

ANTIBODIES AND METHODS FOR TREATING CLAUDIN-ASSOCIATED DISEASES

FIELD OF THE INVENTION

[0001] The present invention relates to antibodies, pharmaceutical compositions and methods for preventing, treating and/or diagnosing CLDN-18-associated diseases.

BACKGROUND

[0002] Claudins (CLDN) are a family of integral membrane proteins, which comprise a major structural protein of tight junctions in polarized cell types such as epithelial or endothelial cell sheets, and have been found to be a biological marker of various tumors.

[0003] CLDNs undergo endocytosis and the turnover time of some CLDNs is short relative to other membrane proteins (Van Raffle et al., 2004, PMID: 15366421). The expression of CLDNs is dysregulated in cancer cells and tight junction structures among tumor cells are disrupted in cancer cells. These properties allow antibodies to selectively bind claudin proteins in neoplastic but not in normal tissues. While antibodies specific to individual claudins are useful, it is also possible that polyreactive claudin antibodies or anti-pan claudin antibodies would be more likely to facilitate the delivery of payloads to a broader patient population due to higher aggregate antigen density that reduces the likelihood of escape of tumor cells with low levels of antigen expression of any individual claudin.

[0004] CLDN18.1, the isoform 1 of CLDN 18, is lung-specific and is markedly decreased in lung adenocarcinoma. CLDN18.2, the isoform 2 of CLDN 18, is physiologically confined to gastric mucosa tight junctions, the epitopes of which

would be exposed on the cancer cell surface upon malignant transformation, and is highly expressed in a significant proportion of gastric and pancreatic adenocarcinomas, which makes it a potential drug target for the treatment of gastric and pancreatic adenocarcinoma. Monoantibodies, bispecific antibodies and antibody drug conjugates etc. that target CLDN18.2 have been researched and developed (Zhu et al., Targeting CLDN18.2 by CD3 Bispecific and ADC Modalities for the Treatments of Gastric and pancreatic Cancer; Tureci et al., Characterization of zolbetuximab in pancreatic cancer models, *Oncoimmunology* 2019, vol.8, no.1, e1523096)). In particular, a monoclonal antibody, zolbetuximab (formerly known as IMAB362), generated against CLDN18.2 obtained preliminary results from the phase II 'FAST' trial in June 2016, which suggests it helpful for advanced gastric cancer.

[0005] However, the amplitude of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) directly correlate with cell surface CLDN18.2 levels (Tureci et al., Characterization of zolbetuximab in pancreatic cancer models, *Oncoimmunology* 2019, vol.8, no.1, e1523096). Therefore, for cancer cells with low expression of CLDN18.2, such as breast cancer, the therapeutic effect of anti-CLDN18.2 antibodies are poor.

[0006] Therefore, there is a need for an anti-CLDN18.2 antibody that has enhanced ADCC and/or CDC for cancer cells, optional cancer cells with low surface expression of CLDN18.2.

BRIEF SUMMARY OF THE INVENTION

[0007] Provided herein are antibodies and antigen-binding fragments and the modification thereof, and pharmaceutical compositions and methods of use for treating/preventing/diagnosing conditions associated with CLDN 18, in particularly, associated with CLDN18.2.

[0008] In one aspect, the present disclosure provides an antibody or antigen-binding fragment which specifically binds to Claudin-18 (CLDN 18), wherein the antibody or antigen-binding fragment comprises at least one heavy or light chain complementarity determining region (CDR) having an amino acid sequence selected from the group consisting of GDY, SEQ ID NOs: 18, 20, 22, 27, 29, 31, 36, 38, 40, 45, 47, 49, 54, 56, 58, 63, 65, 67, 72, 74, 81, 83, 85, 90, 92, 94, 99, 101, 103, 108, 110, 112, 117, 119, 121, 126, 128, 130, 135, 137, 139, 144, 146, 148, 153, 155, 157, 163, 165, 167, 172, 174, 176, 181, 183, 185, 190, 192, 194, 198, 200, 202, 207, 209, 211, 216, 218, 220, 225, 227, 229, 234, 236, 238, 243, 245, 247, 252, 254, 256, 261, 263, 265, 270, 272, 274, 279, 281, 283, 288, 290, 292, 297, 299, 301, 306, 308, 310, 315, 317, 319, 324, 326, 328, 333, 335, 337, 342, 344, 346, 351, 353, 355, 360, 362, 364, 369, 371, 373, 378, 380, 382, 387, 389, 391, 396, 398, 400, 405, 407, 409, 414, 416, 418, 423, 425, 427, 432, 434, 436, 441, 443, 445, 450, 452, 454, 459, 461, 463, 468, 470, 472, 477, 479, 481, 486, 488, 490, 495, 497, 499, 504, 506, 508, 513, 515, 517, 522, 524, 526, 531, 533, 535, 540, 542, 544, 549, 551, 553, 558, 560, 562, 567, 569, 571, 576, 578, 580, 585, 587, 589, 594, 596, 598, 603, 605, 607, 612, 614, 616, 621, 623, 625, 630, 632, 634, 639, 641, 643, 648, 650, 652, 657, 659, 661, 666, 668, 670, 675, 677, 679, 684, 686, 688, 693, 695, 726, 727, 728 and 697.

[0009] In some embodiments, the antibody or antigen-binding fragment provided herein comprises: a heavy chain variable (VH) region comprising 1, 2 or 3 VH-CDR having an amino acid sequence selected from the group consisting of GDY, SEQ ID NOs: 18, 20, 22, 36, 38, 40, 54, 56, 58, 72, 74, 90, 92, 94, 108, 110, 112, 126, 128, 130, 144, 146, 148, 163, 165, 167, 181, 183, 185, 198, 200, 202, 216, 218, 220, 234, 236, 238, 252, 254, 256, 270, 272, 274, 288, 290, 292, 206, 308, 310, 324, 326, 328, 342, 344, 346, 360, 362, 364, 378, 380, 382, 396, 398, 400, 414, 416, 418, 432, 434, 436, 450, 452, 454, 468, 470, 472, 486, 488, 490, 504, 506, 508, 522, 524, 526, 540, 542, 544, 558, 560, 562, 576, 578, 580, 594, 596, 598, 612, 614, 616, 630, 632, 634, 648, 650, 652, 666, 668, 670, 684, 686, 726, 727 and 688.

[0010] In some embodiments, the antibody or antigen-binding fragment provided herein further comprises a light chain variable (VL) region comprising 1, 2 or 3 VL-CDR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 29, 31, 45, 47, 49, 63, 65, 67, 81, 83, 85, 99, 101, 103, 117, 119, 121, 135, 137, 139, 153, 155, 157, 172, 174, 176, 190, 192, 194, 207, 209, 211, 225, 227, 229, 243, 245, 247, 261, 263, 265, 279, 281, 283, 297, 299, 301, 315, 317, 319, 333, 335, 337, 351, 353, 355, 369, 371, 373, 387, 389, 391, 405, 407, 409, 423, 425, 427, 441, 443, 445, 459, 461, 463, 477, 479, 481, 495, 497, 499, 513, 515, 517, 531, 533, 535, 549, 551, 553, 567, 569, 571, 585, 587, 589, 603, 605, 607, 621, 623, 625, 639, 641, 643, 657, 659, 661, 675, 677, 679, 693, 695, 728 and 697.

[0011] In some embodiments, the antibody or antigen-binding fragment provided herein comprises:

- i. a VH-CDR 1 having an amino acid sequence selected from the group consisting of GDY, SEQ ID NOs: 18, 36, 54, 72, 90, 108, 126, 144, 163, 181, 198, 216, 234, 252, 270, 288, 206, 324, 342, 360, 378, 396, 414, 432, 450, 468, 486, 504, 522, 540, 558, 576, 594, 612, 630, 648, 666 and 684;
- ii. a VH-CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 38, 56, 74, 92, 110, 128, 146, 165, 183, 200, 218, 236, 254, 272, 290, 308, 326, 344, 362, 380, 398, 416, 434, 452, 470, 488, 506, 524, 542, 560, 578, 596, 614, 632, 650, 668, 726, 727 and 686; and
- iii. a VH-CDR3 having an amino acid sequence selected from the group consisting of GDY and SEQ ID NOs: 22, 40, 58, 94, 112, 130, 148, 167, 185, 202, 220, 238, 256, 274, 292, 310, 328, 346, 364, 382, 400, 418, 436, 454, 472, 490, 508, 526, 544, 562, 580, 598, 616, 634, 652, 670 and 688.

[0012] In some embodiments, the antibody or antigen-binding fragment provided herein comprises:

- i. a VL-CDR 1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 45, 63, 81, 99, 117, 135, 153, 172, 190, 207, 225, 243, 261, 279, 297, 315, 333, 351, 369, 387, 405, 423, 441, 459, 477, 495, 513, 531, 549, 567, 585, 603, 621, 639, 657, 675, 728 and 693;
- ii. a VL-CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 47, 65, 83, 101, 119, 137, 155, 174, 192, 209, 227, 245, 263, 281, 299, 317, 335, 353, 371, 389, 407, 425, 443, 461, 479, 497, 515, 533, 551, 569, 587, 605, 623, 641, 659, 677 and 695; and
- iii. a VL-CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 49, 67, 85, 103, 121, 139, 157, 176, 194, 211, 229, 247, 265, 283, 301, 319, 337, 355, 373, 391, 409, 427, 445, 463, 481, 499, 517, 535, 553, 571, 589, 607, 625, 643, 661, 679 and 697.

[0013] In some embodiments, the antibody or antigen-binding fragment provided herein comprises:

- i. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 18, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 20, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 22;
- ii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 36, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 38, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 40;
- iii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 54, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 56, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 58;

- iv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 72, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 74, and a VH-CDR 3 having an amino acid sequence of GDY;
- v. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 90, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 92, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 94;
- vi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 108, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 110, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 112;
- vii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 126, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 128, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 130;
- viii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 144, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 146, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 148;
- ix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 163, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 165, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 167;
- x. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 181, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 183, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 185;
- xi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 198, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 200, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 202;
- xii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 216, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 218, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 220;

- xiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 234, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 236, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 238;
- xiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 252, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 254, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 256;
- xv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 270, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 272, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 274;
- xvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 288, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 290, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 292;
- xvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 306, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 308, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 310;
- xviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 324, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 326, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 328;
- xix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 342, a VH-CDR 2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 344, 726 and 727, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 346;
- xx. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 360, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 362, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 364;

- xxi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 378, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 380, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 382;
- xxii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 396, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 398, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 400;
- xxiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 414, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 416, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 418;
- xxiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 432, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 434, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 436;
- xxv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 450, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 452, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 454;
- xxvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 468, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 470, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 472;
- xxvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 486, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 488, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 490;
- xxviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 504, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 506, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 508;
- xxix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 522, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 524, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 526;

- xxx. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 540, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 542, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 544;
 - xxxi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 558, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 560, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 562;
 - xxxii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 576, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 578, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 580;
 - xxxiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 594, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 596, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 598;
 - xxxiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 612, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 614, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 616;
 - xxxv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 630, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 632, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 634;
 - xxxvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 648, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 650, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 652;
 - xxxvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 666, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 668, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 670;
- or

- xxxviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 684, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 686, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 688.

[0014] In some embodiments, the antibody or antigen-binding fragment provided herein further comprises:

- i. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 27, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 29, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 31;
- ii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 45, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 47, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 49;
- iii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 63, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 65, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 67;
- iv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 81, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 83, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 85; or
- v. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 99, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 101, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 103;
- vi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 117, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 119, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 121;
- vii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 135, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 137, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 139;

- viii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 153, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 155, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 157;
- ix. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 172, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 174, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 176;
- x. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 190, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 192, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 194;
- xi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 207, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 209, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 211;
- xii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 225, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 227, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 229;
- xiii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 243, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 245, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 247;
- xiv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 261, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 263, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 265;
- xv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 279, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 281, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 283;
- xvi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 297, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 299, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 301;

- xvii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 315, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 317, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 319;
- xviii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 333, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 335, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 337;
- xix. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 351 or SEQ ID NO: 728, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 353, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 355;
- xx. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 369, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 371, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 373;
- xxi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 387, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 389, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 391;
- xxii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 405, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 407, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 409; or
- xxiii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 423, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 425, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 427;
- xxiv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 441, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 443, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 445;

- xxv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 459, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 461, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 463;
- xxvi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 477, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 479, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 481;
- xxvii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 495, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 497, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 499;
- xxviii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 513, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 515, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 517;
- xxix. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 531, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 533, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 535;
- xxx. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 549, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 551, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 553;
- xxxi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 567, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 569, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 571;
- xxxii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 585, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 587, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 589;
- xxxiii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 603, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 605, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 607;

- xxxiv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 621, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 623, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 625;
- xxxv. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 639, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 641, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 643;
- xxxvi. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 657, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 659, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 661;
- xxxvii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 675, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 677, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 679; or
- xxxviii. a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 693, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 695, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 697.

[0015] In some embodiments, the antibody or antigen-binding fragment provided herein comprises:

- i. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 18, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 20, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 22, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 27, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 29, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 31;
- ii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 36, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 38, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 40, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 45, a

- VL-CDR 2 having an amino acid sequence of SEQ ID NO: 47, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 49;
- iii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 54, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 56, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 58, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 63, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 65, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 67;
- iv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 72, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 74, and
a VH-CDR 3 having an amino acid sequence of GDY, a VL-CDR 1
having an amino acid sequence of SEQ ID NO: 81, a VL-CDR 2
having an amino acid sequence of SEQ ID NO: 83, and a VL-CDR
3 having an amino acid sequence of SEQ ID NO: 85;
- v. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 90, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 92, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 94, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 99, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 101, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 103;
- vi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 108, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 110, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 112, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 117, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 119, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 121;
- vii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 126, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 128, and

- a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 130, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 135, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 137, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 139;
- viii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 144, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 146, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 148, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 153, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 155, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 157;
- ix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 163, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 165, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 167, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 172, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 174, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 176;
- x. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 181, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 183, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 185, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 190, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 192, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 194;
- xi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 198, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 200, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 202, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 207, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 209, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 211;

- xii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 216, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 218, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 220, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 225, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 227, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 229;
- xiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 234, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 236, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 238, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 243, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 245, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 247;
- xiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 252, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 254, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 256, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 261, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 263, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 265;
- xv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 270, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 272, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 274, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 279, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 281, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 283;
- xvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 288, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 290, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 292, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 297, a

- VL-CDR 2 having an amino acid sequence of SEQ ID NO: 299, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 301;
- xvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 306, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 308, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 310, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 315, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 317, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 319;
- xviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 324, a
VH-CDR 2 having an amino acid sequence selected from the group
consisting of SEQ ID NOs: 326, 726 and 727, and a VH-CDR 3
having an amino acid sequence of SEQ ID NO: 328, a VL-CDR 1
having an amino acid sequence of SEQ ID NO: 333 or 728, a VL-
CDR 2 having an amino acid sequence of SEQ ID NO: 335, and a
VL-CDR 3 having an amino acid sequence of SEQ ID NO: 337;
- xix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 342, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 344, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 346, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 351, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 353, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 355;
- xx. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 360, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 362, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 364, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 369, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 371, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 373;

- xxi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 378, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 380, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 382, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 387, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 389, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 391;
- xxii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 396, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 398, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 400, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 405, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 407, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 409;
- xxiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 414, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 416, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 418, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 423, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 425, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 427;
- xxiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 432, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 434, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 436, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 441, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 443, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 445;
- xxv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 450, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 452, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 454, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 459, a

- VL-CDR 2 having an amino acid sequence of SEQ ID NO: 461, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 463;
- xxvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 468, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 470, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 472, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 477, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 479, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 481;
- xxvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 486, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 488, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 490, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 495, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 497, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 499;
- xxviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 504, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 506, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 508, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 513, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 515, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 517;
- xxix. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 522, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 524, and
a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 526, a
VL-CDR 1 having an amino acid sequence of SEQ ID NO: 531, a
VL-CDR 2 having an amino acid sequence of SEQ ID NO: 533, and
a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 535;
- xxx. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 540, a
VH-CDR 2 having an amino acid sequence of SEQ ID NO: 542, and

- a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 544, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 549, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 551, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 553;
- xxxi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 558, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 560, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 562, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 567, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 569, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 571;
- xxxii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 576, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 578, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 580, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 585, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 587, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 589;
- xxxiii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 594, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 596, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 598, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 603, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 605, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 607;
- xxxiv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 612, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 614, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 616, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 621, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 623, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 625;

- xxxv. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 630, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 632, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 634, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 639, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 641, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 643;
- xxxvi. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 648, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 650, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 652, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 657, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 659, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 661;
- xxxvii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 666, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 668, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 670, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 675, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 677, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 679; or
- xxxviii. a VH-CDR 1 having an amino acid sequence of SEQ ID NO: 684, a VH-CDR 2 having an amino acid sequence of SEQ ID NO: 686, and a VH-CDR 3 having an amino acid sequence of SEQ ID NO: 688, a VL-CDR 1 having an amino acid sequence of SEQ ID NO: 693, a VL-CDR 2 having an amino acid sequence of SEQ ID NO: 695, and a VL-CDR 3 having an amino acid sequence of SEQ ID NO: 697.

[0016] In some embodiments, the antibody or antigen-binding fragment provided herein comprises: a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 25/34, SEQ ID NOs: 43/52, SEQ ID NOs: 61/70, SEQ ID NOs: 79/88, SEQ ID NOs: 97/106, SEQ ID NOs: 115/124, SEQ ID NOs: 133/142, SEQ ID NOs: 151/160, SEQ ID NOs:

205/214, SEQ ID NOs: 223/232, SEQ ID NOs: 241/250, SEQ ID NOs: 259/268, SEQ ID NOs: 277/286, SEQ ID NOs: 295/304, SEQ ID NOs: 313/322, SEQ ID NOs: 331/340, SEQ ID NOs: 349/358, SEQ ID NOs: 367/376, SEQ ID NOs: 385/394, SEQ ID NOs: 403/412, SEQ ID NOs: 421/430, SEQ ID NOs: 439/448, SEQ ID NOs: 457/466, SEQ ID NOs: 475/484, SEQ ID NOs: 493/502, SEQ ID NOs: 511/520, SEQ ID NOs: 529/538, SEQ ID NOs: 547/556, SEQ ID NOs: 565/574, SEQ ID NOs: 583/592, SEQ ID NOs: 601/610, SEQ ID NOs: 619/628, SEQ ID NOs: 637/646, SEQ ID NOs: 655/664, SEQ ID NOs: 673/682, SEQ ID NOs: 691/161, SEQ ID NOs: 170/179, SEQ ID NOs: 188/76, or a pair of homologous sequences thereof having at least 80%, 85%, 90%, 95%, 97%, 98%, or 99% sequence identity yet retains specific binding affinity to CLDN 18.

[0017] In some embodiments, the antibody or antigen-binding fragment provided herein comprises:

- a) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 704, SEQ ID NO: 705, SEQ ID NO: 706 and SEQ ID NO: 707, and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 708, SEQ ID NO: 709 and SEQ ID NO: 710; or
- b) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 711, SEQ ID NO: 712, SEQ ID NO: 713 and SEQ ID NO: 714, and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 715, SEQ ID NO: 716 and SEQ ID NO: 717; or
- c) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 718, SEQ ID NO: 719, SEQ ID NO: 720, SEQ ID NO: 721 and SEQ ID NO: 722, and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 723, SEQ ID NO: 724 and SEQ ID NO: 725.

[0018] In some embodiments, the antibody or antigen-binding fragment provided herein further comprises one or more amino acid residue substitutions or modifications that yet retains specific binding affinity to CLDN 18. In some embodiments, at least one of the substitutions or modifications is in one or more of the CDR sequences, and/or in one or more of the non-CDR sequences of the heavy chain variable region or light chain variable region.

[0019] In some embodiments, the antibody or antigen-binding fragment provided herein further comprises one or more non-natural amino acid (NNAA) substitution.

[0020] In some embodiments, the antibody or antigen-binding fragment provided herein is a monoclonal antibody or antigen-binding fragment thereof, a polyclonal antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, a chimeric antibody or antigen-binding fragment thereof, a humanized antibody or antigen-binding fragment thereof, a recombinant antibody or antigen-binding fragment thereof, a human antibody or antigen-binding fragment thereof, a labeled antibody or antigen-binding fragment thereof, a bivalent antibody or antigen-binding fragment thereof, or an anti-idiotypic antibody or antigen-binding fragment thereof.

[0021] In some embodiments, the antibody or antigen-binding fragment provided herein is a camelized single domain antibody, a diabody, a scFv, an scFv dimer, a dsFv, a (dsFv)₂, a dsFv-dsFv', an Fv fragment, a Fab, a Fab', a F(ab')₂, a ds-diabody, a nanobody, a domain antibody, or a bivalent domain antibody.

[0022] In some embodiments, the antibody or antigen-binding fragment provided herein further comprises an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is a λ light chain, κ light chain, γ 1 heavy chain, γ 2 heavy chain, γ 3 heavy chain, or γ 4 heavy chain constant region. In some embodiments, the antibody or antigen-binding fragment provided herein is human IgG1 isotype.

[0023] In some embodiments, immunoglobulin constant region comprises an Fc region having an amino acid sequence selected from the group consisting of SEQ ID NOs. 700-703.

[0024] In some embodiments, the antibody or antigen-binding fragment provided herein specifically binds to CLDN 18.2 protein. In some embodiments, the antibody or antigen-binding fragment provided herein binds to both CLDN 18.1 protein and CLDN 18.2 protein.

[0025] In some embodiments, the binding affinity of the antibody or antigen-binding fragment provided herein to a cell expressing CLDN 18.2 is higher than or comparable with a reference antibody.

[0026] In some embodiments, the max MFI of the antibody or antigen-binding fragment provided herein to a cell expressing CLDN 18.2 is higher than the reference antibody

[0027] In some embodiments, the reference antibody is IMAB362.

[0028] In some embodiments, the surface expression of CLDN 18.2 on the cell is low.

[0029] In some embodiments, the binding affinity is determined by FACS or ELISA.

[0030] In some embodiments, the antibody or antigen-binding fragment provided herein binds to the CLDN 18.2 protein with an EC₅₀ of less than about 10 nM, less than about 8 nM, less than about 6 nM, less than about 4 nM, or less than about 2 nM.

[0031] In some embodiments, the antibody or antigen-binding fragment provided herein is linked to one or more conjugate moieties. In some embodiments, the conjugate moiety comprises an active agent, a radioactive isotope, a detectable label, a pharmacokinetic modifying moiety, or a purifying moiety. In some

embodiments, the conjugate moiety is covalently attached either directly or via a linker.

[0032] In another aspect, the present disclosure also includes the antibody or antigen-binding fragment recognizing the same antigenic determinant site as that of the antibody or antigen-binding fragment provided herein as examples.

[0033] In another aspect, the present disclosure provides a chimeric antigen receptor, comprising the antibody or antigen-binding fragment provided herein, a transmembrane region and an intracellular signal region.

[0034] In some embodiments, the intracellular signal region is selected from the group consisting of: an intracellular signal regions sequence of CD3, FcγRI, CD27, CD28, CD137, CD134, MyD88, CD40, CD278, TLRs, or a combination thereof.

[0035] In some embodiments, the transmembrane region comprises a transmembrane region of CD3, CD4, CD8 or CD28.

[0036] In another aspect, the present disclosure provides an isolated polynucleotide encoding the antibody or antigen-binding fragment or the chimeric antigen receptor provided herein.

[0037] In some embodiments, the isolated polynucleotide provided herein comprises a nucleotide sequence selected from a group consisting of: SEQ ID NOs: 24, 42, 60, 78, 96, 114, 132, 150, 204, 222, 240, 258, 276, 294, 312, 330, 348, 366, 384, 402, 420, 438, 456, 474, 492, 510, 528, 546, 564, 582, 600, 618, 636, 654, 672, 690, 169, 187, or a homologous sequence thereof having at least 80% sequence identity.

[0038] In some embodiments, the isolated polynucleotide provided herein further comprises a nucleotide sequence selected from a group consisting of: SEQ ID NOs: 33, 51, 69, 87, 105, 123, 141, 159, 213, 231, 249, 267, 285, 303, 321, 339, 357, 375, 393, 411, 429, 447, 465, 483, 501, 519, 537, 555, 573, 591, 609, 627, 645, 663, 681, 699, 178, 196, or a homologous sequence thereof having at least 80% sequence identity.

[0039] In another aspect, the present disclosure provides a vector comprising the polynucleotide provided herein.

[0040] In another aspect, the present disclosure provides a host expression system comprising the vector provided herein or having the polynucleotide provided herein integrated into genome thereof. In some embodiments, the host expression system provided herein is a microorganism, a yeast, or a mammalian cell, wherein the microorganism is selected from the group consisting of *E. coli* and *B. subtilis*, wherein the yeast is *Saccharomyces*, and wherein the mammalian cell is selected from the group consisting of COS, CHO-S, CHO-K1, HEK-293, and 3T3 cells.

[0041] In another aspect, the present disclosure provides a virus comprising the vector provided herein.

[0042] In another aspect, the present disclosure provides a method of expressing the antibody or antigen-binding fragment provided herein or the chimeric antigen receptor provided herein, comprising culturing the host expression system provided herein under conditions in which the antibody or antigen-binding fragment or the chimeric antigen receptor is expressed.

[0043] In another aspect, the present disclosure provides an antibody-drug conjugate comprising the antibody or antigen-binding fragment provided herein, linked to one or more therapeutic agents directly or via a linker.

[0044] In another aspect, the present disclosure provides a modified immune cell targeting cells expressing CLDN 18.2, comprising the antibody or antigen-binding fragment thereof provided herein or the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein or the virus provided herein.

[0045] In some embodiments, the cells expressing CLDN 18.2 are selected from the group consisting of: gastric cancer cells, pancreatic cancer cells, esophageal cancer cells, lung cancer cells, gallbladder cancer cells, colorectal cancer, and liver cancer cells.

[0046] In some embodiments, the immune cell is T lymphocyte, NK cell, monocyte, macrophage or NKT lymphocyte.

[0047] In some embodiments, the modified immune cell provided herein, further has one or more features selected from the group consisting of:

- i. carrying an encoding sequence for an exogenous cytokine,
- ii. expressing another chimeric antigen receptor, or a combination thereof,
- iii. expressing a chemokine receptor
- iv. expressing an siRNA that reduces expression of an immune checkpoint inhibitor or a protein that blocks the immune checkpoint inhibitor,
- v. having endogenous immune checkpoint inhibitor knocked out
- vi. expressing secretable antibody sc-fv
- vii. expressing a co-stimulatory protein
- viii. expressing a safety switch.

[0048] In some embodiments, the immune checkpoint inhibitor is selected from the group consisting of PD-1, CTLA-4, LAG-3, TIM-3.

[0049] In another aspect, the present disclosure provides a pharmaceutical composition comprising the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, or the modified immune cell provided herein, and one or more pharmaceutically acceptable carriers.

[0050] In some embodiments, the one or more pharmaceutical acceptable carriers are selected from the group consisting of pharmaceutically acceptable liquid, gel, solid carriers, aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, anesthetics, suspending/dispersing agents,

sequestering or chelating agents, diluents, adjuvants, excipients, and non-toxic auxiliary substances.

[0051] In some embodiments, the pharmaceutical composition provided herein further comprises one or more therapeutic agents.

[0052] In some embodiments, the one or more therapeutic agents are selected from the group consisting of amrubicin, apatinib mesylate, atrasentan, batimast, calcitriol, capecitabine, cilengitide, dasatinib, decatanib, edotecarin, enzastaurin, erlotinib, everolimus, gimatecan, gossypol, ipilimumab, lonafarnib, lucanthone, neuradiab, nolatrexed, oblimersen, olaparib, ofatumumab, oregovomab, panitumumab, pazopanib, regorafenib, talampanel, tegafur, temsirolimus, tesmilifene, tetrandrine, ticilimumab, trametinib, trabectedin, vandetanib, vitespan, zanolimumab, zolendronate, histrelin, azacitidine, dexrazoxane, alemtuzumab, lenalidomide, gemtuzumab, ketoconazole, nitrogen mustard, ibritumomab, tiuxetan, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, editronate, cyclosporine, Edwina-asparaginase, epirubicin, oxaliplatin, an anti-PD1 antibody, an anti-PDL1 antibody, an anti-HER2 antibody, an anti-HER2 ADC, 5-fluorouracil and strontium 89.

[0053] In another aspect, the present disclosure provides a kit comprising: a container, and the pharmaceutical composition provided herein; or a container, and the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, or the modified immune cell provided herein.

[0054] In another aspect, the present disclosure provides a method for treating or preventing a CLDN-related condition in a subject, comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, or the modified immune cell provided herein to the subject.

[0055] In some embodiments, the CLDN-related condition is cancerous condition.

[0056] In some embodiments, the cancerous condition is selected from the group consisting of lung cancer (*e.g.*, small cell lung cancer, non-small cell lung cancer (NSCLC), adenocarcinoma of the lung, or squamous cell carcinoma of the lung), gastric or stomach cancer (*e.g.*, gastrointestinal cancer), pancreatic cancer, esophageal cancer, liver cancer (*e.g.*, hepatocellular carcinoma/hepatoma), squamous cell cancer, cancer of the peritoneum, brain tumor (*e.g.*, glioblastoma/glioblastoma multiforme (GBM), non-glioblastoma brain tumor, or meningioma), glioma (*e.g.*, ependymoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, or mixed glioma such as oligoastrocytoma), cervical cancer, ovarian cancer, liver cancer (*e.g.*, hepatoblastoma, hepatocellular carcinoma/hepatoma, or hepatic carcinoma), bladder cancer (*e.g.*, urothelial cancer), breast cancer, colon cancer, colorectal cancer, rectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer (*e.g.*, rhabdoid tumor of the kidney), prostate cancer, vulval cancer, penile cancer, anal cancer (*e.g.*, anal squamous cell carcinoma), thyroid cancer, head and neck cancer (*e.g.*, nasopharyngeal cancer), skin cancer (*e.g.*, melanoma or squamous cell carcinoma), osteosarcoma, Ewing's sarcoma, chondrosarcoma, soft tissue sarcoma (*e.g.*, rhabdomyosarcoma, fibrosarcoma, Kaposi's sarcoma), carcinoid cancer, eye cancer (*e.g.*, retinoblastoma), mesothelioma, lymphocytic/lymphoblastic leukemia (*e.g.*, acute lymphocytic/lymphoblastic leukemia (ALL) of both T-cell lineage and B-cell precursor lineage, chronic lymphoblastic/lymphocytic leukemia (CLL), acute myelogenous/myeloblastic leukemia (AML), including mast cell leukemia, chronic myelogenous/myelocytic/myeloblastic leukemia (CML), hairy cell leukemia (HCL), Hodgkin's disease, non-Hodgkin's lymphoma, chronic myelomonocytic leukemia (CMML), follicular lymphoma (FL), diffuse large B cell lymphoma (DLCL), mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), mycosis fungoides, Sezary syndrome, cutaneous T-cell lymphoma, mast cell neoplasm, medulloblastoma, nephroblastoma, solitary plasmacytoma, myelodysplastic syndrome, chronic and non-

chronic myeloproliferative disorder, central nervous system tumor, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, gallbladder cancer, idiopathic myofibrosis, and pediatric cancers such as pediatric sarcomas (*e.g.*, neuroblastoma, rhabdomyosarcoma, and osteosarcoma).

