NO: 236, SEQ ID NO: 265, SEQ ID NO: 270, SEQ ID NO: 275, SEQ ID NO: 306, SEQ ID NO: 296, SEQ ID NO: 241, SEQ ID NO: 314, and SEQ ID NO: 223; wherein the antibody or antigen-binding fragment thereof binds to CLEC2D.

[012] The disclosure provides isolated antibodies or antigen-binding fragments thereof comprising a heavy chain and a light chain, wherein the heavy chain comprises a sequence selected from any one of SEQ ID NOs: 1-108.

[013] The disclosure provides isolated antibodies or antigen-binding fragments thereof comprising a heavy chain and a light chain, wherein the light chain comprises a sequence selected from any one of SEQ ID NOs: 217-324.

[014] The disclosure provides isolated antibodies or antigen-binding fragments thereof comprising a heavy chain and a light chain, wherein the heavy chain comprises a sequence selected from any one of SEQ ID NOs: 1-108, and the light chain comprises a sequence selected from any one of SEQ ID NOs: 217-324.

[015] The disclosure provides isolated antibodies or antigen-binding fragments thereof comprising a heavy chain and a light chain, wherein the heavy chain comprises: (i) a heavy chain (HC) CDR1 comprising a sequence selected from SEQ ID NOs: 433-485; (ii) an HC CDR2 comprising a sequence selected from SEQ ID NOs: 486-546; and (iii) an HC CDR3 comprising a sequence selected from SEQ ID NOs: 547-653, wherein the antibody or antigen-binding fragment thereof binds to CLEC2D.

[016] The disclosure provides isolated antibodies or antigen-binding fragments thereof comprising a heavy chain and a light chain, wherein the light chain comprises: (i) a light chain (LC) CDR1 comprising a sequence selected from SEQ ID NOs: 654-726; (ii) an LC CDR2 comprising a sequence selected from SEQ ID NOs: 727-783; and (iii) an LC CDR3 comprising a sequence selected from SEQ ID NOs: 784-885; wherein the antibody or antigen-binding fragment thereof binds to CLEC2D.

[017] The disclosure provides isolated antibodies or antigen-binding fragments thereof, comprising: a heavy chain comprising an HC CDR1 sequence selected from SEQ ID NOs: 433-485, an HC CDR2 sequence selected from SEQ ID NOs: 486-546, and an HC CDR3 sequence selected from SEQ ID NOs: 547-653; a light chain comprising a LC CDR1 sequence selected from SEQ ID NOs: 654-726, a LC CDR2 sequence selected from SEQ ID NOs: 727-783, and a LC CDR3 sequence selected from SEQ ID NOs: 784-885; or a combination thereof.

[017a] In one aspect, the present disclosure refers to an isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein:

a) the VH comprises complementarity determining regions (CDR) HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 1, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:217;

b) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 45, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:261;

c) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 44, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:260;

d) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 58, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:274;

e) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 7, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:223;

f) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 42, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:258;

g) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 73, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:289;

h) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 21, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:237;

i) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 35, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:251;

j) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 75, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:291;

k) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 77, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:293;

l) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 56, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:272;

m) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 64, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:280;

n) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 50, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:266;

o) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 43, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:259;

p) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 80, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:296;

q) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 33, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:249;

r) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 23, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:239;

s) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 24, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:240;

t) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 59, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:275;

u) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 74, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:290;

v) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 25, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:241;

w) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 61, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:277;

x) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 60, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:276;

y) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 28, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:244;

z) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 4, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:220;

aa) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 6, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:222;

bb) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 46, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:262;

cc) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 63, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:279;

dd) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 57, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:273;

ee) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 47, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:263;

ff) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 83, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:299;

gg) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 87, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:245;

hh) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 81, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:297;

ii) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 76, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:292;

jj) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 36, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:252;

kk) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 52, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:268;

ll) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 71, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:287;

mm) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 72, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:288; or

nn) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 62, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:278.

[018] In some examples of the antibodies or antigen binding fragments thereof of the disclosure, the antibody or antigen-binding fragment thereof binds to: a human CLEC2D polypeptide comprising a sequence selected from SEQ ID NOs: 886-909; a human CLEC2D polypeptide comprising a sequence selected from SEQ ID NOs: 930-1003; a cynomolgus CLEC2D polypeptide comprising a sequence selected from SEQ ID NOs: 918-920; a mouse CLEC2D polypeptide comprising a sequence selected from SEQ ID NOs: 911-915; a rat CLEC2D polypeptide comprising a sequence of SEQ ID NO: 910; and/or a dog CLEC2D polypeptide comprising a sequence selected from SEQ ID NOs: 916-917.

[019] The disclosure provides an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain complementarity determining region (CDRH) 1, CDRH2 and CDRH3 amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, as disclosed in Table 9A, and wherein the light chain comprises a light chain complementarity determining region (CDRL)1, CDRL2 and CDRL3 amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, as disclosed in Table 9A.

[020] The disclosure provides an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain and a light chain, wherein the heavy chain comprises a variable heavy chain amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, as disclosed in Table 9A, and wherein the light chain comprises a variable light chain amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, as disclosed in Table 9A.

