney cancer (e.g., renal cell carcinoma), bladder cancer (e.g., urothelial cell carcinoma), pancreatic cancer, and thyroid cancer. See e.g., Zhu, J., et al., Asian Pacific J. Cancer Prev. 14: 3011-3015 (2011), Krambeck A, et al., PNAS 103: 10391-10396 (2006), Fan, M. et al., Int. J. Clin. Exp. Pathol. 7: 6768-6775 (2014), Xu, H., et al., Oncology Letters 11: 1841-1846 (2016), and Liu, W., et al., Oncology Letters 8: 2527-2534 (2014).

[00320] In a subsequent experiment, B7-H4 prevalence in various tumor types was assessed by immunohistochemistry (IHC) (Fig. 1B). The following tumor types and stages of disease were tested: endometrial, breast invasive ductal carcinoma (IDC), breast triple negative (TN), breast triple negative (late stage), ovarian cancer, bladder cancer (early stage), non-small cell lung cancer (sq (squamous), early stage), non-small cell lung cancer (sq, late stage), head and neck cancer, bladder (late stage), small cell lung cancer, cholangiocarcinoma, non-small cell lung cancer (ad (adenocarcinoma)), thyroid cancer, pancreatic cancer, gastric cancer, melanoma, glioblastoma or glioblastoma multiforme (GBM), and merkel cell carcinoma. B7-H4 surface protein expression on tumor cells was evaluated on procured tumor samples from various tumor types and stages of disease where available (early stage (I/II), late stage (III/IV)). IHC intensity with the antibody A57.1 was scored by category 0 to 3, and samples were attributed a single IHC score by the highest intensity observed in a minimum of 10% of all tumor cells per whole

section. A total of 50 to 100 samples per tumor type were evaluated.

Example 2: Generation of novel antibodies against human B7-H4

[00321] B7-H4-specific antibodies were isolated from full-length human IgG1 naïve antibody libraries using an in vitro yeast presentation system. The libraries are designed to mimic the immune system; they do not contain pre-defined heavy and light chain pairs. Libraries were subjected to multiple rounds of positive and negative selection strategies using B7-H4 protein to enrich for IgG that were cross-reactive to human, cynomolgus, and murine B7-H4 target. After four rounds of selection, the resulting IgG were sequenced, and unique antibodies were produced and evaluated for both avid and monomeric binding affinity to recombinant B7-H4 ectodomain, for epitope binning, and for target-specific cell binding.

[00322] A more detailed description of the selection, affinity maturation, and analytical methods that were used to generate and characterize the B7-H4 antibodies is provided below.

Materials and methods

[00323] Antigens were biotinylated using the EZ-Link Sulfo-NHS-Biotinylation Kit from Pierce. Goat F(ab')2 anti-human kappa-FITC (LC-FITC), ExtrAvidin-PE (EA-PE) and Streptavidin-AF633 (SA-633) were obtained from Southern Biotech, Sigma, and Molecular Probes, respectively. Streptavidin MicroBeads and MACS LC separation columns were purchased from Miltenyi Biotec. Goat anti-human IgG-PE (Human-PE) was obtained from Southern Biotech.

Naïve Discovery

[00324] Eight naïve human synthetic yeast libraries each of ~109 diversity were propagated as previously described (see Y. Xu et al, Addressing polyspecificity of antibodies selected from an in vitro yeast presentation system: a FACS-based, high-throughput selection and analytical tool. PEDS 26.10, 663-70 (2013); WO2009036379; WO2010105256; and WO2012009568.) For the first two rounds of selection, a magnetic bead sorting technique utilizing the Miltenyi MACS system was performed, as previously described (see Siegel et al, High efficiency recovery and epitope-specific sorting of an scFv yeast display library." J Immunol Methods 286(1-2), 141-153 (2004).) Briefly, yeast cells (~1010 cells/library) were incubated with 10 ml of 10 nM biotinylated Fc fusion antigen for 30 min at 30°C in wash buffer (phosphate-buffered saline (PBS)/0.1% bovine serum albumin (BSA)). After washing once with 40 ml ice-cold wash buffer, the cell pellet was resuspended in 20 mL wash buffer, and Streptavidin MicroBeads (500 µl)

were added to the yeast and incubated for 15 min at 4°C. Next, the yeast were pelleted, resuspended in 20 mL wash buffer, and loaded onto a Miltenyi LS column. After the 20 mL were loaded, the column was washed 3 times with 3 ml wash buffer. The column was then removed from the magnetic field, and the yeast were eluted with 5 mL of growth media and then grown overnight. The following rounds of selection were performed using flow cytometry. Approximately 2×107 yeast were pelleted, washed three times with wash buffer, and incubated at 30°C with either decreasing concentrations of biotinylated Fc fusion antigen (10 to 1 nM) under equilibrium conditions, 10 nM biotinylated Fc fusion antigens of different species in order to obtain species cross-reactivity, or with a poly-specificity depletion reagent (PSR) to remove non-specific antibodies from the selection. For the PSR depletion the libraries were incubated with a 1:10 dilution of biotinylated PSR reagent as previously described (see Y. Xu et al., addressing polyspecificity of antibodies selected from an in vitro yeast presentation system: a FACS-based, high-throughput selection and analytical tool. PEDS 26.10, 663-70 (2013).) Yeast were then washed twice with wash buffer and stained with LC-FITC (diluted 1:100) and either SA-633 (diluted 1:500) or EAPE (diluted 1:50) secondary reagents for 15 min at 4°C. After washing twice with wash buffer, the cell pellets were resuspended in 0.3 mL wash buffer and transferred to strainer-capped sort tubes. Sorting was performed using a FACS ARIA sorter (BD Biosciences) and sort gates were determined to select for antibodies with desired characteristics. Selection rounds were repeated until a population with all of the desired characteristics was obtained. After the final round of sorting, yeast were plated and individual colonies were picked for characterization.

Antibody Optimization

[00325] Optimization of antibodies was performed via a light chain batch shuffle method, and then by introducing diversities into the heavy chain and light chain variable regions as described below. A combination of some of these approaches was used for each antibody.

[00326] Light chain batch shuffle: Heavy chain plasmids from a naïve selection output were extracted from the yeast via smash and grab, propagated in and subsequently purified from E.coli, and transformed into a light chain library with a diversity of 5 x 106. Selections were performed with one round of MACS and four rounds of FACS employing the same conditions as the naïve discovery.

[00327] CDRH1 and CDRH2 selection: The CDRH3 of a single antibody was recombined into a premade library with CDRH1 and CDRH2 variants of a diversity of 1 x 108 and selections were performed with one round of MACS and four rounds of FACS as described in the naïve

discovery. For each FACS round the libraries were looked at for PSR binding, species cross-reactivity, and affinity pressure, and sorting was performed in order to obtain a population with the desired characteristics. For these selections affinity pressures were applied by using decreasing concentrations of biotinylated HIS-B7-H4 antigen (100 to 1 nM) under equilibrium conditions at 30°C.

[00328] VH Mut selection: The heavy chain variable region (VH) was mutagenized via error prone PCR. The library was then created by transforming this mutagenized VH and the heavy chain expression vector into yeast already containing the light chain plasmid of the parent. Selections were performed similar to previous cycles using FACS sorting for two rounds. For each FACS round the libraries were looked at for PSR binding and affinity pressure, and sorting was performed in order to obtain a population with the desired characteristics. Affinity pressures for these selections were performed as described above in the CDRH1 and CDRH2 selection.

[00329] CDRL1 and CDRL2 selection: The CDRL3 of a single antibody was recombined into a premade library with CDRL1 and CDRL2 variants of a diversity of ~5 x 105 and selections were performed similar to previous cycles using FACS sorting for three rounds. For each FACS round the libraries were looked at for PSR binding and affinity pressure, and sorting was performed in order to obtain a population with the desired characteristics. Affinity pressures for these selections were performed as described above in the CDRH1 and CDRH2 selection.

Antibody production and purification

[00330] Yeast clones were grown to saturation and then induced for 48 h at 30°C with shaking. After induction, yeast cells were pelleted and the supernatants were harvested for purification. IgGs were purified using a Protein A column and eluted with acetic acid, pH 2.0. Fab fragments were generated by papain digestion and purified over KappaSelect (GE Healthcare LifeSciences).

ForteBio K_D measurements

[00331] ForteBio affinity measurements were performed on an Octet RED384 generally as previously described (see Estep et al, High throughput solution-based measurement of antibody-antigen affinity and epitope binning. Mabs 5(2), 270-278 (2013)). Briefly, ForteBio affinity measurements were performed by loading IgGs on-line onto AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen for 3 minutes, and afterwards were transferred to assay buffer for 3 min for off-rate measurement. For monovalent affinity assessment Fabs were used instead of IgGs. For this assessment the

unbiotinylated Fc fusion antigen was loaded on-line onto the AHQ sensors. Sensors were equilibrated off-line in assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded antigen were exposed to 100 nM Fab for 3 minutes, and afterwards they were transferred to assay buffer for 3 min for off-rate measurement. All kinetics were analyzed using the 1:1 binding model.

ForteBio Epitope Binning/Ligand Blocking

[00332] Epitope binning/ligand blocking was performed using a standard sandwich format cross-blocking assay. Control anti-target IgG was loaded onto AHQ sensors and unoccupied Fc-binding sites on the sensor were blocked with an irrelevant human IgG1 antibody. The sensors were then exposed to 100 nM target antigen followed by a second anti-target antibody or ligand. Additional binding by the second antibody or ligand after antigen association indicates an unoccupied epitope (non-competitor), while no binding indicates epitope blocking (competitor or ligand blocking).

[00333] Four non-competing antibodies ("binning antibodies" 1, 2, 3, and 4) were used to identify four distinct portions of the B7-H4 ectodomain by SPR. All of the antibodies generated during this campaign were then assessed for competitive binding with these four binning antibodies to the B7-H4 ectodomain. If a B7-H4 antibody competed with one of the four binning antibodies (e.g., binning antibody 1), the B7-H4 antibody was determined to be in that BIN (e.g., BIN 1). If a B7-H4 antibody competed with two of the four binning antibodies (e.g, binning antibodies 2 and 3), the B7-H4 antibody was determined to be in both of those BINS (e.g., BIN2/3).