[0057] In some embodiments, the administration is through a parenteral route comprising subcutaneous, intraperitoneal, intravenous, intramuscular, or intradermal injection; or a non-parenteral route comprising transdermal, oral, intranasal, intraocular, sublingual, rectal, or topical.

[0058] In some embodiments, the method provided herein further includes administering to the subject in need thereof an additional therapeutic agent.

[0059] In some embodiments, the additional therapeutic agent is selected from the group consisting of: an active agent, an imaging agent, a cytotoxic agent, and angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule agonist, a co-inhibition molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof, a detectable label or reporter, an antimicrobial, a gene editing agent, a beta agonist, an viral RNA inhibitor, a polymerase inhibitor, an interferon, and a microRNA.

[0060] In some embodiments, the additional therapeutic agent is administered to the subject in need before administration of the composition provided herein, after administration of the composition provided herein, and/or at the same time as the composition provided herein.

[0061] In another aspect, the present disclosure provides a method for diagnosing a CLDN-related condition, comprising detecting the CLDN by using the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug

conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein.

[0062] In some embodiments, the CLDN is CLDN 18.2 or CLDN 18.1.

[0063] In some embodiments, condition is selected from the group consisting of: gastric cancer, pancreatic cancer, esophageal cancer, lung cancer, gallbladder cancer, colorectal cancer and liver cancer.

[0064] In another aspect, the present disclosure provides a method for inducing the death of a cell expressing CLDN 18.2, comprising contacting the cell expressing CLDN 18.2 with the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein.

[0065] In some embodiments, the cell is contacted with the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein, *in vitro* or *in vivo*.

[0066] In some embodiments, the cell is a cancer cell. In some embodiments, the cell is a solid tumor cell.

[0067] In another aspect, the present disclosure provides use of the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein in the manufacture of a medicament for treating CLDN-related condition in a subject in need thereof.

[0068] In another aspect, the present disclosure provides use of the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein in the manufacture of a diagnostic reagent for detecting CLDN-related condition.

[0069] In another aspect, the present disclosure provides the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein for use in a method for treating CLDN-related condition in a subject in need thereof.

[0070] In another aspect, the present disclosure provides the antibody or antigen-binding fragment provided herein, the chimeric antigen receptor provided herein, the polynucleotide provided herein, the vector provided herein, the virus provided herein, the modified immune cell provided herein, the antibody-drug conjugate provided herein, the pharmaceutical composition provided herein, or the kit provided herein for use in a method for detecting CLDN-related condition.

BRIEF DESCRIPTION OF THE FIGURES

[0071] Figures 1A and 1B show FACs analysis suggesting that Ab10 binds with human, monkey and mouse Claudine18.2, but does not bind human Claudine18.1.

[0072] Figure 2 shows that chAb10 is more sensitive on Claudin18.2-low expressing cell (i.e., GAXC031 cells) compared with IMAB362. Some of the

GAXC031 cells were negatively stained with IMAB362, while chAb10 stains all GAXC031 cells.

[0073] Figure 3 shows FACs analysis suggesting that the binding affinity of the selected antibodies on CHOK1-18.2 and GAXC031 are higher or comparable with bench mark antibody IMAB362 (Tab1), with higher max MFI. DLE refers to enhanced human IgG1 Fc comprising an amino acid sequence of SEQ ID NO: 702, which is a human IgG1 heavy chain Fc with mutations of S122D, A213L and I215E. 2B1 is the antibody 2B1 included in the patent application No PCT/CN2017/092381; 2C3 is the antibody 2-C3 included in the patent application No PCT/US2019/020872; 3E12 is the antibody 3E12 included in the patent application No PCT/CN2017/092381.

[0074] Figure 4 shows that chAb08 showed more potent ADCC effect compared with IMAB362 on GAXC031 cells.

[0075] Figure 5 shows that our antibodies showed more potent ADCC effect compared with IMAB362 (Tab1) on GAXC031 cells.

[0076] Figure 6 shows that chAb10 and chAb15 showed potent indirect ADC cytotoxicity on GAXC031 cells.

[0077] Figures 7A and 7B show that some of the humanized antibodies showed equal or slightly decreased affinity against GAXC031 Cells.

[0078] Figures 8A-8C show that the antibodies, especially mAb Ab15, displayed detectable binding affinity onto KatoIII and SNU620 cells expressing very low level of Claudin 18.2, which are hardly detected by benchmark antibody IMAB362.

[0079] Figures 9A-9G show binding kinetics of the six humanized antibodies with VLP-Claudin 18.2.

[0080] Figures 10A-10F show ADC cytotoxicity activity of the humanized anti-Claudin 18.2 antibodies against CHOK1 cells or GAXC031 cells overexpressing human Claudin 18.2.

[0081] Figures 11A and 11B show in vivo efficacy and toxicity of mAb Ab15, Ab10, Ab17, Ab06, Ab08 and Ab20.

[0082] Figures 12A-12J show the in vivo ADC efficacy and toxicity of Ab10-vc-MMAF on GAXC03 cells, and Figure 12K shows survival curves of mice treated with Ab10-vc-MMAF.

[0083] Figures 13A-13L show the in vivo ADC efficacy and toxicity of humanized or chimeric antibodies on GAXC03 cells and Figure 13M shows survival curves of mice treated with ADC of humanized or chimeric antibodies.

DETAILED DESCRIPTION

[0084] The following description of the disclosure is merely intended to illustrate various embodiments of the disclosure. As such, the specific modifications discussed are not to be construed as limitations on the scope of the disclosure. It will be apparent to one skilled in the art that various equivalents, changes, and modifications may be made without departing from the scope of the disclosure, and it is understood that such equivalent embodiments are to be included herein. All references cited herein, including publications, patents and patent applications are incorporated herein by reference in their entirety.

[0085] Definitions

[0086] The term “antibody” as used herein refers to any immunoglobulin, monoclonal antibody, polyclonal antibody, diabodies, nanobodies, linear antibodies, single chain antibodies, multivalent antibody, bivalent antibody, monovalent antibody, multispecific antibody, bispecific antibody, the antigen-binding fragment thereof that binds to a specific antigen, mutants thereof, or any other modified configuration of the

immunoglobulin molecule that comprises an antigen binding site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. A “monoclonal antibody” refers to a homogenous antibody population and a “polyclonal antibody” refers to a heterogeneous antibody population. These two terms do not limit the source of an antibody or the manner in which it is made.

[0087] A typical complete antibody comprises two heavy chains and two light chains. Each heavy chain consists of a variable region and a first, second, and third constant region, while each light chain consists of a variable region and a constant region. Mammalian heavy chains are classified as α , δ , ϵ , γ , or μ , and mammalian light chains are classified as λ or κ . The antibody has a “Y” shape, with the stem of the Y consisting of the second and third constant regions of two heavy chains bound together via disulfide bonding. Each arm of the Y includes the variable region and first constant region of a single heavy chain bound to the variable and constant regions of a single light chain. The variable regions of the light and heavy chains are responsible for antigen binding. The variable regions in both chains generally contain three hypervariable loops called the complementarity determining regions (CDRs). In particular, a light chain variable (VL) region in the light chain comprises VL-CDR1, VL-CDR2 and VL-CDR3, and a heavy chain variable (VH) region in the heavy chain comprises VH-CDR1, VH-CDR2 and VH-CDR3. The three CDRs of the light or heavy chain are interposed between flanking stretches known as framework regions (FRs), which are more highly conserved than the CDRs and form a scaffold to support the hypervariable loops. The boundaries of FRs and CDRs may be defined or identified using methodology known in the art, for example, by the Kabat definition, the Chothia definition, the AbM definition, IMGT (see, *e.g.*, Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.*, J Mol Biol. Dec 5;186(3):651-63 (1985); Chothia *et al.*, (1989) Nature 342:877; Chothia, C. *et al.* (1987) J. Mol. Biol. 196:901-917, Al-lazikani *et al* (1997) J. Molec. Biol.

273:927-948; Almagro, J. *Mol. Recognit.* 17:132-143 (2004); Marie-Paule Lefranc et al, *Developmental and Comparative Immunology*, 27: 55-77 (2003); Marie-Paule Lefranc et al, *Immunome Research*, 1(3), (2005); and Marie-Paule Lefranc, *Molecular Biology of B cells* (second edition), chapter 26, 481-514, (2015), hgmp.mrc.ac.uk and bioinf.org.uk/abs). The constant regions of the heavy and light chains are not involved in antigen binding, but exhibit various effector functions. Antibodies are assigned to classes based on the amino acid sequence of the constant region of their heavy chain. The five major classes or isotypes of antibodies are IgA, IgD, IgE, IgG, and IgM, which are characterized by the presence of α , δ , ϵ , γ , and μ heavy chains, respectively. Several of the major antibody classes are divided into subclasses such as IgG1 (γ 1 heavy chain), IgG2 (γ 2 heavy chain), IgG3 (γ 3 heavy chain), IgG4 (γ 4 heavy chain), IgA1 (α 1 heavy chain), or IgA2 (α 2 heavy chain).

[0088] The term “bivalent” as used herein refers to an antibody or an antigen-binding fragment having two antigen-binding sites. The two antigen binding sites may bind to the same antigen, or they may each bind to a different antigen, in which case the antibody or antigen-binding fragment is characterized as “bispecific”.

[0089] The term “monovalent” refers to an antibody or an antigen-binding fragment having only one single antigen-binding site; and the term “multivalent” refers to an antibody or an antigen-binding fragment having multiple (i.e., more than two) antigen-binding sites.

[0090] The term “antigen-binding fragment” as used herein refers to an antibody fragment formed from a portion of an intact antibody comprising one or more CDRs, or any other antibody fragment that can bind to an antigen but does not comprise an intact native antibody structure. Examples of antigen-binding fragment include, without limitation, a camelized single domain antibody, a diabody, a single-chain antibody molecule (scFv), an scFv dimer (bivalent diabody), a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a bispecific dsFv (dsFv-dsFv'), an Fv fragment, a Fab, a Fab', a F(ab')₂, a nanobody, a domain antibody, a bivalent domain antibody, a disulfide stabilized diabody (ds diabody), a bispecific ds diabody, a

multispecific antibody formed from a portion of an antibody comprising one or more CDRs, or any other antibody fragment that binds to an antigen but does not comprise a complete antibody structure. An antigen-binding fragment is capable of binding to the same antigen to which the parent antibody or a parent antibody fragment (e.g., a parent scFv) binds.

[0091] “Fab” with regard to an antibody refers to that portion of the antibody consisting of a single light chain (both variable and constant regions) bound to the variable region and first constant region of a single heavy chain by a disulfide bond.

[0092] “Fab” refers to a Fab fragment that includes a portion of the hinge region.

[0093] “F(ab')₂” refers to a dimer of Fab’.

[0094] “Fv” with regard to an antibody refers to the smallest fragment of the antibody to bear the complete antigen binding site. An Fv fragment consists of the variable region of a single light chain bound to the variable region of a single heavy chain.

[0095] A “dsFv” refers to a disulfide-stabilized Fv fragment that the linkage between the variable region of a single light chain and the variable region of a single heavy chain is a disulfide bond. In some embodiments, a “(dsFv)₂” or “(dsFv-dsFv)” comprises three peptide chains: two V_H moieties linked by a peptide linker (e.g., a long flexible linker) and bound to two V_L moieties, respectively, via disulfide bridges. In some embodiments, dsFv-dsFv’ is bispecific in which each disulfide paired heavy and light chain has a different antigen specificity.

[0096] “Single-chain Fv antibody” or “scFv” refers to an engineered antibody consisting of a light chain variable region and a heavy chain variable region connected to one another directly or via a peptide linker sequence (Huston JS *et al.* Proc Natl Acad Sci USA, 85:5879(1988)).

[0097] “Camelized single domain antibody”, interchangeably used with “heavy chain antibody” or “HCAb”, refers to an antibody that contains two V_H

domains and no light chains (Riechmann L. and Muyldermans S., J Immunol Methods. Dec 10;231(1-2):25-38 (1999); Muyldermans S., J Biotechnol. Jun;74(4):277-302 (2001); WO94/04678; WO94/25591; U.S. Patent No. 6,005,079). Heavy chain antibodies were originally derived from *Camelidae* (camels, dromedaries, and llamas). Although devoid of light chains, camelized antibodies have an authentic antigen-binding repertoire (Hamers-Casterman C. *et al.*, Nature. Jun 3;363(6428):446-8 (1993); Nguyen VK. *et al.* "Heavy-chain antibodies in Camelidae; a case of evolutionary innovation," Immunogenetics. Apr;54(1):39-47 (2002); Nguyen VK. *et al.* Immunology. May;109(1):93-101 (2003). The variable domain of a heavy chain antibody represents the smallest known antigen-binding unit generated by adaptive immune responses (Koch-Nolte F. *et al.*, FASEB J. Nov;21(13):3490-8. Epub 2007 Jun 15 (2007)).

[0098] A "nanobody" refers to an antibody fragment that consists of one V_H domain from a heavy chain antibody of a conventional IgG and two heavy chain constant domains, e.g. CH2 and CH3.

[0099] A "diabody" refers to a small antibody fragment with two antigen-binding sites, wherein the fragment comprises a V_H domain connected to a V_L domain in the same polypeptide chain (V_H-V_L or V_H-V_L) (see, e.g., Holliger P. *et al.*, Proc Natl Acad Sci U S A. Jul 15;90(14):6444-8 (1993); EP404097; WO93/11161). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain, thereby creating two antigen-binding sites. The antigen-binding sites may target the same or different antigens (or epitopes).

[00100] A "domain antibody" refers to an antibody fragment containing only the variable region of a heavy chain or the variable region of a light chain. In certain instances, two or more V_H domains are covalently joined with a peptide linker to create a bivalent or multivalent domain antibody. The two V_H domains of a bivalent domain antibody may target the same or different antigens.

[00101] In certain embodiments, a “bispecific ds diabody” is a diabody targeting two different antigens (or epitopes). In certain embodiments, a “bispecific ds diabody” comprises V_{H1} - V_{L2} (linked by a peptide linker) bound to V_{L1} - V_{H2} (also linked by a peptide linker) via a disulfide bridge between V_{H1} and V_{L1} .

[00102] In certain embodiments, a “bispecific dsFv” or “dsFv-dsFv” comprises three peptide chains: a V_{H1} - V_{H2} moiety wherein the heavy chains are linked by a peptide linker (*e.g.*, a long flexible linker) and bound to V_{L1} and V_{L2} moieties, respectively, via disulfide bridges, wherein each disulfide paired heavy and light chain has a different antigen specificity.

[00103] In certain embodiments, an “scFv dimer” is a bivalent diabody or bivalent ScFv (BsFv) comprising V_H - V_L (linked by a peptide linker) dimerized with another V_H - V_L moiety such that V_H 's of one moiety coordinate with the V_L 's of the other moiety and form two binding sites which can target the same antigens (or epitopes) or different antigens (or epitopes). In specific embodiments, a “scFv dimer” is a bispecific diabody comprising V_{H1} - V_{L2} (linked by a peptide linker) associated with V_{L1} - V_{H2} (also linked by a peptide linker) such that V_{H1} and V_{L1} coordinate and V_{H2} and V_{L2} coordinate and each coordinated pair has a different antigen specificity.

[00104] The term “Fc” with regard to an antibody refers to that portion of the antibody consisting of the second and third constant regions of a first heavy chain bound to the second and third constant regions of a second heavy chain via disulfide bonding. The Fc portion of the antibody is responsible for various effector functions such as ADCC, and CDC, but does not function in antigen binding.

[00105] The term “chimeric” as used herein, means an antibody or antigen-binding fragment, having a portion of heavy and/or light chain derived from one species, and the rest of the heavy and/or light chain derived from a different species. In an illustrative example, a chimeric antibody may comprise a constant region derived from human and a variable region from a non-human animal such as mouse. In some embodiments, the non-human animal is a mammal, for example, a mouse, a rat, a rabbit, a goat, a sheep, a guinea pig, or a hamster.

[00106] The term “humanized” as used herein means that the antibody or antigen-binding fragment comprises CDRs derived from non-human animals, FR regions derived from human, and when applicable, the constant regions are derived from human.

[00107] Unless otherwise specified, the term “Claudin” or “CLDN” as used herein encompasses any or all of tight junction membrane proteins that are expressed in epithelia and endothelia and form paracellular barriers and pores that determine tight junction permeability, and is intended to encompass any form of CLDNs, for example, 1) native unprocessed CLDN molecules, “full-length” CLDN chains or naturally occurring variants of CLDNs, including, for example, allelic variants; 2) any form of CLDN that results from processing in the cell, e.g. different splicing forms, for example, splice variant 1 of Claudin 18 (CLDN18.1), splice variant 2 of Claudin 18 (CLDN18.2), and the like; or 3) a fragment (e.g., a truncated form, an extracellular/transmembrane domain) or a modified form (e.g. a mutated form, a glycosylated/PEGylated, a His-tag/immunofluorescence fused form) of CLDN subunit generated through recombinant methods. “CLDN” as used herein can be derived from any vertebrate source, including mammals such as primates (e.g. humans, monkeys) and rodents (e.g., mice and rats).

[00108] The term “Claudin 18” or “CLDN 18” refers to one family member of CLDN, with a molecular weight of approximately 27.9 KD, which comprises two splicing forms as described above, i.e., CLDN18.1 (identified by NCBI Reference Sequence: NP_057453.1, and/or accession: NM_016369.4 for homo sapiens CLDN18.1) and CLDN18.2 (identified by NCBI Reference Sequence: NP_001002026.1, and/or accession: NM_001002026.3 for homo sapiens CLDN18.2).

[00109] The term “anti-CLDN18 antibodies” refers to an antibody that is capable of specifically binding to CLDN18. In some embodiments, the anti-CLDN18 antibodies provided herein are capable of binding to both CLDN18.2 and CLDN18.1. In some embodiments, the anti-CLDN18 antibodies provided herein are capable of specifically binding to CLDN18.2, but does not bind to CLDN18.1 or bind less well

to CLDN18.1 (e.g., the binding affinity to CLDN18.1 is at least 10-fold lower than that to CLDN18.2, or at least 50-fold lower, or at least 100-fold lower, or at least 200-fold lower). In some embodiments, the anti-CLDN18 antibodies provided herein do not have detectable binding affinity to CLDN18.1. In some embodiments, the binding affinity is determined by FACs. In some embodiments, the binding affinity is determined by MFI detected by FACs.

[00110] The term “specific binding” or “specifically binds” as used herein refers to a non-random binding reaction between two molecules, such as for example between an antibody and an antigen. An antibody that “specifically binds” to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit “specific binding” if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen than it does with alternative targets. An antibody “specifically binds” to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically (or preferentially) binds to an antigen (CLDN18.2) or an antigenic epitope therein is an antibody that binds this target antigen with greater affinity, avidity, more readily, and/or with greater duration than it binds to other antigens or other epitopes in the same antigen. It is also understood with this definition that, for example, an antibody that specifically binds to a first target antigen may or may not specifically or preferentially bind to a second target antigen. As such, “specific binding” or “preferential binding” does not necessarily require (although it can include) exclusive binding. In some examples, an antibody that “specifically binds” to a target antigen or an epitope thereof may not bind to other antigens or other epitopes in the same antigen (*i.e.*, only baseline binding activity can be detected in a conventional method). Alternatively, or in addition, the anti-CLDN18 antibodies described herein may specifically binds human, mouse, or Rhesus monkey CLDN18.2 or a fragment thereof as relative to human CLDN18.1 (*e.g.*, having a binding affinity at least 10-fold higher

to one antigen than the other as determined in the same assay under the same assay conditions).

[00111] As used herein, a “conservative amino acid substitution” refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. For example, conservative substitutions can be made among amino acid residues with hydrophobic side chains (e.g. Met, Ala, Val, Leu, and Ile), among residues with neutral hydrophilic side chains (e.g. Cys, Ser, Thr, Asn and Gln), among residues with acidic side chains (e.g. Asp, Glu), among amino acids with basic side chains (e.g. His, Lys, and Arg), or among residues with aromatic side chains (e.g. Trp, Tyr, and Phe). As known in the art, conservative substitution usually does not cause significant change in the protein conformational structure, and therefore could retain the biological activity of a protein.

[00112] “Percent (%) sequence identity” with respect to amino acid sequence (or nucleic acid sequence) is defined as the percentage of amino acid (or nucleic acid) residues in a candidate sequence that are identical to the amino acid (or nucleic acid) residues in a reference sequence, after aligning the sequences and, if necessary, introducing gaps, to achieve the maximum number of identical amino acids (or nucleic acids). Conservative substitution of the amino acid residues may or may not be considered as identical residues. Alignment for purposes of determining percent amino acid (or nucleic acid) sequence identity can be achieved, for example, using publicly available tools such as BLASTN, BLASTp (available on the website of U.S. National Center for Biotechnology Information (NCBI), see also, Altschul S.F. et al, J. Mol. Biol., 215:403–410 (1990); Stephen F. et al, Nucleic Acids Res., 25:3389–3402 (1997)), ClustalW2 (available on the website of European Bioinformatics Institute, see also, Higgins D.G. et al, Methods in Enzymology, 266:383-402 (1996); Larkin M.A. et al, Bioinformatics (Oxford, England), 23(21): 2947-8 (2007)), and ALIGN or Megalign (DNASTAR) software. Those skilled in the art may use the default parameters provided by the tool, or may customize the parameters as appropriate for the alignment, such as for example, by selecting a suitable algorithm.

[00113] An “isolated” substance has been altered by the hand of man from the natural state. If an “isolated” composition or substance occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living animal is not “isolated,” but the same polynucleotide or polypeptide is “isolated” if it has been sufficiently separated from the coexisting materials of its natural state so as to exist in a substantially pure state. An “isolated polynucleotide sequence” refers to the sequence of an isolated polynucleotide molecule. In certain embodiments, an “isolated antibody” refers to the antibody having a purity of at least 60%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% as determined by electrophoretic methods (such as SDS-PAGE, isoelectric focusing, capillary electrophoresis), or chromatographic methods (such as ion exchange chromatography or reverse phase HPLC).

[00114] “Effector functions” as used herein refer to biological activities attributable to the binding of Fc region of an antibody to its effectors such as C1 complex and Fc receptor. Exemplary effector functions include: complement dependent cytotoxicity (CDC) induced by interaction of antibodies and complement component 1q (C1q) on the C1 complex; antibody-dependent cell-mediated cytotoxicity (ADCC) induced by binding of Fc region of an antibody to Fc receptor on an effector cell; and phagocytosis.

[00115] “Antibody-dependent cell-mediated cytotoxicity” and “ADCC” refer to a cell-mediated reaction in which effector cells that express Fc receptors (FcRs) recognize bound antibody or antigen-binding fragment on a target cell and subsequently cause lysis of the target cell. “ADCC activity” or “ADCC effect” refers to the ability of the antibody or antigen-binding fragment which is bound on the target cell to elicit an ADCC reaction as described above.

[00116] “Target cells” are cells to which antibodies comprising an Fc region specifically bind, generally via the protein part that is C-terminal to the Fc region. “Effector cells” are leukocytes which express one or more Fc receptors and perform

effector functions. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMCs), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source thereof, e.g., from blood or PBMCs as is known in the art.

[00117] As used herein a “vector” refers to a polynucleotide molecule which enables replicating/cloning of a desired nucleic acid fragment contained therein, or enables expressing of a protein encoded by such desired nucleic acid fragment as introduced into an appropriate cell host. Vectors include both cloning vectors and expression vectors. The term “expression vector” as used herein refers to a vehicle into which a polynucleotide encoding a protein may be operably inserted so as to bring about the expression of that protein. An expression vector may contain a variety of elements for controlling expression, including promoter sequences, transcription initiation sequences, enhancer sequences, selectable elements, and reporter genes. In addition, the vector may contain an origin of replication.

[00118] The phrase “host cell” as used herein refers to a cell into which an exogenous polynucleotide and/or a vector has been introduced.

[00119] “Treating” or “treatment” of a condition as used herein includes preventing or alleviating a condition, slowing the onset or rate of development of a condition, reducing the risk of developing a condition, preventing or delaying the development of symptoms associated with a condition, reducing or ending symptoms associated with a condition, generating a complete or partial regression of a condition, curing a condition, or some combination thereof.

[00120] A “CLDN-related” condition as used herein refers to any disease or condition that is susceptible to treatment with a CLDN modulator, or is associated with expression or over-expression of CLDN. In some embodiments, the CLDN-related condition is a CLDN18.2-relating condition. In certain embodiments, the CLDN18.2-relating condition is cancerous condition. In certain embodiments, the cancerous condition is positive for CLDN18.2 expression or elevated expression.

[00121] “Cancerous condition” as used herein refers to any medical condition characterized by malignant cell growth or neoplasm, abnormal proliferation, infiltration or metastasis, and includes both solid tumors and non-solid cancers. As used herein “solid tumor” refers to a solid mass of neoplastic and/or malignant cells. “Non-solid cancer” refers to hematologic malignancies such as leukemia, lymphoma, myeloma and other hematologic malignancies. Examples of cancer or tumor include hematological malignancies (for example, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma and B-cell lymphoma), oral carcinomas (for example of the lip, tongue or pharynx), tumors in digestive organs (for example esophagus, stomach, small intestine, colon, large intestine, or rectum), peritoneum, liver and biliary passages, pancreas, respiratory system such as larynx or lung (small cell and non-small cell), bone, connective tissue, skin (e.g., melanoma), breast, reproductive organs (fallopian tube, uterus, cervix, testicles, ovary, or prostate), urinary tract (e.g., bladder or kidney), brain and endocrine glands such as the thyroid. In certain embodiments, the cancer is selected from the group consisting of lung cancer (e.g., small cell lung cancer, non-small cell lung cancer (NSCLC), adenocarcinoma of the lung, or squamous cell carcinoma of the lung), gastric or stomach cancer (e.g., gastrointestinal cancer), pancreatic cancer, esophageal cancer, liver cancer (e.g., hepatocellular carcinoma/hepatoma), squamous cell cancer, cancer of the peritoneum, brain tumor (e.g., glioblastoma/glioblastoma multiforme (GBM), non-glioblastoma brain tumor, or meningioma), glioma (e.g., ependymoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, or mixed glioma such as oligoastrocytoma), cervical cancer, ovarian cancer, liver cancer (e.g., hepatoblastoma, hepatocellular carcinoma/hepatoma, or hepatic carcinoma), bladder cancer (e.g., urothelial cancer), breast cancer, colon cancer, colorectal cancer, rectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer (e.g., rhabdoid tumor of the kidney), prostate cancer, vulval cancer, penile cancer, anal cancer (e.g., anal squamous cell carcinoma), thyroid cancer, head and neck cancer (e.g., nasopharyngeal cancer), skin cancer (e.g., melanoma or squamous cell carcinoma), osteosarcoma, Ewing's sarcoma, chondrosarcoma, soft tissue sarcoma (e.g., rhabdomyosarcoma, fibrosarcoma,

Kaposi's sarcoma), carcinoid cancer, eye cancer (*e.g.*, retinoblastoma), mesothelioma, lymphocytic/lymphoblastic leukemia (*e.g.*, acute lymphocytic/lymphoblastic leukemia (ALL) of both T-cell lineage and B-cell precursor lineage, chronic lymphoblastic/lymphocytic leukemia (CLL), acute myelogenous/myeloblastic leukemia (AML), including mast cell leukemia, chronic myelogenous/myelocytic/myeloblastic leukemia (CML), hairy cell leukemia (HCL), Hodgkin's disease, non-Hodgkin's lymphoma, chronic myelomonocytic leukemia (CMML), follicular lymphoma (FL), diffuse large B cell lymphoma (DLCL), mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), mycosis fungoides, Sezary syndrome, cutaneous T-cell lymphoma, mast cell neoplasm, medulloblastoma, nephroblastoma, solitary plasmacytoma, myelodysplastic syndrome, chronic and non-chronic myeloproliferative disorder, central nervous system tumor, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, gallbladder cancer, idiopathic myelfibrosis, and pediatric cancers such as pediatric sarcomas (*e.g.*, neuroblastoma, rhabdomyosarcoma, and osteosarcoma).

[00122] The term “pharmaceutically acceptable” indicates that the designated carrier, vehicle, diluent, excipient(s), and/or salt is generally chemically and/or physically compatible with the other ingredients comprising the formulation, and physiologically compatible with the recipient thereof.

[00123] As used herein, “an effective amount” refers to the amount of each active agent required to confer therapeutic effect on the subject, either alone or in combination with one or more other active agents. Determination of whether an amount of the antibody achieved the therapeutic effect would be evident to one of skill in the art. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of

the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

[00124] Anti-CLDN18 antibodies

[00125] The present disclosure provides anti-CLDN18 antibodies, each comprising one or more (e.g. 1, 2, 3, 4, 5, or 6) CDR sequences of each of the exemplary antibodies Ab01-Ab38 as shown in Table 1. The term “Ab01-Ab38” as used herein refers to 38 mouse monoclonal antibodies having a pair of heavy chain variable region and light chain variable region sequences as shown in Table 1. In a particular aspect, the present disclosure provides anti-CLDN18 antibodies that specifically bind to both CLDN18.2 protein and CLDN18.1 protein, such as antibodies, each comprising one or more (e.g. 1, 2, 3, 4, 5, or 6) CDR sequences of each of the exemplary antibodies Ab01, Ab04 and Ab36-Ab38 as shown in Table 1. In another particular aspect, the present disclosure provides anti-CLDN18 antibodies that showing higher binding affinity to CLDN18.2 protein than CLDN18.1 protein, such as antibodies, each comprising one or more (e.g. 1, 2, 3, 4, 5, or 6) CDR sequences of each of the exemplary antibodies Ab02, Ab03 and Ab05-Ab35 as shown in Table 1.