[020a] In one aspect, the present disclosure refers to an isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the antibody or antigen-binding fragment thereof comprises:

a) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 433, 486, and 547, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 654, 727, and 784, respectively;
b) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 590, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 688, 755, and 828, respectively;
c) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 589, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 687, 729, and 827, respectively;
d) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 466, 521, and 603, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 662, 732, and 814, respectively; or
e) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 553, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 660, 733, and 790, respectively;
f) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 473, 495, and 587, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 655, 732, 825, respectively;
g) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 618, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:678, 730, and 852, respectively;
h) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID Nos:446, 501, and 567, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 804, respectively;
i) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID Nos:435, 488, and 581, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:680, 782, and 818, respectively;
j) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:453, 507, and 620, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:700, 760, and 854, respectively;
k) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 622, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:706, 769, and 856, respectively;
l) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:433, 486, and 601, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 754, and 838, respectively;
m) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:469, 525, and 609, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 844, respectively;
n) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:456, 512, and 595, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:692, 759, and 833, respectively;
o) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:473, 495, and 588, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:686, 754, and 826, respectively;
p) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 506, and 625, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:708, 771, and 859, respectively;
q) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:454, 510, and 579, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 816, respectively;
r) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 569, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:670, 744, and 806, respectively;

s) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:448, 504, and 570, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 807, respectively;
t) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 604, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:696, 742, and 840, respectively;
u) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:474, 530, and 619, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:705, 743, and 853, respectively;
v) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:449, 505, and 571, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:671, 745, and 808, respectively;
w) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 529, and 606, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:698, 764, and 842, respectively;
x) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:467, 522, and 605, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:697, 763, and 841, respectively;
y) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:451, 507, and 574, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:674, 747, and 811, respectively;
z) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:436, 489, and 550, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:657, 730, and 787, respectively;
aa) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:438, 491, and 552, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:659, 732, and 789, respectively;
bb) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 591, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:689, 756, and 829, respectively;
cc) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:468, 524, and 608, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 843, respectively;
dd) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 602, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:695, 762, and 839, respectively;
ee) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:462, 517, and 592, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 830, respectively;
ff) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:433, 486, and 628, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 862, respectively;
gg) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:434, 508, and 575, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:675, 748, and 812, respectively;
hh) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:475, 532, and 626, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 729, and 860, respectively;
ii) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:453, 531, and 621, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 732, and 855, respectively;
jj) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:456, 512, and 582, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:681, 751, and 819, respectively;

kk) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:450, 506, and 597, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:667, 734, and 835, respectively;

ll) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 529, and 616, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:703, 767, and 850, respectively;

mm) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:473, 495, and 617, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:704, 768, and 851, respectively; or

nn) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:450, 523, and 607, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 732, and 834, respectively.

[020b] In one aspect, the present disclosure refers to an isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH and VL comprise:

a) SEQ ID NOs: 1 and 217, respectively;

b) SEQ ID NOs: 45 and 261, respectively;

c) SEQ ID NOs: 44 and 260, respectively;

d) SEQ ID NOs: 58 and 274, respectively;

e) SEQ ID NOs: 7 and 223, respectively;

f) SEQ ID NOs: 42 and 258, respectively;

h) SEQ ID NOs: 73 and 289, respectively;

i) SEQ ID NOs: 21 and 237, respectively;

j) SEQ ID NOs: 35 and 251, respectively;

j) SEQ ID NOs: 75 and 291, respectively;

k) SEQ ID NOs: 77 and 293, respectively;

l) SEQ ID NOs: 56 and 272, respectively;

m) SEQ ID NOs: 64 and 280, respectively;

n) SEQ ID NOs: 50 and 266, respectively;

o) SEQ ID NOs: 43 and 259, respectively;

p) SEQ ID NOs: 80 and 296, respectively;

q) SEQ ID NOs: 33 and 249, respectively;

r) SEQ ID NOs: 23 and 239, respectively;

s) SEQ ID NOs: 24 and 240, respectively;

t) SEQ ID NOs: 59 and 275, respectively;

u) SEQ ID NOs: 74 and 290, respectively;

v) SEQ ID NOs: 25 and 241, respectively;

w) SEQ ID NOs: 61 and 277, respectively;

x) SEQ ID NOs: 60 and 276, respectively;

y) SEQ ID NOs: 28 and 244, respectively;

z) SEQ ID NOs: 4 and 220, respectively;

aa) SEQ ID NOs: 6 and 222, respectively;

bb) SEQ ID NOs: 46 and 262, respectively;

cc) SEQ ID NOs: 63 and 279, respectively;

dd) SEQ ID NOs: 57 and 273, respectively;

ee) SEQ ID NOs: 47 and 263, respectively;

ff) SEQ ID NOs: 83 and 299, respectively;

gg) SEQ ID NOs: 87 and 245, respectively;

hh) SEQ ID NOs: 81 and 297, respectively;

ii) SEQ ID NOs: 76 and 292, respectively;

jj) SEQ ID NOs: 36 and 252, respectively;

kk) SEQ ID NOs: 52 and 268, respectively;

ll) SEQ ID NOs: 71 and 287, respectively;

mm) SEQ ID NOs: 72 and 288, respectively; or

nn) SEQ ID NOs: 62 and 278, respectively.

