Description

Title of Invention: ANTIBODIES AND AN TIBODY-DRUG CONJUGATES THEREOF

Field of the Invention

[0001] The present disclosure relates to an antibody binding to cadherin-17 or an antigen binding fragment thereof, an immunoconjugate comprising the antibody or an antigen binding fragment thereof, a pharmaceutical composition comprising the antibody or an antigen binding fragment thereof or the immunoconjuga te, and methods and therapeutic uses of the antibody or an antigen binding fragment t hereof or the immunoconjugate.

Background of the Invention

[0002] Cadherin-17 (CDH17) , also known as liver-intestine cadherin, is specificall y expressed in intestinal epithelial cells and a small fraction of stomach cells. How ever, there is evidence showing that expression of CDH17 is increased in several gast rointestinal tumors including colorectal cancer, pancreatic cancer, esophageal cancer , gastric cancer, cholangiocarcinoma, small intestine cancer, liver cancer and the li ke. The limited expression of CDH17 in normal human tissues and high expression of CDH17 in tumors makes it an ideal target for antibody-based therapeutics. Currently, there are some bispecific antibody products under inve stigation in phase I clinical trials (NCT04137289, and NCT05411133) .

[0003] Therefore, there remains a need for improved methods for treating cancers.

Summary

[0004] In one aspect, provided is an antibody binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody or the antigen bindin g fragment thereof specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166.

[0005] In some embodiments, provided is an antibody binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody has competitive binding activity with the polypeptide having an amino acid sequence shown in SEQ ID NO: 12 7 and/or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody co mprising a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and a l ight chain variable region having an amino acid sequence selected from a group consis

ting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid s equence having at least 80%sequence identity to each thereof.

[0006] In some embodiments, provided is an antibody binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody has competitive binding activity with the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/ or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody selected from a gro up consisting of:

[0007] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino ac id sequence having at least 80%sequence identity to SEQ ID NO: 2;

[0008] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 4;

[0009] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;

[0010] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[0011] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[0012] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[0013] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0014] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0015] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0016] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

[0017] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;

[0018] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

[0019] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[0020] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable re

gion having an amino acid sequence shown in SEQ ID NO: 176 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[0021] In some embodiments, provided is an antibody binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody has competitive binding activity with the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/ or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody selected from a gro up consisting of:

[0022] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 7 or an amino acid sequence having at least 80 %sequence identity to SEQ ID NO: 7, and a light chain having an amin o acid sequence shown in SEQ ID NO: 8 or an amino acid sequence havi ng at least 80%sequence identity to SEQ ID NO: 8;

[0023] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 9 or an amino acid sequence having at least 80 %sequence identity to SEQ ID NO: 9, and a light chain having an amin o acid sequence shown in SEQ ID NO: 10 or an amino acid sequence hav ing at least 80%sequence identity to SEQ ID NO: 10;

[0024] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 11 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 11, and a light chain having an am ino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 12;

[0025] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 20 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 20, and a light chain having an am ino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 30;

[0026] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence id entity to SEQ ID NO: 22, and a light chain having an amino acid sequ ence shown in SEQ ID NO: 32 or an amino acid sequence having at leas t 80%sequence identity to SEQ ID NO: 32;

[0027] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 24 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 24, and a light chain having an am ino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 34;

[0028] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0029] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0030] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 28, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0031] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 38 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 44;

[0032] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 46;

[0033] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 48;

[0034] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 173; and

[0035] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an

amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 177.

[0036] In another aspect, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCD R1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 o f a heavy chain variable region having an amino acid sequence selected from a group c onsisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/ or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 wh ich are same as the LCDR1, LCDR2, and LCDR3 of a light chain variabl e region having an amino acid sequence selected from a group consist ing of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176.

[0037] In some embodiments, the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR 3 are defined according to any one of CDR definition schemes selecte d from a group consisting of IMGT, Kabat, Contact, Chothia, Martin, PyIgClassify, and any combination thereof. Preferably, the HCDR1, HC DR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined according to any one of CDR definition schemes selected from a group consisting of IMGT, Kabat, Contact, Chothia, and any combination thereof.

[0038] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCD R1, HCDR2, and HCDR3 having amino acid sequences selected from a gro up consisting of:

[0039] SEQ ID NO: 49, 50, and 51, respectively;

[0040] SEQ ID NO: 68, 69, and 70, respectively;

[0041] SEQ ID NO: 87, 88, and 89, respectively;

[0042] SEQ ID NO: 109, 50, and 51, respectively;

[0043] SEQ ID NO: 49, 50, and 113, respectively;

[0044] SEQ ID NO: 49, 50, and 116, respectively;

[0045] SEQ ID NO: 178, 179, and 180, respectively; and

[0046] SEQ ID NO: 191, 192, and 193, respectively;

[0047] according to IMGT definition scheme; or a group consisting of:

[0048] SEQ ID NO: 55, 56, and 57, respectively;

[0049] SEQ ID NO: 74, 75, and 76, respectively;

[0050] SEQ ID NO: 93, 94, and 95, respectively;

[0051] SEQ ID NO: 55, 106, and 57, respectively;

[0052] SEQ ID NO: 110, 111, and 57, respectively;

[0053] SEQ ID NO: 55, 106, and 114, respectively;

[0054] SEQ ID NO: 55, 106, and 117, respectively;

[0055] SEQ ID NO: 182, 183, and 184, respectively; and

[0056] SEQ ID NO: 197, 198, and 199, respectively;

[0057] according to Kabat definition scheme; or a group consisting of:

[0058] SEQ ID NO: 60, 61, and 57, respectively;

[0059] SEQ ID NO: 79, 80, and 76, respectively;

[0060] SEQ ID NO: 98, 99, and 95, respectively;

[0061] SEQ ID NO: 60, 61, and 114, respectively;

[0062] SEQ ID NO: 60, 61, and 117, respectively;

[0063] SEQ ID NO: 185, 186, and 184, respectively; and

[0064] SEQ ID NO: 202, 203, and 199, respectively;

[0065] according to Chothia definition scheme; or a group consisting of:

[0066] SEQ ID NO: 62, 63, and 64, respectively;

[0067] SEQ ID NO: 81, 82, and 83, respectively;

[0068] SEQ ID NO: 100, 101, and 102, respectively;

[0069] SEQ ID NO: 62, 107, and 64, respectively;

[0070] SEQ ID NO: 62, 108, and 57, respectively;

[0071] SEQ ID NO: 112, 108, and 64, respectively;

[0072] SEQ ID NO: 62, 107, and 115, respectively;

[0073] SEQ ID NO: 62, 107, and 118, respectively;

[0074] SEQ ID NO: 81, 123, and 83, respectively;