[00126] Table 1. Amino acid sequences of variable regions of the exemplary antibodies of the present disclosure

Antibody ID No.	Variable Chain	Amino Acid Sequence of Each Variable Chain	Amino Acid Sequence of CDR1	Amino Acid Sequence of CDR2	Amino Acid Sequence of CDR3
		SEQ ID NO: 25	SEQ ID NO: 18	SEQ ID NO: 20	SEQ ID NO: 22
Ab01	VH	DVQLQESGPG LVKPSQSLSL TCSVTGYSITS GYYWNWIRQ FPGNKLEWM GYITYDGSNN YNPSLKNRISI TRDTSKNQFF LKLNSVTTED AATYFCARDP	SGYYWN	YITYDGS NNYNPSL KN	DPNYYGTTL PAWFVY

		NYYGTTLPA WFVYWGQGT LTVSA			
		SEQ ID NO: 34	SEQ ID NO: 27	SEQ ID NO: 29	SEQ ID NO: 31
	VL	DIVVTQSHKF MSTSVGDRVS ITCKASQDVG TAVAWYQQK PGQSPKLLIY WASTRHTGV PDRFTGSGSG TDFTLTISNVQ SEDLTDYFCQ QYSSYVTFGA GTKLELK	KASQDV GTAVA	WASTRHT	QQYSSYVT
		SEQ ID NO: 43	SEQ ID NO: 36	SEQ ID NO: 38	SEQ ID NO: 40
Ab02	VH	QVQLKESGPG LVAPSQSLST CTVSGFSLTS YAINWVRQPP GKGLEWLGVI WTGGGTNYN SALKSRLSINK DNSKSQVFLK MNSLQTDDT ARYYCARFY DGYYSWFAY WGQGLVTV SA	SYAIN	VIWTGGG TNYSAL KS	FYDGYYSW FAY
		SEQ ID NO: 52	SEQ ID NO: 45	SEQ ID NO: 47	SEQ ID NO: 49
	VL	DIVMTQSHKF MSTSVGDRVS ITCKASQDVG TAVTWYQQK PGQSPKLLIY WASTRHTGV PDRFTGSGSG TDFTLTISNVQ SEDLADYFCQ QYSSYPFTFG SGTKLEIK	KASQDV GTAVT	WASTRHT	QQYSSYPFT
		SEQ ID NO: 61	SEQ ID NO: 54	SEQ ID NO: 56	SEQ ID NO: 58

Ab03	VH	EVQLQQSGPE LVKPGASVKI ACKASGYTFT DYNMDWVK QSHGKSLEWI GNINSYYGGT IYNQKFKGKA TLTVDKSSST AYMVLRLTS EDNAVYYCA RPHLGNALDY WGQGSITVS S	DYNMD	NINSYYG GTIYNQK FKG	PHLGNALDY
		SEQ ID NO: 70	SEQ ID NO: 63	SEQ ID NO: 65	SEQ ID NO: 67
	VL	DIVVTQSPSSL TVTPGEKVTM SCKSSQSLFN SGNQKNYLS WYQQNPGQP PKLLIYWAST RQSGVPDRFT GSGSGTDFTL TISSVQAEDL AGYYCQNDYI FPLTFGAGTK LELK	KSSQSLF NSGNQK NYLS	WASTRQS	QNDYIFPLT
		SEQ ID NO: 79	SEQ ID NO: 72	SEQ ID NO: 74	
Ab04	VH	EVQLQQSGPE LVKPGASVK MSCMASGYT FTDYNHFWVK RSHGSRLEWI GYISPISGGAG YNQKFMDKA TLTVDKSSNT AYMELRLTS EDSAVYYCTR GDYWGQGT LTVSS	DYNIH	YISPISGG AGYNQKF MD	GDY
		SEQ ID NO: 88	SEQ ID NO: 81	SEQ ID NO: 83	SEQ ID NO: 85
	VL	DIVMTQSPSS LAVTVGEKVT MSCKSSQSL NSGNQKNYL TWYQQKPGQ PPKLLIYWAS	KSSQSLL NSGNQK NYLT	WASTRKS	LNDYGFPLT

		TRKSGVPDRF TGSGSGTDFT LTISSVQAEDL GIYYCLNDYG FPLTFGAGSK LELK			
		SEQ ID NO: 97	SEQ ID NO: 90	SEQ ID NO: 92	SEQ ID NO: 94
Ab05	VH	DVKLVESGED LVKPGGSLKL SCAASGFTFS NYAMSWVRQ TPEKRLEWVA YVSSGGDIY YADTVKGRFI ISRDNARNTL YLQMNSLRSE DTAMYYCAR VYFGNSLDY WGQGTTTLTV SS	NYAMS	YVSSGGD YIYYADT VKG	VYFGNSLDY
		SEQ ID NO: 106	SEQ ID NO: 99	SEQ ID NO: 101	SEQ ID NO: 103
	VL	DIVMTQSPSS LTVTAGEKVT LSCKSSQSLL NGGNQKNYL TWYQQRPGQ PPKLLIYWAS TRESGVPDRF TGSGSGTDFT LISSVQAEDL AVYYCQNDY YYPWTFGGG TKLEIK	KSSQSLL NGGNQK NYLT	WASTRES	QNDYYYPW T
		SEQ ID NO: 115	SEQ ID NO: 108	SEQ ID NO: 110	SEQ ID NO: 112
Ab06	VH	EVQLVASGG GLVKPGGSLK LSCAASGITFR SYAMSWVRQ TPEKRLEWVA TITDGGSYIFY PDNVKGRFTI SGDHAKNNL YLQMSHLKSE DTALYFCVRL YYGNSFAYW GQGTLVTVSA	SYAMS	TITDGGSY IFYPDNV KG	LYYGNSFAY

		SEQ ID NO: 124	SEQ ID NO: 117	SEQ ID NO: 119	SEQ ID NO: 121
	VL	DIVMTQSPSS LTVTAGEKVT LNCKSSQSLF NSGNQKNYL TWYQQKPGQ PPKLLIYWAS TRESGVPDRF TSGSGTDF LTFSSVQAED LAVYYCQNA YIYPFTFGSGT KLEIK	KSSQSLF NSGNQK NYLT	WASTRES	QNAYIYPFT
		SEQ ID NO: 133	SEQ ID NO: 126	SEQ ID NO: 128	SEQ ID NO: 130
Ab07	VH	EVQLQQSGPE LVKPGASVKI SCKASGYSFT DYFMNWVKQ SHGKGLEWIG RINPYNGDTF YNQKFKGKA TLTVDKSSST AHMELLSLTS EDFAVYYCAL YDGYWGAFV YWGQGTSLV VSA	DYFMN	RINPYNG DTFYNQK FKG	LYDGYWGA FVY
		SEQ ID NO: 142	SEQ ID NO: 135	SEQ ID NO: 137	SEQ ID NO: 139
	VL	DIQMTQSPAS LSVFGGETVTI TCRASENIYS NLAWYQQKQ GKSPQLLVYA ATNLADGVPS RFSGSGSGTQ YSLKINSLQSE DFGSYYCQHF WGTPITFGAG TKLELK	RASENIY SNLA	AATNLAD	QHFWDGTPIT
		SEQ ID NO: 151	SEQ ID NO: 144	SEQ ID NO: 146	SEQ ID NO: 148
Ab08	VH	QVQLQQPGA ELVKPGASVK LSCKASGYTF TSYLLHWVK QRPQGGLW	SYLLH	MIHPNGG STNYNEK FKT	VYFGNSFAY

		GMIHPNNGGST NYNEKFKTK ATLTVDKSSS TAYMQLSSLT SEDSAVYYCA PVYFGNSFAY WGQGLVTV SA			
		SEQ ID NO: 160	SEQ ID NO: 153	SEQ ID NO: 155	SEQ ID NO: 157
	VL	DIVMTQSPSS LTVTAGEKVT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIWAS TRESGVPDRF TSGSGTDFT LTISSVQAEDL AVYYCQNDY YYPFTFGSGT KLEKK	KSSQSLL NSGNQK NYLT	WASTRES	QNDYYYPFT
		SEQ ID NO: 205	SEQ ID NO: 198	SEQ ID NO: 200	SEQ ID NO: 202
Ab09	VH	EVQLQQSGPE LVKPGTSVK MSCKASGYTF TDYNMHWVK LSHGKSLEWI GYINPNNGGT IYNQRFKGKA TLTVNKSSRT AYMDLRSLTS EDSAVYYCA RQGYYGNSM DYWGQGNSV TVSS	DYNMH	YINPNNG GTIYNQR FKG	QGYYGNSM DY
		SEQ ID NO: 214	SEQ ID NO: 207	SEQ ID NO: 209	SEQ ID NO: 211
	VL	DIVMTQSPSS LTVTPGERVT MSCKSSQSLL NGGNQRNYL TWYQQKPGQ PPKLLIWAS TRESGVPDRF AGSGSGTDFT LTISRVQAED LSFYQCNSY	KSSQSLL NGGNQR NYLT	WASTRES	QNSYFYPFT

		FYPFTFGSGT KDLR			
		SEQ ID NO: 223	SEQ ID NO: 216	SEQ ID NO: 218	SEQ ID NO: 220
Ab10	VH	EVMLVESGG GLVKPGGSLK LSCAASGFTF SSYTMSWVR QTPEKRLEWV ATISVIGGNTY YVDSVKGRFT ISRDKAKNTL YLQMSSLRSE DTALYYCARL GQTQRNAMD YWGQGTSTV VSS	SYTMS	TISVIGGN TYYVDSV KG	LGQTQRNA MDY
		SEQ ID NO: 232	SEQ ID NO: 225	SEQ ID NO: 227	SEQ ID NO: 229
	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY SYPLTFGAGT KLELK	KSSQSL NSGNQK NYLA	GASTRES	QNDYSYPLT
		SEQ ID NO: 241	SEQ ID NO: 234	SEQ ID NO: 236	SEQ ID NO: 238
Ab11	VH	EVMLVESGG DLVKPGGSLK LSCAASGFTF SRYTMSWVR QTPEKRLEWV ATVSVGSGNT YYLDSVKGRF TISRDNKNT LFLQMNSLR EDTALYYCTR LGQTQRNAV DYWGQGTSTV TVSS	RYTMS	TVSVGSG NTYYLDS VKG	LGQTQRNA VDY

		SEQ ID NO: 250	SEQ ID NO: 243	SEQ ID NO: 245	SEQ ID NO: 247
	VL	DIVMTQSPSF LSVSAGEKVT MSCKSSQSLF NGGNQKNYL AWYQQKPGQ PPKLLIYGAST RDSGVPDRFT GSGSGTDFTL TISNVQAEDL AIYFCQNDHS FPLTFGAGTK LELK	KSSQSLF NGGNQK NYLA	GASTRDS	QNDHSFPLT
		SEQ ID NO: 259	SEQ ID NO: 252	SEQ ID NO: 254	SEQ ID NO: 256
Ab12	VH	EVMLVESGG GLVKPGGSLK LSCAASGFTF SSYTMSWVR QTPEKRLEWV ATIIGGYGNT YYADSVKGR FTISRDSAKNT LYLQMLSLRS EDTALYYCTR LGQTQRNAM DYWGQGTSV TVSS	SYTMS	TIIGGYGN TYYADSV KG	LGQTQRNA MDY
		SEQ ID NO: 268	SEQ ID NO: 261	SEQ ID NO: 263	SEQ ID NO: 265
	VL	DILMTQSPSSL SVSAGEKVT MSCKSSQSLL NSGNQRNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPLTFGAGT KLELK	KSSQSLL NSGNQR NYLA	GASTRES	QNDYYYPLT
		SEQ ID NO: 277	SEQ ID NO: 270	SEQ ID NO: 272	SEQ ID NO: 274
Ab13	VH	EVRLVESGGG LVKPGGSLKL SCAGSGFTFS SYTMSWVRQ	SYTMS	TITIGVNI YYLDSVK G	LGQTQRNA MDY

		TPEKRLEWVA TITIGVNIYYL DSVKGRFTIS RDNAKNTLY LQMNSLRSED TALYYCTRLG QTQRNAMDY WGQGTSVTV SS			
		SEQ ID NO: 286	SEQ ID NO: 279	SEQ ID NO: 281	SEQ ID NO: 283
	VL	DIVMTQSPTS LSVSAGEKVT MTCKSSQSLL NSGNQKNYL AWYQEKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNNH FYPLTFGAGT KLELK	KSSQSLL NSGNQK NYLA	GASTRES	QNNHIFYPLT
		SEQ ID NO: 295	SEQ ID NO: 288	SEQ ID NO: 290	SEQ ID NO: 292
Ab14	VH	QVQLQQPGA ELVKPGASVK LSCKASGYTF TSYLLHWVK QRPQGGLWEI GMIHPNGGST NYNEKFKTK ATLTVDKSSS TAYMQLSSLT SEDSAVYYCA PVYFGNSFAY WGQGLVTV SA	SYLLH	MIHPNGG STNYNEK FKT	VYFGNSFAY
		SEQ ID NO: 304	SEQ ID NO: 297	SEQ ID NO: 299	SEQ ID NO: 301
	VL	DIVMTQSPSS LTVTAGEKVT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIWAS TRESGVPDRF TGSGSGTDFT LTISSVQAEDL	KSSQSLL NSGNQK NYLT	WASTRES	QNDYYYPFT

		AVYYCQNDY YYPFTFGSGT KLEKK			
		SEQ ID NO: 313	SEQ ID NO: 306	SEQ ID NO: 308	SEQ ID NO: 310
Ab15	VH	EVMLVESGG DLVKPGGSLK LSCAASGFTF STYTMSWVR QTPEKRLEWV ATIVGGGGYT YYLDSVKGRF TISRDNAKNT LYLQMISLRS EDTALYYCAR MGLTQRNAL DYWGQGTSIT VSS	TYTMS	TIVGGGG YTYLDS VKG	MGLTQRNA LDY
		SEQ ID NO: 322	SEQ ID NO: 315	SEQ ID NO: 317	SEQ ID NO: 319
	VL	DIVMTQSPSS LSVSEGEKVT LNCKSSQSLF NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGFGTDFTL TISSVQAEDL AVYYCQNDH TYPLTFGAGA KLELK	KSSQSLF NSGNQK NYLA	GASTRES	QNDHTYPLT
		SEQ ID NO: 331	SEQ ID NO: 324	SEQ ID NO: 326	SEQ ID NO: 328
Ab16	VH	EVMLVESGG GLVKPGGSLK LSCAASGFTF NSYTMSWVR QTPEKRLEWV ATITVIGGNT YYLDSVKGRF TISIDNGKNTL YLQMSSLRSE DTALYYCAR MGQTQRNAM DYWGQGTSV TVSS	SYTMS	TITVIGGN TYLDSV KG	MGQTQRNA MDY

		SEQ ID NO: 340	SEQ ID NO: 333	SEQ ID NO: 335	SEQ ID NO: 337
	VL	DIVMTQSPSS LSVSAGQKVT MRCKSSQSLL NSGNQKNYL AWYQQKLGQ PPKLLIYGAST RESGVPDRFS GSGSGTDFTL TITSVQAEDL AVYYCQNDY SFPLTFGAGT KLELK	KSSQSLL NSGNQK NYLA	GASTRES	QNDYSFPLT
		SEQ ID NO: 349	SEQ ID NO: 342	SEQ ID NO: 344	SEQ ID NO: 346
Ab17	VH	QVQLKESGPG LVAPSQSLSIT CTVSGFSLTS YAIWVRQPP GKGLEWLGEI WTGGGTNYN SALKSRLSISK DNSKSQVFLK MNSLQDDT ARYYCGRLSY GNSLDYWGQ GTTLTVSS	SYAIS	EIWTGGG TNYNSAL KS	LSYGNSLDY
		SEQ ID NO: 358	SEQ ID NO: 351	SEQ ID NO: 353	SEQ ID NO: 355
	VL	DIVMTQSPSS LTVTAGEKVT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIYWAS TRESGVPDRF TGSGSGTDFT LTVSSVQAED LAVYYCQNN FIYPLTFGPGT KLELK	KSSQSLL NSGNQK NYLT	WASTRES	QNNFIYPLT
		SEQ ID NO: 367	SEQ ID NO: 360	SEQ ID NO: 362	SEQ ID NO: 364
Ab18	VH	QVQLKESGPG LVAPSQSLSIT CTVSGFSLTT YGINWVRQPP GKGLEWLGVI	TYGIN	VIWGDGS TNYHSALI S	SSYYGNAM DY

		WGDGSTNYH SALISRLSISK DNSKSQVFLK LNSLQTDDTA TYYCVKSSYY GNAMDYWG QGTSVTVSS			
		SEQ ID NO: 376	SEQ ID NO: 369	SEQ ID NO: 371	SEQ ID NO: 373
	VL	DIVMTQSPSS LTVTAGETVT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIYWAS TRESGVPDRF TSGSGTDFT LTISSVQAEDL AVYYCQNVY SYPFTFGSGT KLEI	KSSQSLL NSGNQK NYLT	WASTRES	QNVVSYPT
		SEQ ID NO: 385	SEQ ID NO: 378	SEQ ID NO: 380	SEQ ID NO: 382
Ab19	VH	EVMLVESGG DLVKPGGSLK LSCAASGFSF SRYTMSWVR QTPEKRLEWV ATVSVGSGNT YYLDSVKGRF TISRDNANT LFLQMSSLRS EDTALYYCAR MGQTQRNAV DYWGQGTSV TVSS	RYTMS	TVSVGSG NTYYLDS VKG	MGQTQRNA VDY
		SEQ ID NO: 394	SEQ ID NO: 387	SEQ ID NO: 389	SEQ ID NO: 391
	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSLF NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISNVQAEDL AVYLCQNDH SFPLTFGAGT	KSSQSLL NSGNQK NYLA	GASTRES	QNDHSFPLT

		KLEL			
		SEQ ID NO: 403	SEQ ID NO: 396	SEQ ID NO: 398	SEQ ID NO: 400
Ab20	VH	EVMLVESGG GLVKPGGSLK LSCVASGFTF SSYTMSWVR QTPEKRLEWV ATIIGGYGNT YYSDSVKGR TISRDSAKNT LYLQMISLRS EDTALYYCTR LGQTQRNAM DYWGQGTSV TVSS	SYTMS	TIIGGYGN TYYSDSV KG	LGQTQRNA MDY
		SEQ ID NO: 412	SEQ ID NO: 405	SEQ ID NO: 407	SEQ ID NO: 409
	VL	DILMTQSPSSL SVSAGEKVT MNCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPFTFGAGT KLEL	KSSQSLL NSGNQK NYLA	GASTRES	QNDYYPFT
		SEQ ID NO: 421	SEQ ID NO: 414	SEQ ID NO: 416	SEQ ID NO: 418
Ab21	VH	EVMLVESGG GLVKPGGSLK LSCAASGFTF SSYTMSWVR QTPEKRLEWV ATIIGGYGNT YYVDSVKGR FTISRDSAKNT LYLQMISLRS EDTALYYCTR LGQTQRNAM DYWGQGTSV TVSS	SYTMS	TIIGGYGN TYYVDSV KG	LGQTQRNA MDY
		SEQ ID NO: 430	SEQ ID NO: 423	SEQ ID NO: 425	SEQ ID NO: 427

	VL	DILMTQSPSSL SVSAGEKVT MSCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPFTFGAGT KLEL	KSSQSLL NSGNQK NYLA	GASTRES	QNDYYPFT
		SEQ ID NO: 439	SEQ ID NO: 432	SEQ ID NO: 434	SEQ ID NO: 436
Ab22	VH	EVMLVESGG GLVKPGGSLK LSCAASGFTF SSYTMSWVR QTPEKRLEWV ATIIGGYGNT YYADSVKGR FTISRDSAKNT LYLQMISLRS EDTALYYCTR LGQTQRNAM DYWGQGTSV TVSS	SYTMS	TIIGGYGN TYYADSV KG	LGQTQRNA MDY
		SEQ ID NO: 448	SEQ ID NO: 441	SEQ ID NO: 443	SEQ ID NO: 445
	VL	DILMTQSPSSL SVSAGEKVT MSCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDTFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPFTFGAGT KLEL	KSSQSLL NSGNQK NYLA	GASTRES	QNDYYPFT
		SEQ ID NO: 457	SEQ ID NO: 450	SEQ ID NO: 452	SEQ ID NO: 454
Ab23	VH	EVMLVESGG GLVKPGGSLK LSCVASGFTF SSYTMSWVR QTPEKRLEWV ATLSVVGNT	SYTMS	TLSVVGG NTYYVDS VKG	LGQTQRNA MDY

		YYVDSVKGR FTISRDKAKN TLYLQMSSLR SEDTALYYCA RLGQTQRNA MDYWGQGTS VTVSS			
		SEQ ID NO: 466	SEQ ID NO: 459	SEQ ID NO: 461	SEQ ID NO: 463
	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY SYPLTFGAGT KLEL	KSSQSLL NSGNQK NYLA	GASTRES	QNDYSYPLT
		SEQ ID NO: 475	SEQ ID NO: 468	SEQ ID NO: 470	SEQ ID NO: 472
Ab24	VH	EVKLVESGGG LVKPGGSLKL SCAGSGFTFS SYTMSWVRQ TPEKRLEWVA TITIGVNIYYL DSVKGRFTIS RDNAKNTLY LQMNSLRSED TALYYCTRLG QTQRNAMDY WGQGTSVTV SS	SYTMS	TITIGVNI YYLDSVK G	LGQTQRNA MDY
		SEQ ID NO: 484	SEQ ID NO: 477	SEQ ID NO: 479	SEQ ID NO: 481
	VL	DIVMTQSPTS LSVSAGEKVT MTCKSSQSLF NSGNQKNYL AWYQEKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNVH FYPFTFGAGT	KSSQSLL NSGNQK NYLA	GASTRES	QNVHFYPFT

		KLEL			
		SEQ ID NO: 493	SEQ ID NO: 486	SEQ ID NO: 488	SEQ ID NO: 490
Ab25	VH	EAQLQQSGPE LVKPGASVKI FCKASGYTFT DYYINWVKQ SHGKSLEWIG DINPNNGGTT YNQKFKGKA TLTVDKSSST ASMELRRLTS EDSSVYYCAR RDAMDYWG QGTSVTVSS	DYYIN	DINPNNG GTTYNQK FKG	RDAMDY
		SEQ ID NO: 502	SEQ ID NO: 495	SEQ ID NO: 497	SEQ ID NO: 499
	VL	DIVMTQSQKF MSTTVGDRVS ITCTASQNVG PAVAWYQQK PGQSPKLLIYS ASRRFTGVPD RFTGSGSGTV FTLTINNVQSE DLADYFCQQ YISYPLTFGA GTKLELK	TASQNV GPAVA	SASRRFT	QQYISYPLT
		SEQ ID NO: 511	SEQ ID NO: 504	SEQ ID NO: 506	SEQ ID NO: 508
Ab26	VH	EVMLVESGG GLVKPGGSLK LSCTASGFTF RSYTMSWVR QTPEKRLEWV ATITGGGGNT YFLDSVKGRF TFSRDNAKNA LYLQMNSLRS EDTALYYCAR LGQTQRNAM DYWGQGTSV TVSS	SYTMS	TITGGGG NTYFLDS VKG	LGQTQRNA MDY
		SEQ ID NO: 520	SEQ ID NO: 513	SEQ ID NO: 515	SEQ ID NO: 517

	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSLL NSGNQMNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AIYYCQNDHT YPLTFGAGTK LEL	KSSQSLL NSGNQM NYLA	GASTRES	QNDHTYPLT
		SEQ ID NO: 529	SEQ ID NO: 522	SEQ ID NO: 524	SEQ ID NO: 526
Ab27	VH	QVQLQQSGA ELVRPGSSVKI SCKASGYAFS NYWMNWVK QRPQGGLWEI GQIYPGNGDT NYNGKFKGK ATLTADKSST TAYIQLSSLTS EDSAVYFCTR IYYGNSFAYW GQGTLVTVS	NYWMN	QIYPGNG DTNYNGK FKG	IYYGNSFAY
		SEQ ID NO: 538	SEQ ID NO: 531	SEQ ID NO: 533	SEQ ID NO: 535
	VL	DIVMTQSPSS LTVTAGERT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIWAS TRESGVPDRF TGSGSGTDFT LTISRVQAQD LAVYYCQND YYYPLTFGAG TKLELK	KSSQSLL NSGNQK NYLT	WASTRES	QNDYYYPLT
		SEQ ID NO: 547	SEQ ID NO: 540	SEQ ID NO: 542	SEQ ID NO: 544
Ab28	VH	QVQLKESGPG LVAPSQSLT CTVSGFSLTS HGVHWVRQP PGKGLEWLG VIWAGGSINF NSALMSRLSIS	SHGVH	VIWAGGS INFNSAL MS	DYYYGIGLD Y

		KDNSKNQVFL KMNSLQSD TAMYYCARD YYYGIGLDY WGQGTTLTV S			
		SEQ ID NO: 556	SEQ ID NO: 549	SEQ ID NO: 551	SEQ ID NO: 553
	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPFTFGSGT KLEIK	KSSQSLL NSGNQK NYLA	GASTRES	QNDYYYPFT
		SEQ ID NO: 565	SEQ ID NO: 558	SEQ ID NO: 560	SEQ ID NO: 562
Ab29	VH	EVLLQQSGPE LVKPGASVKI PCKASGYTLT DHSMDWVKQ SHGKSLEWIG NILPNNGGNI YNQKFRGKA TLTVDKSSST AYMELRSLTS EDTAVYNCA RGHYGNSFA YWGQGTTLVI VS	DHSMD	NILPNNG GNIYNQK FRG	GHYGN SFAY
		SEQ ID NO: 574	SEQ ID NO: 567	SEQ ID NO: 569	SEQ ID NO: 571
	VL	DIVMTQSPSS LTVRAGEKVT IYCKSSQSLFN SGNQKNYLT WYQQKPGQP PKLLIYWAST RESGVPHRFT GSGSGTDFTL TISSMQADDL ATYYCQNGY FFPYTFGGGT KLEIK	KSSQSLL NSGNQK NYLT	WASTRES	QNGYFFPYT

		SEQ ID NO: 583	SEQ ID NO: 576	SEQ ID NO: 578	SEQ ID NO: 580
Ab30	VH	QVQLKESGPG LVAPSQSL SITCTVSGFSLTK FGVNWVRQP PGKGLEWLG AIWGDGSTNY HSALISRLSIN KDNSKSQVFL KLSSLQNVDT ATYYCAKSG YGNAMDYW GHGTSVTVSS	KFGVN	AIWGDGS TNYHSALI S	SGYGNAMD Y
		SEQ ID NO: 592	SEQ ID NO: 585	SEQ ID NO: 587	SEQ ID NO: 589
	VL	DIVMTQSPSS LTVTTGEKVT LNCKSSQSLL NSGNLKNYLT WYQQRPGQP PKLLIYWAST RESGVPYRFT GSGSGTDFTL TISNVQAEDL AIYYCQNDYF FPFTFGSGTKL EIK	KSSQSLL NSGNLK NYLT	WASTRES	QNDYFFPFT
		SEQ ID NO: 601	SEQ ID NO: 594	SEQ ID NO: 596	SEQ ID NO: 598
Ab31	VH	QIQLAQSGPE LKKPGETVKI SCKASGYSFT NYGMNWVK QAPGKGLKW MGWINTYSG ETKYADDFK GRFDFSLETS ARTAYLQIKN LKIEDTATYF CARRDAMDY WGQGTSVTV SS	NYGMN	WINTYSG ETKYADD FKG	RDAMDY
		SEQ ID NO: 610	SEQ ID NO: 603	SEQ ID NO: 605	SEQ ID NO: 607
	VL	DIVMTQAAPS VPVTPGESVSI SCRSSKSLLN SNGNTYLYW	RSSKSLL NSNGNT YLY	RMSNLAS	MQHLEFPFT

		FLQRPQGSPQ LLIYRMSNLA SGVPDRFSGS GSGTAFTLRIS RVEAEDVGV YYCMQHLEFP FTFGSGTKLEI K			
		SEQ ID NO: 619	SEQ ID NO: 612	SEQ ID NO: 614	SEQ ID NO: 616
Ab32	VH	QVQLKESGPG LVAPSQSLTIT CTVSGFSLTS HGVHWVRQP PGKGLEWLG VIWAGGSINF NSALMSRLSIS KDNSKNQVFL KMNSLQSD TAMYYCARD YYYGIGLDY WGQGTTTLTV S	SHGVH	VIWAGGS INFNSAL MS	DYYYGIGLD Y
		SEQ ID NO: 628	SEQ ID NO: 621	SEQ ID NO: 623	SEQ ID NO: 625
	VL	DIVMTQSPSS LSVSAGEKVT MSCKSSQSLL NSGNQKNYL AWYQQKPGQ PPKLLIYGAST RESGVPDRFT GSGSGTDFTL TISSVQAEDL AVYYCQNDY YYPFTFGSGT KLEIK	KSSQSLL NSGNQK NYLA	GASTRES	QNDYYPFT
		SEQ ID NO: 637	SEQ ID NO: 630	SEQ ID NO: 632	SEQ ID NO: 634
Ab33	VH	DVNLVESGG GLVKPGGSLK LSCAASGFTF SSYTMSWVR QTPEKRLEWV ATITYGRIYTY YLDVSKGRFT ISRDNKNTL YLMSSLRSE DTAMYYCTR	SYTMS	TITYGRIY TYYLDV KG	MITGNAMDS

		MITGNAMDS WGLGTSVTVS S			
		SEQ ID NO: 646	SEQ ID NO: 639	SEQ ID NO: 641	SEQ ID NO: 643
	VL	DIVMTQSPSS LTVTAGEKVT MSCKSSQSLL NSGNQKNYL TWYQQKPGQ PPKLLIWAS TRESGVPDRF TGSGSGTDFT LTISGVQGED LAVYYCQND YSYPLTFGGG TKLELK	KSSQSLL NSGNQK NYLT	WASTRES	QNDYSYPLT
		SEQ ID NO: 655	SEQ ID NO: 648	SEQ ID NO: 650	SEQ ID NO: 652
Ab34	VH	EVLQQSGPE LVKPGASVKI PCKASGYTFS DYNMDWVK QSHGKSLEWI GHINPNNDNT IYNQKFKGKA TLTVDKSSNT AYMDLRSLSS EDTAVYYCA RGAYYGNSM DYWGQGTSV TVSS	SDYNMD	HINPNND NTIYNQK FKG	GAYYGNSM DY
		SEQ ID NO: 664	SEQ ID NO: 657	SEQ ID NO: 659	SEQ ID NO: 661
	VL	DIVMTQSPSS LTVTAGERT MSCKSSQSLL NGGNQRNYL TWYQQKPGQ SPKLLIWAS TWESGVPDRF TGSGSGTDFT LTISSVQAEDL AVYYCQNAY FYPYTFGGGT KLEIK	KSSQSLL NGGNQR NYLT	WASTWES	QNAYFYPT
		SEQ ID NO: 673	SEQ ID NO: 666	SEQ ID NO: 668	SEQ ID NO: 670

Ab35	VH	DVFLQESGPG LVKPSQSLSL TCTVTGYSITS DYAWNWRQ FPGNKLEWVT YIGYSGTTSY NPSLKSRSIT RDTSKNQFFL QLNSVSTEDT ATYYCVRRGS YYGSYWFFD VWGAGTTVT VSS	SDYAWN	YIGYSGTT SYNPSLKS	RGSYYGSY WFFDV
		SEQ ID NO: 682	SEQ ID NO: 675	SEQ ID NO: 677	SEQ ID NO: 679
	VL	QVVLSQSPAI LSASPGEKVT MTCRASSSVS YMHYQQKP GSSPKPWIYA TSNLASGVPP HFGSGSGSTS YSLTISRVEAE DAATYYCQQ WTSNPPTFGG GTKLEIK	RASSSVS YMH	ATSNLAS	QQWTSNPPT
		SEQ ID NO: 691	SEQ ID NO: 684	SEQ ID NO: 686	SEQ ID NO: 688
Ab36	VH	EVKLEESGGG LVQPGGSMK LSCVASGFTF SNYWMNWV RQSPEKGLEW VAQIRLKSDN YATHYAESV KGMFTISRDD SKSSVYLQMN NLRAEDTGIY YCTAGGDYW GQGTTLTVSS	NYWMN	QIRLKSD NYATHYA ESVKG	GGDY
		SEQ ID NO: 161	SEQ ID NO: 693	SEQ ID NO: 695	SEQ ID NO: 697
	VL	DIVMTQSQKF MSTTVGDRVS ITCKASQNVG TAVAWYHQK PGQSPKLLIYS ASNRYTGVPD RFIGSGSGTDF	KASQNV GTAVA	SASNRYT	QQYINYLLT

		TLTISNVQSED LGNYFCQQYI NYLLTFGSGT KLEIK			
		SEQ ID NO: 170	SEQ ID NO: 163	SEQ ID NO: 165	SEQ ID NO: 167
Ab37	VH	EVKLEESGGG LVQPGGSMK LSCVASGFTF SNYWMNWV RQYPEQGLE WVAQIRLNSD NYATHYAES VKGRFTISRD DSRSTVYLQM NNLRAEDTGI YYCTGGGEY WGQGTTLTV SS	NYWMN	QIRLNSD NYATHYA ESVKG	GGEY
		SEQ ID NO: 179	SEQ ID NO: 172	SEQ ID NO: 174	SEQ ID NO: 176
	VL	DIVMTQSQKF MSTTIGDRVSI TCKASQNVDT AWAWYQQKP GQSPKLLIYS ASTRYTGVPD RFTGSGSGTD FTLTISNMQSE DLADYFCQQ YISYQLTFGA GTKLELK	KASQNV DTAVA	SASTRYT	QQYISYQLT
		SEQ ID NO: 188	SEQ ID NO: 181	SEQ ID NO: 183	SEQ ID NO: 185
Ab38	VH	QIQLVQSGPE LKKPGETVKI SCKASGYTFT NYGMSWVKQ APGKGLKWM GWINTYSGVP TYADDFKGRF VFSLEASAST AYLQINNLIK EDAATYFCSR WSGPDPLEDH WGQGTTLTV SS	NYGMS	WINTYSG VPTYADD FKG	WSGPDPLED H
		SEQ ID NO: 76	SEQ ID NO: 190	SEQ ID NO: 192	SEQ ID NO: 194

	VL	QIVLTQSPAIM SASPGEKVTM TCTASLSLNYI HWYRQRSGT SPKRWIYDTS KLASGVPSRF SGSGSGTSYS LTISSMEAED AATYYCQQW SSNPWTFGGG TKLEIK	TASLSLN YIH	DTSKLAS	QQWSSNPW T
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[00127] Also within the scope of the present disclosure are functional variants of any of the exemplary anti-CLDN18 antibodies as disclosed herein, for example, in Table 1. Such functional variants are substantially similar to the exemplary antibody, both structurally and functionally. A functional variant comprises substantially the same VH- and VL-CDRs as the exemplary antibody. For example, it may comprise only up to 3 (*e.g.*, 2 or 1) amino acid residue variations in the total CDR regions of the antibody and binds the same epitope of CLDN18.2 with substantially similar affinity (*e.g.*, having a mean fluorescence intensity (MFI) value in the same order). Alternatively or in addition, the amino acid residue variations are conservative amino acid residue substitutions.