[00334] The IgG antibodies fell into at least four binding bins, with >90% of the antibodies binding to human/cyno or mouse B7-H4 with an affinity response ranging between >0.1 nm and <100 nM. Of the recombinant protein binders, approximately 75% also bind to B7-H4 on cells.

Cell Binding Analysis

[00335] 100,000 cells overexpressing the antigen were washed with wash buffer and incubated with 100 ul 100 nM IgG for 5 minutes at room temperature. Cells were then washed twice with wash buffer and incubated with 100ul of 1:100 anti-human IgGPE for 15 minutes on ice. Cells were then washed twice with wash buffer and analyzed on a FACS Canto II analyzer (BD Biosciences.)

PSR Binding Assay

[00336] The PSR assay was done as previously described (see Xu Y, et al. (2013) Addressing polyspecificity of antibodies selected from an in vitro yeast presentation system: A FACS-based,

high-throughput selection and analytical tool. *Protein Eng Des Sel* **26(10)**:663–670). In short, soluble membrane proteins were prepared from CHO cells. The enriched membrane fraction was biotinylated using NHS-LCBiotin (Pierce, Thermo Fisher). This polyspecificity reagent was incubated with IgG-presenting yeast, followed by washing. Then secondary labeling mix (Extravidin-R-PE, anti-human LC-FITC, and propidium iodide) was added to the mixture. Samples were analyzed on a FACSCanto II analyzer (BD Biosciences) using an HTS sample injector. Flow cytometry data were analyzed for mean fluorescence intensity (MFI) in the R-PE channel to assess nonspecific binding. MFI values were normalized from 0 to 1 based on three reference antibodies exhibiting low, medium, and high PSR MFI values.

Dynamic Scanning Fluorimetry

[00337] 10 uL of 20x Sypro Orange is added to 20 uL of 0.2-1mg/mL mAb or Fab solution. A RT-PCR instrument (BioRad CFX96 RT PCR) is used to ramp the sample plate temperature from 40 to 95 C at 0.5C increment, with 2min equilibrate at each temperature. The negative of first derivative for the raw data is used to extract Tm.

AC-SINS

[00338] The AC-SINS assay was performed as described previously (see Liu Y, et al. (2014) High-throughput screening for developability during early-stage antibody discovery using self-interaction nanoparticle spectroscopy. *MAbs* **6(2)**:483–492). In short, gold nanoparticles (Ted Pella Inc.) were coated with 80% capturing anti-human goat IgG Fc (Jackson ImmunoResearch) and 20% with polyclonal goat nonspecific antibody (Jackson ImmunoResearch). The antibodies of interest were then incubated with the particles for 2 h and the wavelength shift was measured using Molecular Devices SpectraMax M2 with SoftMax Pro6 software. The self-interacting clones show a higher wavelength shift away from the PBS sample.

Example 3: Structural characterization of human monoclonal antibodies against B7-H4

[00339] The B7-H4 antibodies are human IgG1/kappa isotype. The variable heavy (VH) regions are comprised of alleles from the germline genes VH1, VH3, and VH4, and the variable light (VL) of alleles from germline genes that include Vk1 and Vk3. Some subsets of the antibodies share high identity within the respective CDR regions of the VH and VL that can

range from 72-100%. Antibodies that share the same germline allele have high identity in their VH and VL framework (FR) regions that ranges from 88-100%. Sequences of the B7-H4 antibodies are provided in Tables 1-10.

Example 4: Characterization of monoclonal antibody binding to B7-H4 protein

[00340] Binding affinities of anti-B7-H4 antibodies to B7-H4-extracellular domain (ECD) were determined by biolayer interferometry (BLI). ForteBio affinity assays are described in more detail above in Example 2. Briefly, the recombinant human B7-H4-huIgG1 (SEQ ID NO:409) protein was immobilized on Protein A tips, followed by an isotype control hIgG1 in order to saturate any remaining binding sites on the capturing tip. Anti-B7-H4 antibodies were then evaluated for binding. In addition, antibody binding to cynomolgus monkey (SEQ ID NO: 2) and mouse B7-H4 (SEQ ID NO: 3) was also assessed using the same protocol. The results are summarized in Table 12.

B7-H4-huIgG1:
MASLGQILFWSIISIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKLSDI
VIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDA
GTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWAS
QVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTES
EIKRRSHLQLLNSKASGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO:409)

Table 12: B7-H4 Antibody Binding to Extracellular Domain by Biolayer Interferometry

		Human B7-H4			Cynomolgus B7-H4			Mouse B7-H4		
Anti-body	BIN	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)
15441	2	7.15E-09	1.22E+06	8.72E-03	5.46E-08	1.33E+06	7.27E-02	NB	-	-

15461	2/3	6.29E-08	3.81E+05	2.40E-02	6.21E-08	4.34E+05	2.70E-02	5.57E-08	3.05E+05	1.70E-02
15462	2/3	PF	-	-	6.65E-08	6.72E+05	4.47E-02	8.31E-08	4.59E+05	3.81E-02
15465	2/3	5.13E-08	4.84E+05	2.48E-02	5.11E-08	5.44E+05	2.78E-02	8.96E-08	2.96E+05	2.65E-02
15472	4	7.11E-09	7.00E+05	4.97E-03	7.80E-09	7.46E+05	5.82E-03	3.80E-08	4.22E+05	1.60E-02
15478	4	3.25E-08	4.77E+05	1.55E-02	3.11E-08	5.44E+05	1.69E-02	NB	-	-
15483	2/3	PF	-	-	1.08E-07	3.80E+05	4.09E-02	2.63E-07	2.65E+05	6.95E-02
15489	2/3	6.37E-08	3.66E+05	2.33E-02	7.21E-08	3.98E+05	2.87E-02	2.01E-07	2.93E+05	5.90E-02
15495	2	9.44E-09	2.89E+06	2.72E-02	5.17E-09	3.25E+06	1.68E-02	NB	-	-
15503	2	1.04E-08	1.96E+06	2.05E-02	6.32E-09	1.82E+06	1.15E-02	NB	-	-
20496	other	8.05E-10	6.89E+05	5.55E-04	7.21E-10	7.90E+05	5.69E-04	2.46E-08	6.92E+05	1.71E-02
20500	3	5.97E-09	3.91E+05	2.33E-03	5.47E-09	4.18E+05	2.29E-03	8.25E-09	4.08E+05	3.36E-03
20501	3	2.56E-09	9.80E+05	2.51E-03	2.42E-09	1.02E+06	2.46E-03	3.35E-09	1.12E+06	3.75E-03
20502	3	1.20E-09	9.36E+05	1.15E-03	1.20E-09	9.62E+05	1.12E-03	3.40E-09	6.32E+05	2.13E-03
20502.1	3	3.07E-09	4.87E+05	1.50E-03	2.64E-09	5.28E+05	1.39E-03	3.99E-09	5.20E+05	2.07E-03
20506	3	1.69E-09	4.41E+05	7.46E-04	1.48E-09	4.58E+05	6.78E-04	3.53E-09	4.66E+05	1.64E-03
20513	3	3.98E-09	4.53E+05	1.80E-03	3.67E-09	4.91E+05	1.80E-03	4.57E-09	5.17E+05	2.36E-03
20516	3	1.80E-08	4.10E+05	7.38E-03	1.76E-08	4.45E+05	7.83E-03	4.14E-08	3.98E+05	1.65E-02

22208	3	5.67E-09	1.84E+05	1.04E-03	5.44E-09	1.99E+05	1.08E-03	1.67E-08	9.95E+04	1.67E-03
22213	3	1.44E-08	4.96E+04	7.13E-04	7.48E-09	6.44E+04	4.82E-04	1.37E-08	4.03E+04	5.52E-04
22216	3	1.47E-09	2.45E+05	3.59E-04	1.47E-09	2.45E+05	3.59E-04	1.47E-09	2.45E+05	3.59E-04

[00341] In addition, the binding affinities of selected anti-B7-H4 antibodies to the N-terminal domain of human B7-H4 (B7-H4 IgV-huIgG1; SEQ ID NO:410) were determined by surface plasmon resonance (SPR). Briefly, anti-human Fab antibody was immobilized on a carboxyl-derivatized SPR chip surface, and anti-B7-H4 antibodies were captured on the resulting surface at 5 ug/ml for 30 seconds. B7-H4 IgV-huIgG1 at various concentrations (0 nM, 3.7 nM, 11.1 nM, 33.3 nM, 100 nM , and 300 nM) was then flowed over the surface and allowed to bind to the anti-B7-H4 antibodies during the association phase, followed by a buffer wash during the dissociation phase. Data was fitted using a 1:1 binding model, and the results are summarized in Table 13.

B7-H4 IgV-huIgG1:

MASLGQILFWSIISIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKLSDI
VIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDA
GTYKCYIITSKGKGNANLEYKTGAFSGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:410)

Table 13: B7-H4 Antibody Binding to N-terminal Domain by Surface Plasmon Resonance

		Human B7-H4		
Antibody	BIN	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)
15461	2/3	3.04E-08	1.71E+05	5.19E-03
15462	2/3	1.69E-08	2.95E+05	4.98E-03
15465	2/3	1.73E-08	2.41E+05	4.17E-03

15483	2/3	1.84E-08	2.41E+05	4.43E-03
15489	2/3	2.37E-08	1.64E+05	3.89E-03
20502	3	2.03E-09	1.78E+05	3.61E-04

[00342] Thus, multiple assays demonstrate that the antibodies bind to B7-H4.

Example 5: Epitope Mapping

[00343] Anti-B7-H4 antibody binding bins were determined by biolayer interferometry (BLI). Epitope mapping assays are described in more detail above in Example 2. Briefly, a first anti-B7-H4 antibody was captured on Protein A tips, followed by a control huIgG1 antibody to saturate additional binding sites on the tips. Next, the sensor tips were exposed to the antigen (B7-H4-huIgG1) (SEQ ID NO:409) followed by the second anti-B7-H4 antibody, which was then evaluated for binding. Epitope bins were determined by comparison to binding after a non-B7-H4 antibody was used as the first antibody. Results are summarized in Table 12.