[0075] SEQ ID NO: 187, 188, and 189, respectively; and

[0076] SEQ ID NO: 204, 205, and 206, respectively;

[0077] according to Contact definition scheme;

[0078] and/or a light chain variable region comprising LCDR1, LCDR2, and LC DR3 having amino acid sequences selected from a group consisting of:

[0079] SEQ ID NO: 52, 53, and 54, respectively;

[0080] SEQ ID NO: 71, 72, and 73, respectively;

[0081] SEQ ID NO: 90, 91, and 92, respectively;

[0082] SEQ ID NO: 52, 53, and 181, respectively; and

[0083] SEQ ID NO: 194, 195, and 196, respectively;

[0084] according to IMGT definition scheme; or a group consisting of:

[0085] SEQ ID NO: 58, 59, and 54, respectively;

[0086] SEQ ID NO: 77, 78, and 73, respectively;

[0087] SEQ ID NO: 96, 97, and 92, respectively;

[0088] SEQ ID NO: 58, 120, and 54, respectively;

[0089] SEQ ID NO: 58, 59, and 181, respectively; and

[0090] SEQ ID NO: 200, 201, and 196, respectively;

[0091] according to Kabat definition scheme; or a group consisting of:

[0092] SEQ ID NO: 65, 66, and 67, respectively;

[0093] SEQ ID NO: 84, 85, and 86, respectively;

[0094] SEQ ID NO: 103, 104, and 105, respectively;

[0095] SEQ ID NO: 65, 119, and 67, respectively;

[0096] SEQ ID NO: 65, 121, and 67, respectively;

[0097] SEQ ID NO: 65, 122, and 67, respectively;

[0098] SEQ ID NO: 65, 66, and 190, respectively; and

[0099] SEQ ID NO: 207, 208, and 209, respectively;

[0100] according to Contact definition scheme.

[0101] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0102] SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;

[0103] SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;

[0104] SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;

[0105] SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;

[0106] SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;

[0107] SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;

[0108] SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and

[0109] SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;

[0110] according to IMGT definition scheme; or a group consisting of:

[0111] SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;

[0112] SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;

[0113] SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;

[0114] SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;

[0115] SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;

[0116] SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;

[0117] SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;

[0118] SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;

[0119] SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and

[0120] SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;

[0121] according to Kabat definition scheme; or a group consisting of:

[0122] SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;

[0123] SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;

[0124] SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;

[0125] SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively;

[0126] SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;

[0127] SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;

[0128] SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and

[0129] SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;

[0130] according to Chothia definition scheme; or a group consisting of:

[0131] SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;

[0132] SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;

[0133] SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;

[0134] SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;

[0135] SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;

[0136] SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;

[0137] SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;

[0138] SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;

[0139] SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;

[0140] SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;

[0141] SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and

[0142] SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;

[0143] according to Contact definition scheme.

[0144] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and/or a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to each thereof.

[0145] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody is selected from a group consisting of:

[0146] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 2;

[0147] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 4;

[0148] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;

[0149] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[0150] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[0151] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[0152] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0153] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0154] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable regi

on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0155] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

[0156] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;

[0157] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

[0158] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[0159] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[0160] In some embodiments, the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof; and/or a light chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0161] In some embodiments, the anti-CDH17 antibody is selected from a group consisting of:

[0162] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 8;

[0163] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 10;

[0164] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 11, and a light chain having an amino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 12;

[0165] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 30;

[0166] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 22, and a light chain having an amino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 32;

[0167] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 24, and a light chain having an amino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 34;

[0168] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0169] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an am

ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0170] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 28 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 28, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0171] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 38 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 38, and a light chain having an am ino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 44;

[0172] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 40 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 40, and a light chain having an am ino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 46;

[0173] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 42 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 42, and a light chain having an am ino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 48;

[0174] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 173; and

[0175] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 177.

[0176] In any of the embodiments disclosed herein, the antibody may be a mono-specific antibody, a multi-specific antibody, an intact antibody, a human anti body, a humanized antibody or a chimeric antibody.

[0177] In any of the embodiments disclosed herein, the antigen binding fragment is selected from a group consisting of Fab, Fab', Fv, F (ab') $_2$, scFv, di-scFv and dAb.

[0178] In another aspect, provided is an immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, comprising an antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein, linked to an active agent.

[0179] In another aspect, provided is an antibody-drug conjugate having a formula of Ab- (L- (D) m) n, wherein Ab is the antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein; L is a linker; D is a drug moiety; m is an integer from 1 to 8; and n is any number from 1 to 10.

[0180] In another aspect, provided is a nucleic acid molecule encoding the antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein.

[0181] In another aspect, provided is an expression vector containing the nucleic acid molecule disclosed herein.

[0182] In another aspect, provided is a non-human host cell containing the expression vector disclosed herein.

[0183] In another aspect, provided is a pharmaceutical composition comprising the antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein, or the immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to any of the embodiments disclosed herein; and a pharmaceutically acceptable carrier.

[0184] In another aspect, provided is use of the antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein, or the immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to any of the embodiments disclosed herein in the preparation of a medicament for the treatment of cancer.

[0185] In another aspect, provided is a method for treating a cancer in a subject comprising administering to the subject a therapeutically acceptable amount of the antibody or an antigen binding fragment thereof according to any of the embodiments disclosed herein, or the immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to any of the embodiments disclosed herein, or the pharmaceutical composition according to any of the embodiments disclosed herein.

[0186] Other aspects of the disclosure will be apparent from the detailed descriptions.

Brief Description of the Drawings

[0187] FIG. 1A shows flow cytometry result of examining the binding of anti-CDH17 antibody CL075814 and CL075835 to human colorectal cancer cell line COLO 205. FIG. 1B shows flow cytometry result of examining the

binding of anti-CDH17 antibody CL075814 and CL075942 to human colorectal cancer cell line COLO 205.

[0188] FIG. 2 shows immunofluorescence results of examining the binding specificity of an anti-CDH17 antibody CL075814 to human CDH17 overexpressed on 293T cell.

[0189] FIG. 3 shows immunofluorescence results of examining the binding specificity of an anti-CDH17 antibody CL075835 to human CDH17 overexpressed on 293T cell.

[0190] FIG. 4 shows flow cytometry result of examining the binding affinity (EC50) of anti-CDH17 chimeric antibodies Ch814, Ch835 and Ch942 to human pancreatic cancer cell line AsPC-1.

[0191] FIG. 5A shows flow cytometry result of examining the binding affinity (EC50) of anti-CDH17 chimeric antibodies Ch814 and its humanized variants Hu814-H1L1, Hu814-H2L2, and Hu814-H3L3 to human colorectal cancer cell line COLO 205. FIG. 5B shows flow cytometry result of examining the binding affinity (EC50) of anti-CDH17 chimeric antibody Ch814 and its humanized variants Hu814-H1L4, Hu814-H4L4, and Hu814-H5L4 to human gastric cancer cell line SNU-16.