[020c] In one aspect, the present disclosure refers to an isolated anti-CLEC2D antibody comprising a heavy chain and a light chain, wherein:

a) the heavy chain comprises SEQ ID NO: 1481, 1913, 2129, or 2345, and the light chain comprises SEQ ID NO:1589;

b) the heavy chain comprises SEQ ID NO:1525, 1957, 2713, or 2389, and the light chain comprises SEQ ID NO:1633;

c) the heavy chain comprises SEQ ID NO: 1524, 1956, 2172, or 2388, and the light chain comprises SEQ ID NO:1632;

d) the heavy chain comprises SEQ ID NO: 1538, 1970, 2186, or 2402, and the light chain comprises SEQ ID NO:1646;

e) the heavy chain comprises SEQ ID NO: 1487, 1919, 2135, or 2351, and the light chain comprises SEQ ID NO:1595;

f) the heavy chain comprises SEQ ID NO: 1552, 1954, 2170, or 2386, and the light chain comprises SEQ ID NO:1630;

g) the heavy chain comprises SEQ ID NO: 1553, 1985, 2201, or 2417, and the light chain comprises SEQ ID NO:1661;

h) the heavy chain comprises SEQ ID NO: 1501, 1933, 2149, or 2365, and the light chain comprises SEQ ID NO:1609; or

i) the heavy chain comprises SEQ ID NO: 1515, 1947, 2163, or 2379, and the light chain comprises SEQ ID NO:1623.

[021] The disclosure provides an isolated antibody or antigen-binding fragment thereof, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain frame work region sequence of a Germline family of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9B, as disclosed herein, and wherein the light chain comprises a frame work region sequence of a light chain Germline family of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9B, as disclosed herein.

[022] In some examples of the antibodies or antigen binding fragments thereof of the disclosure, the antibody or antigen-binding fragment thereof is a monoclonal antibody.

[023] In some examples of the antibodies or antigen binding fragments thereof of the disclosure, the antibody or antigen-binding fragment thereof blocks binding of CLEC2D to a receptor. In some examples, the receptor comprises a CD161 receptor, and the CD161 receptor comprises a sequence selected from SEQ ID NOs: 921-929.

[024] In some examples of the antibodies or antigen binding fragments thereof of the disclosure, the antibody or antigen-binding fragment thereof is human, murine or chimeric. In some examples, the antigen-binding fragment is selected from the group consisting of Fv, Fav, F(ab')2, Fab', dsFv, scFv, sc(Fv)2, scFv-CH3, scFv-Fc, and diabody fragments. In some examples, the antibody or antigen-binding fragment thereof binds to human CLEC2D with an affinity (KD) of less than 100 nM.

[025] The disclosure provides pharmaceutical compositions comprising peptides (e.g., antibodies or antigen-binding fragments thereof) or nucleic acids described in the disclosure.

[026] The disclosure provides pharmaceutical compositions comprising antibodies or antigen-binding fragments thereof of the disclosure. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof as disclosed herein and a pharmaceutically acceptable excipient.

[027] The disclosure provides pharmaceutical compositions comprising nucleic acids encoding the antibodies or antigen-binding fragments thereof of the disclosure.

[028] In some examples of the pharmaceutical compositions of the disclosure, the pharamaceutical composition further comprises at least one of a buffer, a pharmaceutically acceptable diluent, a carrier, a solubilizer, an emulsifier, and a preservative.

[029] The disclosure provides isolated nucleic acids comprising a polynucleotide sequence that encodes an amino acid heavy chain sequence selected from SEQ ID NOs: 109-216.

[030] The disclosure provides isolated nucleic acids comprising a polynucleotide sequence that encodes an amino acid light chain sequence selected from SEQ ID NOs: 325-432.

[030a] In one aspect, the present disclosure refers to an isolated nucleic acid comprising a polynucleotide sequence that encodes the isolated antibody or antigen-binding fragment thereof as disclosed herein.

[031] The disclosure provides an isolated nucleic acid, comprising a polynucleotide sequence that encodes a heavy chain comprising a CDRH1, CDRH2 and CDRH3 amino acid sequence according to the CDRH1, CDRH2 and CDRH3 amino acid sequence respectively, of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9A, as disclosed herein.

[032] The disclosure provides an isolated nucleic acid, comprising a polynucleotide sequence that encodes a light chain comprising a CDRL1, CDRL2 and CDRL3 amino acid sequence according to the CDRL1, CDRL2 and CDRL3 amino acid sequence respectively, of an anti-

CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9A, as disclosed herein.

[033] The disclosure provides an isolated nucleic acid, comprising a polynucleotide sequence that encodes a heavy chain amino acid sequence according to variable heavy chain amino acid sequence of an anti-CLEC2D antibody antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9A, as disclosed herein.

[034] The disclosure provides an isolated nucleic acid, comprising a polynucleotide sequence that encodes a light chain amino acid sequence according to variable light chain amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9A, as disclosed herein.

[035] The disclosure provides an isolated nucleic acid, comprising a polynucleotide sequence that encodes a heavy chain comprising a framework region amino acid sequence according to heavy chain framework region amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9B, as disclosed herein.

[036] The disclosure provides an isolated nucleic acid comprising a polynucleotide sequence that encodes a light chain comprising a framework region amino acid sequence according to light chain framework region amino acid sequence of an anti-CLEC2D antibody selected from the group consisting of: A1, B1, E1, P1, U1, Y1, E2, I2 and L2, of Table 9B, as disclosed herein.

[037] The disclosure provides isolated nucleic acids comprising a polynucleotide sequence that encodes a heavy chain amino acid sequence of an antibody or antigen binding fragment thereof of the disclosure.

[038] The disclosure provides isolated nucleic acids comprising a polynucleotide sequence that encodes a light chain amino acid sequence of an antibody or antigen binding fragment thereof of the disclosure.

[039] The disclosure provides compositions comprising a first nucleic acid that encodes a polypeptide selected from SEQ ID NOs: 109-216 and a second nucleic acid that encodes a polypeptide selected from SEQ ID NOs: 325-432.

[040] The disclosure provides vectors comprising the nucleic acids of the disclosure. In one aspect, the present disclosure refers to an expression vector comprising the isolated nucleic acid as disclosed herein.