Example 6: Characterization of monoclonal antibody binding to B7-H4 expressed on the surface of cells

[00344] HEK293T cell lines were transfected to express full-length human, cynomolgus monkey, mouse, or rat B7-H4. In addition, the endogenous human B7-H4 expressing SK-BR-3 breast cancer cell line was used to assess the ability of the antibodies to bind B7-H4 expressed on the cell surface. $1x10^5$ parental HEK293T or transfected HEK293T cell lines were incubated with 100nM of the B7-H4 antibodies. Following incubation, cells were pelleted, washed, and incubated with a secondary labeling antibody, and samples were acquired on a flow cytometer. Fold binding over the parental cell line (FOP) was calculated as follows: MFI transfected HKE293T cells/MFI parental HEK293T cells. A FOP value greater than 10 was considered to demonstrate specific binding.

[00345] To assess the cell binding potency of the B7-H4 antibodies, 1x105 SK-BR-3 cells or 293 cells transfected to express cynomolgus monkey, mouse or rat B7-H4 were incubated with titrating doses of the B7-H4 antibodies. Following incubation, cells were pelleted, washed and incubated with a secondary labeling antibody and samples were acquired on a flow cytometer. Data was analyzed using the FlowJo software and MFI was plotted vs. antibody concentration. The EC50 cell binding potency was calculated using nonlinear regression curve fit (GraphPad

Prism).

[00346] All B7-H4 antibodies demonstrated binding to HEK293T cells that expressed human B7-H4, cynomolgus monkey B7-H4, or mouse B7-H4. Antibodies also demonstrated potent dose-dependent binding to SK-BR-3 cells endogenously expressing human B7-H4 on the cell surface or HEK293T cell lines transfected to express cynomolgus monkey, mouse, or rat B7-H4 on the cell surface. These data demonstrate that the majority of B7-H4 antibodies are fully cross-reactive to cynomolgus monkey, mouse, and rat B7-H4 (Figs. 2A and 2B, Table 14).

[00347]

Table 14: B7-H4 Antibody Binding to Cell-Surface B7-H4

Antibody	BIN	293-huB7-H4 (FOP)	293-cynoB7-H4 (FOP)	293-moB7-H4 (FOP)	SK-BR-3 (EC50; nM)	293-cynoB7-H4 (EC50; nM)	293-mouseB7-H4 (EC50; nM)	293-ratB7-H4 (EC50; nM)
15441	2	67	9	3	34.29	ND	ND	ND
15461	2/3	333	610	887	5.66	6.77	6.37	1.67
15462	2/3	530	416	456	4.55	5.29	5.40	1.13
15465	2/3	626	1324	690	2.13	4.90	5.34	1.47
15472	4	580	1279	685	8.86	-	-	-
15478	4	518	1130	125	PF	-	-	-
15483	2/3	805	1012	1402	14.81	17.4	8.82	1.87
15489	2/3	612	1118	674	31.73	13.7	17.5	4.55
15495	2	619	524	6	61.2	-	-	-
15503	2	289	877	5	PF	-	-	-
20496	other	179	758	604	7.60	7.91	6.70	ND
20500	3	182	630	478	1.54	3.38	4.00	1.14
20501	3	205	728	546	1.90	3.89	4.67	1.15
20502.1	3	200	683	559	2.50	4.94	5.57	1.26

Example 7: Characterization of monoclonal antibody T cell checkpoint blockade activity

[00348] In order to characterize the T cell checkpoint blockade activity of the B7-H4 antibodies, primary human T cells were enriched from peripheral blood mononuclear cells (PBMCs) using the EasySep™ Human T Cell Enrichment Kit based on manufacturer's instructions. Enriched T cells were incubated at $2x10^5$ cell/mL with anti-CD3/anti-CD28 Dynabeads, at a one bead per cell ratio, at 37°C. Six days later, the beads were magnetically removed, and the T cells were washed and incubated at $1x10^6$ cell/mL with 10 U/mL IL-2 at 37°C. Four days later, T cells were washed and incubated at a $1x10^6$ cells/mL along with artificial antigen presenting cells (aAPCs) at $2x10^6$ cells/mL at 37°C in the presence of 10 ug/mL of antibody or an antibody dose titration. aAPCs are a HEK293T cell line that has been transfected to co-express a scFv format of anti-human CD3 clone OKT3 and full-length human B7-H4 on the cell surface. aAPCs were treated with Mitomycin C for one hour at 37°C and then thoroughly washed prior to adding to the T cell co-culture. 72 hours after co-culture of T cells, aAPCs and B7-H4 antibodies, plates were centrifuged, supernatants harvested and assessed for IFNγ production by ELISA, and cells were harvested and stained to assess proliferation by FACS (specifically, the cells in each well were incubated with antibodies against CD4 and CD8). Cells were then washed, fixed, permeabilized, and incubated with the Edu-Click reagent according the manufacturer's instructions. Cells were washed, and the number of proliferating CD4+, CD8+ or total T cells was measured using flow cytometry. Data was analyzed using the FlowJo software. For samples only treated with a single concentration of antibody, the data was calculated and reported as a fold increase over control-huIgG treated samples. For samples treated with a dose titration of antibody, IFNγ production was plotted vs. antibody concentration and the EC50 potency was calculated using nonlinear regression curve fit (GraphPad Prism).

[00349] All BIN2/3 and BIN3 antibodies reproducibly resulted in T cell checkpoint blockade activity as measured by an increase in IFNγ production and/or $CD4^+$, $CD8^+$ or total T cell proliferation. Figure 3A shows that antibody 15441 increases T cell proliferation by at least 3% and increases CD4+ and CD8+ T cell proliferation by at least 2%. Figure 3A also shows that antibody 15461 increases T cell proliferation by at least 21%, increases CD4+ T cell proliferation by at least 9%, and increases CD8+ T cell proliferation by at least 11%. Figures 3B-3D show other dose-dependent T cell checkpoint blockade activities.

Table 15: B7-H4 Antibody – T Cell Checkpoint Blockade Activity

Antibody	BIN	aAPC Assay (EC50 +/-STD; nM)	Donor 1 (Max IFNγ, pg/mL)	Donor 2 (Max IFNγ, pg/mL)	Donor 3 (Max IFNγ, pg/mL)	Donor 4 (Max IFNγ, pg/mL)
15461	2/3	531.18 +/- 403.66	311.64	164.66	1957.34	986.73
15462	2/3	1312.01 +/- 1112.5	205.72	176.33	1661.59	484.8
15465	2/3	4310.72 +/- 7642.6	230.45	133.64	1523.82	865.22
15483	2/3	728.84 +/- 711.1	93.2	87.84	1382.03	939.04
15489	2/3	291.31 +/- 327.82	82.47	96.63	1133.02	799.9

Table 16: B7-H4 Antibody Binding to Cell-Surface B7-H4

Antibody	BIN	aAPC Assay (EC50 +/- STD; nM)	Donor 1 (Max IFNγ, pg/mL)	Donor 2 (Max IFNγ, pg/mL)	Donor 3 (Max IFNγ, pg/mL)	Donor 4 (Max IFNγ, pg/mL)	
20496	other	PF	185.88	ND	ND	ND	
20500	3	0.84 +/- 0.35	821	273.83	117.9	4027.1	
20501	3	0.79 +/- 0.18	849.6	310	135.6	4493.1	
20502.1	3	0.79 +/- 0.03	937	303.9	174.02	4269.7	
20506	3	1.25 +/- 0.26	980.8	258.8	86.1	2301.8	
20513	3	1.16 +/- 0.16	658.8	240.3	91.1	1634.5	
20516	3	PF	ND	441.1	ND	ND	
22213	3	1.79 +/- 1.83	ND	ND	ND	ND	

Example 8: Generation of afucosylated and fucosylated monoclonal antibodies

[00350] Antibodies with Fc regions having reduced fucose content in glycan moieties may exhibit higher ADCC activity compared to a fully fucosylated antibody (Niwa R et al., *Clinical Cancer Research 11(6)*:2327-36 (2005)). B7-H4 antibodies were generated in CHO-x cells (Yamane-Ohnuki N, *et al. Biotechnology and Bioengineering 87(5)*: 614-22 (2004)) to produce normally fucosylated antibodies and in a CHO cell line engineered to produce afucosylated antibodies (CHO-y cells) (*id.*).

Example 9: Characterization of binding of afucosylated and fucosylated monoclonal antibodies

[00351] The fucosylated and afucosylated anti B7-H4 antibodies were characterized by SPR following protocol as described in Example 4. The antibodies showed similar binding to human B7-H4 protein and thus there is no impact of the glycosylation on binding (Table 17).

Table 17: Binding of afucosylated and fucosylated antibodies

			Human B7-H4						
Antibody	BIN		K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)	SK-BR-3 (EC50; nM)	293-cynoB7-H4 (EC50; nM)	293-mouseB7-H4 (EC50; nM)	293-ratB7-H4 (EC50; nM)
20502	3	Fucosylated	2.58E-09	4.28E+05	1.10E-03	0.571	3.291	4.371	2.486
20502	3	Afucosylated	2.74E-09	4.19E+05	1.15E-03	0.483	2.923	1.655	2.446
20506	3	Fucosylated	1.93E-09	3.65E+05	7.03E-04	0.739	1.770	1.77	3.249
20506	3	Afucosylated	2.01E-09	3.60E+05	7.25E-04	0.767	1.769	1.769	PF
22213	3	Fucosylated	5.81E-09	1.53E+05	8.88E-04	0.651	5.199	2.445	4.401
22213	3	Afucosylated	5.11E-09	1.69E+05	8.62E-04	0.667	3.878	2.453	3.545

[00352] The fucosylated and afucosylated anti B7-H4 antibodies were also characterized by flow cytometry. In these experiments, HEK293T cell lines were transfected to express full-length cynomolgus monkey, mouse, or rat B7-H4. In addition, the endogenous human B7-H4 expressing SK-BR-3 breast cancer cell lines were used to assess the cell binding potency of B7-H4 antibodies. 1x105 SK-BR-3 cells or 293 cells transfected to express full-length human, cynomolgus monkey, mouse, or rat B7-H4 were incubated with titrating doses of the B7-H4 antibodies. Following incubation, cells were pelleted, washed, incubated with a secondary labeling antibody, and run on a flow cytometer. Data were analyzed using the FlowJo software. MFI was plotted vs. antibody concentration, and the EC50 cell binding potency was calculated using nonlinear regression curve fit (GraphPad Prism).