[0192] FIG. 6 shows flow cytometry result of examining the binding affinity (EC50) of anti-CDH17 chimeric antibody Ch835 and its humanized variants Hu835-H1L1, Hu835-H2L2, and Hu835-H3L3 to human gastric cancer cell line AGS.

[0193] FIG. 7A shows flow cytometry result of examining the binding affinity (EC50) of humanized anti-CDH17 antibody Hu814-H1L4 to human and cyno monkey CDH17 expressed on 293F cell. FIG. 7B shows flow cytometry result of examining the binding affinity (EC50) of humanized anti-CDH17 antibody Hu814-H5L4 to human and cyno monkey CDH17 expressed on 293F cell.

[0194] FIG. 8A shows flow cytometry result of examining the binding affinity (EC50) of humanized anti-CDH17 antibody Hu814-H1L4, which has been incubated at 40℃ for 0, 14 and 28 days, to human gastric cancer cell line SNU-16. FIG. 8B shows flow cytometry result of examining the binding affinity (EC50) of humanized anti-CDH17 antibody Hu814-H5L4, which has been incubated at 40℃ for 0, 14 and 28 days, to human gastric cancer cell line SNU-16.

[0195] FIG. 9A shows flow cytometry result of examining the binding domain of humanized anti-CDH17 antibody Hu814-H1L4 to domain-swapped CDH17 variants expressed in 293F cells. FIG. 9B shows flow cytometry result of examining the binding domain of humanized anti-CDH17 antibody Hu835-H1L1 to domain-swapped CDH17 variants expressed in 293F cells. FIG. 9C shows flow c

ytometry result of examining the binding domain of chimeric anti-CDH17 antibody Ch 942 to domain-swapped CDH17 variants expressed in 293F cells. FIG . 9D shows flow cytometry result of examining the binding domain of chimeric anti-CDH17 antibody Ch2F12 to domain-swapped CDH17 variants expressed i n 293F cells. FIG. 9E shows flow cytometry result of examining the b inding domain of chimeric anti-CDH17 antibody Ch2E21 to domain-swapped CDH17 variants expressed in 293F cells. FIG. 9F shows flow c ytometry result of examining the binding domain of chimeric anti-CDH17 antibody RAb17 to domain-swapped CDH17 variants expressed in 293F cells.

[0196] FIG. 10A shows the SEC chromatogram of quality control (Hu814-H1L4) ; FIG. 10B shows the HIC chromatogram of quality control (Hu814-H1L4) .

[0197] FIG. 11A shows the SEC result of antibody-drug conjugate Ch814-vc-MMAE; FIG. 11B shows the HIC result of antibody-drug conjugate Ch814-vc-MMAE, wherein Ab is Ch814, linker-payload is vc-MMAE.

[0198] FIG. 12A shows the SEC result of antibody-drug conjugate Ch835-vc-MMAE; FIG. 12B shows the HIC result of antibody-drug conjugate Ch835-vc-MMAE, wherein Ab is Ch835, linker-payload is vc-MMAE.

[0199] FIG. 13 shows the HIC result of antibody-drug conjugate Ch942-vc-MMAE, wherein Ab is Ch942, linker-payload is vc-MMAE.

[0200] FIG. 14A shows the SEC result of antibody-drug conjugate Hu814-H1L4-vc-MMAE; FIG. 14B shows the HIC result of antibody-drug conjugate Hu814-H1L4-vc-MMAE, wherein Ab is Hu814-H1L4, linker-payload is vc-MMAE.

[0201] FIG. 15A shows the SEC result of antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) ; FIG. 15B shows the HIC result of antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) , wherein Ab is Hu814-H1L4, linker-payload is LP1.

[0202] FIG. 16A shows the SEC result of antibody-drug conjugate Hu814-H1L4-LP1 (DAR4) ; FIG. 16B shows the HIC result of antibody-drug conjugate Hu814-H1L4-LP1 (DAR4) , wherein Ab is Hu814-H1L4, linker-payload is LP1.

[0203] FIG. 17A shows the SEC result of antibody-drug conjugate Patritumab-GGFG-DXd; FIG. 17B shows the HIC result of antibody-drug conjugate Patritumab-GGFG-DXd, wherein Ab is Patritumab, linker-payload is GGFG-DXd.

[0204] FIG. 18A shows the SEC result of antibody-drug conjugate Trastuzumab-GGFG-DXd; FIG. 18B shows the HIC result of antibody-drug conjugate Trastuzumab-GGFG-DXd, wherein Ab is Trastuzumab, linker-payload is GGFG-DXd.

[0205] FIG. 19A shows the SEC result of antibody-drug conjugate Datopotamab-GGFG-DXd; FIG. 19B shows the HIC result of antibody-drug conjugate Datopotamab-GGFG-DXd, wherein Ab is Datopotamab, linker-payload is GGFG-DXd.

[0206] FIG. 20A shows the SEC result of antibody-drug conjugate Human IgG-vc-MMAE; FIG. 20B shows the HIC result of antibody-drug conjugate Human IgG-vc-MMAE, wherein Ab is Human IgG, linker-payload is vc-MMAE.

[0207] FIG. 21A shows the SEC result of antibody-drug conjugate Human IgG-LP1 (DAR8) ; FIG. 21B shows the HIC result of antibody-drug conjugate Human IgG-LP1 (DAR8) , wherein Ab is Human IgG, linker-payload is LP1.

[0208] FIG. 22A shows the SEC result of antibody-drug conjugate Human IgG-LP1 (DAR4) ; FIG. 22B shows the HIC result of antibody-drug conjugate Human IgG-LP1 (DAR4) , wherein Ab is Human IgG, linker-payload is LP1.

[0209] FIG. 23A shows the SEC result of antibody-drug conjugate Human IgG-GGFG-DXd; FIG. 23B shows the HIC result of antibody-drug conjugate Human IgG-GGFG-DXd, wherein Ab is Human IgG, linker-payload is GGFG-DXd.

[0210] FIG. 24 shows the results of evaluating the in vitro cell growth inhibition activity of anti-CDH17 chimeric antibody-drug conjugates Ch814-vc-MMAE, Ch835-vc-MMAE and Ch942-vc-MMAE to human gastric cancer cell line SNU-16.

