

[0529] g) a VL2 comprising SEQ ID NO: 29 and a VH2 comprising SEQ ID NO: 30;

[0530] h) a VL2 comprising SEQ ID NO: 33 and a VH2 comprising SEQ ID NO: 34;

[0531] i) a VL2 comprising SEQ ID NO: 37 and a VH2 comprising SEQ ID NO: 38;

[0532] j) a VL2 comprising SEQ ID NO: 41 and a VH2 comprising SEQ ID NO: 42;

[0533] k) a VL2 comprising SEQ ID NO: 45 and a VH2 comprising SEQ ID NO: 46;

[0534] l) a VL2 comprising SEQ ID NO: 49 and a VH2 comprising SEQ ID NO: 50; and

[0535] m) a VL2 comprising SEQ ID NO: 53 and a VH2 comprising SEQ ID NO: 54.

[0536] In one example, the present disclosure is directed to an antigen binding protein that specifically binds and agonizes human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

[0537] the VL comprises a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of:

[0538] SEQ ID NOs: 58, 59, and 60, respectively;

[0539] SEQ ID NOs: 64, 65, and 66, respectively;

[0540] SEQ ID NOs: 70, 71, and 72, respectively;

[0541] SEQ ID NOs: 76, 77, and 78, respectively;

[0542] SEQ ID NOs: 82, 83, and 84, respectively;

[0543] SEQ ID NOs: 88, 89, and 90, respectively;

[0544] SEQ ID NOs: 94, 95, and 96, respectively;

[0545] SEQ ID NOs: 100, 101, and 102, respectively;

[0546] SEQ ID NOs: 106, 107, and 108, respectively;

[0547] SEQ ID NOs: 112, 113, and 114, respectively;

[0548] SEQ ID NOs: 118, 119, and 120, respectively;

[0549] SEQ ID NOs: 124, 125, and 126, respectively; and

[0550] SEQ ID NOs: 130, 131, and 132, respectively;

[0551] and

[0552] the VH comprises a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of:

[0553] SEQ ID NOs: 136, 137, and 138, respectively;

[0554] SEQ ID NOs: 142, 143, and 144, respectively;

[0555] SEQ ID NOs: 148, 149, and 150, respectively;

[0556] SEQ ID NOs: 154, 155, and 156, respectively;

[0557] SEQ ID NOs: 160, 161, and 162, respectively;

[0558] SEQ ID NOs: 166, 167, and 168, respectively;

[0559] SEQ ID NOs: 172, 173, and 174, respectively;

[0560] SEQ ID NOs: 178, 179, and 180, respectively;

[0561] SEQ ID NOs: 184, 185, and 186, respectively;

[0562] SEQ ID NOs: 190, 191, and 192, respectively;

[0563] SEQ ID NOs: 196, 197, and 198, respectively;

[0564] SEQ ID NOs: 202, 203, and 204, respectively; and

[0565] SEQ ID NOs: 208, 209, and 210, respectively.

[0565a] In one aspect, the present disclosure refers to an antigen binding protein that specifically binds human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein: the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs: 100, 101, and amino acids 91 to 101 of SEQ ID NO: 370, respectively; SEQ ID NOs: 100, 101, and 102, respectively; SEQ ID NOs: 58, 59, and 60, respectively; SEQ ID NOs: 64, 65, and 66, respectively; SEQ ID NOs: 70, 71, and 72, respectively; SEQ ID NOs: 76, 77, and 78, respectively; SEQ ID NOs: 82, 83, and 84, respectively; SEQ ID NOs: 88, 89, and 90, respectively; SEQ ID NOs: 94, 95, and 96, respectively; SEQ ID NOs: 106, 107, and 108, respectively; SEQ ID NOs: 112, 113, and 114, respectively; SEQ ID NOs: 118, 119, and 120, respectively; SEQ ID NOs: 124, 125, and 126, respectively; and SEQ ID NOs: 130, 131, and 132, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising an amino acid sequence selected from the group consisting of: SEQ ID NOs: 178, 179, and 180, respectively; SEQ ID NOs: 136, 137, and 138, respectively; SEQ ID NOs: 142, 143, and 144, respectively; SEQ ID NOs: 148, 149, and 150, respectively; SEQ ID NOs: 154, 155, and 156, respectively; SEQ ID NOs: 160, 161, and 162, respectively; SEQ ID NOs: 166, 167, and 168, respectively; SEQ ID NOs: 172, 173, and 174, respectively; SEQ ID NOs: 184, 185, and 186, respectively; SEQ ID NOs: 190, 191, and 192, respectively; SEQ ID NOs: 196, 197, and 198, respectively; SEQ ID NOs: 202, 203, and 204, respectively; and SEQ ID NOs: 208, 209, and 210, respectively.