[00353] The B7-H4 antibodies demonstrated potent dose-dependent binding to SK-BR-3 cells endogenously expressing B7-H4 on the cell surface or 293 cell lines transfected to express cynomolgus monkey, mouse, or rat B7-H4 on the cell surface. Binding potency and species cross-reactivity was not impacted by whether an antibody was fucosylated or afucosylated (Figs. 4A-4D and Table 17).

Example 10: Binding of afucosylated and fucosylated monoclonal antibodies to human Fcγ receptor IIIa (FcγRIIIa) V158 allele

[00354] Antibody 20502 was produced as both fucosylated (Ab-F) and afucosylated (Ab-A) and tested for the binding affinity of the Fc region to FcgRIIIa (V158) by surface plasmon resonance (SPR). Briefly, Protein A was covalently attached to a dextran chip using the amine coupling kit with 100 mM ethylenediamine in 100 mM Sodium Borate buffer, pH 8.0 as the blocking reagent. Ab-A or Ab-F was captured at 2 densities on separate flow cells, and a Protein A derivatized flow served as a reference control. Fc gamma RIIIA (V158) was diluted in HBS-P+ running buffer and injected at 6 concentrations (0 nM, 1.37 nM, 12.3 nM, 37 nM, 111 nM, 333 nM, and 1000 nM) in duplicate. The association constant, dissociation constant, and affinity for Ab-A binding were calculated using the Biacore T200 Evaluation Software 1:1 binding model. The affinity constant for Ab-A and Ab-F binding were determined using the Biacore T200 Evaluation Software steady state affinity model. The afucosylated B7-H4 antibody (Ab-A) has a 140-fold higher affinity for Fc gamma receptor IIIA (V158) than the same antibody with a fucosylated Fc (Ab-F) (Figs. 5A and 5B, Table 18).

Table 18: Fcγ receptor IIIa (FcγRIIIa) V158 allele binding

	ka (1/Ms)	kd (1/s)	K_D (nM)
Ab-A	6.46E+05	9.54E-10	15
Ab-F	N/A	N/A	210

Example 11: Afucosylated and fucosylated monoclonal antibodies T cell checkpoint blockade activity

[00355] Primary human T cells were enriched from PBMCs using the EasySep™ Human T Cell Enrichment Kit based on the manufacturer's instructions. Enriched T cells were incubated at $2x10^5$ cell/mL with anti-CD3/anti-CD28 Dynabeads, at a one bead per cell ratio, at 37°C. Six days later, the beads were magnetically removed, and T cells were washed and incubated at $1x10^6$ cell/mL with 10 U/mL IL-2 at 37°C. Four days later, T cells were washed and incubated at $1x10^6$ cells/mL along with artificial antigen presenting cells (aAPCs) at a $2x10^6$ cells/mL concentration at 37°C in the presence of B7-H4 antibody dose titration. aAPCs were treated with Mitomycin C for one hour at 37°C and then thoroughly washed prior to adding to the T cell co-culture. 72 hours after co-culture of T cells, aAPCs, and B7-H4 antibodies, plates were centrifuged and supernatants were harvested and assessed for IFNγ production by ELISA. IFNγ production was plotted vs. antibody concentration and the EC50 potency was calculated using nonlinear regression curve fit (GraphPad Prism).

[00356] The B7-H4 antibodies demonstrated potent T cell checkpoint blockade activity as measured by an increase in IFNγ production. Moreover, there was no demonstrable difference in potency between afucosylated and fucosylated antibodies (Fig. 6A and Table 19.)

Table 19: T Cell Checkpoint blockade potency

		aAPC Assay (EC50 +/- STD; nM)	
Antibody	BIN	Afucosylated	Fucosylated
20502	3	0.89 +/-0.44	0.74 +/-0.39
20506	3	1.05 +/-0.28	0.95 +/-0.46
22213	3	0.16 +/-0.05	0.17 +/-0.08

[00357] Next, primary human T cells were enriched from HLA-A2+ donor PBMCs using the Human Pan T Cell Isolation Kit following the manufacturer's instructions. MART-I TCR

expressing T cells were generated by first activating 5x106 enriched Pan T cells with 1.5x107 anti-CD3/anti-CD28 Dynabeads, 100ng/mL IL-2 and 15ng/mL IL-7 for 48 hours. 5x106 activated T cells were then transduced with MART-I TCR lentiviral particles in the presence of 200ng/mL IL-2, 30ng/mL IL-7 and 10ug/mL polybrene. 24 hours post transduction, MART-I TCR+ Pan T cells were expanded over a 15-day period in the presence of 33.3ng/mL IL-2 and 5ng/mL IL-7. To generate HLA-A2 expressing target cell lines, the endogenous B7-H4 expressing human breast cancer cell lines MDA-MB-468 and SK-BR-3 were transduced with HLA-A2 lentiviral particles for 48 hours. Furthermore, B7-H4 was knocked-out of the HLA-A2+ SK-BR-3 cell line. MART-I TCR+ Pan T cells were co-cultured in the presence of the various target cell lines at a 1:1 E:T ratio, 500µg/mL of MART-I peptide and 67nM of the B7-H4 antibody 20502 (afucosylated) or a human isotype control. 24 hours post co-incubation, plates were centrifuged and supernatants were harvested and assessed for IL-2 production by AlphaLisa, according to the manufacturer's instructions.

[00358] As shown in Fig. 6B, B7-H4 demonstrated T cell checkpoint ligand activity in this assay when endogenously expressed at physiologic levels as IL-2 production was reduced in wells containing SK-BR-3 B7-H4+ cells relative to SK-BR-3 KO cells. Moreover, the B7-H4 antibody also demonstrated T cell checkpoint blockade activity as measured by an increase in IL-2 production relative to isotype control treated cells (Fig. 6B). Thus, this data confirm the T cell checkpoint blockade activity of B7-H4 antibody 20502 (afucosylated) and show that the B7-H4 antibody 20502 provides T cell checkpoint blockade activity in cells that endogenously express B7-H4.

Example 12: Afucosylated and fucosylated monoclonal antibodies ADCC activity

[00359] B7-H4 antibodies were assessed for ADCC activity against a B7-H4-expressing target cell line. Specifically, primary human PBMCs cells were cytokine activated at $1x10^6$ cells/mL with 200 IU/mL IL-2 at 37°C. The next day, cells were washed and incubated at a 40:1 Effector:Target ratio with SK-BR-3 target cells that were labeled with Calcein-AM. 4 hours after incubation, target cell lysis was quantified using a fluorimeter. A Triton/X treated sample served as the max lysis control sample, whereas a media alone treated sample served as the background lysis control sample. The percent (%) specific lysis was calculated as follows: [1-((sample – media control)/(max lysis – media control))]x100. The percent (%) specific lysis was plotted vs. antibody concentration and the EC50 potency was calculated using nonlinear regression curve fit

(GraphPad Prism).

[00360] The B7-H4 antibodies demonstrated potent dose-dependent ADCC activity against the endogenous B7-H4 expressing breast cell line SK-BR-3. Moreover, the afucosylated antibodies demonstrated significantly more potent ADCC activity in comparison to the fucosylated antibodies (Fig. 7 and Table 20).

Table 20: ADCC activity

		ADCC Assay (EC50 +/- STD; nM)	
Antibody	BIN	Afucosylated	Fucosylated
20502	3	0.0007 +/-1.1x10E-3	0.0370 +/-6.2E-2
20506	3	0.0015 +/-2.5x10E-3	0.0135 +/-2.1E-2
22213	3	0.0015	0.014

Example 13: Correlation of ADCC activity with receptor density

[00361] B7-H4 density was quantified on the surface of SK-BR-3, HCC1569, ZR-75-1, MDA-MB-48, and HCC1964 cells by FACS according to the manufacturer's specifications. Specifically, $1x10^5$ cells were incubated with 15 ug/mL B7-H4 antibody on ice for 25 minutes. In parallel, one drop of Quantum™ Simply Cellular (QSC) microspheres (pre-coated with increasing concentrations of anti-mouse IgG capture antibody) was also incubated with 15 ug/mL B7-H4 antibody on ice for 25 minutes. Following incubation, cells and QSC microspheres were pelleted and washed, and samples were acquired on a flow cytometer. Data was analyzed using the FlowJo software. Mean fluorescence intensity (MFI) was calculated and entered into the QuickCal® spreadsheet. A regression associating each bead's fluorescence channel value to its pre-assigned Antibody Binding Capacity (ABC) value will be calculated automatically. An ABC value was assigned once the MFI values for the labeled cells are also added into the template).

[00362] B7-H4 antibodies were assessed for ADCC activity against B7-H4 expressing target cell lines with different levels of B7-H4 cell surface density. Specifically, 1x104 SK-BR-3, HCC1569, ZR-75-1, MDA-MB-468, or HCC1964 target cells were co-incubated with dose-titrations of B7-H4 antibody at 4oC. 25 minutes later, a single use vial of Jurkat-huCD16 reporter cells from Promega was thawed, and 7.5x104 cells were added to the target cell/B7-H4 antibody mixture and incubated at 37oC. 24 hours later, the samples were brought to room temperature (RT) and incubated with Bio-Glo buffer. The substrate and luminescence were

quantified on an EnVision multi-label reader. The data was plotted as luminescence vs. antibody concentration and the EC50 potency was calculated using nonlinear regression curve fit (GraphPad Prism).