[00128] Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, *e.g.* Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

[00129] CDRs are known to be responsible for antigen binding, however, it has been found that not all of the 6 CDRs are indispensable or unchangeable. In other words, it is possible to replace or change or modify one or more CDRs in Ab01-Ab38,

yet substantially retain the specific binding affinity to CLDN, in particular, to CLDN18.2

[00130] In certain embodiments, the anti-CLDN18 antibodies provided herein comprise a VH-CDR 1 having an amino acid sequence selected from the group consisting of GDY, SEQ ID NOs: 18, 36, 54, 72, 90, 108, 126, 144, 163, 181, 198, 216, 234, 252, 270, 288, 206, 324, 342, 360, 378, 396, 414, 432, 450, 468, 486, 504, 522, 540, 558, 576, 594, 612, 630, 648, 666 and 684, a VH-CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 20, 38, 56, 74, 92, 110, 128, 146, 165, 183, 200, 218, 236, 254, 272, 290, 308, 326, 344, 362, 380, 398, 416, 434, 452, 470, 488, 506, 524, 542, 560, 578, 596, 614, 632, 650, 668 and 686, a VH-CDR3 having an amino acid sequence selected from the group consisting of GDY and SEQ ID NOs: 22, 40, 58, 94, 112, 130, 148, 167, 185, 202, 220, 238, 256, 274, 292, 310, 328, 346, 364, 382, 400, 418, 436, 454, 472, 490, 508, 526, 544, 562, 580, 598, 616, 634, 652, 670 and 688; and optionally a VL-CDR 1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 45, 63, 81, 99, 117, 135, 153, 172, 190, 207, 225, 243, 261, 279, 297, 315, 333, 351, 369, 387, 405, 423, 441, 459, 477, 495, 513, 531, 549, 567, 585, 603, 621, 639, 657, 675 and 693, a VL-CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 47, 65, 83, 101, 119, 137, 155, 174, 192, 209, 227, 245, 263, 281, 299, 317, 335, 353, 371, 389, 407, 425, 443, 461, 479, 497, 515, 533, 551, 569, 587, 605, 623, 641, 659, 677 and 695, a VL-CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 49, 67, 85, 103, 121, 139, 157, 176, 194, 211, 229, 247, 265, 283, 301, 319, 337, 355, 373, 391, 409, 427, 445, 463, 481, 499, 517, 535, 553, 571, 589, 607, 625, 643, 661, 679 and 697, as shown in Table 1.

[00131] In certain embodiments, the anti-CLDN18 antibodies provided herein further comprise suitable framework region (FR) sequences, as long as the antibodies can specifically bind to CLDN18.2. The CDR sequences provided in Table 1 are obtained from a mouse antibody, but they can be grafted to any suitable FR sequences

of any suitable species such as mouse, human, rat, rabbit, among others, using suitable methods known in the art such as recombinant techniques.

[00132] In certain embodiments, the anti-CLDN18 antibodies provided herein further comprise one light chain constant domain and/or one or more heavy chain constant domains. When needed, the anti-CLDN18 antibodies as described herein may comprise a modified constant region. For example, it may comprise a modified constant region that can enhance antibody-dependent cell mediated cytotoxicity (ADCC). ADCC activity can be assessed using methods disclosed in U.S. Pat. No. 5,500,362. In certain embodiments, the modified constant region comprises an amino acid sequence of SEQ ID NOs: 701-702 as shown in Table 2, wherein S122D, A213L and I215E were bolded and underlined.

[00133] Table 2. Amino acid sequences of Fc regions.

SEQ ID NO	Name	Amino acid sequence
700	Human IgG1 Heavy Chain Fc-wt	ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVDVSH DPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVSVLTVLH QDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPP SRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPP VLDSGDGSFFLYSKLTVDKSRW QQGNVFSFSVMHEALHNHYT QKSLSLSPGK
701	Human IgG1 Heavy Chain Fc-DE Mutation	ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGP <u>D</u> VFLFPPKPK KDTLMISRTPEVTCVVDVSH EDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVSVLTVL HQDWLNGKEYKCKVSNKALP A <u>P</u> EEKTISKAKGQPREPQVYTL

		PPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTP PVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
702	Human IgG1 Heavy Chain Fc- DLE Mutation	ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPDVFLFPPKP KDTLMISRTPEVTCVVDVSH EDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALP LPEEKISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTP PVLDSGDSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
703	Mouse IgG2a Heavy Chain Fc	AKTTAPSVYPLAPVCGDTTGSS VTLGCLVKGYFPEPVTLTWNS GSLSSGVHTFPAVLQSDLYTLS SSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPC KCPAPNLLGGPSVFIFPPKIKDV LMISLSPIVTCVVDVSEDDPD VQISWFWNNVEVHTAQTQTHR EDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLPAPIERTI SKPKGSVRAPQVYVLPPEEE MTKKQVTLTCMVTDFMPEDIY VEWTNNGKTELNYKNTEPVLD SDGSYFMYSKLRVEKKNWVE RNSYSCSVVHEGLHNHHTTKS FSRTPGK

[00134] Antibody heavy and light chain constant regions are well known in the art, *e.g.*, those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php, both of which are incorporated by reference herein.

[00135] In one example, the antibodies described herein are a humanized antibody. Humanized antibodies refer to forms of non-human (*e.g.*, murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or

antigen-binding fragments thereof that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin.

[00136] Methods for constructing humanized antibodies are also well known in the art (see, *e.g.*, Queen *et al.*, Proc. Natl. Acad. Sci. USA, 86:10029-10033 (1989)). In one example, variable regions of V_H and V_L of a parent non-human antibody are subjected to three-dimensional molecular modeling analysis following methods known in the art. Next, framework amino acid residues predicted to be important for the formation of the correct CDR structures are identified using the same molecular modeling analysis. In parallel, human V_H and V_L chains having amino acid sequences that are homologous to those of the parent non-human antibody are identified from any antibody gene database using the parent V_H and V_L sequences as search queries. Human V_H and V_L acceptor genes are then selected.

[00137] In another example, the antibody described herein is a chimeric antibody, which can include a heavy constant region or a part thereof and/or a light constant region or a part thereof from a human antibody. Chimeric antibodies refer to

antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (*e.g.*, a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

[00138] “chAb01-chAb38” as used herein refers to chimeric antibodies based on Ab01-Ab38, each of which comprises a mouse heavy chain variable region as shown in Table 1, and a mouse light chain variable region as shown in Table 1, fused respectively to human heavy chain constant region and human light chain constant region. In certain embodiments, the human heavy chain constant region and human light chain constant region are from human IgG1. In certain embodiments, the human heavy chain constant region and human light chain constant region are from wild-type human IgG1 having an amino acid sequence of SEQ ID NO: 700 as shown in Table 2.

[00139] In certain embodiments, the anti-CLDN18 antibodies provided herein may contain one or more modifications or substitutions in one or more variable region sequences provided herein, yet retaining specific binding affinity to CLDN18. In certain embodiments, at least one (or all) of the substitution(s) in the CDR sequences, FR sequences, or variable region sequences is a conservative substitution(s).

[00140] Various methods known in the art can be used to achieve this purpose. For example, a library of antibody variants (such as Fab or scFv variants) can be generated and expressed with phage display technology, and then screened for the binding affinity to human CLDN18. For another example, computer software can be used to virtually simulate the binding of the antibodies to CLDN18, and identify the amino acid residues on the antibodies which form the binding interface. Such residues may be either avoided in the substitution so as to prevent reduction in binding affinity, or targeted for substitution to provide for a stronger binding.

[00141] In some embodiments, the anti-CLDN18 antibodies may comprise heavy chain CDRs that are at least 80% (e.g., 85%, 90%, 95%, or 98%) sequence identity, individually or collectively, as compared with the VH-CDRs of the exemplary antibodies described herein and as shown in Table 1. Alternatively or in addition, the anti-CLDN18 antibodies may comprise light chain CDRs that are at least 80% (e.g., 85%, 90%, 95%, or 98%) sequence identity, individually or collectively, as compared with the VL-CDRs of the exemplary antibodies described herein and as shown in Table 1.

[00142] In certain embodiments, the anti-CLDN18 antibodies provided herein comprise a constant region capable of inducing effector function such as ADCC or CDC. Effector functions such as ADCC and CDC can lead to cytotoxicity to cells expressing CLDN18, and can be evaluated using various assays such as Fc receptor binding assay, C1q binding assay, and cell lysis assay. In certain embodiments, the constant region is of IgG1 isotype, which is known to induce ADCC.

[00143] In certain embodiments, the anti-CLDN18 antibodies comprise one or more modifications in the constant region that renders enhanced ADCC. As used herein, the term “enhanced ADCC” is defined as either an increase in the number of target cells that are lysed in a given time, at a given concentration of antibody in the medium surrounding the target cells, by the mechanism of ADCC defined above, and/or a reduction in the concentration of antibody, in the medium surrounding the target cells, required to achieve the lysis of a given number of target cells in a given time, by the mechanism of ADCC.

[00144] **Characterization of Anti-CLDN18 antibodies**

[00145] Binding affinity

[00146] In certain embodiments, the anti-CLDN18 antibodies provided herein specifically bind to human CLDN18, mouse CLDN18, and Ehesus monkey CLDN18. In certain embodiments, the anti-CLDN18 antibodies provided herein more

specifically bind to human CLDN18.2, mouse CLDN18.2, and Ehesus monkey CLDN18.2 than corresponding CLDN18.1.

[00147] In certain embodiments, specific binding of the antibodies provided herein to human CLDN18.2 is represented by “half maximal effective concentration” (EC_{50}) value, which refers to the concentration of an antibody where 50% of its maximal effect (e.g., binding) is observed. The EC_{50} value can be measured by methods known in the art, for example, sandwich assay such as ELISA, Western Blot, flow cytometry assay, and other binding assay. In certain embodiments, the antibodies provided herein specifically bind to human CLDN18.2 at an EC_{50} (i.e. 50% binding concentration) of no more than 6 nM, no more than 5 nM, no more than 4 nM, no more than 3 nM, no more than 2 nM, no more than 1.5 nM, no more than 1 nM, no more than 0.9 nM, no more than 0.8 nM, no more than 0.7 nM, no more than 0.6 nM, no more than 0.5 nM, no more than 0.4 nM, no more than 0.3 nM, no more than 0.2 nM or no more than 0.1 nM measured by FACs.

[00148] In certain embodiments, specific binding of the antibodies to human CLDN18.2 is represented by median fluorescence intensity (MFI) or maximum MFI (MAX MFI) as measured by FACs. Higher MAX MFI indicates higher binding affinity when the measurement conditions remain the same among different samples. Differences in binding affinity (e.g., for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold.

[00149] In certain embodiments, the antibodies provided herein have a specific binding affinity to human CLDN18.2 which is sufficient to provide for diagnostic and/or therapeutic use. In certain embodiments, the antibodies provided herein have a specific binding affinity to human CLDN18.2, the expression of which is too low to be specifically bound by existing anti-CLDN18.2 antibodies, such as IMAB362. In certain embodiments, the antibodies provided herein specifically bind to CLDN18.2 low-expressing cells with less than 10000 anti-CLDN18.2 antibody binding sites per cell, less than 9000 anti-CLDN18.2 antibody binding sites per cell, less than 8000 anti-CLDN18.2 antibody binding sites per cell, less than 7000 anti-

CLDN18.2 antibody binding sites per cell, less than 6000 anti-CLDN18.2 antibody binding sites per cell, or less than 5000 anti-CLDN18.2 antibody binding sites per cell, or less than 4000 anti-CLDN18.2 antibody binding sites per cell.

[00150] ADCC

[00151] To assess ADCC activity of a molecule of interest, an in vitro ADCC assay, such as that described in U.S. Pat. No. 5,500,362; Hellstrom et al. Proc Natl Acad Sci USA 83, 7059-7063 (1986) and Hellstrom et al, Proc Natl Acad Sci USA 82, 1499-1502 (1985); U.S. Patent No. 5,821,337; or Bruggemann et al, J Exp Med 166, 1351-1361 (1987) may be performed. Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (Cell Technology Inc., Mountain View, CA); and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI)). Additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al., PNAS (USA) 95:652-656 (1998).

[00152] ADCC activity of an antibody can be enhanced by engineering the glycosylation forms of the antibody. A number of glycosylation forms have been reported to enhance ADCC activity of an antibody through enhancing its binding to the Fc receptor of the effector cells. The different glycosylation form includes any of several forms of glycans attached to the antibody, with different saccharides (e.g., lacks one type of saccharide such as fucose, or has a high level of one type of saccharide such as mannose), or having a different structure (e.g., various branched structure, such as biantennary (two branches), triantennary (three branches) or tetraantennary (four branches) structures).

[00153] In certain embodiments, the anti-CLDN18 antibodies provided herein are glyco-engineered. A “glyco-engineered” antibody or antigen-binding fragment may have an increased or decreased glycosylation level, a change in the glycosylation form, or both, as compared to its non-glyco-engineered counterpart. In certain embodiments, the glyco-engineered antibodies exhibit enhanced ADCC activity than its non-engineered counterpart. In some embodiments, the enhanced ADCC activity

is characterized in at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 65%, 70%, or 75% higher lysis of CLDN18.2 expressing cell.

[00154] The antibodies can be glyco-engineered by methods known in the art, including any manipulation to the peptide backbone (e.g., modifications to the amino acid sequence, and/or to the side chain group of individual amino acids), and/or, manipulation to the post-translational modifications through a host cell line (e.g., modifications to glycosylation pattern). Methods of altering ADCC activity by engineering of glycosylation of an antibody have also been described in the art, see for example, Weikert et al. (1999) *Nature Biotech.*, 17:116- 121; Shields R. L. et al. (2002), *J. Biol. Chem.*, 277: 26733-26740; Shinkawa et al. (2003), *J Biol Chem.*, 278, 3466-3473; Ferrara et al. (2006), *Biotech. Bioeng.*, 93, 851-861; Yamane-Ohnuki et al.(2004), *Biotech Bioeng.*, 87, 614-622; Niwa et al.(2006), *J Immunol Methods* 306, 151-160; Shinkawa T. et al, *J. Biol. Chem*, (2003), 278: 3466-3473.

[00155] In some embodiments, the glyco-engineered antibodies provided herein are afucosylated (i.e. contain no fucose). Several studies have shown that afucosylated (i.e., fucose deficient, or non-fucosylated) antibody exhibited an increased binding to CLDN18.2 and thus provoked a higher ADCC activity (Shields et al. (2002) *J. Biol. Chem.*, 277:26733-26740; Shinkawa et al. (2003) *J. Biol. Chem.*, 278:3466-3473; and European Patent Appln. Pub. No. 1176195). In some embodiments, the afucosylated antibody provided herein lacks fucose at asparagine 297 (Asn297) of the heavy chain (based on Kabat numbering). Asn297 is a conserved N-linked glycosylation site found in each CH2 domain of the Fc region of IgG1 isotype of antibodies (Arnold et al., *Glycobiology and Medicine*, 564:27-43, 2005).

[00156] In some embodiments, the glyco-engineered antibodies provided herein are characterized in a high mannose glycosylation form (e.g., mannose e5, mannose 7, 8, 9 glycan). High mannose glycosylation form has been proved to enhance ADCC activity (Yu et al. (2012), *Landes Bioscience, mAbs* 4:4, 475-487).

[00157] In some embodiments, the antibody provided herein further comprises within its constant region one or more modifications which: a) introduces or removes

a glycosylation site, b) introduces a free cysteine residue, c) enhances binding to an activating Fc receptor, and/or d) enhances ADCC.

[00158] Antigen-binding fragments

[00159] The present disclosure also provides antigen-binding fragments that can specifically bind to CLDN18. Various types of antigen-binding fragments are known in the art and can be developed based on the anti-CLDN18 antibodies provided herein, including for example, the exemplary antibodies whose CDR and variable sequences are shown in Table 1, and their different variants containing modification or substitution.

[00160] In certain embodiments, an anti-CLDN18 antigen-binding fragment provided herein is a camelized single domain antibody, a diabody, a single chain Fv fragment (scFv), an scFv dimer, a dsFv, a (dsFv)₂, a dsFv-dsFv', an Fv fragment, a Fab, a Fab', a F(ab')₂, a ds-diabody, a nanobody, a domain antibody, or a bivalent domain antibody.

[00161] Various techniques can be used for the production of such antigen-binding fragments. Illustrative methods include, enzymatic digestion of intact antibodies (see, e.g., Morimoto et al., *Journal of Biochemical and Biophysical Methods* 24:107-117 (1992); and Brennan et al., *Science*, 229:81 (1985)), recombinant expression by host cells such as *E. Coli* (e.g. for Fab, Fv and ScFv antibody fragments), screening from a phase display library as discussed above (e.g. for ScFv), and chemical coupling of two Fab'-SH fragments to form F(ab')₂ fragments (Carter et al., *Bio/Technology* 10:163-167 (1992)). Other techniques for the production of antibody fragments will be apparent to a skilled practitioner.

[00162] In certain embodiments, the antigen-binding fragment is a scFv. Generation of scFv is described in, for example, WO 93/16185; U.S. Pat. Nos. 5,571,894; and 5,587,458. ScFv may be fused to an effector protein at either the amino or the carboxyl terminus to provide for a fusion protein (see, for example, *Antibody Engineering*, ed. Borrebaeck).

[00163] Conjugates

[00164] In some embodiments, the anti-CLDN18 antibodies further comprise a conjugate moiety. The conjugate moiety can be linked to an antibody provided herein. A conjugate moiety is a non-proteinaceous or peptic moiety that can be attached to the antibody. It is contemplated that a variety of conjugate moieties may be linked to the antibodies provided herein (see, for example, “Conjugate Vaccines”, Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr. (eds.), Carger Press, New York, (1989)). The conjugate moiety may be linked to the antibody by covalent binding, affinity binding, intercalation, coordinate binding, complexation, association, blending, or addition, among other methods.

[00165] In certain embodiments, the anti-CLDN18 antibodies is linked to one or more conjugates via a linker. In certain embodiments, the linker is a hydrazine linker, a disulfide linker, a bifunctional linker, dipeptide linker, glucuronide linker, or a thioether linker. In certain embodiments, the linker is a lysosomally cleavable dipeptide, e.g. valine-citrulline (vc).

[00166] The conjugate moiety can be a therapeutic agent (e.g., a cytotoxic agent), a radioactive isotope, a detectable label (e.g., a lanthanide, a luminescent label, a fluorescent label, or an enzyme-substrate label), a pharmacokinetic modifying moiety, or a purifying moiety (such as a magnetic bead or nanoparticle).

[00167] Examples of detectable label may include a fluorescent label (e.g. fluorescein, rhodamine, dansyl, phycoerythrin, or Texas Red), enzyme-substrate label (e.g. horseradish peroxidase, alkaline phosphatase, luciferases, glucoamylase, lysozyme, saccharide oxidases or β -D-galactosidase), radioisotope, luminescent label, chromophoric moiety, digoxigenin, biotin/avidin, a DNA molecule or gold for detection.

[00168] Examples of radioisotopes may include ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{35}S , ^3H , ^{111}In , ^{112}In , ^{14}C , ^{64}Cu , ^{67}Cu , ^{86}Y , ^{88}Y , ^{90}Y , ^{177}Lu , ^{211}At , ^{186}Re , ^{188}Re , ^{153}Sm , ^{212}Bi , ^{32}P

and other lanthanides. Radioisotope labelled antibodies are useful in receptor targeted imaging experiments.

[00169] In certain embodiments, the pharmacokinetic modifying moiety can be a clearance-modifying agent which helps increase half-life of the antibody. Illustrative examples include water-soluble polymers, such as PEG, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, copolymers of ethylene glycol/propylene glycol, and the like. The polymers may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules.

[00170] In certain embodiments, the conjugate moiety can be a purification moiety such as a magnetic bead or a nanoparticle.

[00171] Antibody-Drug Conjugates

[00172] In certain embodiments, the conjugates provided herein are antibody-drug conjugates (ADC) comprising any of the above anti-CLDN18 antibodies conjugated to a cytotoxic agent. In other words, the conjugate moiety comprises a cytotoxic agent.

[00173] ADCs can be useful for local delivery of a cytotoxic agent, for example, in the treatment of cancer. This allows for targeted delivery of cytotoxic agents to tumors and intracellular accumulation therein, which is particularly useful where systemic administration of these unconjugated cytotoxic agents may result in unacceptable levels of toxicity to normal cells as well as the tumor cells sought to be eliminated (Baldwin et al., (1986), *Lancet*, 603-05; Thorpe, (1985), *Monoclonal Antibodies*, 84; Pinchera et al. (ed.s), *Biological And Clinical Applications*, 475-506; Syrigos and Epenetos (1999), *Anticancer Research* 19:605-614; Niculescu-Duvaz and Springer (1997) *Adv. Drg Del. Rev.* 26:151-172; and U.S. Pat. No. 4,975,278).

[00174] A “cytotoxic agent” can be any agent that is detrimental to cancer cells or that can damage or kill cancer cells. In certain embodiments, the cytotoxic agent is

optionally a chemotherapeutic agent (such as a growth inhibitory agent, a DNA-alkylators, a topoisomerase inhibitor, a tubulin-binders, or other anticancer drugs), a toxin, or a highly reactive radioactive isotope.

[00175] Examples of cytotoxic agent include large molecular bacterial toxins and plant toxins, such as for example, diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin, abrin, modeccin, alpha-sarcin, Aleurites fordii, proteins, dianthin proteins, *Phytolaca americana* proteins (PARI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, restrictocin, phenomycin, enomycin, and the tricothecenes (see, e.g., WO 93/21232). Such a large molecule toxin can be conjugated to the antibodies provided herein using methods known in the art, for example, as described in Vitetta et al (1987) Science, 238:1098.

[00176] The cytotoxic agent can also be small molecule toxins and chemotherapeutic drugs, such as geldanamycin (Mandler et al (2000) Jour. of the Nat. Cancer Inst. 92(19):1573-1581; Mandler et al (2002) Bioconjugate Chem. 13:786-791), maytansinoids (EP 1391213; Liu et al., (1996) Proc. Natl. Acad. Sci. USA 93:8618-8623), calicheamicin (Lode et al (1998) Cancer Res. 58:2928; Hinman et al (1993) Cancer Res. 53:3336-3342), taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, vindesine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin and analogs thereof, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic

agents (e.g., vincristine and vinblastine), calicheamicin, maytansinoids, dolastatins, auristatins (such as monomethyl auristatin E (MMAE) and Monomethyl auristatin F (MMAF)), a trichothecene, and CC1065, and the derivatives thereof having cytotoxic activity. Such toxin can be conjugated to the antibodies provided herein using methods known in the art, for example, as described in US7,964,566; Kline, T. et al, *Pharmaceutical Research*, 32(11): 3480-3493.

[00177] The cytotoxic agent can also be a highly radioactive isotope. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. Methods of conjugation of a radioisotope to an antibody is known in the art, for example, via a suitable ligand reagent (see, e.g., WO94/11026; *Current Protocols in Immunology*, Volumes 1 and 2, Coligen et al, Ed. Wiley-Interscience, New York, N.Y., Pubs. (1991)). A ligand reagent has a chelating ligand that can bind, chelate or otherwise complex a radioisotope metal, and also has a functional group that is reactive with a thiol of cysteine of an antibody or antigen-binding fragment. Exemplary chelating ligands include DOTA, DOTP, DOTMA, DTPA and TETA (Macrocyclics, Dallas, Tex.).

[00178] In certain embodiments, the antibodies are attached to the conjugate moiety via a linker, for example, a hydrazine linker, a disulfide linker, a bifunctional linker, dipeptide linker, glucuronide linker, or a thioether linker.

[00179] Exemplary bifunctional linkers include, such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene).

[00180] In certain embodiments, the linker is cleavable under a particular physiological environment, thereby facilitating release of the cytotoxic agent in the cell. For example, the linker can be an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Research* 52:127-131 (1992); U.S. Pat. No. 5,208,020). In some embodiments, the linker may comprise amino acid residues, such as a dipeptide, a tripeptide, a tetrapeptide or a pentapeptide. The amino acid residues in the linker may be natural or non-naturally occurring amino acid residues. Examples of such linkers include: valine-citrulline (ve or val-cit), alanine-phenylalanine (af or ala-phe), glycine-valine-citrulline (gly-yl-cit), glycine-glycine-glycine (gly-gly-gly), an valine-citrullin-p-aminobenzyloxycarbonyl ("vc-PAB"). Amino acid linker components can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzyme, for example, a tumor-associated protease, cathepsin B, C and D, or a plasmin protease.

[00181] The ADC provided herein may be prepared by any suitable methods known in the art. In certain embodiments, a nucleophilic group of the antibody is first reacted with a bifunctional linker reagent and then linked to the cytotoxic agent, or the other way around, i.e., first reacting a nucleophilic of the cytotoxic agent with a bifunctional linker and then linking to the antibody.

[00182] In certain embodiments, the cytotoxic agent may contain (or modified to contain) a thiol reactive functional group which may react with a cysteine thiol of a free cysteine of the antibodies provided herein. Exemplary thiol-reactive functional group include, for example, a maleimide, an iodoacetamide, a pyridyl disulfide, haloacetyl, succinimidyl ester (e.g., NHS, N-hydroxysuccinimide), isothiocyanate, sulfonyl chloride, 2,6-dichlorotriazinyl, pentafluorophenyl ester, or phosphoramidite (Haugland, 2003, *Molecular Probes Handbook of Fluorescent Probes and Research Chemicals*, Molecular Probes, Inc.; Brinkley, 1992, *Bioconjugate Chem.* 3:2; Garman, 1997, *Non-Radioactive Labelling: A Practical Approach*, Academic Press, London; Means (1990) *Bioconjugate Chem.* 1:2; Hermanson, G. in *Bioconjugate Techniques* (1996) Academic Press, San Diego, pp. 40-55, 643-671).

[00183] The cytotoxic agent or the antibody may react with a linking reagent before being conjugated to form the ADC. For example, N-hydroxysuccinimidyl ester (NHS) of a cytotoxic agent may be performed, isolated, purified, and/or characterized, or it may be formed in situ and reacted with a nucleophilic group of an antibody.

[00184] In some embodiments, the cytotoxic agent and the antibody may be linked by in situ activation and reaction to form the ADC in one step. In another example, the antibody may be conjugated to biotin, then indirectly conjugated to a second conjugate that is conjugated to avidin.

[00185] In certain embodiments, the conjugate moiety is randomly attached to a specific type of surface-exposed amino acid residue in the antibody, for example a cysteine residue or a lysine residue.