[0211] FIG. 25A shows concentration-dependent cell growth inhibition activities of Ch814-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F12-LP1 (DAR8) , and RAb17-LP1 (DAR8) in CDH17-positive AsPC-1 pancreatic cancer cell line. FIG. 25B shows concentration-dependent cell growth inhibition activities of Ch814-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F12-LP1 (DAR8) , and RAb17-LP1 (DAR8) in CDH17-positive SNU5 gastric cancer cell line. FIG. 25C shows concentration-dependent cell growth inhibition activities of Ch814-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F12-LP1 (DAR8) , and RAb17-LP1 (DAR8) in CDH17-positive SNU16 gastric cancer cell line.. FIG. 25D shows the internalization of Hu814-H1L4-LP1 (DAR8) and Hu814-H1L4-vc-MMAE by SNU-16 cells. FIG. 25E shows the internalization of Hu814-H1L4-LP1 (DAR8) and Hu814-H1L4-vc-MMAE by SNU-5 cells.

[0212] FIG. 26A shows the results of evaluating the in vitro cell growth inhibition activity of anti-CDH17 antibody-drug conjugate Hu814-H1L4-vc-MMAE to human gastric cancer cell line SNU-16. FIG. 26B shows the results of evaluating the in vitro cell growth inhibition activity of anti-CDH17 antibody-drug conjugates Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) to human gastric cancer cell line SNU-16.

[0213] FIG. 27A shows the in vivo antitumor effects of two humanized anti-CDH17 antibody-drug conjugates (Hu814-H1L4-vc-MMAE, Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using animal model in which CDH17-positive human gastric cancer cell line SNU-5 was inoculated into immunodeficient mice. FIG. 27B shows the effect on body weight of mice of two humanized anti-

CDH17 antibody-drug conjugates (Hu814-H1L4-vc-MMAE, Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using animal model in which CDH17-positive human gastric cancer cell line SNU-5 was inoculated into immunodefici ent mice.

[0214] FIG. 28A shows the in vivo antitumor effects of three antibody-drug conjugates (Patritumab-GGFG-DXd, Transtuzumab-GGFG-DXd, Datopotamab-GGFG-DXd, Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using a nimal model in which the HER3, HER2, Trop2 and CDH17-positive human ga stric cancer patient derived xenograft tumor was inoculated into immunodeficient mice . FIG. 28B shows the effect on body weight of mice of three antibody-drug conjugates (Patritumab-GGFG-DXd, Transtuzumab-GGFG-DXd, Datopotamab-GGFG-DXd Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using a nimal model in which HER3, HER2, Trop2 and CDH17-positive human ga stric cancer patient derived xenograft tumor was inoculated into immunodeficient mice .

[0215] FIG. 29A shows the in vivo antitumor effects of two humanized anti-CDH17 antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human pancreatic cancer cell line AsPC-1 was inoculated into immunodefici ent mice. FIG. 29B shows the effect on body weight of mice of two humanized anti-CDH17 antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human pancreatic cancer cell line AsPC-1 was inoculated into immunodefici ent mice.

[0216] FIG. 30A shows the in vivo antitumor effects of two humanized anti-CDH17 antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human colorectal cancer patient derived xenograft tumor was in oculated into immunodeficient mice. FIG. 30B shows the effect on bod y weight of mice of two humanized anti-CDH17 antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) and two isotype contr ol (IgG-LP1 (DAR8) , IgG-LP1 (DAR4)) . The evaluation was conducted using a nimal model in which CDH17-positive human colorectal cancer patient derived xe nograft tumor was inoculated into immunodeficient mice.

[0217] FIG. 31A shows the in vivo antitumor effects of two antibody-drug conjugates (Patritumab-GGFG-DXd, Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using animal model in which HER3 and CDH17-positive human co lorectal cancer patient derived xenograft tumor was inoculated into immunodeficient m

ice. FIG. 31B shows the effect on body weight of mice of two antibody-drug conjugates (Patritumab-GGFG-DXd, Hu814-H1L4-LP1 (DAR8)) . The evaluation was conducted using animal model in which HER3 and CDH17-positive human colorectal cancer patient derived xenograft tumor was inoculated into immunodeficient mice.

[0218] FIG. 32A shows the in vivo antitumor effects of two humanized antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human cholangiocarcinoma cancer patient derived xenograft tumor was inoculated into immunodeficient mice. FIG. 32B shows the effect on body weight of mice of two humanized antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human cholangiocarcinoma cancer patient derived xenograft tumor was inoculated into immunodeficient mice.

[0219] FIG. 33A shows the in vivo antitumor effects of two humanized antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human liver cancer patient derived xenograft tumor was inoculated into immunodeficient mice. FIG. 33B shows the effect on body weight of mice of two humanized antibody-drug conjugates (Hu814-H1L4-LP1 (DAR8) , Hu814-H5L4-LP1 (DAR4)) . The evaluation was conducted using animal model in which CDH17-positive human liver cancer patient derived xenograft tumor was inoculated into immunodeficient mice.

[0220] FIG. 34 shows the detection of CDH17 expression in gastric cancer (A) , colorectal cancer (B) , pancreatic cancer (C) , esophageal adenocarcinoma (D) , cholangiocarcinoma (E) and neuroendocrine cancer (F) by immunohistochemistry using CL075814 as primary antibody.

[0221] FIG. 35A shows that Ch814 and Ch2F12 compete with Ch814-Biotin. FIG. 35B shows that Ch2F12 and Ch814 compete with Ch2F12-Biotin. FIG. 35C shows that Ch835 and Ch942 compete with Ch835-Biotin. FIG. 35D shows that Ch942, as a positive control, competes with Ch942-Biotin, while Ch835 has lower but still detectable competition activity against Ch942-Biotin.

[0222] FIG. 36 shows the structure of the Hu814-H5L4-LP1.

Detailed Description

[0223] Definition

[0224] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0225] As used herein, the term "antibody" generally refers to a polypeptid e of the immunoglobulin family that is capable of binding a corresponding antigen non -covalently, reversibly, and in a specific manner. For example, a naturally occurring IgG antibody is a tetramer comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain (HC) is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant r egion. The heavy chain constant region is comprised of three domains , CH1, CH2 and CH3. Each light chain (LC) is comprised of a light chain variable regi on (abbreviated herein as VL) and a light chain constant region. The light chain cons tant region is comprised of one domain, CL. The VH and VL regions ca n be further subdivided into regions of hypervariability, termed complementarity dete rmining regions (CDR) , interspersed with regions that are more conserved, termed fra mework regions (FR) . Each VH and VL is composed of three CDRs and f our FRs arranged from amino-terminus to carboxy-terminus in the following order: F R1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to h ost tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[0226] The term "antibody" includes, but is not limited to, monoclonal anti bodies, human antibodies, humanized antibodies, camelid antibodies, and chimeric anti bodies. The antibodies can be of any isotype/class (e.g., IgG, IgE, IgM, IgD, IgA and IgY) or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) .