[0566] In one example, the multispecific antibody construct comprises mutations limiting Fc receptor binding and thus decreases Fc receptor-dependent CD40 agonism.

[0567] In one example,

[0568] the VL and VH are selected from the group consisting of:

[0569] a) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 58, 59, and 60, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 136, 137, and 138, respectively;

[0570] b) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 64, 65, and 66, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 142, 143, and 144, respectively;

[0571] c) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 70, 71, and 72, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 148, 149, and 150, respectively;

- [0572]** d) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 76, 77, and 6780, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 154, 155, and 156, respectively;
- [0573]** e) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 82, 83, and 84, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 160, 161, and 162, respectively;
- [0574]** f) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 88, 89, and 90, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 166, 167, and 168, respectively;
- [0575]** g) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 94, 95, and 96, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 172, 173, and 174, respectively;
- [0576]** h) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 100, 101, and 102, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 178, 179, and 180, respectively;
- [0577]** i) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 106, 107, and 108, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 184, 185, and 186, respectively;

[0578] j) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 112, 113, and 114, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 190, 191, and 192, respectively;

[0579] k) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 118, 119, and 120, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 196, 197, and 198, respectively;

[0580] l) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 124, 125, and 126, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 202, 203, and 204, respectively; and

[0581] m) a VL comprising a CDRL1, a CDRL2, and a CDRL3 selected from the group consisting of SEQ ID NOs: 130, 131, and 132, respectively; and a VH comprising a CDRH1, a CDRH2, and a CDRH3 selected from the group consisting of SEQ ID NOs: 208, 209, and 210, respectively.

[0581a] In one aspect, the present disclosure refers to an antigen binding protein that specifically binds human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein: (i) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising the amino acid sequences of: SEQ ID NOs: 100, 101, and amino acids 91 to 101 of SEQ ID NO: 370, respectively; or SEQ ID NOs: 100, 101, and 102, respectively; and (ii) the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 178, 179, and 180, respectively.

[0582] In one example,

[0583] the VL comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53; and

[0584] the VH comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54.

[0585] In one example,

[0586] the VL and VH are selected from the group consisting of:

[0587] a) a VL comprising SEQ ID NO: 5 and a VH comprising SEQ ID NO: 6;

[0588] b) a VL comprising SEQ ID NO: 9 and a VH comprising SEQ ID NO: 10;

[0589] c) a VL comprising SEQ ID NO: 13 and a VH comprising SEQ ID NO: 14;

[0590] d) a VL comprising SEQ ID NO: 17 and a VH comprising SEQ ID NO: 18;

[0591] e) a VL comprising SEQ ID NO: 21 and a VH comprising SEQ ID NO: 22;

[0592] f) a VL comprising SEQ ID NO: 25 and a VH comprising SEQ ID NO: 26;

[0593] g) a VL comprising SEQ ID NO: 29 and a VH comprising SEQ ID NO: 30;

[0594] h) a VL comprising SEQ ID NO: 33 and a VH comprising SEQ ID NO: 34;

[0595] i) a VL comprising SEQ ID NO: 37 and a VH comprising SEQ ID NO: 38;

[0596] j) a VL comprising SEQ ID NO: 41 and a VH comprising SEQ ID NO: 42;

[0597] k) a VL comprising SEQ ID NO: 45 and a VH comprising SEQ ID NO: 46;

[0598] l) a VL comprising SEQ ID NO: 49 and a VH comprising SEQ ID NO: 50; and

[0599] m) a VL comprising SEQ ID NO: 53 and a VH comprising SEQ ID NO: 54.