[00186] In certain embodiments, the conjugate moiety is attached to a specifically defined site to provide ADC populations with high homogeneity and batch-to-batch consistency with respect to drug-to-antibody ratio (DAR) and attachment site. In certain embodiments, the conjugate moiety is attached to specifically defined sites in antibody molecules via natural amino acids, unnatural amino acid, short peptide tags, or Asn297 glycans. For example, the conjugation may be at a specific site outside the epitope binding portion.

[00187] Site-specific attachment can be achieved by substituting a native amino acid at a specific site of the antibody with, or introducing before/after a specific site of the antibody, an amino acid such as cysteine to which a drug moiety can be conjugated (see Stimmel et al. (2000), JBC, 275(39):30445-30450; Junutula et al. (2008), Nature Biotechnology, 26(8):925-932; and WO2006/065533). Alternatively, site-specific conjugation can be achieved by engineering antibodies to contain unnatural amino acids (e.g., p-acetylphenylalanine (pAcF), N6-((2-azidoethoxy)carbonyl)-L-lysine, p-azidomethyl-L-phenylalanine (pAMF), and selenocysteine (Sec)) at specific sites in their heavy and/or light chains as described by Axup et al. ((2012), Proc Natl Acad Sci USA. 109(40):16101-16116), wherein the unnatural amino acids provide the additional advantage that orthogonal chemistry can

be designed to attach the linker reagent and drug. Exemplary specific sites (e.g., light chain V205, heavy chain A114, S239, H274, Q295, S396, etc.) useful in the two above-described site-specific conjugation method are described in many prior arts, for example, Strop et al. (2013), *Chemistry & Biology*, 20, 161-167; Qun Zhou (2017), *Biomedicines*, 5, 64; Dimasi et al. (2017), *Mol. Pharm.*, 14, 1501–1516; WO2013/093809 and WO2011/005481. Another site-specific ADC conjugation method is glycan-mediated conjugation, in which a drug-linker can be conjugated to Asn297 glycans (such as fucose, galactose, N-acetylgalactosamine, N-acetylglucosamine, sialic acid) located in CH2 domain instead of coupling the relatively hydrophobic cytotoxic agent into amino acid backbone of the antibody. Efforts have also been made to introduce unique short peptide tags (such as LLQG, LPETG, LCxPxR) into antibodies via specific sites (e.g., sites in N terminal or C terminal regions), which then allow specific amino acids in the peptide tags to be functionalized and coupled to the drug-linkers (Strop et al. (2013), *Chemistry & Biology*, 20, 161-167; Beerli et al. (2015), *PLoS ONE*, 10, e0131177; Wu et al. (2009), *Proc. Natl. Acad. Sci.* 106, 3000–3005; Rabuka (2012), *Nat. Protoc.* 7, 1052–1067).

[00188] Polynucleotides and Recombinant Methods

[00189] The present disclosure provides isolated polynucleotides that encode the anti-CLDN18 antibodies provided herein.

[00190] The term “polynucleotide” as used herein refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses polynucleotides containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular polynucleotide sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically,

degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (see Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

[00191] In certain embodiments, the isolated polynucleotides comprise one or more nucleotide sequences as shown in Table 3, and/or a homologous sequence thereof having at least 80% (e.g. at least 85%, 88%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) sequence identity, and/or a variant thereof having only degenerate substitutions, and encodes the variable region of the exemplary antibodies provided herein. DNA encoding the monoclonal antibody is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). The encoding DNA may also be obtained by synthetic methods.

[00192] Table 3. Polynucleotides of variable regions of the exemplary antibodies

Antibody ID No.	Variable Chain	Polynucleotide of Each Variable Chain
		SEQ ID NO: 24
Ab01	VH	GATGTACAGCTTCAGGAGTCAGGACCTGGCCTCGT GAAACCTTCTCAGTCTCTGTCTCTC ACCTGCTCTGTCACTGGCTACTCCATCACCAGTGGT TATTACTGGAAGTGGATCCGGCAG TTTCCAGGAAACAAATTGGAATGGATGGGCTACAT AACCTACGATGGTAGCAATAACTAC AACCCATCTCTCAAAAATCGAATCTCCATCACTCGT GACACATCTAAGAACCAGTTTTTC CTGAAGTTGAATTCTGTGACTACTGAGGACGCAGC CACATATTTCTGTGCAAGAGATCCA AATTACTACGGTACTACCCTACCGGCCTGGTTTGT TACTGGGGCCAAGGGACTCTGGTC ACTGTCTCTGCA
		SEQ ID NO: 33

	VL	GACATTGTGGTGACCCAGTCTCACAAATTCATGTCC ACATCAGTAGGAGACAGGGTCAGC ATCACCTGCAAGGCCAGTCAGGATGTGGGTACTGC TGTAGCCTGGTATCAACAGAAACCA GGGCAATCTCCTAAATTACTGATTTACTGGGCATCC ACCCGGCACACTGGAGTCCCTGAT CGCTTCACAGGCAGTGGATCTGGGACAGATTTAC TCTCACCATTAGCAATGTGCAGTCT GAAGACTTGACAGATTATTTCTGTCAAGCAATATAGC AGCTATGTCACGTTTCGGTGCTGGG ACCAAGCTGGAGCTGAAA
		SEQ ID NO: 42
Ab02	VH	CAGGTGCAGCTGAAGGAGTCAGGACCTGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATC ACATGCACTGTCTCTGGGTTCTCATTAACCAGCTAT GCTATAAACTGGGTTTCGCCAGCCA CCAGGAAAGGGTCTGGAGTGGCTTGGAGTAATTTG GACTGGTGGAGGCACAAATTATAAT TCAGCTCTCAAATCCAGACTGAGCATCAACAAAGA CAACTCCAAGAGTCAAGTTTTCTTA AAAATGAACAGTCTGCAAATGATGACACAGCCAG GTACTACTGTGCCCATTCTATGAT GGTACTACTCCTGGTTTGCTTACTGGGGCCAAGGG ACTCTGGTCACTGTCTCTGCA
		SEQ ID NO: 51
	VL	GACATTGTGATGACCCAGTCTCACAAATTCATGTCC ACATCAGTAGGAGACAGGGTCAGC ATCACCTGCAAGGCCAGTCAGGATGTGGGTACTGC TGTAACCTGGTATCAACAGAAACCA GGGCAATCTCCTAAACTACTGATTTACTGGGCATCC ACCCGGCACACTGGAGTCCCTGAT CGCTTCACAGGCAGTGGATCTGGGACAGATTTAC TCTCACCATTAGCAATGTGCAGTCT GAAGACTTGGCAGATTATTTCTGTCAACAATATAGT AGCTATCCATTACGTTTCGGCTCG GGGACAAAGTTGGAAATAAAA
		SEQ ID NO: 60
Ab03	VH	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGT GAAGCCTGGGGCTTCAGTGAAGATA GCCTGCAAGGCTTCTGGATACACATTCACTGACTAC AACATGGACTGGGTGAAGCAGAGC CATGGAAAGAGCCTTGAGTGGATTGGAAATATTAA TTCTTATTATGGTGGTACTATCTAT AATCAGAAATTCAAAGGCAAGGCCACATTGACTGT AGACAAGTCTTCCAGCACAGCCTAC ATGGTCCTCCGCAGCCTGACATCTGAGGACAATGC

		AGTCTATTACTGTGCAAGACCCAC TTGGGGAATGCTCTGGACTACTGGGGTCAAGGAAC CTCAATCACCGTCTCCTCA
		SEQ ID NO: 69
	VL	GACATTGTGGTGACACAGTCTCCATCCTCCCTGACT GTGACACCAGGAGAAAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTTAACAG TGGAAATCAAAAGAACTACTTGTC TGGTACCAGCAGAACCCAGGGCAGCCTCCTAAACT GTTGATCTACTGGGCATCCACTAGG CAATCTGGGGTCCCTGATCGCTTCACTGGCAGTGGA TCTGGAACAGATTTCCTCTCACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGGTTA TTACTGTCAGAATGATTATATTTTT CCGCTCACGTTCCGGTGCTGGGACCAAGCTGGAGCT GAAA
		SEQ ID NO: 78
Ab04	VH	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGT GAAGCCTGGGGCTTCAGTGAAGATG TCCTGCATGGCTTCTGGATACACATTCACTGACTAC AACATACACTGGGTGAAGCGGAGC CATGGATCCCGTCTTGAGTGGATTGGATATATTAGT CCTATCAGTGGTGGTGCTGGCTAC AACCAGAAGTTCATGGACAAGGCCACATTGACTGT AGACAAGTCCTCCAACACAGCCTAC ATGGAGCTCCGCAGCCTGACATCGGAAGATTCTGC AGTCTATTACTGTACAAGAGGGGAC TACTGGGGCCAGGGCACCACTCTCACAGTCTCCTCA
		SEQ ID NO: 87
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGGCT GTGACAGTAGGAGAGAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAAATCAAAAGAACTACTTGACC TGGTATCAGCAGAAACCAGGGCAGCCTCCTAAATT GTTGATCTACTGGGCATCCACTAGG AAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACAGATTTCCTCTCACC ATCAGCAGTGTGCAGGCTGAAGACCTGGGAATTTA TTACTGTCTGAATGATTATGGTTTT CCGCTCACGTTCCGGTGCTGGGTCCAAGCTGGAGCT GAAA
		SEQ ID NO: 96

Ab05	VH	GACGTGAAGTTGGTGGAGTCTGGGGAAGACTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCTGCCTCTGGGTTCACTTTCAGTAACTAT GCCATGTCTTGGGTTCCGCCAGACT CCAGAGAAGAGGCTGGAGTGGGTCGCATATGTTAG TAGTGGTGGTGATTACATCTACTAT GCAGACACTGTGAAGGGCCGATTCATCATCTCCAG AGACAATGCCAGGAACACCCTGTAC CTGCAAATGAACAGTCTGAGGTCTGAGGACACAGC CATGTATTACTGTGCAAGAGTCTAC TTTGGTAACTCCCTTGACTACTGGGGCCAAGGCACC ACTCTCACAGTCTCCTCA
		SEQ ID NO: 105
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCT CTGAGCTGCAAGTCCAGTCAGAGTCTCTTAAATGGT GGAAATCAAAAGAACTACTTGACC TGGTACCAGCAGAGACCAGGACAGCCTCCTAAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACAGATTTCACTCTCATC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATTATTATTAT CCGTGGACGTTCCGTGGAGGCACCAAGCTGGAAAT CAAA
		SEQ ID NO: 114
Ab06	VH	GAAGTGCAGCTGGTGGCGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGCCTCTGGAATCACTTTCAGAAGTTAT GCCATGTCTTGGGTTCCGCCAGACT CCGGAAAAGAGGCTGGAGTGGGTCGCAACCATTAC TGATGGTGGTAGTTACATCTTCTAT CCAGACAATGTAAAGGGCCGATTCACCATCTCCGG AGACCATGCCAAGAACAACCTGTAC CTGCAAATGAGCCATCTGAAGTCTGAGGACACAGC CTTGTATTTCTGTGTAAGACTCTAC TATGGAAACTCGTTTGCTTACTGGGGCCAAGGGAC TCTGGTCACTGTCTCTGCA
		SEQ ID NO: 123
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCT TTGAACTGCAAGTCCAGTCAGAGTCTGTTCAACAGT GGAAATCAAAAGAACTACTTGACC TGGTACCAGCAGAAACCAGGGCAGCCTCCTAAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG

		ATCTGGAACAGATTTCCTCTCACC TTCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TACTGTCAGAATGCTTATATTTAT CCATTACGTTTCGGCTCGGGGACAAAATTGGAAAT AAAA
		SEQ ID NO: 132
Ab07	VH	GAGGTTTCAGCTGCAGCAGTCTGGACCTGAGCTGGT GAAGCCTGGGGCTTCAGTGAAGATA TCCTGCAAGGCTTCTGGTTACTCATTTACTGACTAC TTTATGAACTGGGTGAAGCAGAGC CATGGAAAGGGCCTTGAGTGGATTGGACGTATTAA TCCTTACAATGGTGATACTTTCTAC AACCAGAAAGTTCAAGGGCAAGGCCACATTGACTGT AGACAAATCCTCTAGCACAGCCAC ATGGAGCTCCTGAGCCTGACATCTGAGGACTTTGC AGTCTATTATTGTGCCCTCTATGAT GGTACTGGGGGGCTTTTGTCTTACTGGGGCCAAGGG ACTCTGGTCACTGTCTCTGCA
		SEQ ID NO: 141
	VL	GACATCCAGATGACTCAGTCTCCAGCCTCCCTCTCT GTATTTGTGGGAGAACTGTCACC ATCACATGTCGAGCAAGTGAGAATATTTACAGTAA TTTAGCATGGTATCAGCAGAAACAG GGAAATCTCCTCAGCTCCTGGTCTATGCTGCAACA AACTTAGCAGATGGTGTGCCATCA AGGTTTCAGTGGCAGTGGATCAGGCACACAGTATTC CCTCAAGATCAACAGCCTGCAGTCT GAAGATTTTGGGAGTTATTACTGTCAACATTTTGG GGTACTCCGCTCACGTTTCGGTGCT GGGACCAAGCTGGAGCTGAAA
		SEQ ID NO: 150
Ab08	VH	CAGGTCCAAGTGCAGCAGCCTGGGGCTGAGTTGGT AAAGCCTGGGGCTTCAGTGAAGTTG TCCTGCAAGGCTTCTGGCTACACTTTCACCAGCTAC TACTACACTGGGTGAAACAGAGG CCTGGACAAGGCCTTGAGTGGATTGGAATGATTCA TCCTAATGGTGGTAGTACTAACTAC AATGAGAAGTTCAAGACCAAGGCCACACTGACTGT AGACAAATCCTCCAGCACAGCCTAC ATGCAACTCAGCAGCCTGACATCTGAGGACTCTGC GGTCTATTACTGTGCCCCTGTCTAC TTTGGTAACTCGTTTGCTTACTGGGGCCAAGGGACT CTGGTCACTGTCTCTGCA
		SEQ ID NO: 159

	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAAATCAAAGAAGTACTTGACC TGGTACCAGCAAAAACCAGGGCAGCCTCCTAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACAGATTTCCTCTCACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATTATTATTAT CCATTACGTTTCGGTTCGGGGACAAAGTTGGAAAA AAAA
		SEQ ID NO: 204
Ab09	VH	GAGGTCCAAGTCAACAGTCTGGACCTGAGCTGGT GAAGCCTGGGACTTCAGTGAAGATG TCCTGCAAGGCTTCTGGATACACATTCACTGACTAC AACATGCACTGGGTGAACTGAGC CATGGAAAGAGCCTTGAGTGGATTGGATATATTAA CCCTAATAATGGGGGTACTATCTAC AACCAGCGATTCAAGGGCAAGGCCACATTGACTGT AAACAAGTCCTCCAGAACAGCCTAC ATGGACCTCCGCAGCCTGACATCGGAGGATTCTGC AGTCTATTACTGTGCGCGACAGGGT TACTACGGTAACTCTATGGACTACTGGGGTCAAGG AAATTCAGTCACCGTCTCCTCA
		SEQ ID NO: 213
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACACCAGGAGAGAGGGTCACT ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACGG TGGAAATCAAAGGAAGTACTTGACC TGGTACCAGCAAAAACCAGGGCAGCCTCCTAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCGCAGGCAGTGG ATCTGGAACAGATTTCCTCTCACC ATCAGCAGAGTGCAGGCTGAAGACCTGTCATTTTA TTACTGTCAGAATTCTTATTTTAT CCGTTACGTTTCGGCTCGGGGACAAAGTTGGACCT AAGA
		SEQ ID NO: 222
Ab10	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGCCTCTGGATTCACTTTCAGTAGCTAT ACCATGTCTTGGGTTCGCCAGACT CCGGAGAAGAGGCTGGAGTGGGTGCGCAACCATTAG TGTTATTGGTGGTAACACCTACTAT GTAGACAGTGTGAAGGGTCGATTACCATCTCCAG

		AGACAAAGCCAAGAACACCCTGTAC CTGCAAATGAGCAGTCTGAGGTCTGAGGACACGGC CTTATATTACTGTGCAAGACTGGGA CAGACACAGAGAAATGCTATGGACTACTGGGGTCA AGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 231
	VL	GACATTGTGATGACACAGTCTCCATCCTCTCTGAGT GTGTCAGCAGGAGAGAAGGTCACA ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAAATCAAAAGAACTACTTGGCC TGGTACCAGCAGAAACCAGGGCAGCCTCCTAAACT GTTGATCTACGGGGCATCTACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACCGATTTCCTCTTACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATTATAGTTAT CCGCTCACGTTCCGGTGCTGGGACCAAGCTGGAGCT GAAA
		SEQ ID NO: 240
Ab11	VH	GAAGTGATGTTGGTGGAAATCTGGGGGAGACTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGCCTCTGGATTCACTTTCAGTCGTTAT ACCATGTCTTGGGTTCGCCAGACT CCGGAGAAGAGGCTGGAGTGGGTCGCAACCGTTAG TGTTGGTTCTGGTAACACCTACTAT TTAGACAGTGTGAAGGGTCGATTACCATCTCCAG AGACAATGCCAAGAACACCCTGTTC CTGCAAATGAACAGTCTGAGGTCTGAGGACACGGC CTTATATTACTGTACAAGACTGGGA CAGACACAGAGAAATGCTGTGGACTACTGGGGTCA AGGCACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 249
	VL	GACATTGTGATGACACAGTCTCCATCCTTCCTGAGT GTGTCAGCGGGAGAGAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTTC AACGG TGGAAATCAAAAGAACTACTTGGCC TGGTACCAGCAGAAACCAGGGCAGCCTCCTAAACT GTTGATCTACGGGGCATCCACTAGG GACTCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACCGATTTCCTCTTACC ATCAGCAATGTGCAGGCTGAAGACCTGGCAATTTA TTTCTGTCAGAATGATCATA
		SEQ ID NO: 258

Ab12	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGCCTCTGGATTCACTTTCAGTAGCTAT ACCATGTCTTGGGTTCGCCAGACT CCGGAGAAGAGGCTGGAGTGGGTCGCAACCATTAT TGGTGGTTATGGTAACACCTACTAT GCAGACAGTGTGAAGGGTCGATTACCATCTCCAG AGACAGTGCCAAGAACACCCTGTAC CTACAAATGCTCAGTCTGAGGTCTGAGGACACGGC CTTGTATTACTGTACAAGACTGGGA CAGACACAGAGAAATGCTATGGACTACTGGGGTCA AGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 267
	VL	GACATTTTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAATCAAAGGAACTATTTGGCC TGGTACCAACAGAAACCAGGGCAGCCTCCTAAATT GTTGATCTATGGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACCGATTTCCTCTTACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTATTGTCAGAATGATTATTATTAT CCACTCACGTTCCGGTGCTGGGACCAAGCTGGAGCT GAAA
		SEQ ID NO: 276
Ab13	VH	GAAGTGAGGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGGCTCTGGATTCACTTTCAGTAGCTAT ACCATGTCTTGGGTTCGCCAGACT CCGGAGAAGAGGCTGGAGTGGGTCGCAACCATTAC TATTGGTGTAAACATCTACTATCTA GACAGTGTGAAGGGTCGATTACCATCTCCAGAGA CAATGCCAAGAACACCCTGTACCTG CAAATGAACAGTCTGAGGTCTGAGGACACGGCCTT GTATTATTGTACAAGACTGGGACAG ACACAGCGAAATGCTATGGACTACTGGGGTCAAGG AACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 285
	VL	GACATTGTGATGACACAGTCTCCAACCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCCT ATGACCTGCAAGTCCAGTCAGAGTCTATTAAACAG TGGAATCAAAGAACTACTTGGCC TGGTACCAGGAGAAACCAGGGCAGCCTCCTAAACT GTTGATCTACGGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG

		ATCTGGAACCGATTTCCTTACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATAATCATTTTTAT CCGCTCACTTTCGGTGCTGGGACCAAGCTGGAAC GAAA
		SEQ ID NO: 294
Ab14	VH	CAGGTCCAAGTGCAGCAGCCTGGGGCTGAGTTGGT AAAGCCTGGGGCTTCAGTGAAGTTG TCCTGCAAGGCTTCTGGCTACACTTTCACCAGCTAC TTACTACACTGGGTGAAACAGAGG CCTGGACAAGGCCTTGAGTGGATTGGAATGATTCA TCCTAATGGTGGTAGTACTAACTAC AATGAGAAGTTCAAGACCAAGGCCACACTGACTGT AGACAAATCCTCCAGCACAGCCTAC ATGCAACTCAGCAGCCTGACATCTGAGGACTCTGC GGTCTATTACTGTGCCCCTGTCTAC TTTGTTAACTCGTTTGCTTACTGGGGCCAAGGGACT CTGGTCACTGTCTCTGCA
		SEQ ID NO: 303
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCT ATGAGCTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAATCAAAAGAACTACTTGACC TGGTACCAGCAAAAACCAGGGCAGCCTCCTAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGG ATCTGGAACAGATTTCACTCTCACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATTATTATTAT CCATTCACGTTTCGGTTCGGGGACAAAGTTGGAAAA AAAA
		SEQ ID NO: 312
Ab15	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGACTTAGT GAAGCCTGGAGGGTCCCTGAAACTC TCCTGTGCAGCCTCTGGATTCACTTTCAGTACCTAT ACCATGTCTTGGGTTCGCCAGACT CCGAGAAGAGGCTGGAGTGGGTGCAACCATTGT TGGTGGTGGTGGTTACACCTACTAT CTAGACAGTGTGAAGGGTCGATTACCATCTCCAG AGACAATGCCAAGAACACCCTGTAC CTGCAAATGATCAGTCTGAGGTCTGAGGACACGGC CTTATATTACTGTGCAAGAATGGGA CTGACACAGAGAAATGCTCTGGACTACTGGGGTCA AGGAACCTCAATCACCGTCTCCTCA
		SEQ ID NO: 321

	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGAAGGAGAGAAGGTCCT CTGAACTGCAAGTCCAGTCAGAGTCTGTTCAACAG TGGAAATCAAAAGAACTACTTGGCC TGGTACCAGCAGAAACCAGGGCAGCCTCCTAACT GTTAATCTACGGGGCATCCACTAGA GAATCTGGGGTCCCTGATCGTTTCACAGGCAGTGG ATTTGGCACCGATTTCCTCTTACC ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATCATACTTAT CCGCTCACGTTTCGGTGCTGGGGCCAAGCTGGAGCT GAAA
		SEQ ID NO: 330
Ab16	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAACTC TCCTGTGCAGCCTCTGGATTCACTTTCAATAGTTAT ACCATGTCTTGGGTTCGCCAGACT CCGGAGAAGAGGCTGGAGTGGGTCGCAACCATTAC TGTTATTGGTGGTAACACCTACTAT TTAGACAGTGTGAAGGGTCGATTACCATTTCCATA GACAATGGCAAGAACACCCTGTAC CTGCAAATGAGCAGTCTGAGGTCTGAGGACACGGC CTTGTATTACTGTGCAAGAATGGGA CAGACACAGAGAAATGCTATGGACTACTGGGGTCA AGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 339
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGACAGAAGGTCCT ATGAGGTGCAAGTCCAGTCAGAGTCTGTTAAACAG TGGAAATCAAAAGAACTACTTGGCC TGGTATCAGCAGAACTAGGGCAGCCTCCTAACT ACTGATCTACGGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGTTTCTCAGGCAGTGG ATCTGGAACCGATTTCCTCTTACC ATCACCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATGATTATAGTTTT CCGCTCACGTTTCGGTGCTGGGACCAAGCTGGAGCT GAAA
		SEQ ID NO: 348
Ab17	VH	CAGGTGCAGCTGAAGGAGTCAGGACCTGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATC ACATGCACTGTCTCTGGGTCTCATTAACCAGCTAT GCTATAAGCTGGGTTCGCCAGCCA CCAGGAAAGGGTCTGGAGTGGCTTGGAGAAATATG GACTGGTGGAGGCACAAATTATAAT TCAGCTCTCAAATCCAGACTGAGCATCAGCAAAGA

		CAACTCCAAGAGTCAAGTTTTCTTA AAAATGAACAGTCTGCAAAGTATGACACAGCCAG GTACTACTGTGGCAGACTTTCCTAT GGTAATTCCTTGACTACTGGGGCCAAGGCACCAC TCTCACAGTCTCCTCA
		SEQ ID NO: 357
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCT ATGAGTTGCAAGTCCAGTCAGAGTCTGTAAACAG TGGAAATCAAAAGAACTACTTGACC TGGTACCAGCAGAAACCAGGGCAGCCTCCTAACT GTTGATCTACTGGGCATCCACTAGG GAATCTGGGGTCCCTGATCGCTTCACTGGCAGTGG ATCTGGAACAGATTTCACTCTCACC GTCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTA TTACTGTCAGAATAATTTTATTTAT CCTCTCACGTTCCGGTCTGGGACCAAGCTGGAGTTG AAA
		SEQ ID NO: 366
Ab18	VH	CAGGTGCAGCTGAAGGAGTCAGGACCTGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATCACATGCACTGT CTCAGGGTTCTCATTAACCACCTATGGTATAAACTG GGTTCGCCAGCCTCCAGGAAAGGGTCTGGAGTGGC TGGGAGTCATATGGGGTGACGGGAGCACAAATTAT CATTCAGCTCTCATATCCAGACTGAGCATCAGCAA GGATAACTCCAAGAGCCAAGTTTTCTTAAACTGA ACAGTCTGCAAAGTATGACACAGCCACGTACTAC TGTGTCAAATCCTCTTACTACGGTAATGCTATGGAC TACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 375
	VL	GACATTGTGATGACTCAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGACGGTCACTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAAATCAAA AGAACTACTTGACCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAACTGTTGATCTACTGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCAACAGGCAG TGGATCTGGAACAGATTCACTCTCACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGTTTATAGTTATCCATTCACGTTCCGGCTCGGG GACAAAGTTGGAAATAAAA
		SEQ ID NO: 384
Ab19	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGACTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAG CCTCTGGATTCAAGTTTCAGTCGCTATACCATGTCTT GGGTTCCGCCAGACTCCGGAGAAGAGGCTGGAGTGG

		GTCGCAACCGTTAGTGTGGTTCTGGTAACACCTAC TATTTAGACAGTGTGAAGGGTCGATTCACCATCTCC AGAGACAATGCCAAGAACACCCTGTTCTGCAAAT GAGTAGTCTGAGGTCTGAGGACACGGCCTTATATT ACTGTGCAAGAATGGGACAGACACAGAGAAATGCT GTGGACTACTGGGGTCAAGGCACCTCAGTCACCGT CTCCTCA
		SEQ ID NO: 393
	VL	GACATTGTGATGACACAGTCTCCATCCTCCTTGAGT GTGTCAGCAGGAGAGAAGGTCAGTATGAGCTGCAA GTCCAGTCAGAGTCTGTTCAACAGTGGAAATCAAA AGAACTACTTGGCCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAAGCTGTTGATCTACGGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACCGATTTCCTTACCATCAGCAA TGTGCAGGCTGAAGACCTGGCAGTTTATCTCTGTCA GAATGATCATAGTTTTCCGCTGACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAGA
		SEQ ID NO: 402
Ab20	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGTAG CCTCTGGATTCACTTTCAGTAGTTATAACCATGTCTT GGGTTCCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACCATTATTGGTGGTTATGGTAACACCTAC TATTCAGACAGTGTGAAGGGTCGAATCACCATCTC CAGAGACAGCGCCAAGAACACCCTGTACCTGCAAA TGATCAGTCTGAGGTCTGAGGACACGGCCTTGTATT ACTGTACAAGACTGGGACAGACACAGAGAAATGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGT CTCCTCA
		SEQ ID NO: 411
	VL	GACATTTTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCAGTATGAACTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAAATCAAA AGAACTATTTGGCCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAAATTGTTGATCTATGGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACCGATTTCCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATTATTATCCATTACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAAA
		SEQ ID NO: 420
Ab21	VH	GAAGTGATGCTGGTGGAAATCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCTATAACCATGTCTT

		GGGTTCCGCCAGACTCCGGAGAAGAGACTGGAGTGG GTCGCAACCATTATTGGTGGTTATGGTAACACCTAC TATGTAGACAGTGTGAAGGGTCGATTACCATCTCC AGAGACAGTGCCAAGAACACCCTCTACCTACAAAT GATCAGTCTGAGGTCTGAGGACACGGCCTTGTATT ACTGTACAAGACTGGGACAGACACAGAGAAATGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGT CTCCTCA
		SEQ ID NO: 429
	VL	GACATTTTGTATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCACCTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAAATCAAA AGAACTATTTGGCCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAAATTATTGATCTATGGGGCATCTACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACCGATTTCACCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTATTGTCA GAATGATTATTATTATCCGTTACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAAA
		SEQ ID NO: 438
Ab22	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCTATAACCATGTCTT GGGTTCCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACCATTATTGGTGGTTATGGTAACACCTAC TATGCAGACAGTGTGAAGGGTCGATTACCATCTC CAGAGACAGTGCCAAGAACACCCTGTACCTGCAAA TGATCAGTCTGAGGTCTGAGGACACGGCCTTGTATT ACTGTACAAGACTGGGACAGACACAGAGAAATGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGT CTCCTCA
		SEQ ID NO: 447
	VL	GACATTTTGTATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCACCTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAAATCAAA AGAACTATTTGGCCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAAATTGTTGATCTATGGGGCATCCACT AGGGAATCTGGGGTCCCTGATACCTTCACAGGCAG TGGATCTGGAACCGATTTCACCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATTATTATCCGTTACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAAG
		SEQ ID NO: 456