[0227] As used herein, the term "Complementarity determining domains" is us ed herein interchangeably with the term "complementary determining r egions" ("CDRs") , and generally refers to the hypervariable regions of VL and VH. The CDRs are the target protein-binding site of the antibody chains that harbors sp ecificity for such target protein. There are three CDRs (CDR1-3, numbered seque ntially from the N-terminus) in each human VL or VH, constituting about 15- 20%of the variable domains. CDRs can be referred to by their region and order. For ex ample, "VH CDR1" or "HCDR1" both refer to the first CDR of the heavy chain variable region. The CDRs are structurally complementary to the epitope of the target protein and are thus directly responsible for the binding specificity. The re maining stretches of the VL or VH, the so-called framework regions, exhibit less variation in amino acid sequence (Kuby, Immunology, 4th ed., Ch apter 4. W. H. Freeman &Co., New York, 2000) . In the art, the CDR o f the antibody can be defined by various methods/schemes, such as a Kabat definition scheme based on sequence variability (see Kabat et al., protein sequence in immunolog

y, 5th edition, National Institutes of Health, Bethesda, Maryland (1991)) , a Chothi a definition scheme based on the position of a structural loop region (see A1-Lazikani et al., JMol Biol 273: 927-48, 1997) and a IMGT definition sc heme based on the concept of IMGT-ONTOLOGY and IMGT Scientific chart rules. In certain embodiments, the present application uses the IMGT rules to define the CDRs of an antibody. The definition rules of Martin, PyIgClassi fy and Combined definition rules of Kabat, Chothia, IMGT, Martin and PyIgClassify are also included in this application (see Mark L. Chiu et al., Antibod ies 8 (4) , 55, 2019) .

[0228] Table A. Comparation of CDR numbering among different definition sch emes (in Chothia numbering)

CDR	Kabat	Chothia	IMGT	Contact	Martin	PyIgClassify	Combined
LCDR1	L24-L34	L24-L34	L27-L32	L30-L36	L24-L34	L24-L34	L24-L36
LCDR2	L50-L56	L50-L56	L50 L52	L46-L55	L50 L56	L49-L56	L46-L56
LCDR3	L89-L97	L89-L97	L89-L97	L89-L96	L89-L97	L89 L97	L89-L97
HCDR1	H31-H35	H26-H32	H26-H33	H30-H35	H26-H35	H23-H35	H23-H35
HCDR2	H50-H65	H52-H56	H51-H57	H47-H58	H50-H58	H50 H58	H47-H65
HCDR3	H95-H102	H95-H102	H93-H102	H93-H101	H95-H102	H93-H102	H93-H102

[0229] wherein, Laa-Lbb or Haa-Hbb may refer to, from N-terminal, the ami no acids sequence from NO. aa to NO. bb of light chain or heavy chain respectively. F or example, L24-L34 refers to the amino acid sequence from NO. 24 to NO. 34 of light chain.

[0230] Both the light and heavy chains are divided into regions of structural and functional homology. The terms "constant" and "variable" are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (V H) chain portions determine antigen recognition and specificity. Conversely, the cons tant domains of the light chain (CL) and the heavy chain (CH1, CH2 o r CH3) confer important biological properties such as secretion, transplacental mobil ity, Fc receptor binding, complement binding, and the like. By convention, the number ing of the constant region domains increases as they become more distal from the anti gen binding site or amino-terminus of the antibody. The N-terminus is a var iable region and at the C-terminus is a constant region; the CH3 and CL domai

ns actually comprise the carboxy-terminal domains of the heavy and light chain, resp ectively.

[0231] As used herein, the term "antigen binding fragment" generally refers to a polypeptide including one or more portions of an antibody that retain the ability to specificall y interact with (e.g., by binding, steric hindrance, stabilizing/destabilizing, spati al distribution) an epitope of an antigen. Examples of binding fragments include, but are not limited to, single-chain Fvs (scFv) , disulfide-linked Fvs (sdFv) , Fab fragments, F (ab') fragments, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F (ab') 2 fragment, a bivalent fragment compri sing two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragmen t consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward et al., Nature 341: 544-546, 1989) , which consists of a VH domain; and an isolated complementarity determining region (CDR) or other epitope-binding fragments of an antibody.

[0232] Antigen binding fragments also comprises single domain antibodies, m axibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies an d bis-scFv (see, e.g., Hollinger and Hudson, Nature Biotechnology 23: 1126 -1136, 2005) . Antigen binding fragments can also comprise single cha in molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of anti gen binding regions (Zapata et al, Protein Eng. 8: 1057-1062, 1995) . A f ragment of a conventional antibody may also be a single domain antibody, such as a he avy chain antibody or VHH.

[0233] As used herein, the term "monoclonal antibody" as used herein generally refers to pol ypeptides, including antibodies and antigen binding fragments that have substantially identical amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity fo r a particular epitope.

[0234] As used herein, the term "humanized antibody" generally refers to an antibody which includes sequences of heavy chain variable regions and light chain va riable regions derived from non-human species (e.g., mice) , but in which at least a portion of the VH and/or VL sequences have been changed to be simi lar to the human germline variable sequences. For example, the term "humanized antibody" is an antibody or a variant, derivative, analogue or fragment th ereof that can bind to a related antigen with immune specificity and includes a frame work region (FR) which includes substantially an amino acid sequence

of a human antibody and a complementary determining region (CDR) wh ich includes substantially an amino acid sequence of a non-human antibody. I n the context of CDR, the term “substantially” means that the amino acid sequence of CDR has at least 80%, e.g., at least 85%, at least 90%, at least 95% , at least 98%or at least 99%identity with an amino acid sequence of CDR of a non-human antibody. The humanized antibodies include substantially at least one, typicall y two variable domains (Fab, Fab’, F (ab’) 2, Fab, Fv) , wherein all or substantially all CDR regions correspond to the CDR region of a non-human immunoglobu lin and all or substantially all framework regions are frame regions with consensus s equence of human immunoglobulin. In some embodiments, the humanized antibody can further include at least a portion of a constant region of immunoglobuli n (Fc) , typically a constant region of human immunoglobulin.

[0235] As used herein, the term "human antibody" generally refers to an ant ibody with variable and constant regions derived from the sequence o f immunoglobulin of human germ line. Human antibodies are well known in the prior art (e.g., van Dijk, M. A. and van de Winkel, J.G., Curr. Opin. Chem. B iol. 5 (2001) 368-374) . The human antibodies can also be generated in transgenic anim als (e.g., mice) which can generate a complete or selected set of human antibodies in absence of generated endogenous immunoglobulin after immunization (e.g., Jakobovits, A. et al., Proc. Natl. Acad. Sci. USA 90 (1993) 2551-2555; Jakobovits, A. et al., Nature 362 (1993) 255-258; Brueggemann, M. et al., YearI mmunol. 7 (1993) 33-40) . The human antibodies can also be generated in a phage display library (e.g., Hoogenboom, H. R. and Winter, G., J. Mol. Biol. 227 (1992) 381-388; Marks, J.D. et al., J. Mol. Biol. 222 (1991) 581-597) . The term “ human antibody” can also include antibodies modified in the constant regions.