[041] The disclosure provides cells comprising the nucleic acids, nucleic acid compositions or vectors of the disclosure. In some examples, the cell is a eukaryotic cell. In one aspect, the present disclosure refers to a host cell comprising the isolated nucleic acid as disclosed herein or the expression vector as disclosed herein, wherein the cell is a eukaryotic cell. In some examples, the eukaryotic cell is a mammalian cell. In some examples, the mammalian

cell is selected from the group consisting of a CHO cell, a 293 cell, an NSO cell, a PER.C6 cell, and a B cell. In some examples, the mammalian cell is a 293-6E cell or a DG44 cell. In some examples, the cells express the antibodies or antigen binding fragments thereof of the disclosure. In some examples, the cell is a germline cell.

[042] The disclosure provides cells producing the antibodies or antigen-binding fragments thereof of the disclosure

[043] The disclosure provides a method of treating a disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibodies or antigen-binding fragments thereof of the disclosure.

[044] The disclosure provides a composition for use in treating a disease in a subject in need thereof, comprising a therapeutically effective amount of the antibodies or antigen-binding fragments thereof of the disclosure or the nucleic acids encoding the antibodies or antigen-binding fragments thereof of the disclosure.

[044a] In one aspect, the present disclosure refers to use of the isolated antibody or antigen-binding fragment thereof as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a cancer, modulating the activation of an immune response, increasing the cytotoxicity of a natural killer cell, or eliciting anti-tumour response in a subject in need thereof.

[045] The disclosure provides a composition for use in the manufacture of a medicament for the prevention or treatment of a disease in a subject in need thereof, comprising a therapeutically effective amount of the antibodies or antigen-binding fragments thereof of the disclosure or the nucleic acids encoding the antibodies or antigen-binding fragments thereof of the disclosure.

[046] In some examples of the methods or compositions for use of the disclosure, the disease is rheumatoid arthritis. In some examples, the subject exhibits bone loss as a result of having rheumatoid arthritis. In some examples, administration of a therapeutically effective amount of the antibody or antigen-binding fragment thereof slows or reverses the bone loss in the subject.

[047] In some examples of the methods or compositions for use of the disclosure, the disease is a cancer. In some examples, the cancer is selected from the group consisting of breast cancer, prostate cancer, endometrial cancer, uterine cancer, bladder cancer, kidney cancer, esophageal cancer, squamous cell carcinoma, uveal melanoma, glioma, glioblastoma, myeloma, pheochromocytoma, paraganglioma, follicular lymphoma, renal cell carcinoma, cendcal cancer, ovarian cancer, cervical cancer, lung cancer, colorectal cancer, brain cancer, pancreatic cancer, gastric cancer, intestinal cancer, testicular cancer, skin cancer, thyroid cancer, thymoma, head and neck cancer, liver cancer, pharynx cancer, adrenocortical cancer, cholangiocarcinoma, mesothelioma, sarcoma, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, melanoma,

astrocytoma, stomach cancer, and pulmonary adenocarcinoma. In some examples, a cell of the cancer expresses CLEC2D on the cell surface. In some examples, administration of a therapeutically effective amount of the antibodies or antigen-binding fragments thereof results in an anti-tumor response in the subject.

[048] In some examples of the methods or compositions for use of the disclosure, the antibodies or antigen-binding fragments thereof are administered as a monotherapy. In some examples, the antibodies or antigen-binding fragments thereof are administered in combination with at least one of a T cell targeted immunomodulatory agent, a second immunomodulatory agent, a cancer vaccine, an adoptive cell therapy, an oncolytic virus, a second antibody therapy, a radiotherapy, an antibody drug conjugate, a small interfering RNA, a chemotherapy, an immunotherapy, an immune checkpoint inhibitor, a mitotic inhibitor, or a combination thereof. In some examples, the adoptive cell therapy comprises a CAR-T therapy. In some examples, administration of a therapeutically effective amount of the antibody or antigen-binding fragment thereof alleviates a sign or a symptom of the disease.

[049] In one example, the present disclosure refers to an antibody library comprising at least about 108 unique monoclonal antibody clones, wherein at least about 80% of the antibody clones detectably and specifically bind a CLEC2D antigen. In one aspect, the present disclosure refers to an antibody library comprising at least about 108 unique monoclonal antibody clones, wherein the antibody library comprises an isolated antibody or antigen-binding fragment thereof as disclosed herein, and wherein at least about 80% of the antibody clones detectably and specifically bind a CLEC2D antigen.

[050] In some examples of the antibody library of the disclosure, the CLEC2D antigen comprises an amino acid sequence selected from SEQ ID NOs: 886-920 and SEQ ID NOs: 930-1003. In some examples of the antibody library of the disclosure, the CLEC2D antigen comprises an amino acid sequence selected from SEQ ID NOs: 886-909 and SEQ ID NOs: 930-1003. In some examples, the CLEC2D antigen comprises a CLEC2D antigen expressed on a tumor cell surface, a variant of the CLEC2D antigen, or a homolog of the CLEC2D antigen. In some examples, the variant of the CLEC2D antigen comprises a fragment of the CLEC2D protein. In some examples, the homolog of the CLEC2D antigen comprises a human, a mouse, a dog, a rat or a cynomolgus CLEC2D.

[051] The disclosure provides a method of modulating immunity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibodies or antigen-binding fragments of the disclosure or the nucleic acids encoding the antibodies or antigen-binding fragments thereof of the disclosure.

yeast cells expressing antibody genes that bind to the CLEC2D antigen with flow cytometry. In some examples, the method further comprises repeating the flow cytometry isolation at least 1x, at least 2x, at least 3x, at least 4x or at least 5x. In some examples, the method further comprises cloning the antibody genes that bind to CLEC2D into a mammalian expression vector.