Ab23	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGTAG CCTCTGGATTCACTTTCAGTAGCTATAACCATGTCTT GGGTTCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACCCTTAGTGTTGTTGGTGGTAACACCTAC TATGTAGACAGTGTGAAGGGTCGATTCACCATCTCC AGAGACAAAGCCAAGAACACCCTGTACCTGCAAAT GAGCAGTCTGAGGTCTGAGGACACGGCCTTATATT ACTGTGCAAGACTGGGACAGACACAGAGAAATGCT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGT CTCCTCA
		SEQ ID NO: 465
	VL	GACATTGTGATGACACAGTCTCCATCCTCTCTGAGT GTGTCAGCAGGAGAGAAGGTCACAATGAGTTGCAA GTCCAGTCAGAGTCTGTTAAACAGTGGAATCAAA AGAACTACTTGGCCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAAACTGTTGATCTACGGGGCATCTACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACCGATTTCACTCTTACCATCAGTAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATAGTTATCCGCTCACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAAA
		SEQ ID NO: 474
Ab24	VH	GAAGTGAAGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAG GCTCTGGATTCACTTTCAGTAGCTATAACCATGTCTT GGGTTCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACCATTACTATTGGTGTTAACATCTACTAT CTAGACAGTGTGAAGGGTCGATTCACCATCTCCAG AGACAATGCCAAGAACACCTTGTACCTGCAAATGA ACAGTCTGAGGTCTGAGGACACGGCCTTGTATTATT GTACAAGACTGGGACAGACACAGCGAAATGCTATG GACTACTGGGGTCAAGGAACCTCAGTCACCGTCTC CTCA
		SEQ ID NO: 483
	VL	GACATTGTGATGACACAGTCTCCAACCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCAGTATGACCTGCAA GTCCAGTCAGAGTCTGTTCAACAGTGGAATCAAA AGAACTACTTGGCCTGGTATCAGGAGAAACCAGGA CAGCCTCCTAAACTGTTGATCTACGGGGCATCCACT AGGGAGTCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACCGATTTCACTCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCCGTTTATTACTGTCA GAATGTTTATTTTATCCGTTTACGTTCCGGTGCTGG GACCAAGCTGGAGCTGAAA

		SEQ ID NO: 492
Ab25	VH	GAGGCCAGCTGCAACAATCTGGACCTGAGCTGGT GAAGCCTGGGGCGTCAGTGAAGATATTCTGTAAGG CTTCTGGATACACGTTCACTGACTACTACATCAACT GGGTGAAACAGAGCCATGGAAAGAGCCTTGAGTGG ATTGGAGATATTAATCCTAACAATGGTGGTACTACC TACAACCAGAAGTTCAAGGGCAAGGCCACATTGAC TGTAGACAAGTCCTCCAGCACAGCCTCCATGGAGC TCCGCAGACTGACATCTGAAGACTCTTCAGTCTATT ACTGTGCAAGACGCGATGCTATGGACTACTGGGGT CAAGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 501
	VL	GACATTGTGATGACCCAGTCTCAAAAATTCATGTCC ACAACAGTAGGAGACAGGGTCAGCATCACCTGCAC GGCCAGTCAGAATGTGGGTCTGCTGTTGCCTGGTA TCAACAGAAACCAGGACAATCTCCTAACTACTGA TTTACTCAGCATCCCGTCGGTTCCTGGAGTCCCTG ATCGCTTACAGGCAGTGGATCTGGGACAGTTTCA CTCTCACCATTAACAATGTGCAGTCTGAAGACCTGG CAGATTATTTCTGTCAGCAATATATCAGCTATCCTC TCACGTTTCGGTCTGGGACCAAGCTGGAGCTGAAA
		SEQ ID NO: 510
Ab26	VH	GAAGTGATGCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTACAG CCTCTGGATTCACTTTCAGAAGCTATACCATGTCTT GGGTTCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACTATTACTGGTGGTGGTGGAAATACCTA CTTTCTAGACAGTGTGAAGGGTCGATTCACCTTCTC CAGAGACAATGCCAAGAACGCCCTGTACCTGCAAA TGAACAGTCTGAGGTCTGAGGACACGGCCTTGAT TACTGTGCAAGACTGGGACAGACACAGAGAAATGC TATGGACTACTGGGGTCAAGGAACCTCAGTCACCG TCTCCTCA
		SEQ ID NO: 519
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCCGGAGAGAAGGTCATGAGCTGCAA GTCCAGTCAGAGTCTATTAAACAGTGGAAATCAAA TGAACACTTGGCCTGGTACCAGCAGAAACCAGGA CAGCCTCCTAAATTGTTGATCTATGGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTACAGGCAG TGGATCTGGAACCGATTTCACTCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAATTTATTACTGTCA GAATGATCATACTTATCCGCTCACGTTTCGGTCTGG GACCAAACCTGGAGCTGAAA

		SEQ ID NO: 528
Ab27	VH	CAGGTTTCAGCTGCAGCAGTCTGGGGCTGAACTGGT GAGGCCTGGGTCCCTCAGTGAAGATTTCTGCAAGG CTTCTGGCTATGCATTCAGTAACTACTGGATGAACT GGGTGAAGCAGAGGCCTGGACAGGGTCTTGAGTGG ATTGGACAGATTTATCCTGGAAATGGTGATACTAAC TACAATGGAAAGTTCAAGGGTAAAGCCACACTGAC TGCAGACAAATCCTCCACCACAGCCTACATTCAGCT CAGCAGCCTAACTTCTGAGGACTCTGCGGTCTATTT CTGTACAAGGATCTACTATGGTAACTCTTTTGCTTA CTGGGGCCAAGGCACTCTGGTCACTGTCTCTGCA
		SEQ ID NO: 537
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAGGGTCACTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAATCAAA AGAACTACTTGACCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAACTGTTGATCTACTGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACAGATTTACCCCTACCATCAGCA GGGTGCAGGCTCAAGACCTGGCAGTTTATTACTGTC AGAATGATTATTATTATCCACTCACGTTCCGGTGCTG GGACCAAGCTGGAGCTGAAA
		SEQ ID NO: 546
Ab28	VH	CAGGTGCAGTTGAAGGAGTCAGGACCAGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATCACTTGCACTGT CTCCGGGTTTTTCATTAACCAGCCATGGTGTACACTG GGTTCGCCAGCCTCCAGGAAAGGGTCTGGAGTGGC TGGGAGTAATATGGGCTGGAGGAAGCATAACTTT AATTCGGCTCTCATGTCCAGACTGAGCATCAGCAA AGACAACTCCAAAAACCAGGTTTTCTTAAAAATGA ACAGTCTGCAAAGTGATGACACAGCCATGTACTAC TGTGCCAGAGACTATTACTACGGTATTGGTCTTGAC TATTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA
		SEQ ID NO: 555
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCCTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAATCAAA AGAACTACTTGGCCTGGTACCAGCAGAAACCAGGA CAGCCTCCTAACTGTTGATCTACGGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGGTCTGGAACCGATTTCACTCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATTATTATCCATTCACGTTCCGGCTCGGG GACAAAGTTGGAAATAAAA

		SEQ ID NO: 564
Ab29	VH	GAGGTCCTGCTGCAACAGTCTGGACCTGAACTGGT GAAGCCTGGGGCTTCAGTGAAGATACCCTGCAAGG CTTCTGGATACACTTTGACTGACCACAGCATGGACT GGGTGAAGCAGAGCCATGGAAAGAGCCTTGAGTGG ATTGGAAATATTCTTCCTAATAATGGTGGTAATATA TACAACCAGAAGTTCAGGGGCAAGGCCACACTGAC TGTCGACAAGTCCTCCAGCACAGCCTACATGGAGC TCCGCAGCCTGACATCTGAAGACACTGCAGTCTAT AACTGTGCAAGGGGCCACTATGGTAACTCATTGCT TACTGGGGCCAAGGGACTCTGGTCATAGTCTCTGC A
		SEQ ID NO: 573
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGAGAGCAGGAGAGAAGGTCACTATATACTGCAA GTCCAGTCAGAGTCTGTTTAACAGTGGAAATCAAA AAAACACTTGTGACCTGGTACCAGCAGAAACCGGGC CAGCCTCCTAAATTGTTGATCTACTGGGCATCCACT AGGGAATCTGGGGTCCCTCATCGCTTCACAGGCAG TGGATCTGGGACAGATTTCACTCTCACCATCAGCAG TATGCAGGCTGATGACCTGGCAACTTATTACTGTCA GAATGGTTATTTTTTCCGTACACGTTCCGAGGGGG GACCAAGCTGGAGATAAAA
		SEQ ID NO: 582
Ab30	VH	CAGGTACAACCTGAAGGAGTCAGGACCTGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATCACATGCACTGT CTCAGGGTTCTCATTAACCAAGTTTGGTGTAACTG GGTTCGCCAGCCTCCAGGAAAGGGTCTGGAGTGGC TGGGAGCAATATGGGGTGACGGGAGCACAAATTAT CATTCACTCTCATATCCAGACTGAGCATCAACAA GGATAACTCCAAGAGCCAAGTTTTCTTAAACTGA GCAGTCTGCAAAATGTTGACACAGCCACTTACTACT GTGCCAAAAGTGGGTACGGTAATGCTATGGACTAC TGGGGTCACGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 591
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAACAGGAGAGAAGGTCACTCTGAACTGCAA GTCCAGTCAGAGTCTGTTAAACAGTGGAAATCTAA AGAACTACTTGTGACCTGGTACCAGCAGAGACCGGGG CAGCCTCCTAAACTGTTGATCTACTGGGCATCCACT AGGGAATCTGGGGTCCCTTATCGCTTCACAGGCAG TGGATCTGGAACAGATTTCACTCTCACCATCAGCAA TGTGCAGGCTGAAGACCTGGCAATTTATTACTGTCA GAATGATTATTTTTTCCATTACGTTCCGGCTCGGG GACAAAGTTGGAAATTTAAA

		SEQ ID NO: 600
Ab31	VH	CAGATCCAGTTGGCGCAGTCTGGACCTGAGCTGAA GAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGG CTTCTGGGTATAGTTTCACAACTATGGAATGAACT GGGTGAAGCAGGCTCCAGGAAAGGGCTTAAAGTGG ATGGGCTGGATAAACACCTACAGTGGAGAGACAAA ATATGCTGATGACTTCAAGGGACGGTTCGACTTTTC ATTGAAACCTCTGCCAGGACAGCCTATTTGCAGA TCAAAAACCTCAAAATTGAGGACACGGCTACATAT TTCTGTGCAAGACGGGATGCTATGGACTACTGGGG TCAAGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 609
	VL	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCT GTCACCTCTGGAGAGTCAGTGTCCATTTCTTGCAGG TCTAGTAAGAGTCTCCTGAATAGTAATGGTAACACT TATTTGTATTGGTTCCTACAGAGGCCAGGCCAGTCT CCTCAGCTCCTGATATATCGGATGTCTAACCTTGCC TCAGGAGTCCCAGACAGGTTTCAGTGGCAGTGGGTC AGGGACTGCTTTCACACTGAGAATCAGTAGAGTGG AGGCTGAGGATGTGGGTGTTTATTATTGTATGCAAC ATCTAGAATTTCCATTACGTTTCGGCTCGGGGACAA AGTTGGAAATAAAA
		SEQ ID NO: 618
Ab32	VH	CAGGTGCAGTTGAAGGAGTCAGGACCAGGCCTGGT GGCGCCCTCACAGAGCCTGTCCATCACTTGCAGTGT CTCCGGGTTTTTCATTAACCAGCCATGGTGTACACTG GGTTCGCCAGCCTCCAGGAAAGGGTCTGGAGTGGC TGGGAGTAATATGGGCTGGAGGAAGCATAACTTT AATTCGGCTCTCATGTCCAGACTGAGCATCAGCAA AGACAACTCCAAAAACCAGGTTTTCTTAAAAATGA ACAGTCTGCAAAGTGATGACACAGCCATGTACTAC TGTGCCAGAGACTATTACTACGGTATTGGTCTTGAC TATTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA
		SEQ ID NO: 627
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGAGT GTGTCAGCAGGAGAGAAGGTCAGTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAATCAAA AGAACTACTTGGCCTGGTACCAGCAGAAACCAGGA CAGCCTCCTAACTGTTGATCTACGGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGGTCTGGAACCGATTTCACTCTTACCATCAGCAG TGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATTATTATCCATTACGTTTCGGCTCGGG GACAAAGTTGGAAATAAAA

		SEQ ID NO: 636
Ab33	VH	GACGTGAACCTGGTGGAGTCTGGGGGAGGCTTAGT GAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCTATACCATGTCTT GGGTTCGCCAGACTCCGGAGAAGAGGCTGGAGTGG GTCGCAACCATTACTTATGGTCGTATTTACACCTAC TATCTAGACAGTGTAAGGGCCGATTCACCATCTCC AGAGACAATGCCAAAAACACCCTGTACCTGCAGAT GAGCAGTCTGAGGTCTGAGGACACAGCCATGTATT ACTGTACAAGGATGATTACGGGGAATGCTATGGAC TCCTGGGGTCTAGGAACCTCAGTCACCGTCTCCTCA
		SEQ ID NO: 645
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAAGGTCCTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACAGTGGAAATCAAA AAAATACTTGACCTGGTACCAGCAGAAACCAGGG CAGCCTCCTAACTGTTGATCTACTGGGCATCCACT AGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGATCTGGAACAGATTTCACTCTCACCATCAGCGG TGTGCAGGGTGAAGACCTGGCAGTTTATTACTGTCA GAATGATTATAGTTATCCGCTCACGTTCCGGTGGTGG GACCAAGCTGGAGCTGAAA
		SEQ ID NO: 654
Ab34	VH	GAGGTCCTGCTGCAACAGTCTGGACCTGAGTTGGT GAAGCCTGGGGCTTCAGTGAAAATACCCTGCAAGG CTTCTGGATACACATTCTCTGACTACAACATGGACT GGGTGAAGCAGAGCCATGGAAAGAGCCTTGAGTGG ATTGGACATATTAATCCTAACAATGATAATACTATC TACAACCAGAAGTTCAAGGGCAAGGCCACATTGAC TGTAACAAGTCCTCCAATACAGCCTACATGGACC TCCGCAGCCTGTCATCTGAGGACACTGCAGTCTATT ACTGTGCAAGAGGGGCCTACTATGGTAACTCTATG GACTACTGGGGTCAAGGAACCTCAGTCACCGTCTC CTCA
		SEQ ID NO: 663
	VL	GACATTGTGATGACACAGTCTCCATCCTCCCTGACT GTGACAGCAGGAGAGAGGGTCACTATGAGCTGCAA GTCCAGTCAGAGTCTGTAAACGGTGGAAATCAAA GGAATACTTGACCTGGTACCAGCAGAAACCAGGG CAGTCTCCTAACTGTTGATCTACTGGGCATCCACT TGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAG TGGGTCTGGAACAGATTTCACTCTCACCATCAGCAG TGTGCAGGCTGAGGACCTGGCAGTTTATTACTGTCA AAATGCTTATTTTATCCGTACACGTTCCGAGGGGG GACCAAGCTGGAAATAAAA

		SEQ ID NO: 672
Ab35	VH	GATGTGTTTCTTCAGGAGTCGGGACCTGGCCTGGTG AAACCTTCTCAGTCTCTGTCCCTCACCTGCACCGTC ACTGGCTACTCAATCACCAGTGATTATGCCTGGAAC TGGATCCGGCAGTTTCCAGGAAACAACTGGAGTG GGTGACCTACATAGGCTACAGTGGTACCACTAGCT ACAACCCATCTCTCAAAAGTCGAATCTCTATCACTC GAGACACATCCAAGAACCAGTTCTTCTGTCAGTTG AATTCTGTGTCTACTGAGGACACAGCCACATATTAC TGTGTAAGAAGGGGGAGTTACTATGGGAGTTACTG GTTCTTCGATGTCTGGGGCGCAGGGACCACGGTCA CCGTCTCCTCA
		SEQ ID NO: 681
	VL	CAAGTTGTTCTCTCCCAGTCTCCAGCAATCCTGTCT GCATCTCCAGGGGAGAAGGTCACAATGACTTGCAG GGCCAGTTCAAGTGTAAAGTTACATGCACTGGTATC AGCAGAAGCCAGGATCCTCCCCCAAACCCTGGATT TATGCCACATCCAACCTGGCTTCTGGAGTCCCTCCT CACTTCAGTGGCAGTGGGTCTGGGACCTCGTACTCT CTCACAATCAGCAGAGTGGAGGCTGAAGATGCTGC CACTTATTACTGCCAGCAGTGGACTAGTAACCCACC CACGTTCCGAGGGGGGACCAAGTTGGAAATAAAA
		SEQ ID NO: 690
Ab36	VH	GAAGTGAAGCTTGAGGAGTCTGGAGGAGGCTTGGT GCAGCCTGGAGGATCCATGAAACTCTCCTGTGTGTC CTCTGGATTCACTTTCAGTAACTACTGGATGAACTG GGTCCGCCAGTCTCCAGAGAAGGGGCTTGAGTGGG TTGCTCAAATTAGATTGAAATCTGATAATTATGCAA CACATTATGCGGAGTCTGTGAAAGGGATGTTACCC ATCTCAAGAGATGATTCCAAAAGTAGTGTCTACCT GCAAATGAACAACCTTAAGGGCTGAAGACACTGGAA TTTATTACTGCACAGCAGGCGGGGACTACTGGGGC CAAGGCACCACTCTCACAGTCTCCTCA
		SEQ ID NO: 699
	VL	GACATTGTGATGACCCAGTCTCAAAAATTCATGTCC ACAACAGTAGGAGACAGGGTCAGCATCACCTGCAA GGCCAGTCAGAATGTGGGTACTGCTGTAGCCTGGT ATCACCAGAAACCAGGACAATCTCCTAAACTCCTG ATTTACTCAGCATCCAATCGGTACACTGGAGTCCCT GATCGCTTCATAGGCAGTGGATCTGGGACAGATTT CACTCTCACCATTAGCAATGTGCAGTCTGAAGACCT GGGAAATTATTTCTGTGCAATATATCAACTATCT TCTCACGTTTCGGCTCGGGGACAAAGTTGGAAATAA AA

		SEQ ID NO: 169
Ab37	VH	GAAGTGAAGCTTGAGGAGTCTGGAGGAGGCTTGGT GCAACCTGGAGGATCCATGAAACTCTCCTGTGTTGC CTCTGGATTCACTTTCAGTAACTACTGGATGAACTG GGTCCGCCAGTATCCAGAGCAGGGGCTTGAGTGGG TTGCTCAAATTAGATTGAATTCTGATAATTATGCAA CGCATTATGCGGAGTCTGTGAAAGGGAGGTTACCC ATCTCAAGAGATGATTCCAGAAAGTACTGTCTACCTA CAAATGAACAACTTAAGGGCTGAAGACACTGGAAT TTATTACTGCACAGGCGGGGGGGAGTACTGGGGCC AAGGCACCACTCTCACAGTCTCCTCA
		SEQ ID NO: 178
	VL	GACATTGTGATGACCCAGTCTCAAAAATTCATGTCC ACAACAATAGGAGACAGGGTCAGCATCACCTGCAA GGCCAGTCAGAATGTGGATACTGCTGTAGCCTGGT ATCAACAGAAACCAGGACAATCTCCTAACTACTG ATTTACTCAGCATCCACTCGGTACACTGGAGTCCCT GATCGCTTCACAGGCAGTGGATCTGGGACAGATTT CACTCTCACCATTAGTAATATGCAGTCTGAAGACCT GGCAGATTATTTCTGTCAGCAATATATCAGTTATCA GCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGA AA
		SEQ ID NO: 187
Ab38	VH	CAGATCCAGTTGGTACAGTCTGGACCTGAGCTGAA GAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGG CTTCTGGATATACCTTCACAACTATGGAATGAGTT GGGTGAAACAGGCTCCAGGAAAGGGATTAAAGTGG ATGGGCTGGATAAACACCTATTCTGGAGTGCCAAC ATATGCTGATGACTTCAAGGGACGGTTTGTCTTCTC TTTGGAAGCCTCTGCCAGCACTGCCTATTTGCAGAT CAACAACCTCAAAAATGAGGACGCGGCTACATATT TCTGTTCAAGGTGGTCTGGGCCCCGATCCGCTTGAGG ACCACTGGGGCCAAGGCACCACTCTCACAGTCTCC TCA
		SEQ ID NO: 196
	VL	CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCT GCATCTCCAGGGGAGAAGGTCACCATGACCTGCAC TGCCAGTTTAAGTCTAAATTACATTCAGTGGTACCG ACAGAGGTCAGGCACCTCCCCCAAACGATGGATTT ATGACACATCCAAGCTGGCTTCTGGAGTCCCTTCTC GTTTCAGTGGCAGTGGATCTGGGACCTCTTACTCTC TCACAATCAGCAGCATGGAGGCTGAAGATGCTGCC ACTTATTACTGCCAGCAGTGGAGTAGTAACCCCTG GACGTTTCGGTGGAGGCACCAAGCTGGAAATCAAA

[00193] The isolated polynucleotide that encodes the anti-CLDN18 antibodies (e.g. including the sequences as shown in Table 3) can be inserted into a vector for further cloning (amplification of the DNA) or for expression, using recombinant techniques known in the art. Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter (e.g. SV40, CMV, EF-1 α), and a transcription termination sequence. A vector may also include materials to aid in its entry into the cell, including but not limited to a viral particle, a liposome, or a protein coating.

[00194] The present disclosure provides vectors (e.g., cloning vectors or expression vectors) containing the nucleic acid sequence provided herein encoding the antibodies, at least one promoter (e.g., SV40, CMV, EF-1 α) operably linked to the nucleic acid sequence, and at least one selection marker. Examples of vectors include, but are not limited to, plasmids, phagemids, cosmids, and artificial chromosomes such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), or P1-derived artificial chromosome (PAC), bacteriophages such as lambda phage or M13 phage, and animal viruses. Categories of animal viruses used as expression vectors include retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpesvirus (e.g., herpes simplex virus), poxvirus, baculovirus, papillomavirus, and papovavirus (e.g., SV40). Exemplary plasmids include, pcDNA3.3, pMD18-T, pOptivec, pCMV, pEGFP, pIRES, pQD-Hyg-GSeu, pALTER, pBAD, pcDNA, pCal, pL, pET, pGEMEX, pGEX, pCI, pEGFT, pSV2, pFUSE, pVITRO, pVIVO, pMAL, pMONO, pSELECT, pUNO, pDUO, Psg5L, pBABE, pWPXL, pBI, p15TV-L, pPro18, pTD, pRS10, pLexA, pACT2.2, pCMV-SCRIPT.RTM., pCDM8, pCDNA1.1/amp, pcDNA3.1, pRc/RSV, PCR 2.1, pEF-1, pFB, pSG5, pXT1, pCDEF3, pSVSPORT, and pEF-Bos etc.

[00195] Vectors comprising the polynucleotide sequence encoding the antibody or antigen-binding fragment can be introduced to a host cell for cloning or gene

expression. Suitable host cells for cloning or expressing the DNA in the vectors herein are the prokaryote, yeast, or higher eukaryote cells described above. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, *Enterobacteriaceae* such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis*, *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*.

[00196] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-CLDN18 antibodies-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[00197] Suitable host cells for the expression of antibodies or antigen-fragment provided here are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for

transfection of *Spodoptera frugiperda* cells. Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco can also be utilized as hosts.

[00198] However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); mouse myeloma cell line (NS0, Galfrè and Milstein (1981), *Methods in Enzymology*, 73:3-46; Sp2/0-Ag14, ATCC CRL-1581;); Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); mouse sertoli cells (TM4, *Mather, Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (*Mather et al., Annals N.Y. Acad. Sci.* 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2). In some preferable embodiments, the host cell is mammalian cultured cells, such as CHO cells, BHK cells, or NS0 cells.

[00199] In some embodiments, the host cell is capable of producing a glyco-engineered antibody. For example, a host cell line can provide for the required glycosylation machinery during post-translation modification. Examples of such host cell lines includes but are not limited to those with altered (increased or decreased) activity of glycosylation related enzymes, such as, glucosaminyltransferase (e.g., $\beta(1,4)$ -N-acetylglucosaminyltransferase III (GnTIII)), glycosyltransferase (e.g., $\beta(1,4)$ -galactosyltransferase (GT)), sialyltransferase (e.g., $\alpha(2,3)$ -sialyltransferase (ST)), mannosidase (e.g., α -mannosidase II (ManII)), fucosyltransferase (e.g., alpha-1,6-fucosyltransferase gene (FUT8), (1,3) fucosyltransferase), prokaryotic GDP-6-

deoxy-D-lyxo-4-hexulose reductase (RMD), GDP- fucose transporter (GFT), natively or through genetic engineering.

[00200] In some embodiments, the host cell is characterized in lack of functional FUT8, overexpression of a heterologous GnTIII, expression of a prokaryotic GDP-6-deoxy-D-lyxo-4-hexulose reductase (RMD), or lack of functional GFT. A FUT8 knock out host cell line is fucosylation-deficient and produces afucosylated antibodies. Overexpression of GnTIII in a host cell line (see for example, the Glycart technology by Roche) results in the formation of bisected, non-fucosylated glycosylation form of an antibody. Expression of RMD (e.g. as in GlymaxX[®] system from ProBioGen AG) inhibits fucose de-novo biosynthesis, and as a consequence, antibodies generated by such host cell lines also exhibit reduced fucosylation. GFT knockout in CHO cell line (see for example, technology by Beijing Mabworks Biotech) block both fucose de-novo and fucose salvage biosynthesis pathways and results in reduced fucosylation.

[00201] Host cells are transformed with the above-described expression or cloning vectors for anti-CLDN18 antibodies production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In another embodiment, the antibody may be produced by homologous recombination known in the art.

[00202] The host cells used to produce the antibodies provided herein may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium (MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium (DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham *et al.*, *Meth. Enz.* 58:44 (1979), Barnes *et al.*, *Anal. Biochem.* 102:255 (1980), U.S. Pat. No. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Pat. Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such

as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCINTM drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[00203] When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration. Carter et al., *Bio/Technology* 10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[00204] The anti-CLDN18 antibodies prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, DEAE-cellulose ion exchange chromatography, ammonium sulfate precipitation, salting out, and affinity chromatography, with affinity chromatography being the preferred purification technique.

[00205] Pharmaceutical Composition

[00206] The present disclosure further provides pharmaceutical compositions comprising an anti-CLDN18 antibodies or antigen-binding fragment thereof, the chimeric antigen receptor, the polynucleotides, the vector, or the modified immune cells provided herein and one or more pharmaceutically acceptable carriers.

[00207] Pharmaceutical acceptable carriers for use in the pharmaceutical compositions disclosed herein may include, for example, pharmaceutically acceptable liquid, gel, or solid carriers, aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, anesthetics, suspending/dispersing agents, sequestering or chelating agents, diluents, adjuvants, excipients, or non-toxic auxiliary substances, other components known in the art, or various combinations thereof. Suitable components may include, for example, antioxidants, fillers, binders, disintegrants, buffers, preservatives, lubricants, flavorings, thickeners, coloring agents, emulsifiers or stabilizers such as sugars and cyclodextrins. Suitable antioxidants may include, for example, methionine, ascorbic acid, EDTA, sodium thiosulfate, platinum, catalase, citric acid, cysteine, thioglycerol, thioglycolic acid, thiosorbitol, butylated hydroxyanisole, butylated hydroxytoluene, and/or propyl gallate. As disclosed herein, inclusion of one or more antioxidants such as methionine in a composition comprising an antibody or antigen-binding fragment and conjugates as provided herein decreases oxidation of the antibody or antigen-binding fragment. This reduction in oxidation prevents or reduces loss of binding affinity, thereby improving antibody stability and maximizing shelf-life. Therefore, in certain embodiments compositions are provided that comprise one or more antibodies as disclosed herein and one or more antioxidants such as methionine. Further provided are methods for preventing oxidation of, extending the shelf-life of, and/or improving the efficacy of an antibody or antigen-binding fragment as provided herein by mixing the antibody or antigen-binding fragment with one or more antioxidants such as methionine.

[00208] The pharmaceutical compositions can be a liquid solution, suspension, emulsion, pill, capsule, tablet, sustained release formulation, or powder. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol,

lactose, starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate, etc.

[00209] In certain embodiments, the pharmaceutical compositions are formulated into an injectable composition. The injectable pharmaceutical compositions may be prepared in any conventional form, such as for example liquid solution, suspension, emulsion, or solid forms suitable for generating liquid solution, suspension, or emulsion. Preparations for injection may include sterile and/or non-pyretic solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use, and sterile and/or non-pyretic emulsions. The solutions may be either aqueous or nonaqueous.

[00210] In certain embodiments, unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration should be sterile and not pyretic, as is known and practiced in the art.

[00211] In certain embodiments, a sterile, lyophilized powder is prepared by dissolving an antibody or antigen-binding fragment as disclosed herein in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological components of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, water, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides a desirable formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial can contain a single dosage or multiple dosages of the anti-CLDN18 antibodies or composition thereof. Overfilling vials with a small amount above that needed for a dose or set of doses (e.g., about 10%) is acceptable so

as to facilitate accurate sample withdrawal and accurate dosing. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

[00212] Reconstitution of a lyophilized powder with water for injection provides a formulation for use in parenteral administration. In one embodiment, for reconstitution the sterile and/or non-pyretic water or other liquid suitable carrier is added to lyophilized powder. The precise amount depends upon the selected therapy being given, and can be empirically determined. The antibodies, as well as the encoding nucleic acids or nucleic acid sets, vectors comprising such, or host cells comprising the vectors, as described herein can be mixed with a pharmaceutically acceptable carrier (excipient) to form a pharmaceutical composition for use in treating a target disease. “Acceptable” means that the carrier must be compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. Pharmaceutically acceptable excipients (carriers) including buffers, which are well known in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover.

[00213] In some examples, the pharmaceutical composition described herein comprises liposomes containing the antibodies (or the encoding nucleic acids) which can be prepared by methods known in the art, such as described in Epstein, et al., *Proc. Natl. Acad. Sci. USA* 82:3688 (1985); Hwang, et al., *Proc. Natl. Acad. Sci. USA* 77:4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

[00214] The antibodies, or the encoding nucleic acid(s), may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial

polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are known in the art, see, *e.g.*, Remington, The Science and Practice of Pharmacy 20th Ed. Mack Publishing (2000).

[00215] In other examples, the pharmaceutical composition described herein can be formulated in sustained-release format. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.* films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

[00216] The pharmaceutical compositions to be used for *in vivo* administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Therapeutic antibody compositions are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[00217] The pharmaceutical compositions described herein can be in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

[00218] In certain embodiments, the pharmaceutical composition of the present disclosure further comprises one or more therapeutic agents. In certain embodiments, the one or more therapeutic agents are selected from the group consisting of

amrubicin, apatinib mesylate, atrasentan batabulin, calcitriol, capecitabine, cilengitide, dasatinib, decatanib, edotecarin, enzastaurin, erlotinib, everolimus, gimatecan, gossypol ipilimumab, lonafarnib, lucanthone, neuradiab, nolatrexed, oblimersen, olaparib, ofatumumab, oregovomab, panitumumab, pazopanib rubitecan, regorafenib, talampanel, tegafur, temsirolimus, tesmilifene, tetrandrine, ticilimumab, trametinib, trabectedin, vandetanib, vitespan, zanolimumab, zolendronate, histrelin, azacitidine, dexrazoxane, alemtuzumab, lenalidomide, gemtuzumab, ketoconazole, nitrogen mustard, ibritumomab tiuxetan, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, editronate, cyclosporine, Edwina-asparaginase, epirubicin, oxaliplatin, an anti-PD1 antibody, an anti-PDL1 antibody, an anti-HER2 antibody, an anti-HER2 ADC and 5-fluorouracil and strontium 89.