[0236] As used herein, the term "chimeric antibody" generally refers to an engineered antibo dy which in its broadest sense contains one or more regions from one antibody and one or more regions from one or more other antibody (ies) . In particular a chimeric ant ibody comprises a VH domain and a VL domain of an antibody derived f rom a non-human animal, in association with a CH domain and a CL domain of ano ther antibody, in particular a human antibody. As the non-human animal, any animal such as mouse, rat, hamster, rabbit or the like can be used. A chimeric antib ody may also denote a multispecific antibody having specificity for at least two diff erent antigens.

[0237] By "purified" and "isolated" it is meant, when referring to a polypeptide (i.e. the a ntibody of the invention) or a nucleotide sequence, that the indicated molecule is pr esent in the substantial absence of other biological macromolecules of the same type. The term "purified" as used herein in particular means at least 75%, 85

%, 95%or 98%by weight, of biological macromolecules of the same type are present. An "isolated" nucleic acid molecule that encodes a particular polypeptide refers to a nucleic acid molecule that is substantially free of other nucleic acid molecules that do not encode the subject polypeptide; however, the molecule may include some additional bases or moieties, which do not deleteriously affect the basic characteristics of the composition. The present invention may contain, for example, an isolated antigen-binding protein, an isolated antibody or an antigen-binding fragment thereof, an isolated polypeptide, an isolated nucleic acid molecule or molecules.

[0238] As used herein, the term "affinity" is generally defined by the equilibrium association between the whole antibody and the antigen. Affinity may be expressed for example in half-maximal effective concentration (EC50) or the equilibrium dissociation constant (KD) . Affinity can be experimentally assessed by a variety of known methods, such as measuring association and dissociation rates with surface Plasmon resonance or measuring the EC50 in an immunochemical assay (ELISA, FACS) .

[0239] The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variant refers to those nucleic acids which encode identical or essentially identical amino acid sequences or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations, " which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0240] For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles. The following eight gro

ups contain amino acids that are conservative substitutions for one another: 1) Alani ne (A) , Glycine (G) ; 2) Aspartic acid (D) , Glutamic acid (E) ; 3) Asparagine (N) , Glutamine (Q) ; 4) Arginine (R) , Lysine (K) ; 5) Isoleucine (I) , Leucine (L) , Met hionine (M) , Valine (V) ; 6) Phenylalanine (F) , Tyrosine (Y) , Tryptophan (W) ; 7) Serine (S) , Threonine (T) ; and 8) Cysteine (C) , Methionine (M) (see, e.g., Creight on, Proteins (1984)) . In some aspects, the term "conservative sequence modification s" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0241] As used herein, the term "percent identical" or "percent identity, " in the context o f two or more nucleic acids or polypeptide sequences, refers to the extent to whi ch two or more sequences or subsequences that are the same. Two sequ ences are "identical" if they have the same sequence of amino acids or nucleotides ov er the region being compared. Two sequences are "substantially identical" if two sequ ences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60%identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95 %or 99%identity over a specified region or, when not specified, over the entire seque nce) , when compared and aligned for maximum correspondence over a c omparison window or designated region as measured using one of the f ollowing sequence comparison algorithms or by manual alignment and v isual inspection. Optionally, the identity exists over a region that is at least abou t 30 nucleotides (or 10 amino acids) in length or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in len gth. Two examples of algorithms that are suitable for determining percent sequence id entity and sequence similarity are the BLAST and BLAST 2.0 algorithm s, which are described in Altschul et al, Nuc. Acids Res. 25: 3389-3402, 1977; and A ltschul et al , J. Mol. Biol. 215: 403-410, 1990, respectively.

[0242] Other than percentage of sequence identity noted above, another indication that two n ucleic acid sequences or polypeptides are substantially identical is that the polypep tide encoded by the first nucleic acid is immunologically cross reactive with the ant ibodies raised against the polypeptide encoded by the second nucleic acid. Thus, a po lypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions. Yet another indication that two nucleic acid sequences are substantially identical is that the s ame primers can be used to amplify the sequence.

[0243] As used herein, the term "nucleic acid molecule" is used herein interchangeably with the term "polynucleotide" and generally refers to deoxyribonucleotides or ribonucleot

ides and polymers thereof in either single-or double-stranded form. Th e term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the re ference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs) .

[0244] As used herein, the term "polypeptide" is used herein interchangeably with the term " protein" and refers to a polymer of amino acid residues. The terms apply to amino aci d polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless othe rwise indicated, a particular polypeptide sequence also implicitly encompasses conser vatively modified variants thereof.

[0245] As used herein, the term "immunoconjugate" as used herein generally refers to the lin kage of an antibody or an antigen binding fragment thereof with another agent, such a s a payload, a drug moiety, a chemotherapeutic agent, a toxin, an immunotherapeutic a gent, an imaging probe, and the like. The linkage can be a covalent bond or non-covalent interactions such as through electrostatic forces. Various linkers, known i n the art, can be employed in order to form the immunoconjugate. Additionally, the im munoconjugate can be provided in the form of a fusion protein that may be expressed f rom a polynucleotide encoding the immunoconjugate. As used herein, " fusion protein" refers to a protein created through the joining of two or more genes or gene fragments which originally coded for separate proteins (including peptides an d polypeptides) . Translation of the fusion gene results in a single protein with fun ctional properties derived from each of the original proteins.

[0246] The term "active moiety" or "payload" as used herein generally refer s to the portion of a conjugated compound that constitutes an active agent, which med iates a pharmaceutical effect including but not limited to prophylactic, therapeutic, and/or diagnostic effects, for example, an anti-cancer, anti-inflammatory, ant i-infective (e.g., anti-fungal, antibacterial, anti-parasitic, anti-viral) or an anes thetic agent. Methods for attaching each of these to a linker compatible with the ant ibodies and method of the present disclosure are known in the art. See, e.g., Singh e t al., (2009) Therapeutic Antibodies: Methods and Protocols, vol. 525, 445-457. In addition, an "active moiety" or a “payload” can be a biophysical probe, a flu orophore, a spin label, an infrared probe, an affinity probe, a chelator, a spectrosc opic probe, a radioactive probe, a lipid molecule, a polyethylene glycol, a polymer,

DNA, RNA, a protein, a peptide, a surface, an antibody, an antibody fragment, a nanop article, a quantum dot, a liposome, a PLGA particle, a saccharide or a polysaccharide.