[056a] In one aspect, the present disclosure refers to a method of screening a high diversity antibody gene library for antibodies that bind to a CLEC2D antigen, comprising: a) inserting a library of antibody genes into a phage protein gene and transforming a plurality of phages to produce a phage library, wherein the phages in the phage library display the library of antibody genes on the surface of the phages; b) panning the phage library with a CLEC2D antigen for individual phages that bind to the CLEC2D antigen, thereby producing an enriched phage library that is enriched for antibody genes that encode antibodies that bind to the CLEC2D antigen; c) repeating step (b) at least once or at least twice; d) transferring the antibody genes from the enriched phage library to a yeast surface display library; e) isolating individual yeast cells that bind to the CLEC2D antigen from the yeast surface display library; f) culturing the isolated individual yeast cells that bind to the CLEC2D antigen to produce yeast surface display library clones; and g) sequencing the yeast surface display library clones; thereby isolating antibody genes that bind to the CLEC2D antigen, wherein the antibody genes comprise the amino acid sequence of an isolated antibody or antigen-binding fragment thereof as disclosed herein.

[057] The disclosure provides methods of making a composition comprising anti-CLEC2D antibodies or antigen binding fragments thereof, comprising (a) transforming mammalian cells with a vector comprising a sequence encoding a promoter and a sequence encoding an anti-CLEC2D antibody or antibody fragment, wherein the sequence encoding the promoter and the anti-CLEC2D antibody or antibody fragment are operably linked; (b) culturing the mammalian cells under conditions suitable for the expression of the anti-CLEC2D antibody or antibody fragment; (c) centrifuging the cultured mammalian cells to produce a supernatant; (d) filtering the supernatant; and (e) purifiying the filtered supernatant using liquid chromatography.

[057a] In one aspect, the present disclosure refers to a method of making a composition comprising an anti-CLEC2D antibody or antigen-binding fragment thereof, comprising a) transforming mammalian cells with a vector comprising a sequence encoding a promoter and a sequence encoding an anti-CLEC2D antibody or antigen-binding fragment thereof, wherein the sequence encoding the promoter and the anti-CLEC2D antibody or antigen-binding fragment thereof are operably linked; b) culturing the mammalian cells under conditions suitable for the expression of the anti-CLEC2D antibody or antigen-binding fragment thereof; and c) obtaining the anti-CLEC2D antibody or antigen-binding fragment thereof from the cultured mammalian cells to produce a supernatant, wherein the anti-CLEC2D antibody or antigen-binding fragment thereof comprises the isolated antibody or antigen-binding fragment thereof as disclosed herein.

[058] In some examples of the methods of the disclosure, the filration step (d) comprises a 3 µm - 30 µm filter. In some examples, the filtration step (d) further comprises a 0.22 µm filter. In some examples, the purifying step (e) comprises a Protein A column. In some examples, the protein A column is treated with a high salt wash buffer to remove host cell proteins. In some examples, the ani-CLEC2D antibody of fragment thereof is eluted using 30 mM Phosphate buffer at pH.3.0-4.0. In some examples, the purifying step (e) further comprises an anion exchange chromatography (AEX) step. In some examples, the AEX step comprises a Q Sepharose column. In some examples, the Q Sepharose is pre-equilibrated in a pre-equilibration buffer comprising 10-100 mM Histidine. In some examples, the pre-equilibration buffer further comprises citrate, phosphate 2-(N-morpholino)ethanesulfonic acid (MES), acetate or a combination thereof. In some examples, the pre-equilibration buffer comprises a pH of 4.5-6.5. In some examples, the anti-CLEC2D antibody is eluted at step (e) with an elution buffer comprising 200-1000 mM NaCl, KCl or a combination thereof. In some examples, the elution buffer comprises a pH of 4.5-6.5.

[059] In one example, this disclosure relates to the isolation of novel monoclonal antibodies that bind specifically to a CLEC2D antigen. The novel antibodies modulate (e.g., inhibit) the interaction of CD161 and CLEC2D to modify NK cell/immune cell mediated cytotoxicity and/or cytokine production.

[060] In another example, this disclosure relates to cancer cells expressing CLEC2D are specifically recognized by these novel antibodies which may kill the tumor cells via ADCC (antibody dependent cellular cytotoxicity) and/or CDC (complement dependent cytotoxicity) and/or ADCP (antibody dependent cellular phagocytosis).

[061] In a related example, this disclosure relates to methods of making an anti-CLEC2D antibody, comprising selecting from a high diversity antibody gene library an anti-CLEC2D antibody. In one example, the high diversity antibody gene library is displayed through phage and/or yeast surface display. In one example, the phage- and/or yeast-displayed high diversity antibody gene library is selected using purified CLEC2D antigen as a target. In one example, the selected anti-CLEC2D antibody genes are expressed in a mammalian cell (e.g., Chinese hamster ovary (CHO) cell). In one example, a single cell clone expressing an anti-CLEC2D antibody is expanded into a cell line and verified for anti-CLEC2D antibody expression. In one example, overexpression of selected antibody clones is achieved through defined culture media, supplements, and specific bioreactor processes cumulatively described herein as upstream process development. In one example, the anti-CLEC2D antibodies expressed from the cell line are purified to homogeneity, for example, through various filtration and chromatography, referred to herein as downstream purification processes.