[00219] Therapeutical application

[00220] The present disclosure also provides therapeutic methods comprising: administering a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the chimeric antigen receptor, the polynucleotides, the vector, or the modified immune cells as provided herein to a subject in need thereof, thereby treating or preventing a CLDN18.2-related condition or disorder. In some embodiments, the CLDN18.2-related condition or disorder is cancer, optionally the cancer is characterized in expressing or over-expressing CLDN18.2. Expression or over-expression may be determined in a diagnostic or prognostic assay by evaluating increased levels of CLDN18.2 in a biological sample (such as a sample derived from cancer cell or tissue, or tumor infiltrating immune cells) from a subject. Various methods can be used. For example, diagnostic or prognostic assay can be used to evaluate expression levels of CLDN18.2 present on the surface of a cell (e.g. via an immunohistochemistry assay; IHC). Alternatively, or additionally, one may measure levels of CLDN-encoding nucleic acid in the cell, e.g. via fluorescent in situ hybridization (FISH; see WO98/45479 published October, 1998), southern blotting, or polymerase chain reaction (PCR) techniques, such as real time quantitative PCR (RT-PCR). Methods 132: 73-80 (1990)). Aside from the above assays, various in vivo

assays are available to the skilled practitioner. For example, one may expose cells within the body of the patient to an antibody which is optionally labeled with a detectable label, e.g. a radioactive isotope, and binding of the antibody to cells in the patient can be evaluated, e.g. by external scanning for radioactivity or by analyzing a biopsy taken from a patient previously exposed to the antibody. In some embodiments, the CLDN18.2-related condition or disorder is cancer, wherein the cancer is characterized in expressing CLDN18.2 at a level of less than 10000 antibody binding sites per cell, less than 9000 antibody binding sites per cell, less than 8000 antibody binding sites per cell, less than 7000 antibody binding sites per cell, less than 6000 antibody binding sites per cell, less than 5000 antibody binding sites per cell, or less than 4000 antibody binding sites per cell.

[00221] In some embodiments, the CLDN18.2-related condition or disorder is cancer, wherein the cancer is selected from the group consisting of lung cancer (*e.g.*, small cell lung cancer, non-small cell lung cancer (NSCLC), adenocarcinoma of the lung, or squamous cell carcinoma of the lung), gastric or stomach cancer (*e.g.*, gastrointestinal cancer), pancreatic cancer, esophageal cancer, liver cancer (*e.g.*, hepatocellular carcinoma/hepatoma), squamous cell cancer, cancer of the peritoneum, brain tumor (*e.g.*, glioblastoma/glioblastoma multiforme (GBM), non-glioblastoma brain tumor, or meningioma), glioma (*e.g.*, ependymoma, astrocytoma, anaplastic astrocytoma, oligodendroglioma, or mixed glioma such as oligoastrocytoma), cervical cancer, ovarian cancer, liver cancer (*e.g.*, hepatoblastoma, hepatocellular carcinoma/hepatoma, or hepatic carcinoma), bladder cancer (*e.g.*, urothelial cancer), breast cancer, colon cancer, colorectal cancer, rectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer (*e.g.*, rhabdoid tumor of the kidney), prostate cancer, vulval cancer, penile cancer, anal cancer (*e.g.*, anal squamous cell carcinoma), thyroid cancer, head and neck cancer (*e.g.*, nasopharyngeal cancer), skin cancer (*e.g.*, melanoma or squamous cell carcinoma), osteosarcoma, Ewing's sarcoma, chondrosarcoma, soft tissue sarcoma (*e.g.*, rhabdomyosarcoma, fibrosarcoma, Kaposi's sarcoma), carcinoid cancer, eye cancer (*e.g.*, retinoblastoma),

mesothelioma, lymphocytic/lymphoblastic leukemia (*e.g.*, acute lymphocytic/lymphoblastic leukemia (ALL) of both T-cell lineage and B-cell precursor lineage, chronic lymphoblastic/lymphocytic leukemia (CLL), acute myelogenous/myeloblastic leukemia (AML), including mast cell leukemia, chronic myelogenous/myelocytic/myeloblastic leukemia (CML), hairy cell leukemia (HCL), Hodgkin's disease, non-Hodgkin's lymphoma, chronic myelomonocytic leukemia (CMML), follicular lymphoma (FL), diffuse large B cell lymphoma (DLCL), mantle cell lymphoma (MCL), Burkitt's lymphoma (BL), mycosis fungoides, Sezary syndrome, cutaneous T-cell lymphoma, mast cell neoplasm, medulloblastoma, nephroblastoma, solitary plasmacytoma, myelodysplastic syndrome, chronic and non-chronic myeloproliferative disorder, central nervous system tumor, pituitary adenoma, vestibular schwannoma, primitive neuroectodermal tumor, ependymoma, choroid plexus papilloma, polycythemia vera, thrombocythemia, gallbladder cancer, idiopathic myofibrosis, and pediatric cancers such as pediatric sarcomas (*e.g.*, neuroblastoma, rhabdomyosarcoma, and osteosarcoma). In certain embodiments, the cancer is selected from the group consisting of gastric cancer, pancreatic cancer, esophageal cancer, lung cancer, gallbladder cancer, colorectal cancer and liver cancer.

[00222] The therapeutically effective amount of an antibody or antigen-binding fragment thereof, the chimeric antigen receptor, the polynucleotides, the vector, or the modified immune cells as provided herein will depend on various factors known in the art, such as for example body weight, age, past medical history, present medications, state of health of the subject and potential for cross-reaction, allergies, sensitivities and adverse side-effects, as well as the administration route and extent of disease development. Dosages may be proportionally reduced or increased by one of ordinary skill in the art (*e.g.*, physician or veterinarian) as indicated by these and other circumstances or requirements.

[00223] The antibodies disclosed herein may be administered by any route known in the art, such as for example parenteral (*e.g.*, subcutaneous, intraperitoneal, intravenous, including intravenous infusion, intramuscular, or intradermal injection)

or non-parenteral (e.g., oral, transdermal, intranasal, intraocular, sublingual, rectal, or topical) routes.

[00224] The present disclosure further provides methods of using the anti-CLDN18 antibodies.

[00225] In some embodiments, the present disclosure provides methods of detecting presence or amount of CLDN18.2 in a sample, comprising contacting the sample with the antibody, and determining the presence or the amount of CLDN18.2 in the sample.

[00226] In some embodiments, the present disclosure provides methods of diagnosing a CLDN18.2-related disease or condition in a subject, comprising: a) contacting a sample obtained from the subject with the antibody provided herein; b) determining presence or amount of CLDN18.2 in the sample; c) correlating the presence or the amount of CLDN18.2 to existence or status of the CLDN18.2-related disease or condition in the subject.

[00227] In some embodiments, the present disclosure provides kits comprising the antibody provided herein, optionally conjugated with a detectable moiety. The kits may be useful in detection of CLDN18.2 or diagnosis of CLDN18.2 related disease.

[00228] In some embodiments, the present disclosure also provides use of the antibody provided herein in the manufacture of a medicament for treating a disease or condition that would benefit from modulation of CLDN18.2 expression in a subject, in the manufacture of a diagnostic/prognostic reagent for diagnosing/prognosing a CLDN18.2-related disease or condition. To practice the method disclosed herein, an effective amount of the pharmaceutical composition described herein can be administered to a subject (*e.g.*, a human) in need of the treatment *via* a suitable route, such as intravenous administration, *e.g.*, as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, inhalation or topical routes.

Commercially available nebulizers for liquid formulations, including jet nebulizers and ultrasonic nebulizers are useful for administration. Liquid formulations can be directly nebulized and lyophilized powder can be nebulized after reconstitution. Alternatively, the antibodies as described herein can be aerosolized using a fluorocarbon formulation and a metered dose inhaler, or inhaled as a lyophilized and milled powder.

[00229] The subject to be treated by the methods described herein can be a mammal, more preferably a human. Mammals include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats. A human subject who needs the treatment may be a human patient having, at risk for, or suspected of having a target disease/disorder, such as a cancer or an immune disorder such as an autoimmune disease.

[00230] A subject having a target cancer can be identified by routine medical examination, *e.g.*, laboratory tests, organ functional tests, CT scans, or ultrasounds. In some embodiments, the subject to be treated by the method described herein may be a human cancer patient who has undergone or is subjecting to an anti-cancer therapy, for example, chemotherapy, radiotherapy, immunotherapy, or surgery.

[00231] Treatment efficacy for a target disease/disorder can be assessed by methods well-known in the art.

[00232] Combined Therapy

[00233] The anti-CLDN18 antibodies described herein may be utilized in conjunction with other types of therapy for the target disease such as cancer. The anti-CLDN18 antibodies described herein can be combined with an anti-cancer therapy, for example, those known in the art. Additional anti-cancer therapy includes chemotherapy, surgery, radiation, immunotherapy, gene therapy, and so forth.

[00234] Alternatively, the treatment of the present disclosure can be combined with a chemotherapeutic agent, for example, pyrimidine analogs (5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine), purine analogs, folate

antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (etoposide, teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, hexamethylnelamineoxaliplatin, iphosphamide, melphalan, merchlorhtamine, mitomycin, mitoxantrone, nitrosourea, plicamycin, procarbazine, taxol, taxotere, teniposide, triethylenethiophosphoramidate and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes-dacarbazine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (*e.g.*, TNP-470, genistein, bevacizumab) and growth factor inhibitors (*e.g.*, fibroblast

growth factor (FGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; and chromatin disruptors. In certain embodiments, the treatment of the present disclosure can be combined with one or more therapeutic agents are selected from the group consisting of amrubicin, apatinib mesylate, atrasentan batabulin, calcitriol, capecitabine, cilengitide, dasatinib, decatanib, edotecarin, enzastaurin, erlotinib, everolimus, gimatecan, gossypol ipilimumab, lonafarnib, lucanthone, neuradiab, nolatrexed, oblimersen, olaparib, ofatumumab, oregovomab, panitumumab, pazopanib rubitecan, regorafenib talampanel, tegafur, temsirolimus, tesmilifene, tetrandrine, ticilimumab, trametinib, trabectedin, vandetanib, vitespan, zanolimumab, zolendronate, histrelin, azacitidine, dexrazoxane, alemtuzumab, lenalidomide, gemtuzumab, ketoconazole, nitrogen mustard, ibritumomab tiuxetan, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, editronate, cyclosporine, Edwina-asparaginase, epirubicin, oxaliplatin, an anti-PD1 antibody, an anti-PDL1 antibody, an anti-HER2 antibody, an anti-HER2 ADC and 5-fluorouracil and strontium 89.

[00235] When a second therapeutic agent is used, such an agent can be administered simultaneously or sequentially (in any order) with the therapeutic agent described herein. When co-administered with an additional therapeutic agent, suitable therapeutically effective dosages for each agent may be lowered due to the additive action or synergy.

[00236] Kits for Therapeutical Uses

[00237] The present disclosure also provides kits for use in treating or alleviating a target diseases, such as cancer and immune disorders as described herein.

Such kits can include one or more containers comprising an anti-CLDN18 antibodies, *e.g.*, any of those described herein, and optionally a second therapeutic agent to be co-used with the anti-CLDN18 antibodies, which is also described herein.

[00238] In some embodiments, the kit can comprise instructions for use in accordance with any of the methods described herein. The included instructions can comprise a description of administration of the anti-CLDN18 antibodies, and optionally the second therapeutic agent, to treat, delay the onset, or alleviate a target disease as those described herein. The kit may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has the target disease, *e.g.*, applying the diagnostic method as described herein. In still other embodiments, the instructions comprise a description of administering an antibody to an individual at risk of the target disease.

[00239] The instructions relating to the use of an anti-CLDN18 antibodies generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the disclosure are typically written instructions on a label or package insert (*e.g.*, a paper sheet included in the kit), but machine-readable instructions (*e.g.*, instructions carried on a magnetic or optical storage disk) are also acceptable.

[00240] The label or package insert indicates that the composition is used for treating, delaying the onset and/or alleviating the disease, such as cancer or immune disorders (*e.g.*, an autoimmune disease). Instructions may be provided for practicing any of the methods described herein.

[00241] The kits of this disclosure are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (*e.g.*, an atomizer) or an infusion device such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial

having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-CLDN18 antibodies as those described herein.

[00242] Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container. In some embodiments, the disclosure provides articles of manufacture comprising contents of the kits described above.

[00243] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. All specific compositions, materials, and methods described below, in whole or in part, fall within the scope of the present invention. These specific compositions, materials, and methods are not intended to limit the invention, but merely to illustrate specific embodiments falling within the scope of the invention. One skilled in the art may develop equivalent compositions, materials, and methods without the exercise of inventive capacity and without departing from the scope of the invention. It will be understood that many variations can be made in the procedures herein described while still remaining within the bounds of the present invention. It is the intention of the inventors that such variations are included within the scope of the invention.

EXAMPLES

[00244] Example 1: Hybridoma Development

[00245] 1. Methods

[00246] 1.1. Immunization and Serum Titer Determination

[00247] The immunogen and immunization strategies applied in the present disclosure include cell immunization (human Claudin18.2 (CLDN18.2) overexpressing cells, e.g. HEK293F-hCLDN18.2), genetic immunization (full length human CLDN18.2 expression construct), and protein immunization (recombinant human CLDN18.2 protein).

[00248] Balb/c or SJL mice were divided into 5 groups, with 5 mice in each group. Each group of mice were immunized with human Claudin18.2 (CLDN18.2) overexpressing cells (Claudin18.2 cells, e.g. HEK293F-hCLDN18.2), full length human CLDN18.2 expression construct (Claudin18.2 expression construct), or recombinant human CLDN18.2 protein (Recombinant Claudin18.2 protein). The outline of the immunization strategies were summarized in Table 4. The primary immunization were followed by several boosts until animals developed satisfactory antiserum titers suitable for hybridoma development. All the immunization strategies were carried out in parallel in order to compare the performance and immune response in serum level.

[00249] Table 4. The outline of the immunization strategies

Group	Immunogen	Route	Animal/Strain	Group size	Dosage
1	Claudin18.2 cells	I.P.	SJL	5	$0.5-1 \times 10^7$ cells
2	Claudin18.2 cells	I.P.	Balb/c	5	$0.5-1 \times 10^7$ cells
3	Claudin18.2 expression construct	Gene gun	SJL	5	4 μ g
4	Claudin18.2 expression construct	Gene gun	Balb/c	5	4 μ g
5	Recombinant Claudin18.2 protein	I.P	SJL	5	25-50 μ g

[00250] 1.1.2. Immunization schedules

[00251] The detailed immunization schedule for cell immunization was shown in Table 5 below.

[00252] Table 5. Immunization schedule (Cell immunization)

Day 0	Pre-bleed (15-30 μ L serum/mouse) Primary: $0.5-1 \times 10^6$ /mouse, IP
14	Boost 1: $0.5-1 \times 10^7$ cell per mouse, IP
21	Test Bleed (15-30 μ L serum/mouse) (TB1)
22	Test bleed FACS
35	Boost 2: $0.5-1 \times 10^7$ cell per mouse, IP
42	Test Bleed (15-30 μ L serum/mouse) (TB2)
43	Test bleed FACS
44	Data analysis and phase conclusion
56	Pre-fusion (final) Boost: $0.5-1 \times 10^7$ cell per mouse, IP
Animals not selected for cell fusion will be maintained in cage and may be given additional boost immunizations.	

[00253] The detailed immunization schedule for genetic immunization was shown in Table 6 below.

[00254] Table 6. Immunization schedule (Genetic immunization)

Day 0	Pre-bleed (15-30 μ L serum/mouse) Primary: 1 μ g/shot, 4 shots/animal
14	Boost 1: 1 μ g/shot, 4 shots/animal
21	Test Bleed (15-30 μ L serum/mouse)
22	Test bleed FACS
28	Boost 2: 1 μ g/shot, 4 shots/animal
35	Test Bleed (15-30 μ L serum/mouse)
36	Test bleed FACS
42	Boost 3: 1 μ g/shot, 4 shots/animal

49	Test Bleed (15-30 μ L serum/mouse)
50	Test bleed FACS
51	Data analysis and phase conclusion
63	Pre-fusion (final) Boost: $0.5-1 \times 10^6$ per mouse
67	Fusion
Animals not selected for cell fusion will be maintained in cage and may be given additional boost immunizations.	

[00255] The detailed immunization schedule for protein immunization was shown in Table 7 below.

[00256] Table 7. Immunization schedule (Protein immunization)

Day 0	Pre-bleed (15-30 μ L serum/mouse) Primary: 50 μ g/mouse, IP, CFA
14	Boost 1: 25 μ g/mouse, IP, IFA
21	Test Bleed (15-30 μ L serum/mouse) (TB1)
22	Test bleed FACS
35	Boost 2: 25 μ g/mouse, IP, IFA
42	Test Bleed (15-30 μ L serum/mouse) (TB2)
43	Test bleed FACS
44	Data analysis and phase conclusion
56	Pre-fusion (final) Boost, 25 μ g/mouse, IP
Animals not selected for cell fusion will be maintained in cage and may be given additional boost immunizations.	

[00257] 1.1.3. Test bleed antiserum analysis

[00258] Test bleeds were performed and evaluated by testing using FACS on CHO-K1 cell line stably over-expressing human Claudine18.2 (i.e., CHOK1-18.2).

[00259] 1.2. Hybridoma Generation and Screening

[00260] 1.2.1. Cell fusion and screening

[00261] **Fusion:** Splenocyte fusions were performed on the mice which show the best response to the immunizations as determined by test bleed FACS. The lymphocytes from spleens and lymph nodes were fused to a Sp2/0-Ag14 cell line using an optimized electrofusion protocol. Multiple fusions were performed to ensure success of the project.

[00262] **Screening and Expansion:** The fusion was plated (10^4 to 10^5 per well) into a stack of 96-well plates. Plates were monitored for growth and fed weekly. Wells with cell growth were screened by primary screening assays in 10-14 days with

Acumen (HCI488NM) and/or other feasible assays. Multiple fusions for each targeting antigen were performed and screened by Acumen. The positive parental clones which showed positive binding with CHOK1-18.2 from primary screening were expanded into 24-well plates for secondary screening.

[00263] Additional Antibody Screening: Following primary screening, positive parental clones expanded into 24-well plates were screened again by the assay described in the hybridoma screening funnel below in section 1.2.2.

[00264] Hybridomas of interest were chosen to proceed to subcloning.

[00265] 1.2.2. Hybridoma subcloning, screening and cryopreservation

[00266] Subcloning: The parental hybridomas with desired reactivity and isotypes from the screening funnel above were then subcloned by multiple rounds of limiting dilution or single cell sorting until monoclones were obtained.

[00267] Screening & Expansion: The subcloning plates were screened by Acumen assay and the subclones with good binding ability were expanded to 24-wells for confirmation tests. The specificity and cross-reactivity of these subclones were confirmed with FACs analysis. Briefly, parental CHO-K1 cells, CHOK1-18.2, CHO-K1 cell line stably over-expressing human Claudine18.1 (CHOK1-18.1), CHO-K1 cell line stably over-expressing Rhesus monkey Claudine18.2 (CHOK1-rh18.2), and CHO-K1 cell line stably over-expressing mouse Claudine18.2 (CHOK1-m18.2) were incubated with antibodies produced by each subclone respectively. Fluorescent dye-conjugated secondary antibody was used to detect the binding of the primary antibody with the cells. Median fluorescence intensity (MFI) was measured by FACs analysis.

[00268] Cryopreservation: The desired subclonal cell lines were sequenced and further expanded into culture flasks for cryopreservation. 4-6 vials per cell line at $0.5-1.0 \times 10^7$ cells/vial were initially cryopreserved. Master cell bank and working cell bank can be established for the selected most valuable cell lines if desired.

[00269] 2. Results

[00270] We discovered 38 antibodies with unique sequences showing positive binding with CHO-K1 cell stably over-expressing human Claudine18.2 protein (CHOK1-18.2). Among which, 33 antibodies did not bind with CHO-K1 cell line stably over-expressing human Claudine18.1 protein (CHOK1-18.1), which suggested that these antibodies specifically recognize Claudine 18.2. Five antibodies had positive binding with both CHOK1-18.2 and CHOK1-18.1, but did not bind to parental CHOK1 cells, suggesting these antibodies are Pan-Claudine 18 recognizing antibody. All 38 antibodies could bind with monkey and mouse Claudin18.2 protein. The MFI of the antibodies staining CHOK1-18.2, CHOK1-18.1, CHOK1-rh18.2, CHOK1-m18.2, detected by FACs were summarized in Table 8 below. Anti-Pan-Claudine18 antibodies were underlined.

[00271] Table 8. MFI of antibodies binding to different cell lines

Clone	SEQ ID NOs of VH-CDR 1, VH-CDR 2, VH-CDR 3 (upper) and VL-CDR 1, VL-CDR 2, VL-CDR 3 (lower)	FACS MFI (CHOK1-18.1)	FACS MFI (CHOK1-18.2)	FACS MFI (CHOK1-rh18.2)	FACS MFI (CHOK1-m18.2)
<u>Ab01</u>	<u>SEQ ID NOs: 18, 20, 22</u>	<u>7247.1</u>	<u>12315.7</u>	<u>8383.4</u>	<u>12698.6</u>
	<u>SEQ ID NOs: 27, 29, 31</u>				
<u>Ab02</u>	<u>SEQ ID NOs: 36, 38, 40</u>	101.4	1378.9	1402.4	2036
	<u>SEQ ID NOs: 45, 47, 49</u>				
<u>Ab03</u>	<u>SEQ ID NOs: 54, 56, 58</u>	95.6	1957.3	1434.7	2973.8
	<u>SEQ ID NOs: 63, 65, 67</u>				
<u>Ab04</u>	<u>SEQ ID</u>	<u>6920</u>	<u>17564.3</u>	<u>2133</u>	<u>8444</u>

	<u>NOs: 72 and 74, GDY</u>				
	<u>SEQ ID</u>				
	<u>NOs: 81, 83, 85</u>				
Ab05	<u>SEQ ID</u>	97	16003.9	9851.9	12520.7
	<u>NOs: 90, 92, 94</u>				
	<u>SEQ ID</u>				
	<u>NOs: 99, 101, 103</u>				
Ab06	<u>SEQ ID</u>	789.4	46072.7	13988.5	13203.5
	<u>NOs: 108, 110, 112</u>				
	<u>SEQ ID</u>				
	<u>NOs: 117, 119, 121</u>				
Ab07	<u>SEQ ID</u>	764.4	13716.6	9042	15007.2
	<u>NOs: 126, 128, 130</u>				
	<u>SEQ ID</u>				
	<u>NOs: 135, 137, 139</u>				
Ab08	<u>SEQ ID</u>	97	19354	8351.8	13100.6
	<u>NOs: 144, 146, 148</u>				
	<u>SEQ ID</u>				
	<u>NOs: 153, 155, 157</u>				
Ab09	<u>SEQ ID</u>	95.6	17055.7	8104.1	12561.9
	<u>NOs: 198, 200, 202</u>				
	<u>SEQ ID</u>				
	<u>NOs: 207, 209, 211</u>				
Ab10	<u>SEQ ID</u>	80.8	8401.8	7071.4	17133.6
	<u>NOs: 216, 218, 220</u>				
	<u>SEQ ID</u>				
	<u>NOs: 225, 227, 229</u>				
Ab11	<u>SEQ ID</u>	80.8	9799	7803.5	11248.4
	<u>NOs: 234, 236, 238</u>				
	<u>SEQ ID</u>				
	<u>NOs: 243, 245, 247</u>				
Ab12	<u>SEQ ID</u>	83.8	8816.3	7613.1	13134.5
	<u>NOs: 252</u>				

	<u>254, 256</u> <u>SEQ ID</u> <u>NOs: 261,</u> <u>263, 265</u>				
Ab13	<u>SEQ ID</u> <u>NOs: 270,</u> <u>272, 274</u> <u>SEQ ID</u> <u>NOs: 279,</u> <u>281, 283</u>	82.3	7463.2	5627.9	12543.5
Ab14	<u>SEQ ID</u> <u>NOs: 288,</u> <u>290, 292</u> <u>SEQ ID</u> <u>NOs: 297,</u> <u>299, 301</u>	97	21360.6	6845.1	13628.4
Ab15	<u>SEQ ID</u> <u>NOs: 306,</u> <u>308, 310</u> <u>SEQ ID</u> <u>NOs: 315,</u> <u>317, 319</u>	80.8	7386.8	6319.5	12165.7
Ab16	<u>SEQ ID</u> <u>NOs: 324,</u> <u>326, 328</u> <u>SEQ ID</u> <u>NOs: 333,</u> <u>335, 337</u>	80.8	8170.3	6662	14313.4
Ab17	<u>SEQ ID</u> <u>NOs: 342,</u> <u>344, 346</u> <u>SEQ ID</u> <u>NOs: 351,</u> <u>353, 355</u>	82.3	11454.2	6681.1	13289.5
Ab18	<u>SEQ ID</u> <u>NOs: 360,</u> <u>362, 364</u> <u>SEQ ID</u> <u>NOs: 369,</u> <u>371, 373</u>	79.4	9910.7	7885.1	13519.6
Ab19	<u>SEQ ID</u> <u>NOs: 378,</u> <u>380, 382</u> <u>SEQ ID</u> <u>NOs: 387,</u> <u>389, 391</u>	80.8	7343.4	6293.1	13391.7
Ab20	<u>SEQ ID</u> <u>NOs: 396,</u> <u>398, 400</u>	82.3	7580.8	7047.2	13845.9

	<u>SEQ ID</u> <u>NOs: 405,</u> <u>407, 409</u>				
Ab21	<u>SEQ ID</u> <u>NOs: 414,</u> <u>416, 418</u>	79.4	10079.8	8239.4	15216.7
	<u>SEQ ID</u> <u>NOs: 423,</u> <u>425, 427</u>				
Ab22	<u>SEQ ID</u> <u>NOs: 432,</u> <u>434, 436</u>	82.3	9024.3	7329.4	15518.1
	<u>SEQ ID</u> <u>NOs: 441,</u> <u>443, 445</u>				
Ab23	<u>SEQ ID</u> <u>NOs: 450,</u> <u>452, 454</u>	82.3	8597.3	7242.7	16527.2
	<u>SEQ ID</u> <u>NOs: 459,</u> <u>461, 463</u>				
Ab24	<u>SEQ ID</u> <u>NOs: 468,</u> <u>470, 472</u>	80.8	10085.7	7519.1	12839.7
	<u>SEQ ID</u> <u>NOs: 477,</u> <u>479, 481</u>				
Ab25	<u>SEQ ID</u> <u>NOs: 486,</u> <u>488, 490</u>	82.3	12559.7	11970.9	23445
	<u>SEQ ID</u> <u>NOs: 495,</u> <u>497, 499</u>				
Ab26	<u>SEQ ID</u> <u>NOs: 504,</u> <u>506, 508</u>	80.8	9731.4	8292.3	15676.1
	<u>SEQ ID</u> <u>NOs: 513,</u> <u>515, 517</u>				
Ab27	<u>SEQ ID</u> <u>NOs: 522,</u> <u>524, 526</u>	97	7147.1	9241.9	8236.4
	<u>SEQ ID</u> <u>NOs: 531,</u> <u>533, 535</u>				
Ab28	<u>SEQ ID</u> <u>NOs: 540,</u> <u>542, 544</u>	205.8	8878.8	11085.3	9531.5
	<u>SEQ ID</u>				

	<u>NOs: 549,</u> <u>551, 553</u>				
Ab29	<u>SEQ ID</u> <u>NOs: 558,</u> <u>560, 562</u> <u>SEQ ID</u> <u>NOs: 567,</u> <u>569, 571</u>	97	19077.7	25720.6	21851.6
Ab30	<u>SEQ ID</u> <u>NOs: 576,</u> <u>578, 580</u> <u>SEQ ID</u> <u>NOs: 585,</u> <u>587, 589</u>	98.5	7563.2	10476.7	9613.8
Ab31	<u>SEQ ID</u> <u>NOs: 594,</u> <u>596, 598</u> <u>SEQ ID</u> <u>NOs: 603,</u> <u>605, 607</u>	97	5524.3	8010	7789.5
Ab32	<u>SEQ ID</u> <u>NOs: 612,</u> <u>614, 616</u> <u>SEQ ID</u> <u>NOs: 621,</u> <u>623, 625</u>	172	8731.1	11070.6	9237.5
Ab33	<u>SEQ ID</u> <u>NOs: 630,</u> <u>632, 634</u> <u>SEQ ID</u> <u>NOs: 639,</u> <u>641, 643</u>	97	8195.3	9659.4	9753.5
Ab34	<u>SEQ ID</u> <u>NOs: 648,</u> <u>650, 652</u> <u>SEQ ID</u> <u>NOs: 657,</u> <u>659, 661</u>	91.1	9072.8	6719.4	10670.7
Ab35	<u>SEQ ID</u> <u>NOs: 666,</u> <u>668, 670</u> <u>SEQ ID</u> <u>NOs: 675,</u> <u>677, 679</u>	92.6	11264.6	8339.3	9613.8
Ab36	<u>SEQ ID</u> <u>NOs: 684,</u> <u>686, 688</u> <u>SEQ ID</u> <u>NOs: 693,</u>	<u>4304.2</u>	<u>18040.7</u>	<u>17420.4</u>	<u>21601.1</u>

<u>Ab37</u>	<u>695, 697</u> <u>SEQ ID</u> <u>NOs: 163,</u> <u>165, 167</u>	<u>4589.9</u>	<u>15168.3</u>	<u>16699.4</u>	<u>18634.8</u>
	<u>SEQ ID</u> <u>NOs: 172,</u> <u>174, 176</u>				
<u>Ab38</u>	<u>SEQ ID</u> <u>NOs: 181,</u> <u>183, 185</u>	<u>4472.6</u>	<u>15683.7</u>	<u>15612.6</u>	<u>20379.2</u>
	<u>SEQ ID</u> <u>NOs: 190,</u> <u>192, 194</u>				

[00272] Example 2: Antibody Characterization: Affinity

[00273] 1. Methods

[00274] Sequences of 15 mouse antibodies from Table 8 were selected to generate and produce human IgG1 chimeric antibodies. The binding affinity of these antibodies and the bench mark antibody (i.e., IMAB362 (Zolbetuximab)) with CHOK1-18.2 cells and human patient derived gastric cancer cell line (i.e., GAXC031) was determined by FACs analysis. The protocol for FACs analysis was described as follows:

[00275] a. Digested cells using TrypLE™ Express Enzyme (1X), and then centrifuged the harvested cells at 400g for 5 min and discarded the supernatant.

[00276] b. Washed the cells twice with cold FACS buffer by centrifuging at 400g for 5 min and discarded the supernatant.