[0247] As used herein, the term “drug moiety” or “D” generally refers to an y compound possessing a desired biological activity and a reactive functional group t hat may be used to incorporate the drug into the conjugate of the disclosure. In some embodiments, the drug moiety indicate a cytotoxic drug useful in cancer therapy; a p rotein or polypeptide possessing a desired biological activity, such as a toxin, e.g. , abrin, ricin A, pseudomonas exotoxin, and diphtheria toxin; other suitable proteins include tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, p latelet derived growth factor, tissue plasminogen activator, and biological response modifiers, for example, lymphokines, interleukin-1 (IL-1) , interleukin-2 (IL-2) , interleukin-6 (IL-6) , granulocyte macrophage colony stimulating factor (GM-CSF) , granulocyte colony stimulating factor (G-CSF) or other growth factors. In s ome embodiments, the term “drug moiety” may be a chemical moiety. In certain aspects, a drug moiety is selected from a V-ATPase inhibitor, a HSP90 inhibito r, an IAP inhibitor, an mTor inhibitor, a microtubule stabilizer, a microtubule desta bilizer, an auristatin, a dolastatin, a maytansinoid, a MetAP (methionine aminopeptid ase) , an inhibitor of nuclear export of proteins CRM1, a DPPIV inhibitor, an inhibit or of phosphoryl transfer reactions in mitochondria, a protein synthesis inhibitor, a kinase inhibitor, a CDK2 inhibitor, a CDK9 inhibitor, a proteasome inhibitor, a kine sin inhibitor, an HDAC inhibitor, a DNA damaging agent, a DNA alkyla ting agent, a DNA intercalator, a DNA minor groove binder and a DHFR inhibitor.

[0248] In one embodiment, the drug moiety can be microtubule disrupting dru gs such as auristatin, e.g., monomethyl auristatin E (MMAE) , monome thyl auristatin F (MMAF) , and auristatin F (AF) . In another embodi ment, the drug moiety can be microtubule disrupting drugs such as maytansinoids, e.g. , DM1, DM3, and DM4. In another embodiment, the drug moiety can be D NA damaging agents such as calicheamicins, duocarmycins, SN-38, and pyrrolo [2, 1-c] [1, 4] benzodi-azepines (PBDs) . Still in other embodiments, the drug moiety can be amanitins, anthracyclines, baccatins, camptothecins, cemadotins, colchicines, colcim ids, combretastatins, cryptophycins, discodermolides, docetaxel, doxorubicin, echino mycins, eleutherobins, epothilones, estramustines, lexitropsins, maytansines, methotr exate, netropsins, puromycins, rhizoxins, taxanes, tubulysins or vinca alkaloids.

[0249] As used herein, the term “topoisomerase inhibitor” usually refers to a compound that inhibits topoiosmerase activity. Compounds known as topoisomerase I inhibitors have activity against topoisomerase I, and the topoiosmerase II inhibitors have activity against topoisomerase II. Some compounds have activity against both to poisomerase I and topoisomerase II and are known as topoisomerase I/

II inhibitors. Preferred topoisomerase I inhibitors for use in the present invention are camptothecin and analogs of camptothecin. Camptothecin is a pent acyclic alkaloid initially isolated from the wood and bark of Camptotheca acuminata, a tree indigenous to China (Wall, M.E. et al, J. Am. Chem. Soc, 94: 388 (1966)) . Ca mptothecin exerts its pharmacological effects by irreversibly inhibiting topoisomeras e I. Methods for the synthesis of camptothecin and camptothecin analogs or derivative s are known and are summarized and as set forth in U.S. Patent No. 5,244,903, which i s herein incorporated by reference in its entirety.

[0250] As used herein, the term “camptothecin” generally includes camptothe cin and camptothecin derivatives including irinotecan, topotecan, lurtotecan, silatec an, etirinotecan pegol, TAS 103, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10, 11-methylenedioxycamptothecin, 9-amino- 10, 11-methylenedioxycamptothecin, 9-chloro-10, 11-methylenedioxycam ptothecin, 7- (4-methylpiperazinomethylene) -10, 1 1-ethylenedioxy-20 (S) -camptothecin, 7- (4-methylpiperazinomethylene) -10, 1 1-methylenedioxy-20 (S) -camptothecin, and 7- (2- (N-isopropylamino) ethyl) - (20S) -camptothecin, and stereoisomers, salts and esters thereof.

[0251] As used herein, the term “linker” described in the present disclosure includes a clea vable linker or a noncleavable linker. Cleavable linkers can be chemically labile and enzyme-labile linkers. Due to the high plasma stability and good intracellu lar cleaving selectivity and efficiency, enzyme-labile linkers are broadly selecte d as cleavable linker candidates in ADCs. In some embodiments, enzyme-labile linkers may include a peptide unit (-AAs-) selected from a group consisting of -valline-citruline- (-Val-Cit-) , -valline-lysine- (-Val-Lys-) , -valline-arginine- (-Val-Arg-) , -phenylalanine-citruline- (-Phe-Cit-) , -phenylalanine-lysine- (-Phe-Lys-) , and -phenylalanine-arginine- (-Phe-Arg-) . Typical enzyme-labile linkers in clude -Val-Cit-and -Phe-Lys-, which can be recognized by cathepsin B. In some e mbodiments, the noncleavable linker may be linkers that are capable of increasing the hydrophilicity of the resulting ADC. In one embodiment, the noncleavable linker may include one or more poly (ethylene glycol) (PEG) . In other embodime nt, the noncleavable linker may be PEG, PEG diamine (NH2-PEG-NH2) , amine-PEG-hydroxyl (NH2-PEG-OH) , amine-PEG-COOH (NH2-PEG-COOH) , diethylen e triamine or a combination thereof. In some embodiments, PEG may be represented by - $(CH_2CH_2O)_x$-, wherein x may be an integer ranging from 1 to 20.

[0252] As used herein, the term "toxin, " "cytotoxin" or "cytotoxic agent" as used herein, g enerally refers to any agent that is detrimental to the growth and proliferation of c ells and may act to reduce, inhibit or destroy a cell or malignancy.