[062] The disclosure provides a method of treating a disease in a subject in need thereof, comprising: determining a level of CLEC2D protein in the subject; and administering a therapeutically effective amount of an anti-CLEC2D antibody to the subject. In one aspect, the present disclosure refers to use of the isolated antibody or antigen-binding fragment thereof as disclosed herein or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject in need thereof has an aberrant or differential cellular expression of CLEC2D.

[063] In some examples of the methods of the disclosure, the disease is a cancer. In some examples, the cancer comprises breast cancer, prostate cancer, endometrial cancer, uterine cancer, bladder cancer, kidney cancer, esophageal cancer, squamous cell carcinoma, uveal melanoma, glioma, glioblastoma, myeloma, pheochromocytoma, paraganglioma, follicular lymphoma, renal cell carcinoma, cendcal cancer, ovarian cancer, cervical cancer, lung cancer, colorectal cancer, brain cancer, pancreatic cancer, gastric cancer, intestinal cancer, testicular cancer, skin cancer, thyroid cancer, thymoma, head and neck cancer, liver cancer, pharynx cancer, adrenocortical cancer, cholangiocarcinoma, mesothelioma, sarcoma, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, melanoma, astrocytoma, stomach cancer, pulmonary adenocarcinoma, adenocarcinoma, acinic cell adenocarcinoma, adrenal cortical carcinomas, alveoli cell carcinoma, anaplastic carcinoma, basaloid carcinoma, basal cell

CLAIMS

1. An isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein:

a) the VH comprises complementarity determining regions (CDR) HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 1, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:217;

b) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 45, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:261;

c) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 44, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:260;

d) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 58, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:274;

e) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 7, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:223;

f) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 42, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:258;

g) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 73, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:289;

h) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 21, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:237;

i) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 35, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:251;

j) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 75, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:291;

k) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 77, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:293;

l) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 56, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:272;

m) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 64, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:280;

n) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 50, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:266;

o) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 43, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:259;

p) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 80, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:296;

q) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 33, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:249;

r) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 23, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:239;

s) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 24, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:240;

t) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 59, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:275;

u) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 74, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:290;

v) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 25, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:241;

w) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 61, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:277;

x) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 60, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:276;

y) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 28, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:244;

z) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 4, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:220;

aa) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 6, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:222;

bb) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 46, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:262;

cc) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 63, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:279;

dd) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 57, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:273;

ee) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 47, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:263;

ff) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 83, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:299;

gg) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 87, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:245;

hh) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 81, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:297;

ii) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 76, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:292;

jj) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 36, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:252;

kk) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 52, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:268;

ll) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 71, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:287;

mm) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 72, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:288; or

nn) the VH comprises HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 62, and the VL comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NO:278.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a) a VH comprising HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 1, and a VL comprising LCDR1, LCDR2, and LCDR3 of SEQ ID NO:217;

b) a VH comprising HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 45, and a VL comprising LCDR1, LCDR2, and LCDR3 of SEQ ID NO:261;

c) a VH comprising HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 44, and a VL comprising LCDR1, LCDR2, and LCDR3 of SEQ ID NO:260;

d) a VH comprising HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 58, and the VL comprising LCDR1, LCDR2, and LCDR3 of SEQ ID NO:274; or

e) a VH comprising HCDR1, HCDR2, and HCDR3 of SEQ ID NO: 7, and a VL comprising LCDR1, LCDR2, and LCDR3 of SEQ ID NO:223.

3. An isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL),
wherein the antibody or antigen-binding fragment thereof comprises:

a) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 433, 486, and 547, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 654, 727, and 784, respectively;

b) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 590, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 688, 755, and 828, respectively;

c) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 589, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 687, 729, and 827, respectively;

d) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 466, 521, and 603, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 662, 732, and 814, respectively; or

e) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 439, 492, and 553, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 660, 733, and 790, respectively;

f) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 473, 495, and 587, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs: 655, 732, 825, respectively;

g) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 618, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:678, 730, and 852, respectively;

h) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID Nos:446, 501, and 567, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 804, respectively;

i) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID Nos:435, 488, and 581, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:680, 782, and 818, respectively;

j) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:453, 507, and 620, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:700, 760, and 854, respectively;

k) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 622, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:706, 769, and 856, respectively;

l) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:433, 486, and 601, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 754, and 838, respectively;

m) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:469, 525, and 609, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 844, respectively;

n) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:456, 512, and 595, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:692, 759, and 833, respectively;

o) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:473, 495, and 588, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:686, 754, and 826, respectively;

p) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 506, and 625, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:708, 771, and 859, respectively;

q) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:454, 510, and 579, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 816, respectively;

r) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:439, 492, and 569, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:670, 744, and 806, respectively;

s) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:448, 504, and 570, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 807, respectively;

t) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 604, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:696, 742, and 840, respectively;

u) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:474, 530, and 619, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:705, 743, and 853, respectively;

v) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:449, 505, and 571, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:671, 745, and 808, respectively;

w) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 529, and 606, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:698, 764, and 842, respectively;

x) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:467, 522, and 605, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:697, 763, and 841, respectively;

y) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:451, 507, and 574, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:674, 747, and 811, respectively;

z) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:436, 489, and 550, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:657, 730, and 787, respectively;

aa) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:438, 491, and 552, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:659, 732, and 789, respectively;

bb) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 591, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:689, 756, and 829, respectively;

cc) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:468, 524, and 608, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 735, and 843, respectively;

dd) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:461, 516, and 602, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:695, 762, and 839, respectively;

ee) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:462, 517, and 592, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 830, respectively;

ff) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:433, 486, and 628, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:656, 729, and 862, respectively;

gg) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:434, 508, and 575, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:675, 748, and 812, respectively;

hh) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:475, 532, and 626, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:655, 729, and 860, respectively;

ii) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:453, 531, and 621, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 732, and 855, respectively;

jj) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:456, 512, and 582, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:681, 751, and 819, respectively;

kk) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:450, 506, and 597, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:667, 734, and 835, respectively;

ll) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:437, 529, and 616, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:703, 767, and 850, respectively;

mm) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:473, 495, and 617, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:704, 768, and 851, respectively; or

nn) a VH comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:450, 523, and 607, respectively, and a VL comprising CDR1, CDR2, and CDR3 of SEQ ID NOs:662, 732, and 834, respectively.