[0600] In one example, the heavy chain comprises an amino acid substitution selected from the group consisting of:

[0601] (i) N297G or N297A;

CLAIMS

We claim:

1. An antigen binding protein that specifically binds human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising an amino acid sequence selected from the group consisting of:

SEQ ID NOs: 100, 101, and amino acids 91 to 101 of SEQ ID NO: 370, respectively;
SEQ ID NOs: 100, 101, and 102, respectively;
SEQ ID NOs: 58, 59, and 60, respectively;
SEQ ID NOs: 64, 65, and 66, respectively;
SEQ ID NOs: 70, 71, and 72, respectively;
SEQ ID NOs: 76, 77, and 78, respectively;
SEQ ID NOs: 82, 83, and 84, respectively;
SEQ ID NOs: 88, 89, and 90, respectively;
SEQ ID NOs: 94, 95, and 96, respectively;
SEQ ID NOs: 106, 107, and 108, respectively;
SEQ ID NOs: 112, 113, and 114, respectively;
SEQ ID NOs: 118, 119, and 120, respectively;
SEQ ID NOs: 124, 125, and 126, respectively; and
SEQ ID NOs: 130, 131, and 132, respectively;

and

the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising an amino acid sequence selected from the group consisting of:

SEQ ID NOs: 178, 179, and 180, respectively;
SEQ ID NOs: 136, 137, and 138, respectively;
SEQ ID NOs: 142, 143, and 144, respectively;
SEQ ID NOs: 148, 149, and 150, respectively;
SEQ ID NOs: 154, 155, and 156, respectively;
SEQ ID NOs: 160, 161, and 162, respectively;
SEQ ID NOs: 166, 167, and 168, respectively;
SEQ ID NOs: 172, 173, and 174, respectively;
SEQ ID NOs: 184, 185, and 186, respectively;
SEQ ID NOs: 190, 191, and 192, respectively;
SEQ ID NOs: 196, 197, and 198, respectively;

SEQ ID NOs: 202, 203, and 204, respectively; and
SEQ ID NOs: 208, 209, and 210, respectively.

2. The antigen binding protein of claim 1, wherein

a) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 100, 101, and amino acids 91 to 101 of SEQ ID NO: 370, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 178, 179, and 180, respectively;

b) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 100, 101, and 102, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 178, 179, and 180, respectively;

c) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 58, 59, and 60, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 136, 137, and 138, respectively;

d) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 64, 65, and 66, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 142, 143, and 144, respectively;

e) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 70, 71, and 72, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 148, 149, and 150, respectively;

f) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 76, 77, and 6780, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 154, 155, and 156, respectively;

g) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 82, 83, and 84, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 160, 161, and 162, respectively;

h) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 88, 89, and 90, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 166, 167, and 168, respectively;

i) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 94, 95, and 96, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 172, 173, and 174, respectively;

j) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 106, 107, and 108, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 184, 185, and 186, respectively;

k) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 112, 113, and 114, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 190, 191, and 192, respectively;

l) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 118, 119, and 120, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 196, 197, and 198, respectively;

m) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 124, 125, and 126, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 202, 203, and 204, respectively; or

n) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising SEQ ID NOs: 130, 131, and 132, respectively; and the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising SEQ ID NOs: 208, 209, and 210, respectively.

3. The antigen binding protein of claim 1 or 2, wherein:

the VL comprises an amino acid sequence comprising amino acids 1 to 112 of SEQ ID NO: 370, or the VL comprises the amino acid sequence of SEQ ID NO: 33, 5, 9, 13, 17, 21, 25, 29, 37, 41, 45, 49, or 53; and

the VH comprises an amino acid sequence of SEQ ID NO: 34, 6, 10, 14, 18, 22, 26, 30, 38, 42, 46, 50, or 54.

4. The antigen binding protein of any one of claim 1-3, wherein:

a) the VL comprises an amino acid sequence comprising amino acids 1 to 112 of SEQ ID NO: 370 and the VH comprises an amino acid sequence comprising SEQ ID NO: 34;

b) the VL comprises an amino acid sequence comprising SEQ ID NO: 33 and the VH comprises an amino acid sequence comprising SEQ ID NO: 34;

c) the VL comprises an amino acid sequence comprising SEQ ID NO: 5 and the VH comprises an amino acid sequence comprising SEQ ID NO: 6;

d) the VL comprises an amino acid sequence comprising SEQ ID NO: 9 and the VH comprises an amino acid sequence comprising SEQ ID NO: 10;

e) the VL comprises an amino acid sequence comprising SEQ ID NO: 13 and the VH comprises an amino acid sequence comprising SEQ ID NO: 14;