[00277] c. Resuspended the cells, and seeded 2×10^5 cell/well into the assay plate in 50 μ l FACS buffer, then added 50 μ l primary antibody (primary antibody final concentration: 50.00, 16.67, 5.56, 1.85, 0.62, 0.21, 0.07, 0.02, 0.01, 0.00 μ g/ml) and incubated at 40°C for 1 hour.

[00278] d. Washed the cells twice by using the condition in step b, and then resuspended the cells with 100 μ l/well diluted secondary antibody (i.e. AlexaFluor488-anti-human IgG), and incubated at 4 °C for 1 hour in the dark.

[00279] e. Washed the cells twice by using the condition in step b, and then resuspended the cells with 100 μ l/well cold FACS buffer. Kept the cells in dark for FACS analysis.

[00280] 2. Results

[00281] The binding affinity of the selected antibodies on CHOK1-18.2 were higher than or comparable with the bench mark antibody IMAB362 (see Table 9 and Figure 3).

[00282] Compared with IMAB362, the max MFI (primary antibody concentration at 50 μ g/ml) of the selected antibodies on Claudin18.2-low expressing cells GAXC031 and CHOK1-18.2 were much higher (see Table 9).

[00283] The selected antibodies were more sensitive on Claudin18.2-low expressing cells GAXC031 compared with IMAB362 (see Figure2), with higher max MFI and higher or comparable EC₅₀ (see Table 9 and Figure 3).

[00284] Table 9. Binding affinity of the antibodies on GAXC031 and CHOK1-18.2 (“ch” refers to chimeric)

Clones	SEQ ID NOs of VH-CDR 1, VH-CDR 2, VH-CDR 3 (upper) and VL-CDR 1, VL-CDR 2, VL-CDR 3 (lower)	GAXC031		CHOK1-18.2	
		MAX MFI	EC ₅₀ (nM)	MAX MFI	EC ₅₀ (nM)
IMAB362	<u>SEQ ID NOs: 2, 4, 6</u>	742	36.11	49613	5.686
	<u>SEQ ID NOs: 10, 12, 14</u>				
chAb06	<u>SEQ ID NOs: 108, 110, 112</u>	5462	/	92848	5.425
	<u>SEQ ID NOs: 117, 119, 121</u>				
chAb10	<u>SEQ ID NOs: 216, 218, 220</u>	6937	29.24	80356	2.274
	<u>SEQ ID NOs: 225, 227, 229</u>				

chAb15	<u>SEQ ID NOs: 306, 308, 310</u>	6112	31.86	94002	4.645
	<u>SEQ ID NOs: 315, 317, 319</u>				
chAb17	<u>SEQ ID NOs: 342, 344, 346</u>	4231	94.18	83797	4.736
	<u>SEQ ID NOs: 351, 353, 355</u>				
chAb04	<u>SEQ ID NOs: 72 and 74, GDY</u>	3864	/	75326	2.14
	<u>SEQ ID NOs: 81, 83, 85</u>				
chAb05	<u>SEQ ID NOs: 90, 92, 94</u>	4599	73.81	83869	5.001
	<u>SEQ ID NOs: 99, 101, 103</u>				
chAb08	<u>SEQ ID NOs: 144, 146, 148</u>	5834	/	71852	3.6
	<u>SEQ ID NOs: 153, 155, 157</u>				
chAb11	<u>SEQ ID NOs: 234, 236, 238</u>	6425	/	85566	3.635
	<u>SEQ ID NOs: 243, 245, 247</u>				
chAb18	<u>SEQ ID NOs: 360, 362, 364</u>	3686	/	60243	7.715
	<u>SEQ ID NOs: 369, 371, 373</u>				
chAb24	<u>SEQ ID NOs: 468, 470, 472</u>	5859	/	64484	4.989
	<u>SEQ ID NOs: 477, 479, 481</u>				
chAb25	<u>SEQ ID NOs: 486, 488, 490</u>	3015	/	56138	8.266
	<u>SEQ ID NOs: 495, 497, 499</u>				
chAb20	<u>SEQ ID NOs: 396, 398, 400</u>	6265	42.94	65685	3.882
	<u>SEQ ID NOs: 405, 407, 409</u>				
chAb30	<u>SEQ ID NOs: 576, 578, 580</u>	4462	/	65007	9.761
	<u>SEQ ID NOs: 585, 587, 589</u>				
chAb29	<u>SEQ ID NOs: 558, 560, 562</u>	5635	/	63401	6.629
	<u>SEQ ID NOs: 567, 569, 571</u>				
chAb31	<u>SEQ ID NOs: 594, 596, 598</u>	3773	/	59932	5.165
	<u>SEQ ID NOs: 603, 605, 607</u>				

[00285] **Example 3: Antibody characterization: ADCC**

[00286] **1. Methods**

[00287] GAXC031 cells were labeled with fluorescence enhancing ligand (DELFIATM BATDA Reagent, Perkin Elmer, AD0116) according to operational manuscript (i.e., 1×10^6 /ml cells were labeled with 2 μ L/ml fluorescence enhancing ligand (DELFIATM BATDA Reagent) and incubate for 20 min at 37 °C in a cell incubator) and 10,000 cells/well in 100 μ L were seeded to 96 wells V-bottom sterile plate (Corning, cat: 3894). After that, added 50 μ L serial diluted antibodies listed in Table 9 (at a concentration gradient of 100 nM, 20 nM, 4 nM, 0.8 nM, 0.16 nM, 0.032 nM, 0.0064 nM, 0.00128 nM, 0.000256 nM, and 0 nM) to each well and incubated the plate at 37°C, 5% CO₂ for 5-10 min, meanwhile, harvested NK-92 CD16a 176V cells and resuspended them in no pheno red RPMI1640 medium (Gibco, Cat No.#11835-030)+10% FBS to 1×10^6 /ml. 50 μ L NK92/CD16a cells as mentioned were supply into each well of the assay plate. After 2 hours incubated in 37°C, 5% CO₂, transferred 25 μ L of the supernatant to a new flat-bottom detection plate (PERKIN ELMER, Cat No.#AAAND-0001). Added 200 μ L of Europium Solution (Perkin Elmer, Envision 2105, AD0116-B, Lot#2610848) and shaken the plate at 250 rpm for 15 min at room temperature and detected the values by Envision (Perkin Elmer, Envision 2105).

[00288] 2. Results

[00289] All our antibodies showed potent ADCC effect on GAXC031 cells. Our antibodies showed higher max ADCC induced cell killing on GAXC031 cells, and lower EC₅₀ compared with bench mark antibody (i.e., IMAB362) (see Table 10 and Figure 4).

[00290] Table 10. Max GAXC031 killing percentage and EC₅₀ of antibody induced ADCC effect

Samples ID.	SEQ ID NOs of VH-CDR 1, VH-CDR 2, VH-CDR 3 (upper) and VL-CDR 1, VL-CDR 2, VL-CDR 3 (lower)	Max tumor cell killing (% of control)	EC ₅₀ (nM)
IMAB362	SEQ ID NOs: 2, 4, 6	30.68	36.08
	SEQ ID NOs: 10, 12, 14		
chAb06	SEQ ID NOs: 108, 110, 112	40.56	3.008
	SEQ ID NOs: 117, 119, 121		

chAb10	SEQ ID NOs: 216, 218, 220	55.17	1.68
	SEQ ID NOs: 225, 227, 229		
chAb15	SEQ ID NOs: 306, 308, 310	36.52	2.652
	SEQ ID NOs: 315, 317, 319		
chAb17	SEQ ID NOs: 342, 344, 346	60.62	2.456
	SEQ ID NOs: 351, 353, 355		
chAb04	SEQ ID NOs: 72 and 74, GDY	/	/
	SEQ ID NOs: 81, 83, 85		
chAb05	SEQ ID NOs: 90, 92, 94	57.91	5.925
	SEQ ID NOs: 99, 101, 103		
chAb08	SEQ ID NOs: 144, 146, 148	69.35	2.216
	SEQ ID NOs: 153, 155, 157		
chAb11	SEQ ID NOs: 234, 236, 238	54.68	3.702
	SEQ ID NOs: 243, 245, 247		
chAb18	SEQ ID NOs: 360, 362, 364	61.5	5.07
	SEQ ID NOs: 369, 371, 373		
chAb24	SEQ ID NOs: 468, 470, 472	66.59	4.457
	SEQ ID NOs: 477, 479, 481		
chAb25	SEQ ID NOs: 486, 488, 490	76.85	8.38
	SEQ ID NOs: 495, 497, 499		
chAb20	SEQ ID NOs: 396, 398, 400	62.86	4.141
	SEQ ID NOs: 405, 407, 409		
chAb30	SEQ ID NOs: 576, 578, 580	80.2	7.441
	SEQ ID NOs: 585, 587, 589		
chAb29	SEQ ID NOs: 558, 560, 562	60.94	5.267
	SEQ ID NOs: 567, 569, 571		
chAb31	SEQ ID NOs: 594, 596, 598	78.84	8.159
	SEQ ID NOs: 603, 605, 607		

[00291] Example 4: Antibody characterization: CDC

[00292] 1. Methods

[00293] GAXC031 cells were adjusted to 1×10^5 /ml in L-15 medium (GE HYCLONE, Cat No#SH30525.01), then seeded 50 μ L cells into 96-flat well plate (Corning, Cat No.#3903), 25 μ L serial diluted antibody (at a concentration gradient of 1000 nM, 333.33 nM, 111.11 nM, 37.04 nM, 12.35 nM, 4.12 nM, 1.37 nM, 0.46 nM, 0.15 nM, and 0 nM) were added to each well. After incubating the plate at 37°C, 5% CO₂ for 30 min, 25 μ L normal human serum complement (Quidel corporation, Cat A113) (final concentration is 20%) were supplied into each well and incubated overnight. On day 2, added 50 μ L Cell Titer-Glo Luminescent Buffer (Promega, Cat

No.#G7572) to the wells and shake the plate for 2 minutes and put the plate at room temperature for 10 minutes. Signals were measured by Spectra Max M5.

[00294] 2. Results

[00295] All our antibodies showed potent CDC effect on GAXC031 cells. Our antibody showed higher max CDC induced cell killing on GAXC031 cells, and lower EC₅₀ compared with bench mark antibody (i.e., IMAB362) (see Table 11 and Figure 3).

[00296] Table 11. Max GAXC031 killing percentage and EC₅₀ of antibody induced CDC effect

Samples ID.	SEQ ID NOs of VH-CDR 1, VH-CDR 2, VH-CDR 3 (upper) and VL-CDR 1, VL-CDR 2, VL-CDR 3 (lower)	Max CDC induced tumor cell killing (% of control)	EC ₅₀ (nM)
IMAB362	SEQ ID NOs: 2, 4, 6	52.52	809.4
	SEQ ID NOs: 10, 12, 14		
chAb06	SEQ ID NOs: 108, 110, 112	75.38	9.722
	SEQ ID NOs: 117, 119, 121		
chAb10	SEQ ID NOs: 216, 218, 220	82.745	2.695
	SEQ ID NOs: 225, 227, 229		
chAb15	SEQ ID NOs: 306, 308, 310	77.44	8.155
	SEQ ID NOs: 315, 317, 319		
chAb17	SEQ ID NOs: 342, 344, 346	70.81	9.925
	SEQ ID NOs: 351, 353, 355		
chAb05	SEQ ID NOs: 90, 92, 94	78.86	17.75
	SEQ ID NOs: 99, 101, 103		
chAb08	SEQ ID NOs: 144, 146, 148	68.37	13.6
	SEQ ID NOs: 153, 155, 157		
chAb11	SEQ ID NOs: 234, 236, 238	71.15	19.41
	SEQ ID NOs: 243, 245, 247		
chAb18	SEQ ID NOs: 360, 362, 364	75.3	35.02
	SEQ ID NOs: 369, 371, 373		
chAb24	SEQ ID NOs: 468, 470, 472	70.73	12.81
	SEQ ID NOs: 477, 479, 481		
chAb25	SEQ ID NOs: 486, 488, 490	72.88	25.39
	SEQ ID NOs: 495, 497, 499		
chAb20	SEQ ID NOs: 396, 398, 400	72.96	8.82
	SEQ ID NOs: 405, 407, 409		
chAb30	SEQ ID NOs: 576, 578, 580	76.08	23.17
	SEQ ID NOs: 585, 587, 589		

chAb29	SEQ ID NOs: 558, 560, 562	67.83	12.72
	SEQ ID NOs: 567, 569, 571		
chAb31	SEQ ID NOs: 594, 596, 598	60.74	37.86
	SEQ ID NOs: 603, 605, 607		

[00297] Example 5: Antibody characterization: Indirect ADC cytotoxicity

[00298] 1. Methods

[00299] GAXC031 cells were incubated with selected chimeric antibodies (primary antibody) and vc-MMAF-conjugated anti-human IgG (secondary antibody), to evaluate the antibody-drug conjugation induced cytotoxicity efficacy of the antibodies. The method is described as follows:

[00300] a. GAXC031 cells were seeded at 2000 cells/well in 65 μ l assay medium;

[00301] b. Treated the cell with primary antibody with a series dilutions in 25 μ l assay medium follow the design layout the next day (final starting working concentration 100 nM, 1:5 serial dilution), then added 10 μ l of secondary antibody (final working concentration: 2 μ g/ml);

[00302] c. Continued to culture for 120 hours; and

[00303] d. Measured the cell viability at 120-hour time point according to the celltiter Glo manual.

[00304] 2. Results

[00305] All our antibodies showed potent indirect ADC effect on GAXC031 cells, with higher max cell killing (max growth inhibition), and lower IC₅₀ compared with bench mark antibody (i.e., IMAB362) (see Table 12 and Figure 6).

[00306] Table 12. Max GAXC031 growth inhibition % and IC₅₀ of indirect ADC cytotoxicity

Samples ID.	SEQ ID NOs of VH-CDR 1, VH-CDR 2, VH-CDR 3 (upper) and VL-CDR 1, VL-CDR 2,	IC50 (nM)	Max inhibition%
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	VL-CDR 3		
IMAB362	<u>SEQ ID NOs: 2, 4, 6</u>	4.75	81.80
	<u>SEQ ID NOs: 10, 12, 14</u>		
chAb06	<u>SEQ ID NOs: 108, 110,</u>	0.61	91.78
	<u>112</u>		
	<u>SEQ ID NOs: 117, 119,</u>		
chAb10	<u>121</u>	0.24	92.83
	<u>SEQ ID NOs: 216, 218,</u>		
	<u>220</u>		
chAb15	<u>SEQ ID NOs: 225, 227,</u>	0.38	92.43
	<u>229</u>		
	<u>SEQ ID NOs: 306, 308,</u>		
chAb17	<u>310</u>	0.88	92.40
	<u>SEQ ID NOs: 315, 317,</u>		
	<u>319</u>		
chAb05	<u>SEQ ID NOs: 342, 344,</u>	0.99	92.28
	<u>346</u>		
	<u>SEQ ID NOs: 351, 353,</u>		
chAb08	<u>355</u>	0.45	92.52
	<u>SEQ ID NOs: 90, 92, 94</u>		
	<u>SEQ ID NOs: 99, 101,</u>		
chAb11	<u>103</u>	0.87	93.49
	<u>SEQ ID NOs: 144, 146,</u>		
	<u>148</u>		
chAb18	<u>SEQ ID NOs: 153, 155,</u>	1.58	90.72
	<u>157</u>		
	<u>SEQ ID NOs: 234, 236,</u>		
chAb24	<u>238</u>	0.85	92.72
	<u>SEQ ID NOs: 243, 245,</u>		
	<u>247</u>		
chAb25	<u>SEQ ID NOs: 360, 362,</u>	0.86	92.91
	<u>364</u>		
	<u>SEQ ID NOs: 369, 371,</u>		
chAb20	<u>373</u>	0.47	92.83
	<u>SEQ ID NOs: 468, 470,</u>		
	<u>472</u>		
chAb30	<u>SEQ ID NOs: 477, 479,</u>	1.58	92.38
	<u>481</u>		
	<u>SEQ ID NOs: 486, 488,</u>		
chAb20	<u>490</u>	0.47	92.83
	<u>SEQ ID NOs: 495, 497,</u>		
	<u>499</u>		
chAb30	<u>SEQ ID NOs: 396, 398,</u>	0.47	92.83
	<u>400</u>		
	<u>SEQ ID NOs: 405, 407,</u>		
chAb30	<u>409</u>	1.58	92.38
	<u>SEQ ID NOs: 576, 578,</u>		
	<u>580</u>		
chAb30	<u>SEQ ID NOs: 585, 587,</u>	1.58	92.38
	<u>580</u>		
	<u>SEQ ID NOs: 585, 587,</u>		

	<u>589</u>		
chAb29	<u>SEQ ID NOs: 558, 560,</u>	0.91	93.53
	<u>562</u>		
	<u>SEQ ID NOs: 567, 569,</u>		
	<u>571</u>		
chAb31	<u>SEQ ID NOs: 594, 596,</u>	2.35	91.69
	<u>598</u>		
	<u>SEQ ID NOs: 603, 605,</u>		
	<u>607</u>		

[00307] Example 6: Antibody humanization

[00308] Lead candidates Ab15, Ab10 and Ab17 were selected for antibody humanization. Briefly, mouse antibody sequences were analyzed and then

- 1) Modelling of the mouse antibody VH and VL domains;
- 2) Alignment with a range of preferred human germline sequences;
- 3) Assessment of conflicts between non-human CDRs and human FRs and design of back mutations to prevent a loss of affinity in the final products;
- 4) CDR grafting onto preferred germline backbones;
- 5) ~5 different humanized sequences generated, cloning and small-scale production of all humanized variants and chimeric in mammalian expression system;

[00309] The finally obtained heavy chains and light chains of the humanized sequences were listed below (the amino acids in red refer to the amino acids of CDRs):

>Ab15 HM-VH1

EVMLVESGGGLVQPGGSLRLSCAASGFTFSTYTMSWVRQTPEKRLEWVATIVGGGGY
 TTYLDSVKGRFTISRDNKNTLYLQMNSLRAEDTALYYCARMGLTQRNALDYWGQGT
 LITVSS (SEQ ID NO: 704)

>Ab15 HM-VH2

EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYTMSWVRQTPEKRLEWVATIVGGGGY
 TTYLDSVKGRFTISRDNKNTLYLQMNSLRAEDTALYYCARMGLTQRNALDYWGQGT
 LITVSS (SEQ ID NO: 705)

>Ab15 HM-VH3

EVMLVESGGGVVQPGGSLRLSCAASGFTFSTYTMSWVRQTPEKRLEWVATIVGGGGY
TYYLDSVKGRFTISRDNKNTLYLQMNSLRTEDTALYYCARMGLTQRNALDYWGQGT
LITVSS (SEQ ID NO: 706)

>Ab15-HM-VH-N1

EVMLVESGGGLVQPGGSLRLSCAASGFTFSTYTMSWVRQTPGKRLEWVATIVGGGGY
TYYLDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARMGLTQRNALDYWGQGT
SITVSS (SEQ ID NO: 707)

>Ab15 HM-VL1

DIVMTQSPDSLAVSLGERATINCKSSQSLFNSGNQKNYLAWYQQKPGQPPKLLIYGA
STRESGVPDRFTGSGFGTDFTLTISLQAEDVAVYYCQNDHTYPLTFGAGTKLEIK
(SEQ ID NO: 708)

>Ab15 HM-VL2

DIVMTQSPSLPVTGPGEPAISCKSSQSLFNSGNQKNYLAWYLQKPGQPPKLLIYGA
STRESGVPDRFTGSGFGTDFTLKISRVEAEDVGVYYCQNDHTYPLTFGAGTKLEIK
(SEQ ID NO: 709)

>Ab15-HM-VL-N1

DIVMTQSPDSLAVSLGERATINCKSSQSLFNSGNQKNYLAWYQQKPGQPPKLLIYGA
STRESGVPDRFSGSGFGTDFTLTISLQAEDVAVYYCQNDHTYPLTFGAGTKLEIK
(SEQ ID NO: 710)

>Ab10-HM-VH2

EVMLVESGGGLVKPGGSLRLSCAASGFTFSSYTMSWVRQAPEKRLEWVATISVIGGN
TYYVDSVKGRFTISRDKAKNTLYLQMNSLRAEDTALYYCARLGQTQRNAMDYWGQGT
LVTVSS (SEQ ID NO: 711)

>Ab10-HM-VH3

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPEKRLEWVATISVIGGN
TYYVDSVKGRFTISRDKAKNTLYLQMNSLRAEDTALYYCARLGQTQRNAMDYWGQGT
LVTVSS (SEQ ID NO: 712)

>Ab10-HM-VH4

EVMLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQTPEKRLEWVATISVIGGN
TTYVDSVKGRFTISRDKAKNTLYLQMNSLRAEDTALYYCARLGQTQRNAMDYWGQGT
LVTVSS (SEQ ID NO: 713)

>Ab10-HM-VH-N1

EVMLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQTPGKRLEWVATISVIGGN
TTYVDSVKGRFTISRDKSKNTLYLQMNSLRAEDTAVYYCARLGQTQRNAMDYWGQGT
LVTVSS (SEQ ID NO: 714)

>Ab10 HM-VL1

DIVMTQSPDSLAVSLGERATINCKSSQSLNLSGNQKNYLAWYQQKPGQPPKLLIYGA
STRESGVPDRFTGSGSGTDFTLTISLQAEDVAVYYCQNDYSYPLTFGAGTKLEIK
(SEQ ID NO: 715)

>Ab10 HM-VL2

EIVMTQSPATLSLSPGERATLSCKSSQSLNLSGNQKNYLAWYQQKPGQPPKLLIYGA
STRESGIPARFTGSGSGTDFTLTISLQPEDFAVYYCQNDYSYPLTFGAGTKLEIK
(SEQ ID NO: 716)

>Ab10-HM-VL-N1

DIVMTQSPDSLAVSAGERATMNCKSSQSLNLSGNQKNYLAWYQQKPGQPPKLLIYGA
STRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQNDYSYPLTFGAGTKLEIK
(SEQ ID NO: 717)

>Ab17 HM-VH1

QVQLKESGPGLVKPSSETLSLTCTVSGFSLTSYAISWVRQPPGKGLEWLGEIWTGGGT
NYSALKSRVSIKDNSKSQVFLKLSSVQAADTARYYCGRLSYGNSLDYWGQGT LVT
VSS (SEQ ID NO: 718)

>Ab17 HM-VH2

QVQLQESGPGLVKPSQTLSTCTVSGFSLTSYAISWVRQPAGKGLEWLGEIWTGGGT
NYSALKSRVSIKDNSKSQVFLKLSSVQAADTARYYCGRLSYGNSLDYWGQGT LVT
VSS (SEQ ID NO: 719)

>Ab17 HM-VH3

QVQLQESGPGLVKPSQTLSTCTVSGFSLTSYAISWVRQPPGKGLEWLGEIWTGGGT
NYNPALKSRVSISKDNSKSQVFLKLSSVTAADTARYYCGRLSYGNSLDYWGQGTLVTVSS (SEQ ID NO: 720)

>Ab17 HM-VH3-CDR2

EIWTGGGTNYNPALKS (SEQ ID NO: 726)

>Ab17 HM-VH5

QVQLQESGPGLVKPSQTLSTCTVSGFSLTSYAISWVRQPPGKGLEWLGEIWTGGGT
NYSALKSRVSISKDNSKSQVFLKLSSVTAADTARYYCGRLSYGNSLDYWGQGTLVTVSS (SEQ ID NO: 721)

>Ab17 HM-VH1-N1

QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYAISWVRQPPGKLEWIGEIWTGGGT
NYNSSLKSRVTISKDNSKSQVSLKLSSVQAADTARYYCGRLSYGNSLDYWGQGTLVTVSS (SEQ ID NO: 722)

>Ab17 HM-VH1-N1-CDR2

EIWTGGGTNYNSSLKS (SEQ ID NO: 727)

>Ab17 HM-VL1

DIVMTQSPDSLTVSLGERATINCKSSQSLNLSGNQKNYLTWYQQKPGQPPKLLIYWA
STRESGVPDRFTGSGSGTDFTLTISSLQAEDVAVYYCQNNFIYPLTFGPGTKLEIK
(SEQ ID NO: 723)

>Ab17 HM-VL2

DIVMTQSPSLPVTLGEPASISCKSSQSLNLSGNQKNYLTWYLQKPGQPPKLLIYWA
STRESGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCQNNFIYPLTFGPGTKLEIK
(SEQ ID NO: 724)

>Ab17 HM-VL1-N

DIVMTQSPDSTTVLLGERATINCKSSQSLNLSGNQKNYLAWYQQKPGQPPKLLIYWA
STRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNNFIYPLTFGPGTKLEIK
(SEQ ID NO: 725)

>Ab17 HM-VL1-N-CDR1

KSSQSLNLSGNQKNYLA (SEQ ID NO: 728)

[00310] 1. Cell based binding affinity (GAXC031)

[00311] Humanized antibodies with different combination of light and heavy chains were expressed. Cell based affinity was tested using GAXC031 cells. Some of the humanized antibody showed equal or slightly decreased affinity against GAXC031 cells as shown in Figure 7.

[00312] 2. Cell based binding affinity (KatoIII and SNU620)

[00313] KatoIII and SNU620 cells that express very low level Claudin 18.2 were tested for the binding affinity with Ab15, Ab10 and Ab17. Briefly, these gastric cancer cells were collected and washed twice with 1x PBS buffer and then incubated with mAbs of this disclosure at a series of concentrations for 1 hour. Samples were washed twice and incubated with FITC-labeled secondary antibody for the following flow cytometry analysis.

[00314] These two gastric cancer cell lines actually expressed relatively low levels of Claudin 18.2, which was detected by antibodies of this disclosure while the reference antibody IMAB362 could hardly detect the signal (see Figure 8). Again, mAb Ab15 displayed the highest affinity.

[00315] 3. SPR analysis for Lead candidates

[00316] The affinity of antibodies with VLP-Claudin 18.2-biotin was determined by BIAcore 8K (GE Healthcare). 200 µg/ml VLP-Claudin 18.2-biotin was immobilized to Series S Sensor Chip SA at a flow rate of 10 µl/min for 120s to reach the immobilization level around 1200RU. Antibodies were injected at a flow rate of 30 µl/min at room temperature with the concentration gradient (1.56~50 nM). The contact time was set to 180s and dissociation time was 400s. At the end of each cycle, 10 mM Glycine pH=1.5 was injected to remove the tested antibody from the surface. At last, binding kinetics was calculated using BIAcore Insight Evaluation Software and a 1:1 binding model was used for curve fitting.

[00317] As shown in Figure 9, the humanized Ab15 (VH3xVLN1), humanized Ab15 (VHN1xVL2), humanized Ab10 (VHN1xVLN1), humanized Ab10

(VH3xVLN1), humanized Ab17 (VH5xVLN1) and humanized Ab17 (VH1xVLN1) have a KD of 7.07×10^{-13} , 9.40×10^{-12} , 1.39×10^{-10} , 4.41×10^{-10} , 4.60×10^{-10} and 4.95×10^{-10} , respectively.

[00318] Example 7: efficacy assay of antibody drug conjugates

[00319] 1. *In vitro* efficacy assay (ADC efficacy included)

[00320] Target tumor cells were seeded at 2000 cells/well in 75 μ L assay medium and were then treated with an antibody drug conjugate (ADC) in the form of antibody-vc-MMAE with a series dilution in 25 μ L assay medium following the design layout the next day (final starting working concentration 100 nM, 1:5 serial dilution). The Cells were continued to be cultured for 120 hours and the cell viability was measured at 120 hours time point according to the celltiter Glo manual.

[00321] CHOK1 cells over-expressing hClaudin18.2 (HOK1-hClaudin18.2) and GAXC031 cells were treated with ADC derived from Ab15, Ab10 and Ab17 chimeric antibodies (or with their humanized sequences) and human IgG1-vc-MMAE. Survival percentage was measured after 120 hours incubation.

[00322] Cytotoxicity could be detected when target cells were incubated with ADCs derived from antibody of the present disclosure conjugating vc-MMAE. Sub-nanomolar or nanomolar efficacy could be observed for the *in vitro* cytotoxicity assay (see Figure 10).

[00323] 2. *In vivo* efficacy evaluation:

[00324] 1) *in vivo* study for mAbs

[00325] Briefly, MC38-hClaudin18.2 cells were inoculated into C57BL/6 mice. The mice were randomly divided into 10 groups when the tumor volume was $\sim 100 \text{ mm}^3$. Antibodies (Ab15, Ab10, Ab17, 6E8A2, 25G1F4, 51E3H5 and reference antibody IMAB362) with a mIgG2a Fc were administrated into mice at a dosage of 5 mg/kg.

[00326] Compared with PBS control group, most of the antibodies administrated showed inhibition of tumor growth. Tumor growth inhibition (TGI) ranged from 15.3% to 38.6%, among which, Ab15 showed best monotherapy efficacy (see Figure 11A). All the antibodies administrated did not show toxicity to mice as the body weight didn't decline (see Figure 11B).

[00327] 2) *in vivo* efficacy study for ADC

[00328] Firstly, Ab10-vc-MMAF was tested for *in vivo* efficacy study. Briefly, GAXC031 cells were inoculated to BABL/c nude mice (female, 6-8 weeks). When the mean tumor volume reached $\sim 120\text{mm}^3$, ADC drugs (Ab10-vc-MMAF and IMAB362-vc-MMAF) as well as the controls (PBS vehicle and hIgG-vc-MMAF) were administrated via intravenous injection at a Quality to be delivered every 2 weeks (Q2W) frequency for twice. Tumor volume was measured twice a week for 3 weeks.

[00329] TGI and body weight as well as survival proportions were detected.

[00330] Compared with control and reference antibody ADC, Ab10-vc-MMAF showed much better efficacy and high dose group (10 mg/kg) showed total tumor regression (see Figure 12A and 12C-12J). Survival curve showed that ADC dosed groups mice lived for longer time (see Figure 12K). Again, the ADC drugs did not show any toxicity since the body weight did not decrease (see Figure 12B).

[00331] 3) *in vivo* efficacy study for humanized antibody ADC (vc-MMAE as linker-payload).

[00332] GAXC031 cells were inoculated to BABL/c nude mice (female, 6-8w). When the mean tumor volume reached $\sim 120\text{mm}^3$, ADC drugs (vc-MMAE conjugated Ab15, Ab10, Ab17 and their humanized antibodies) as well as PBS vehicle control were administrated via intravenous injection only once at the dosage of 3 mg/kg. Tumor volume was measured twice a week for 3 weeks. TGI and body weight as well as survival proportions were detected.

[00333] All the ADCs were quite potent against the GAXC031 model. Tumor regression could be observed in most of the ADC treatment groups (see Figure 13).