[00363] B7-H4 antibody ADCC activity was dependent on B7-H4 cell surface density: as the numbers of cell surface molecules decreased, the amount of maximal ADCC activity also decreased. Moreover, afucosylated antibodies demonstrated improved ADCC activity in comparison to the fucosylated antibodies, especially against target cells with lower levels of B7-H4 cell surface density (Fig. 8).

Example 14: *In vivo* anti-tumor efficacy

[00364] Seven week old female BALB/c mice were purchased from Charles River Laboratories (Hollister, CA) and were acclimated for up to three weeks before the start of the studies. The murine colorectal carcinoma cell line CT26 was engineered to express a chimeric protein consisting of the extracellular domain of murine B7-H4 with the transmembrane domain of murine B7H3. These tumor cells were implanted subcutaneously over the right flank of the mice at $1.0x10^6$ cells/200 µl/mouse. Prior to inoculation, the cells were cultured for no more than three passages in RPMI 1640 medium supplemented with 10% heat-inactivated Fetal Bovine Serum (FBS), 2mM L-Glutamine. Cells were grown at 37°C in a humidified atmosphere with 5% CO_2. Upon reaching 80-85% confluence, cells were harvested and resuspended in a 1:1 mixture of serum-free RPMI 1640 and Matrigel at 5 $x10^6$ cells per milliliter).

[00365] Mice were monitored twice weekly following cell implantation for tumor growth. For tumor measurements, the length and width of each tumor was measured using calipers and volume was calculated according to the formula: tumor volume (mm3) = (width (mm) x length (mm2)/2. On the day of treatment initiation, all tumors were measured, outliers were excluded, and mice were randomly assigned to treatment groups. For anti-B7-H4 treatment, antibodies used include 20502 (Fig. 9A) and 22213 (Fig. 9B). As controls, mice were administered polyclonal human IgG (Bio X Cell, BE0092) or mouse IgG2a (Bio X Cell, BE0085). The antibodies were administered four times via intravenous (i.v.) injection twice weekly beginning on Day 4 or 5 after inoculation.

[00366] Tumors continued to be measured at least twice per week until tumor volume exceeded 10% of animal weight, or approximately 2000 mm3. The change in tumor size is shown by graphing individual tumors relative to the day upon which animals were inoculated

with CT26 cells. P-values were calculated using unpaired, two-tailed t-test analyses of the calculated tumor volumes on each day of the study. Treatment with 20502 or 22213 significantly reduced tumor growth compared to human IgG control ($p<0.05$) when administered between doses of 10-20 mg/kg (Figs. 9A and 9B).

[00367] Similar experiments were performed using mice with implanted 4T1 cells (a murine breast carcinoma cell line) or B16 (a murine melanoma cell line). These mice were treated with 20 mg/kg of a mouse surrogate of 20502 called 20502-msIgG2a-F, which contains the 20502 variable region fused to fucosylated mouse IgG2a, or with murine IgG control antibody. Treatment with 20502-msIgG2a-F significantly reduced tumor growth compared to the murine IgG control in both the 4T1 breast carcinoma and B16 melanoma models (Fig. 10).

[00368] Additional experiments were also performed using afucosylated 20502 in a MX-1 human breast cancer xenograft model. Female NSG (NOD-scid, IL2R gammanull) mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and were acclimated for one week before the start of the studies. The human breast cancer cell line MX-1 had previously been shown to endogenously express cell-surface B7H4 protein. These tumor cells were implanted subcutaneously over the right flank of the mice at 1.0x106 cells/100 µl/mouse in a 1:1 mixture of serum-free RPMI 1640 and Matrigel at 5 x106 cells per milliliter.

[00369] Mice were monitored twice weekly following cell implantation for tumor growth. For tumor measurements, the length and width of each tumor was measured using calipers, and volume was calculated according to the formula: Tumor volume (mm3) = (width (mm) x length (mm)2)/2. On Day 7 after inoculation, all tumors were measured, outliers were excluded, and mice were randomly assigned to treatment groups. All animals were administered a DNA construct that induced constitutive human IL-15 expression in the circulation for the remainder of the study. On Day 9, half of the mice received an intravenous (i.v.) injection of 20x106 human peripheral blood monocytic cells (PBMCs), acquired from StemCell Technologies (Tukwila, WA). Beginning on Day 11, mice were administered afucosylated 20502 (20 mg/kg) or saline as a negative control. Therapeutics were administered four times via intravenous (i.v.) injection twice weekly.

[00370] Tumors continued to be measured at least twice per week until tumor volume exceeded 10% of animal weight or until the animals demonstrated a 15% or greater loss of initial body weight. P-values were calculated using One-Way ANOVA comparing the mean tumor volumes across all treatment groups on Day 28. As shown in Figure 11, treatment with afucosylated 20502 significantly reduced tumor growth compared to saline control ($p<0.05$) only

when administered to mice previously injected with human PBMCs.

Example 15: *In vivo* anti-tumor efficacy in combination with anti-PD-1 antibody

Methods

[00371] Eight week old female BALB/c mice were purchased from Charles River Laboratories (Hollister, CA) and were acclimated for up to two weeks before the start of the study. The murine breast carcinoma cell line 4T1 was engineered to express a chimeric protein containing the extracellular domain of murine B7-H4 and the transmembrane domain of murine B7H3. Tumor cells were implanted orthotopically in the mammary fat pad of the mice at 0.5x105 cells/50 µl/mouse. Prior to inoculation, the cells were cultured for no more than three passages in RPMI 1640 medium supplemented with 10% heat-inactivated Fetal Bovine Serum (FBS). Cells were grown at 37□C in a humidified atmosphere with 5% CO2. Upon reaching 80-85% confluence, cells were harvested and resuspended in serum-free RPMI 1640 on the ventral flank of each mouse into the mammary fat pad.

[00372] Mice were monitored twice weekly following cell implantation for tumor growth. The length and width of each tumor was measured using calipers, and the volume was calculated according to the formula: Tumor volume (mm3) = (width (mm) x length (mm)2)/2. On the day of treatment initiation, all tumors were measured, outliers were excluded, and mice were randomly assigned to treatment groups. For the anti-B7-H4 treatment, a mouse surrogate of 20502 called 20502-msIgG2a-F, which contains the 20502 variable region fused to fucosylated mouse IgG2a, was utilized. As a control, mice were administered msIgG2a (anti-HEL). 20502-msIgG2a-F or msIgG2a were administered four times via intravenous (i.v.) injection twice weekly beginning on Day 11 after inoculation. Anti-PD-1 (a modified version of RMP1-14 (Bio X Cell) containing a Fc silent msIgG2a domain) was administered three times via intraperitoneal (i.p.) injection twice weekly beginning on Day 11 after inoculation. Tumors continued to be measured at least twice per week until tumor volume exceeded 10% of animal weight, or approximately 2000 mm^3.

Results

[00373] The change in tumor size, the change in mean tumor volume, and the percent survival are shown in Figs. 12A, 12B and 12C, respectively. Treatment with either 20502-msIgG2a-F or anti-PD-1 significantly reduced tumor growth compared to msIgG2a control ($p<0.05$). The co-administration of 20502-msIgG2a-F and anti-PD-1 significantly enhanced tumor growth

inhibition compared to either monotherapy ($p<0.05$). Moreover, combination therapy resulted in complete tumor regression in 5 of 12 mice. P-values were calculated using One-Way ANOVA analyses of the calculated tumor volumes on each day of the study with multiple comparisons between each group.

Example 16: Anti-B7-H4 antibody increases NK-cell and T-cell infiltration and up-regulates PD-L1

[00374] Eight week old female BALB/c mice were purchased from Charles River Laboratories (Hollister, CA) and implanted orthotopically in the mammary fat pad of the mice with 4T1+moB7-H4/H3 cells at 0.5x105 cells/50 µl/mouse. On the day of treatment initiation, all tumors were measured, outliers were excluded, and mice were randomly assigned to treatment groups. Mice were administered huIgG1 (anti-HEL) or afucosylated 20502 at 20 mg/kg via intravenous (i.v.) injection twice (Day 11 and Day 14 post-inoculation).

[00375] At 24 hours after the second dose administration, mice were euthanized and perfused with phosphate-buffered saline (PBS). Tumors were then extracted, fixed in 10% formalin for five hours, rinsed in PBS, and placed in a 30% sucrose solution for at least 24 hours. Tumors were embedded in Tissue-Tek® O.C.T. Compound and sectioned at 20 µm in a -15°C chamber (cryostat). Tissue-mounted slides were rinsed in 0.3% Triton in PBS, blocked with 5% normal goat serum, and stained with primary antibody (anti-NKp46, anti-CD3, or anti-PD-L1; 1:500) overnight. Two serial sections from each tumor were stained.

[00376] Following overnight incubation, slides were rinsed in 0.3% Triton then incubated with secondary antibody (1:400) for three hours in a dark humid chamber and rinsed. The tissue was then fixed in 1% paraformaldehyde and rinsed in PBS. Coverslips were mounted using Vectashield® with DAPI, sealed with Cytoseal™, and left to dry in a dark chamber. Images were acquired manually with a fluorescence microscope and camera. As shown in Figure 13, treatment with afucosylated 20502 resulted in increased natural killer (NK) cells (as measured by the anti-NKp46 antibody) and increased CD3+ T cells at tumor edges with a moderate increase of CD3+ T cells in the tumor core. Increased PD-L1 expression was also observed.

Example 17: Anti-B7-H4 antibody significantly reduces tumor growth *in vivo* in

4T1- and B16-moB7-H4/H3 models in a dose dependent manner

[00377] Six- to eight-week old female BALB/c or C57Bl/6 mice were purchased from Charles River Laboratories (Hollister, CA) and were acclimated for up to three weeks before the start of the studies. The murine breast carcinoma cell line 4T1 and melanoma cell line B16-F10 were engineered to express murine a chimeric protein consisting of the extracellular domain of murine B7-H4 with the transmembrane domain of murine B7-H3. These tumor cells were implanted orthotopically in the mammary fat pad at $0.05x10^6$ cells/50 µl/mouse for 4T1+moB7-H4/H3 or subcutaneously over the right flank of the mice at $0.5x10^6$ cells/100 µl/mouse for B16+moB7-H4/H3. Prior to inoculation, the cells were cultured for no more than three passages in RPMI-1640 or DMEM medium supplemented with 10% heat-inactivated Fetal Bovine Serum (FBS) and 2mM L-Glutamine. Cells were grown at 37°C in a humidified atmosphere with 5% CO_2.