f) the VL comprises an amino acid sequence comprising SEQ ID NO: 17 and the VH comprises an amino acid sequence comprising SEQ ID NO: 18;

g) the VL comprises an amino acid sequence comprising SEQ ID NO: 21 and the VH comprises an amino acid sequence comprising SEQ ID NO: 22;

h) the VL comprises an amino acid sequence comprising SEQ ID NO: 25 and the VH comprises an amino acid sequence comprising SEQ ID NO: 26;

i) the VL comprises an amino acid sequence comprising SEQ ID NO: 29 and the VH comprises an amino acid sequence comprising SEQ ID NO: 30;

j) the VL comprises an amino acid sequence comprising SEQ ID NO: 37 and the VH comprises an amino acid sequence comprising SEQ ID NO: 38;

k) the VL comprises an amino acid sequence comprising SEQ ID NO: 41 and the VH comprises an amino acid sequence comprising SEQ ID NO: 42;

l) the VL comprises an amino acid sequence comprising SEQ ID NO: 45 and the VH comprises an amino acid sequence comprising SEQ ID NO: 46;

m) the VL comprises an amino acid sequence comprising SEQ ID NO: 49 and the VH comprises an amino acid sequence comprising SEQ ID NO: 50; or

n) the VL comprises an amino acid sequence comprising SEQ ID NO: 53 and the VH comprises an amino acid sequence comprising SEQ ID NO: 54.

5. The antigen binding protein according to any one of claims 1-4, wherein the heavy chain comprises an amino acid substitution selected from the group consisting of:

(i) N297G or N297A;

(ii) L234A and L235A; and

(iii) R292C and V302C;

wherein the amino acid numbering is EU numbering according to Kabat.

6. The antigen binding protein according to claim 5, wherein the heavy chain comprises N297G, R292C, and V302C mutations, wherein the amino acid numbering is EU numbering according to Kabat.

7. The antigen binding protein according to any one of claims 1-6, wherein the antigen binding protein further comprises a light chain CL polypeptide linked to the VL, wherein the CL polypeptide is selected from the group consisting of SEQ ID NO: 883 and SEQ ID NO: 884.

8. The antigen binding protein according to any one of claims 1-7, wherein the antigen binding protein further comprises a heavy chain CH1-hinge-CH2-CH3 polypeptide wherein the CH1-hinge-CH2-CH3 polypeptide is selected from the group consisting of SEQ ID NO: 885 and SEQ ID NO: 886.

9. An antigen binding protein that specifically binds human CD40 (SEQ ID NO: 1), the antigen binding protein comprising a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

- (i) the VL comprises a CDRL1, a CDRL2, and a CDRL3 comprising the amino acid sequences of: SEQ ID NOs: 100, 101, and amino acids 91 to 101 of SEQ ID NO: 370, respectively; or
SEQ ID NOs: 100, 101, and 102, respectively;
and
- (ii) the VH comprises a CDRH1, a CDRH2, and a CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 178, 179, and 180, respectively.

10. The antigen binding protein of claim 9, wherein:

- a) the VL comprises an amino acid sequence comprising amino acids 1 to 112 of SEQ ID NO: 370 and the VH comprises an amino acid sequence comprising SEQ ID NO: 34; or
- b) the VL comprises an amino acid sequence comprising SEQ ID NO: 33 and the VH comprises an amino acid sequence comprising SEQ ID NO: 34.

11. The antigen binding protein according to any one of claims 1 to 10, wherein the antigen binding protein further comprises a second antigen binding portion that specifically binds a second antigen.

12. The antigen binding protein according to claim 11, wherein the second antigen is a tumor associated antigen (TAA).

13. The antigen binding protein according to any one of claims 1 to 12, wherein said VH comprises a human framework (FR) sequence, and said VL comprises a human framework (FR) sequence.

14. The antigen binding protein according to any one of claims 1 to 13, wherein said antigen binding protein comprises a human constant domain.

15. The antigen binding protein according to claim 14, wherein said antigen binding protein comprises:

- (a) a human light chain constant domain (CL); optionally wherein said CL is kappa CL or lambda CL; and/or
- (b) a human heavy chain constant domain CH1; optionally wherein said CH1 is an IgG CH1 or an IgG1 CH1.

16. The antigen binding protein according to any one of claims 1 to 15, wherein said antigen binding protein comprises a human heavy chain Fc domain; optionally wherein said Fc is an IgG1 Fc.