4. An isolated anti-CLEC2D antibody or antigen-binding fragment thereof comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH and VL comprise:

a) SEQ ID NOs: 1 and 217, respectively;

b) SEQ ID NOs: 45 and 261, respectively;

c) SEQ ID NOs: 44 and 260, respectively;

d) SEQ ID NOs: 58 and 274, respectively;

e) SEQ ID NOs: 7 and 223, respectively;

f) SEQ ID NOs: 42 and 258, respectively;

h) SEQ ID NOs: 73 and 289, respectively;

i) SEQ ID NOs: 21 and 237, respectively;

j) SEQ ID NOs: 35 and 251, respectively;

j) SEQ ID NOs: 75 and 291, respectively;

k) SEQ ID NOs: 77 and 293, respectively;

l) SEQ ID NOs: 56 and 272, respectively;

m) SEQ ID NOs: 64 and 280, respectively;

n) SEQ ID NOs: 50 and 266, respectively;

o) SEQ ID NOs: 43 and 259, respectively;

p) SEQ ID NOs: 80 and 296, respectively;

q) SEQ ID NOs: 33 and 249, respectively;

r) SEQ ID NOs: 23 and 239, respectively;

s) SEQ ID NOs: 24 and 240, respectively;

t) SEQ ID NOs: 59 and 275, respectively;

u) SEQ ID NOs: 74 and 290, respectively;

v) SEQ ID NOs: 25 and 241, respectively;

w) SEQ ID NOs: 61 and 277, respectively;

x) SEQ ID NOs: 60 and 276, respectively;

y) SEQ ID NOs: 28 and 244, respectively;

z) SEQ ID NOs: 4 and 220, respectively;

aa) SEQ ID NOs: 6 and 222, respectively;

bb) SEQ ID NOs: 46 and 262, respectively;

cc) SEQ ID NOs: 63 and 279, respectively;

dd) SEQ ID NOs: 57 and 273, respectively;

ee) SEQ ID NOs: 47 and 263, respectively;

ff) SEQ ID NOs: 83 and 299, respectively;

gg) SEQ ID NOs: 87 and 245, respectively;

hh) SEQ ID NOs: 81 and 297, respectively;

ii) SEQ ID NOs: 76 and 292, respectively;

jj) SEQ ID NOs: 36 and 252, respectively;

kk) SEQ ID NOs: 52 and 268, respectively;

ll) SEQ ID NOs: 71 and 287, respectively;

mm) SEQ ID NOs: 72 and 288, respectively; or

nn) SEQ ID NOs: 62 and 278, respectively.

5. An isolated anti-CLEC2D antibody comprising a heavy chain and a light chain, wherein:

a) the heavy chain comprises SEQ ID NO: 1481, 1913, 2129, or 2345, and the light chain comprises SEQ ID NO:1589;

b) the heavy chain comprises SEQ ID NO:1525, 1957, 2713, or 2389, and the light chain comprises SEQ ID NO:1633;

c) the heavy chain comprises SEQ ID NO: 1524, 1956, 2172, or 2388, and the light chain comprises SEQ ID NO:1632;

d) the heavy chain comprises SEQ ID NO: 1538, 1970, 2186, or 2402, and the light chain comprises SEQ ID NO:1646;

e) the heavy chain comprises SEQ ID NO: 1487, 1919, 2135, or 2351, and the light chain comprises SEQ ID NO:1595;

f) the heavy chain comprises SEQ ID NO: 1552, 1954, 2170, or 2386, and the light chain comprises SEQ ID NO:1630;

g) the heavy chain comprises SEQ ID NO: 1553, 1985, 2201, or 2417, and the light chain comprises SEQ ID NO:1661;

h) the heavy chain comprises SEQ ID NO: 1501, 1933, 2149, or 2365, and the light chain comprises SEQ ID NO:1609; or

i) the heavy chain comprises SEQ ID NO: 1515, 1947, 2163, or 2379, and the light chain comprises SEQ ID NO:1623.

6. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody is afucosylated.

7. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4 or 6, wherein the antibody comprises an IgG1 Fc region, an IgG2 Fc region, an IgG4 Fc region, or an IgG1 Fc region comprising an N297A substitution.

8. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-7, wherein the antibody or antigen-binding fragment thereof recognizes and binds to a conformational epitope of CLEC2D antigen comprised of amino acids positions overlapping and/or non-overlapping with CD161 receptor interacting amino acid residues.

9. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-8, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that inhibit or abrogate or compete with another antibody that recognizes and binds to a conformational epitope of CLEC2D antigen comprised of amino acids positions either overlapping and/or non-overlapping with CD161 receptor interacting amino acid residues.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that bind to a conformational epitope of CLEC2D antigen comprising any of the amino acid positions ARG175; TYR177; GLU179; ARG153; ARG84; HIS190; ARG101; GLU150; GLN154; THR152; GLN141; SER105; ASP107; ASP92; THR93; LYS94; LYS144; GLU138; CYS176; GLN139; ARG180; SER187; LYS181; PHE116; ASN95, or a combination thereof of SEQ ID NOs: 886-920 and 930-1003.

11. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that inhibit or abrogate or competes with the binding of another antibody to a conformational epitope of CLEC2D antigen comprising any of the amino acid positions ARG175; TYR177; GLU179; ARG153; ARG84; HIS190; ARG101; GLU150; GLN154; THR152; GLN141; SER105; ASP107; ASP92; THR93; LYS94; LYS144; GLU138; CYS176; GLN139; ARG180; SER187; LYS181; PHE116; ASN95 or a combination thereof of SEQ ID NOs: 886-920 and 930-1003.

12. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that bind to a conformational epitope of CLEC2D antigen comprising at least one of the amino acids positions ARG175; TYR177; GLU179; ARG153; ARG84; HIS190; ARG101; GLU150; GLN154; THR152; GLN141; SER105; ASP107; ASP92; THR93; LYS94; LYS144; GLU138; CYS176; GLN139; ARG180; SER187; LYS181; PHE116; ASN95 of SEQ ID NOs: 886-920 and 930-1003, constituting non-linear scaffolds for CD161 receptor interacting amino acid residues, thereby blocking the interaction between CLEC2D and CD161 receptors.

13. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that bind to a conformational epitope of CLEC2D antigen comprising at least one of the amino acids positions ARG175; TYR177; GLU179; ARG153; ARG84; HIS190; ARG101; GLU150; GLN154; THR152; GLN141; SER105; ASP107; ASP92; THR93; LYS94; LYS144; GLU138; CYS176; GLN139; ARG180; SER187; LYS181; PHE116; ASN95 of SEQ ID NOs: 886-920

and 930-1003, constituting allosteric and non-linear scaffolds for CD161 receptor non-interacting amino acid residues, thereby blocking the interaction between CLEC2D and CD161 receptors.

14. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof comprises a VH and a VL that when bound to CLEC2D selected from SEQ ID NOs: 886-920 and 930-1003, bind to at least one of the amino acids positions ARG175; TYR177; GLU179; ARG153; ARG84; HIS190; ARG101; GLU150; GLN154; THR152; GLN141; SER105; ASP107; ASP92; THR93; LYS94; LYS144; GLU138; CYS176; GLN139; ARG180 SER187; LYS181; PHE116; ASN95, independently or in combination to induce tumour killing or cytotoxicity.

15. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-14 and a pharmaceutically acceptable excipient.

16. An isolated nucleic acid comprising a polynucleotide sequence that encodes the isolated antibody or antigen-binding fragment thereof of any one of claims 1-14.

17. An expression vector comprising the isolated nucleic acid of claim 16.

18. A host cell comprising the isolated nucleic acid of claim 16 or the expression vector of claim 17, wherein the cell is a eukaryotic cell.

19. Use of the isolated antibody or antigen-binding fragment thereof of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a cancer, modulating the activation of an immune response, increasing the cytotoxicity of a natural killer cell, or eliciting anti-tumour response in a subject in need thereof.

20. An antibody library comprising at least about 108 unique monoclonal antibody clones, wherein the antibody library comprises an isolated antibody or antigen-binding fragment thereof

of any one of claims 1-14, and wherein at least about 80% of the antibody clones detectably and specifically bind a CLEC2D antigen.

21. A method of screening a high diversity antibody gene library for antibodies that bind to a CLEC2D antigen, comprising:

a) inserting a library of antibody genes into a phage protein gene and transforming a plurality of phages to produce a phage library, wherein the phages in the phage library display the library of antibody genes on the surface of the phages;
b) panning the phage library with a CLEC2D antigen for individual phages that bind to the CLEC2D antigen, thereby producing an enriched phage library that is enriched for antibody genes that encode antibodies that bind to the CLEC2D antigen;
c) repeating step (b) at least once or at least twice;
d) transferring the antibody genes from the enriched phage library to a yeast surface display library;
e) isolating individual yeast cells that bind to the CLEC2D antigen from the yeast surface display library;
f) culturing the isolated individual yeast cells that bind to the CLEC2D antigen to produce yeast surface display library clones; and
g) sequencing the yeast surface display library clones;

thereby isolating antibody genes that bind to the CLEC2D antigen,

wherein the antibody genes comprise the amino acid sequence of an isolated antibody or antigen-binding fragment thereof of any one of claims 1-14.

22. A method of making a composition comprising an anti-CLEC2D antibody or antigen-binding fragment thereof, comprising

a) transforming mammalian cells with a vector comprising a sequence encoding a promoter and a sequence encoding an anti-CLEC2D antibody or antigen-binding fragment thereof, wherein the sequence encoding the promoter and the anti-CLEC2D antibody or antigen-binding fragment thereof are operably linked;
b) culturing the mammalian cells under conditions suitable for the expression of the anti-CLEC2D antibody or antigen-binding fragment thereof; and

c) obtaining the anti-CLEC2D antibody or antigen-binding fragment thereof from the cultured mammalian cells to produce a supernatant,

wherein the anti-CLEC2D antibody or antigen-binding fragment thereof comprises the isolated antibody or antigen-binding fragment thereof of any one of claims 1-14.

23. Use of the isolated antibody or antigen-binding fragment thereof of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject in need thereof has an aberrant or differential cellular expression of CLEC2D.