[00378] Mice were monitored twice weekly following cell implantation for tumor growth. For tumor measurements, the length and width of each tumor was measured using calipers, and volume was calculated according to the formula: Tumor volume (mm3) = (width (mm) x length (mm)2)/2. On the day of treatment initiation, all tumors were measured, outliers were excluded, and mice were randomly assigned to treatment groups. Mice were administered 20502-msIgG2a-F antibody (anti-B7-H4, msIgG2a, fucosylated (also called "cmFPA150-F") or a mouse IgG2a control antibody four times via intravenous (i.v.) injection twice weekly beginning on Day 11 (4T1+moB7-H4/H3) or Day 6 (B16+moB7-H4/H3) after inoculation, except for the 20 mg/kg group, which was administered continuously twice weekly until the end of study.

[00379] Tumors continued to be measured at least twice per week until tumor volume exceeded 10% of animal weight, or approximately 2000 mm3. The change in tumor size is shown by graphing mean tumor volume relative to the day upon which animals were inoculated. Treatment with 20502-msIgG2a-F significantly reduced tumor growth compared to mouse IgG2a control ($p < 0.05$) when administered at doses of 1 mg/kg or greater in the 4T1+moB7-H4/H3 model (see Figs. 14A and 14B) and at doses of 3 mg/kg or greater in the B16+moB7-H4/H3 model (Figs. 15A and 15B). Statistical significance was calculated using OneWay ANOVA comparing all treatment groups to msIgG2a.

[00380] Figs. 14A and 14B show that 20502-msIgG2a-F antibody significantly reduces growth of 4T1 expressing B7-H4/H3. BALB/c mice were inoculated orthotopically with 4T1 breast carcinoma cells engineered to express murine B7-H4 ECD fused to B7-H3 TM. Mice were administered 20502-msIgG2a-F antibody (anti-B7-H4, msIgG2a, fucosylated) twice weekly

beginning on Day 11 after inoculation. 20502-msIgG2a-F antibody demonstrated a dose-dependent reduction in tumor growth, with significant tumor growth inhibition at 30 mg/kg ($p = 0.0003$), 20 mg/kg ($p = 0.0103$), 10 mg/kg ($p = 0.0419$), 3 mg/kg ($p = 0.0277$), and 1 mg/kg ($p = 0.0333$) as assessed by OneWay ANOVA on Day 30.

[00381] Figs. 15A and 15B show that 20502-msIgG2a-F antibody significantly reduces growth of B16 expressing B7-H4/H3. C57Bl/6 mice were inoculated subcutaneously with B16-F10 melanoma cells engineered to express murine B7-H4 ECD fused to B7-H3 TM. Mice were administered 20502-msIgG2a-F antibody (anti-B7-H4, msIgG2a, fucosylated) twice weekly beginning on Day 6 after inoculation. 20502-msIgG2a-F antibody demonstrated a dose-dependent reduction in tumor growth (Fig. 15A), with significant tumor growth inhibition at 30 mg/kg ($p = 0.0085$), 20 mg/kg ($p = 0.0041$), 10 mg/kg ($p = 0.0017$), and 3 mg/kg ($p = 0.0420$) as assessed by OneWay ANOVA on Day 23 (Fig. 15B).

[00382] Thus, the 20502-msIgG2a-F antibody significantly reduced tumor size in a dose-dependent manner in two different cancer models. This data in breast carcinoma and melanoma cell lines indicate that the 20502-msIgG2a-F antibody can be used to treat patients with cancer.

Sequence Tables

GITR Antibody Sequences

SEQ ID NO	Sequence
411	SGSVFSIDAM
412	LSGISSAK
413	YADVSTGWGRDAHGYW
414	EVQLLESGGGEVQPGGSLRLSCAASGSVFSIDAMGWYRQAPGKQRELVA VLSGISSAKYAASAPGRFTISRDNAKNTVYLQMSSLRAEDTAVYYCYADV STGWGRDAHGYWGQGTLVTV
415	EVQLLESGGGEVQPGGSLRLSCAASGSVFSIDAMGWYRQAPGKQRELVA VLSGISSAKYAASAPGRFTISRDNAKNTVYLQMSSLRAEDTAVYYCYADV STGWGRDAHGYWGQGTLVTVKPGGSGGSEVQLLESGGGEVQPGGSLRLS CAASGSVFSIDAMGWYRQAPGKQRELVAVLSGISSAKYAASAPGRFTISR DNAKNTVYLQMSSLRAEDTAVYYCYADVSTGWGRDAHGYWGQGTLVT VKPGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD

	WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
416	EPKSSDKTHTCPPC
417	DKTHTCPPC
418	ESKYGPPCPPC
419	GGSGGS
420	GGSGGSGGS
421	GGSGGSGGSGGS
422	GGSGGSGGSGGSGGS
423	GGGG
424	GGGGG
425	GGGGGG

CD80 Sequences

SEQ ID NO	Sequence
426	VIHVTKEVKEVATLSCGHNVSVEELAQTRIYWQKEKKMVLTMMSGD MNIWPEYKNRTIFDITNNLSIVILALRPSDEGTYECVVLKYEKDAFKREH LAEVTLSVKADFPTPSISDFEIPTSNIRRIICSTSGGFPEPHLSWLENGEEL NAINTTVSQDPETELYAVSSKLDFNMTTNHSFMCLIKYGHLRVNQTFN WNTTKQEHFPDN
427	VIHVTKEVKEVATLSCGHNVSVEELAQTRIYWQKEKKMVLTMMSGD MNIWPEYKNRTIFDITNNLSIVILALRPSDEGTYECVVLKYEKDAFKREH LAEVTLSVKADFPTPSISDFEIPTSNIRRIICSTSGGFPEPHLSWLENGEEL NAINTTVSQDPETELYAVSSKLDFNMTTNHSFMCLIKYGHLRVNQTFN WNTTKQEHFPDNEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

428	VIHVTKEVKEVATLSCGHNVSVEELAQTRIYWQKEKKMVLTMMSGD MNIWPEYKNRTIFDITNNLSIVILALRPSDEGTYECVVLKYEKDAFKREH LAEVTLSVKADFPTPSISDFEIPTSNIRRIICSTSGGFPEPHLSWLENGEEL NAINTTVSQDPETELYAVSSKLDFNMTTNHSFMCLIKYGHLRVNQTFN WNTTKQEHFPDNEPKSSDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

CSFR1 Sequences

SEQ ID NO	Sequence
429	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV SS
430	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI K
431	GYTFTDNYMI
432	DINPYNGGTT FNQKFKG
433	ESPYFSNLYV MDY
434	KASQSVDYDG DNYMN
435	AASNLES
436	HLSNEDLST
437	QVQLVQSGAE VKKPGSSVKV SCKASGYTFT DNYMIWVRQA PGQGLEWMGD INPYNGGTTF NQKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARES PYFSNLYVMD YWGQGTLVTV

	SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK
438	EIVLTQSPAT LSLSPGERAT LSCKASQSVD YDGDNYMNWY QQKPGQAPRL LIYAASNLES GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YCHLSNEDLS TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

PD-1 (nivolumab) Antibody Sequences

SEQ ID NO:	Descrip-tion	Sequence
440	heavy chain variable region	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYA DSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS
441	heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK
442	light chain variable region	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIK
443	light chain constant	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

	region	
444	heavy FR1	QVQLVESGGGVVQPGRSLRLDCKASGITFS
445	heavy CDR1	NSGMH
446	heavy FR2	WVRQAPGKGLEWVA
447	heavy CDR2	VIWYDGSKRYYADSVKG
448	heavy FR3	RFTISRDNSKNTLFLQMNSLRAEDTAVYYCAT
449	heavy CDR3	NDDY
450	heavy FR4	WGQGTLVTVSS
451	light FR1	EIVLTQSPATLSLSPGERATLSC
452	light CDR1	RASQSVSSYLA
453	light FR2	WYQQKPGQAPRLLIY
454	light CDR2	DASNRAT
455	light FR3	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC
456	light CDR3	QQSSNWPRT
457	light FR4	FGQGTKVEIK

* * *

[00383] The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00384] All references (e.g., publications or patents or patent applications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual reference (e.g., publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00385] Other embodiments are within the following claims.

WHAT IS CLAIMED:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences selected from the group consisting of:
   (a) SEQ ID NOs:458-463, respectively;
   (b) SEQ ID NOs:5-10, respectively;
   (c) SEQ ID NOs:15-20, respectively;
   (d) SEQ ID NOs:25-30, respectively;
   (e) SEQ ID NOs:35-40, respectively;
   (f) SEQ ID NOs:45-50, respectively;
   (g) SEQ ID NOs:55-60, respectively;
   (h) SEQ ID NOs:65-70, respectively;
   (i) SEQ ID NOs:75-80, respectively;
   (j) SEQ ID NOs:85-90, respectively;
   (k) SEQ ID NOs:95-100, respectively;
   (l) SEQ ID NOs:105-110, respectively;
   (m) SEQ ID NOs:115-120, respectively;
   (n) SEQ ID NOs:125-130, respectively;
   (o) SEQ ID NOs:135-140, respectively;
   (p) SEQ ID NOs:145-150, respectively;
   (q) SEQ ID NOs:155-160, respectively;
   (r) SEQ ID NOs:165-170, respectively;
   (s) SEQ ID NOs:175-180, respectively;
   (t) SEQ ID NOs:185-190, respectively; and
   (u) SEQ ID NOs:195-200, respectively.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201.

3. The antibody or antigen-binding fragment thereof of claim 1 or claim 2, wherein the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, or 202.

4. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201.

5. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody comprises a heavy chain variable region and a light chain variable region, wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, or 202.

6. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences of:
   (a) SEQ ID NOs:464 and 42, respectively;
   (b) SEQ ID NOs:11 and 12, respectively;
   (c) SEQ ID NOs:21 and 22, respectively;
   (d) SEQ ID NOs:31 and 32, respectively;
   (e) SEQ ID NOs:41 and 42, respectively;
   (f) SEQ ID NOs:51 and 52, respectively;
   (g) SEQ ID NOs:61 and 62, respectively;
   (h) SEQ ID NOs:71 and 72, respectively;
   (i) SEQ ID NOs:81 and 82, respectively;
   (j) SEQ ID NOs:91 and 92, respectively;
   (k) SEQ ID NOs:101 and 102, respectively;
   (l) SEQ ID NOs:111 and 112, respectively;
   (m) SEQ ID NOs:121 and 122, respectively;

(n) SEQ ID NOs:131 and 132, respectively;
(o) SEQ ID NOs:141 and 142, respectively;
(p) SEQ ID NOs:151 and 152, respectively;
(q) SEQ ID NOs:161 and 162, respectively;
(r) SEQ ID NOs:171 and 172, respectively;
(s) SEQ ID NOs:181 and 182, respectively;
(t) SEQ ID NOs:191 and 192, respectively; or
(u) SEQ ID NOs:201 and 202, respectively.

7. The antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment further comprises a heavy chain constant region.

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the heavy chain constant region is selected from the group consisting of human immunoglobulins IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2 heavy chain constant regions.

9. The antibody or antigen-binding fragment thereof of any one of claims 1-8, wherein the antibody or antigen-binding fragment further comprises a light chain constant region.

10. The antibody or antigen-binding fragment thereof of claim 9, wherein the light chain constant region is selected from the group consisting of human immunoglobulins IgGκ and IgGλ light chain constant regions.

11. The antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment further comprises a heavy chain constant region and a light chain constant region, wherein the heavy chain constant region is a human IgG_1 heavy chain constant region, and wherein the light chain constant region is a human IgGκ light chain constant region.

12. The antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:13, 23, 33, 43, 469, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 153, 163, 173, 183, 193, or 203.

13. The antibody or antigen-binding fragment thereof of any one of claims 1-6 or 12, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising the amino acid sequence of SEQ ID NO:14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, or 204.

14. The antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain and light chain comprising the amino acid sequences of:
    (a) SEQ ID NOs:469 and 44, respectively;
    (b) SEQ ID NOs:13 and 14, respectively;
    (c) SEQ ID NOs:23 and 24, respectively;
    (d) SEQ ID NOs:33 and 34, respectively;
    (e) SEQ ID NOs:43 and 44, respectively;
    (f) SEQ ID NOs:53 and 54, respectively;
    (g) SEQ ID NOs:63 and 64, respectively;
    (h) SEQ ID NOs:73 and 74, respectively;
    (i) SEQ ID NOs:83 and 84, respectively;
    (j) SEQ ID NOs:93 and 94, respectively;
    (k) SEQ ID NOs:103 and 104, respectively;
    (l) SEQ ID NOs:113 and 114, respectively;
    (m) SEQ ID NOs:123 and 124, respectively;
    (n) SEQ ID NOs:133 and 134, respectively;
    (o) SEQ ID NOs:143 and 144, respectively;
    (p) SEQ ID NOs:153 and 154, respectively;
    (q) SEQ ID NOs:163 and 164, respectively;
    (r) SEQ ID NOs:173 and 174, respectively;
    (s) SEQ ID NOs:183 and 184, respectively;
    (t) SEQ ID NOs:193 and 194, respectively; or
    (u) SEQ ID NOs:203 and 204, respectively.

15. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody or antigen-binding fragment thereof comprises the VH CDR1,

VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of an antibody selected from the group consisting of 15461, 20500, 20501, 20502, 20502.1, 22208, 15462, 22213, 15465, 20506, 15483, 20513, 22216, 15489, 20516, 15472, 15503, 15495, 15478, 15441, and 20496.

16. The antibody or antigen-binding fragment thereof of claim 15, wherein the CDRs are the Kabat-defined CDRs, the Chothia-defined CDRs, or the AbM-defined CDRs.

17. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, wherein the antibody or antigen-binding fragment thereof comprises the Chothia-defined or AbM-defined VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3 of 20502.1.

18. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 458-463, respectively.

19. The antibody or antigen-binding fragment thereof of claim 18, wherein (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

20. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively.

21. The antibody or antigen-binding fragment thereof of claim 20, wherein (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the

amino acid sequence of SEQ ID NO:44.

22. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4, comprising the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively.

23. The antibody or antigen-binding fragment thereof of claim 22, wherein (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:72 or (ii) wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

24. An isolated antibody or antigen-binding fragment thereof that binds to the same epitope of human B7-H4 as the antibody or antigen-binding fragment thereof of any one of claims 1-23.

25. The antibody or antigen-binding fragment thereof of any one of claims 1-24, wherein the antibody or antigen-binding fragment thereof is a human antibody or antigen-binding fragment thereof.

26. The antibody or antigen-binding fragment thereof of any one of claims 1, 15-20, 22, or 24, wherein the antibody or antigen-binding fragment thereof is a murine, humanized, or chimeric antibody or antigen-binding fragment thereof.

27. The antibody or antigen-binding fragment thereof of any one of claims 1-26, wherein the antibody or antigen-binding fragment thereof induces T cell proliferation.

28. The antibody of antigen-binding fragment thereof of claim 27, wherein the antibody or antigen-binding fragment increases T cell proliferation by at least 21% as compared to treatment with a control antibody.

29. The antibody of antigen-binding fragment thereof of claim 27, wherein the antibody or antigen-binding fragment increases T cell proliferation by about 5% to about 35% as

compared to treatment with a control antibody.

30. The antibody or antigen-binding fragment thereof of any one of claims 1-29, wherein the antibody or antigen-binding fragment thereof induces CD4+ T cell proliferation.

31. The antibody or antigen-binding fragment thereof of claim 30, wherein the antibody or antigen-binding fragment thereof increases CD4+ T cell proliferation by at least 9% as compared to treatment with a control antibody.

32. The antibody or antigen-binding fragment thereof of claim 30, wherein the antibody or antigen-binding fragment thereof increases CD4+ T cell proliferation by about 5% to about 15% as compared to treatment with a control antibody.

33. The antibody or antigen-binding fragment thereof of any one of claims 1-32, wherein the antibody or antigen-binding fragment thereof induces CD8+ T cell proliferation.

34. The antibody or antigen-binding fragment thereof of claim 33, wherein the antibody or antigen-binding fragment thereof increases CD8+ T cell proliferation by at least 11% as compared to treatment with a control antibody.

35. The antibody or antigen-binding fragment thereof of claim 34, wherein the antibody or antigen-binding fragment thereof increases CD8+ T cell proliferation by about 5% to about 15% as compared to treatment with a control antibody.

36. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof induces interferon-gamma (IFNγ) production.

37. The antibody or antigen-binding fragment thereof of claim 36, wherein the antibody or antigen-binding fragment thereof is capable of increasing production of IFNγ by at least 2 fold, at least 3 fold, at least 4 fold, and at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, about 2 fold to about 10 fold, or about 3 fold to about 10 fold.

38. The antibody or antigen-binding fragment thereof of any one of claims 1-37, wherein the antibody or antigen-binding fragment thereof is capable of inducing antibody dependent cell mediated cytotoxicity (ADCC) in a B7-H4-expressing cell.

39. The antibody or antigen-binding fragment thereof of claim 38, wherein the antibody or antigen-binding fragment thereof induces specific lysis in at least 20%, at least 30%, at least 40%, about 20% to about 50%, or about 30% to about 50% of B7-H4 expressing cells.

40. The antibody or antigen-binding fragment thereof of any one of claims 1-39, wherein the antibody or antigen-binding fragment thereof inhibits tumor growth in a murine CT26 colorectal carcinoma model, a murine breast carcinoma 4T1 model, or a melanoma cell line B16-moB7-H4/H3 model.

41. The antibody or antigen-binding fragment thereof of claim 40, wherein the antibody or antigen-binding fragment thereof reduces tumor growth by at least 25%, at least 30%, at least 40%, at least 45%, or at least 50% as compared to treatment with a control antibody.

42. The antibody or antigen-binding fragment thereof of any one of claims 27-41, wherein the induction of T cell proliferation, the induction of CD4+ T cell proliferation, the induction of CD8+ T cell proliferation, the induction of IFNγ production, the ADCC activity, and/or the inhibition of tumor growth is dose-dependent.

43. The antibody or antigen-binding fragment thereof of any one of claims 1-42, wherein the antibody or antigen-binding fragment thereof binds to cynomolgus monkey B7-H4.

44. The antibody or antigen-binding fragment thereof of any one of claims 1-43, wherein the antibody or antigen-binding fragment thereof binds to rat B7-H4.

45. The antibody or antigen-binding fragment thereof of any one of claims 1-44 wherein the antibody or antigen-binding fragment thereof binds to mouse B7-H4.

46. The antibody or antigen-binding fragment thereof of any one of claims 1-45, wherein the antibody or antigen-binding fragment thereof binds to the IgV domain of human B7-H4.

47. The antibody or antigen-binding fragment thereof of any one of claims 1-46, wherein the antibody or antigen-binding fragment thereof is afucosylated.

48. The antibody or antigen binding fragment thereof of any one of claims 1-47, which is a full length antibody.

49. The antibody or antigen binding fragment thereof of any one of claims 1-47, which is an antigen binding fragment.

50. The antigen binding fragment of claim 49, wherein said antigen binding fragment comprises a Fab, Fab', $F(ab')_2$, single chain Fv (scFv), disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGΔCH2, minibody, $F(ab')_3$, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb^2, $(scFv)_2$, or scFv-Fc.

51. The antibody or antigen-binding fragment thereof of any one of claims 1-50, further comprising a detectable label.

52. An isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the antibody or antigen-biding fragment thereof of any one of claims 1-51.

53. The isolated polynucleotide of claim 52, wherein the nucleic acid molecule encodes the VH of SEQ ID NO:11, 21, 31, 41, 464, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, or 201 or the heavy chain of SEQ ID NO:13, 23, 33, 43, 469, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 153, 163, 173, 183, 193, or 203.

54. The isolated polynucleotide of claim 52, wherein the nucleic acid molecule comprises the sequence of SEQ ID NO:213, 223, 233, 243, 470, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 383, 393, or 403.

55. The isolated polynucleotide of claim 52, wherein the nucleic acid molecule comprises (i) the sequence of SEQ ID NO:213, 223, 233, 243, 470, 253, 263, 273, 283, 293, 303, 313, 323, 333, 343, 353, 363, 373, 383, 393, or 403 and (ii) the sequence of SEQ ID NO:408.

56. An isolated polynucleotide comprising a nucleic acid molecule encoding the light chain variable region or light chain of the antibody or antigen-biding fragment thereof of any one of claims 1-51.

57. The isolated polynucleotide of claim 56, wherein the nucleic acid molecule encodes the VL of SEQ ID NO:12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182,

192, or 202 or the light chain of SEQ ID NO:14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, or 204.

58. The isolated polynucleotide of claim 56, wherein the nucleic acid molecule comprises the sequence of SEQ ID NO:214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 384, 394, or 404.

59. The isolated polynucleotide of claim 56, wherein the nucleic acid molecule comprises (i) the sequence of SEQ ID NO:214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, 344, 354, 364, 374, 384, 394, or 404 and (ii) the sequence of SEQ ID NO:406.

60. An isolated polynucleotide comprising a nucleic acid molecule encoding the heavy chain variable region or heavy chain of the antibody or antigen-binding fragment thereof of any one of claims 1-51 and the light chain variable region or light chain of the antibody or antigen-binding fragment thereof of any one of claims 1-51.

61. An isolated vector comprising the polynucleotide of any one of claims 52-60.

62. A host cell comprising the polynucleotide of any one of claims 52-60, the vector of claim 61, or a first vector comprising the polynucleotide of any one of claims 52-55 and a second vector comprising the polynucleotide of any one of claims 56-59.

63. The host cell of claim 62, which is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.

64. The host cell of claim 62 or 63, wherein the host cell lacks a functional alpha-1,6-fucosyltransferase gene (FUT8) gene.

65. A method of producing an antibody or antigen-binding fragment thereof that binds to human B7-H4 comprising culturing the host cell of any one of claims 62-64 so that the nucleic acid molecule is expressed and the antibody or antigen-binding fragment thereof is produced.

66. An isolated antibody or antigen-binding fragment thereof that specifically binds to human B7-H4 and is encoded by the polynucleotide of any one of claims 52-60.

67. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 and a pharmaceutically acceptable excipient.

68. A pharmaceutical composition comprising (i) antibodies or antigen-binding fragments of any one of claims 1-51 or 66 and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

69. A pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:458-460, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

70. The pharmaceutical composition of claim 69, wherein (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:464 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:469 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

71. A pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:35-40, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

72. The pharmaceutical composition of claim 71, wherein (i) the antibody or antigen-binding

fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:41 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:42 or (ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:43 and a light chain comprising the amino acid sequence of SEQ ID NO:44.

73. A pharmaceutical composition comprising (i) antibodies or antigen-binding fragments thereof that specifically bind to human B7-H4 and comprise the heavy chain variable region (VH) complementarity determining region (CDR) 1, VH CDR2, VH CDR3 and light chain variable region (VL) CDR1, CDR2, and CDR3 sequences of SEQ ID NOs:65-70, respectively and (ii) a pharmaceutically acceptable excipient, wherein at least 95% of the antibodies or antigen-binding fragments thereof in the composition are afucosylated.

74. The pharmaceutical composition of claim 73, wherein (i) the antibody or antigen-binding fragment thereof comprises a variable heavy chain region comprising the amino acid sequence of SEQ ID NO:71 and a variable light chain region comprising the amino acid sequence of SEQ ID NO:72 or (ii) wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:73 and a light chain comprising the amino acid sequence of SEQ ID NO:74.

75. The pharmaceutical composition of any one of claims 67-74, wherein fucosylation is undetectable in the composition.

76. The pharmaceutical composition of any one of claims 67-75 further comprising an anti-PD-1 antibody or antigen-binding fragment thereof.

77. The pharmaceutical composition of claim 76, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is nivolumab, or pembrolizumab.

78. The pharmaceutical composition of claim 76, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is AMP-514, camrelizumab, tislelizumab, and spartalizumab.

79. The pharmaceutical composition of any one of claims 67-75 further comprising an anti-PD-L1 antibody or antigen-binding fragment thereof.

80. A method for inducing T cell proliferation comprising contacting a T cell with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

81. The method of claim 80, wherein T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80%.

82. A method for inducing CD4+ T cell proliferation comprising contacting a CD4+ T cell with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

83. The method of claim 82, wherein CD4+ T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80%.

84. A method for inducing CD8+ T cell proliferation comprising contacting a CD8+ T cell with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

85. The method of claim 84, wherein CD8+ T cell proliferation is reduced by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80%.

86. A method for inducing interferon gamma production comprising contacting a T cell with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

87. The method of claim 86, wherein interferon gamma production is increased by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, or at least 80%.

88. A method for killing a cell expressing B7-H4 comprising contacting the cell the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

89. A method for depleting B7-H4-expressing cells from a population of cells comprising contacting the population of cells with the antibody or antigen-binding fragment thereof of

any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

90. The method of claim 88 or 89, wherein the killing or depletion occurs via ADCC.

91. The method of any one of claims 80-90, further comprising contacting the T cell, the CD4+ T cell, the CD8+ T cell, the cell, or the population of cells with an anti-PD-1 antibody or antigen-binding fragment thereof.

92. The method of claim 91, wherein the contacting with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-78 and the contacting with the anti-PD-1 antibody or antigen-binding fragment thereof occur simultaneously.

93. The method of claim 91, wherein the contacting with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-78 and the contacting with the anti-PD-1 antibody or antigen-binding fragment thereof occur sequentially.

94. The method of any one of claims 80-90, further comprising contacting the T cell, the CD4+ T cell, the CD8+ T cell, the cell, or the population of cells with an anti-PD-L1 antibody or antigen-binding fragment thereof.

95. The method of claim 94, wherein the contacting with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-75 and the contacting with the anti-PD-L1 antibody or antigen-binding fragment thereof occur simultaneously.

96. The method of claim 94, wherein the contacting with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-75 and the contacting with the anti-PD-L1 antibody or antigen-binding fragment thereof occur sequentially.

97. The method of any one of claims 80-96, wherein the contacting is *in vitro*.

98. The method of any one of claims 80-96, wherein the contacting is in a subject.

99. A method of treating a B7-H4 expressing cancer in a subject, the method comprising administering to the subject an effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79.

100. The method of claim 99, wherein the cancer is selected from the group consisting of breast cancer, ductal carcinoma, endometrial carcinoma, ovarian cancer, non-small cell lung cancer, pancreatic cancer, thyroid cancer, kidney cancer and bladder cancer.

101. The method of claim 100, wherein the breast cancer is triple negative breast cancer or wherein the non-small cell lung cancer is squamous cell carcinoma.

102. The method of claim 100, wherein the non-small cell lung cancer is an adenocarcinoma.

103. The method of claim 99, wherein the cancer is selected from the group consisting of head and neck cancer, small cell lung cancer, gastric cancer, and melanoma.

104. The method of claim 100, wherein the cancer is ovarian cancer that is a serous adenocarcinoma.

105. The method of claim 101, wherein the cancer is breast cancer that is a ductal adenocarcinoma.

106. The method of any one of claims 99-105, wherein the cancer is a PD-1 inhibitor inadequate responder.

107. The method of any one of claims 99-106, wherein the cancer is a PD-L1 inhibitor inadequate responder.

108. The method of any one of claims 99-107, wherein the cancer expresses a low level of PD-L1.

109. The method of any one of claims 99-108, wherein the subject is human.

110. The method of any one of claims 99-109, further comprising administering to the subject an anti-PD-1 antibody or antigen-binding fragment thereof.

111. The method of claim 110, wherein the administration of the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-78 and the administration of the anti-PD-1 antibody or antigen-binding fragment thereof occur simultaneously.

112. The method of claim 110, wherein the administration of the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-78 and the administration of the anti-PD-1 antibody or antigen-binding fragment thereof occur sequentially.

113. The method of claim 112, wherein the administration of the anti-PD-1 antibody or antigen-binding fragment thereof occurs after the administration of the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-78.

114. The method of any one of claims 91-93, 97, 98 and 110-113, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is nivolumab or pembrolizumab.

115. The method of any one of claims 91-93, 97, 98 and 110-113, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is AMP-514, camrelizumab, tislelizumab, or spartalizumab.

116. A method for detecting B7-H4 in a sample comprising contacting said sample with the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66.

117. The method of claim 116, wherein the sample is obtained from a cancer in a human subject.

118. A kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66 or the pharmaceutical composition of any one of claims 67-79 and a) a detection reagent, b) a B7-H4 antigen, c) a notice that reflects approval for use or sale for human administration, or d) a combination thereof.

119. An isolated antibody or antigen-binding fragment thereof of any one of claims 1-51 or 66, wherein the antibody or antigen-binding fragment thereof inhibits T cell checkpoint blockade activity of B7-H4.

120. The isolated antibody or antigen-binding fragment thereof of claim 119, wherein the T cell checkpoint blockade activity is measured by an increase in IL-2 production relative to control cells.

121. A pharmaceutical composition comprising (i) antibodies or antigen-binding fragments of any one of claims 1-51 or 66 and (ii) a pharmaceutically acceptable excipient, wherein the antibodies or antigen-binding fragments inhibit T cell checkpoint blockade activity of B7-H4.

122. The pharmaceutical composition of claim 121, wherein the T cell checkpoint blockade activity is measured by an increase in IL-2 production relative to control cells.