[0253] As used herein, “cancer” or “tumor” as used interchangeably herein i s meant to a group of diseases which can be treated according to the disclosure and i nvolve abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumors are cancerous; benign tumors do not spread to other parts of the body. Possible signs and symptoms include: a new lump, abnormal bleeding, a prolonged cough, unexplained weight loss, and a change in bowel movements among others. There are over 100 different known cancers that affect humans. As used herein, “cancer” includes, without limitation, a solid cancer (e.g., a tumor) and a hematologic malignancy. A “hematologic malignancy” , also known as a blood cancer, is a cancer that originates in blood-forming tissue, such as the bone marrow or other cells of the immune system. Hematologic malignancies include, without limitation, leukemias (such as acute myeloid leukemia (ANIL) , acute promyelocytic leukemia, acute lymphoblastic leukemia (ALL) , acute mixed lineage leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia (CLL) , hairy, cell leukemia and large granular lymphocytic leukemia) , myelodysplastic syndrome (MDS) , myeloproliferative disorders (polycythemia vera, essential thrombocytosis, primary myelofibrosis and chronic myeloid leukemia) , lymphomas, multiple myeloma, MGUS and similar disorders, Hodgkin’s lymphoma, non-Hodgkin lymphoma (NHL) , primary mediastinal large B-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, transformed follicular lymphoma, splenic marginal zone lymphoma, lymphocytic lymphoma, T-cell lymphoma, and other B-cell malignancies. “Solid cancers” include, without limitation, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon cancer, colorectal cancer, kidney cancer, pancreatic cancer, bone cancer, breast cancer, ovarian cancer, prostate cancer, esophogeal cancer, stomach cancer, oral cancer, nasal cancer, throat cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms'tumor, cervical cancer, uterine cancer, testicular cancer, small cell lung carcinoma, bladder carcinoma, lung cancer, epithelial carcinoma, glioma, glioblastoma multiforme, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, skin cancer, melanoma, neuroblastoma, retinoblastoma.

[0254] As used herein, the term "anti-tumor agent" or "antitumor drug" as used herein gen erally refers to any agent that can be used to treat a cell proliferative disorder su ch as cancer, including but not limited to, cytotoxic agents, chemotherapeutic agents , radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, an d immunotherapeutic agents.

[0255] As used herein, the term "anti-tumor activity" means a reduction in the rate of tu mor cell proliferation, viability or metastatic activity. A possible way of showing a nti-tumor activity is to show a decline in growth rate of tumor cells, tumor size stasis or tumor size reduction. Such activity can be assessed using accepted in vitro or in vivo tumor models, including but not limited to xenograft models, allograft models, M MTV models, and other known models known in the art to investigate anti-tumor activity.

[0256] As used herein, the term CDH17 refers to “cadherin-17” . CDH17 is a member of the cadherin superfamily of calcium-dependent, membrane-associated glycoproteins. The encoded protein is cadherin-like, consisting of an extracellular region, containing 7 cadherin domains (i.e., ECD 1 through 7) , a nd a transmembrane region and a short cytoplasmic domain. Human CDH17 is represented by SEQ ID NO: 126 as well as in database accession n umber UniProt Q12864.3. Human CDH17 ECD1 is represented by amino aci d positions 30 to 128 in SEQ ID NO: 126. Human CDH17 ECD2 is represe nted by amino acid positions 129 to 244 in SEQ ID NO: 126. Human CDH 17 ECD3 is represented by amino acid positions 245 to 340 in SEQ ID NO: 126 and has an amino acid sequence shown in SEQ ID NO: 127 and E CD4 is represented by amino acid positions 341 to 449 in SEQ ID NO: 126 and has an amino acid sequence shown in SEQ ID NO: 128. Human CD H17 ECD5 is represented by amino acid positions 450 to 566 in SEQ ID NO: 126. Human CDH17 ECD6 is represented by amino acid positions 56 7 to 667 in SEQ ID NO: 126. Human CDH17 ECD7 is represented by amino acid positions 668 to 777 in SEQ ID NO: 126.

[0257] In the present description, the term “epitope” is generally used to mean the partial peptide or partial three-dimensional structure of CDH17, to which a specific anti-CDH17 antibody binds.

[0258] The terms "CDH17 expressing tumor " or "CDH17 positive tumor " gener ally refers to a tumor that express CDH17 and/or a mutant form of CD H17 on the surface of tumor cells.

[0259] As used herein, the term "subject" includes human and non-human animals. Non-human animals include all vertebrates, e.g., mammals and non-mammals, such as

non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

[0260] As used herein, the term "pharmaceutically acceptable" generally refers to one or more non-toxic substances that do not interfere with the effectiveness of the biological activity of the active ingredient. Such formulations may typically contain salts, buffers, preservatives, compatible carriers, and optionally other therapeutic agents. Such pharmaceutically acceptable formulations may also typically contain compatible solid or liquid fillers, diluents, or encapsulating materials suitable for administration to humans. When used in medicine, the salt should be a pharmaceutically acceptable salt, but non-pharmaceutically acceptable salts can be conveniently used to prepare pharmaceutically acceptable salts and cannot be excluded from the scope of the present invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, salts prepared from the following acids: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, maleic acid, acetic acid, salicylic acid, citric acid, boric acid, formic acid, malonic acid, succinic acid, etc. Pharmacologically acceptable salts can also be prepared as alkali metal salts or alkaline earth metal salts, such as sodium, potassium or calcium salts. The term "solvate" is used herein in the conventional sense to refer to a complex of a solute (e.g., an active compound, a salt of an active compound) and a solvent. Solvates usually do not significantly alter the physiological activity or toxicity of the compound and therefore can act as pharmacological equivalents. If the solvent is water, the solvent compound may be conveniently referred to as a hydrate, e.g., monohydrate, dihydrate, trihydrate, etc.

[0261] As used herein, the terms "treat, " "treating, " or "treatment" of any disease or disorder generally refer in one aspect, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof) . In another aspect, "treat, " "treating, " or "treatment " refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another aspect, "treat, " "treating, " or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom) , physiologically, (e.g., stabilization of a physical parameter) or both. In yet another aspect, "treat, " "treating, " or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

[0262] As used herein, the term "therapeutically acceptable amount" or "therapeutically effective dose" interchangeably refers to an amount sufficient to effect the desired result (i.e., a reduction in tumor size, inhibition of tumor growth, prevention of metastasis, inhibition or prevention of viral, bacterial, fungal or parasitic infection) .

In some aspects, a therapeutically acceptable amount does not induce or cause undesir able side effects. A therapeutically acceptable amount can be determined by first adm inistering a low dose, and then incrementally increasing that dose until the desired effect is achieved. A "prophylactically effective dosage, " and a "therapeutically ef fective dosage, " of the molecules of the present disclosure can prevent the onset of or result in a decrease in severity of, respectively, disease symptoms, including sy mptoms associated with cancer.

[0263] As used herein, the term "co-administer" generally refers to the simultaneous pr esence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

[0264] As used herein, the terms "comprising" , "containing" , "having" , "include" , and "i ncluding" are to be construed as "including, but not limited to" unless otherwise not ed. The terms "a, " "an, " and "the" and similar referents in the context of describi ng the invention and, specifically, in the context of the appended claims, are to be construed to cover both the singular and the plural unless otherwise noted. The use o f any and all examples or exemplary language ("for example" , "e.g. " , "such as") is intended merely to illustrate aspects or embodiments of the invention, and is not to be construed as limiting the scope thereof, unless otherwise claimed.

[0265] As used herein, the term "about" when referring to a measurable valu e such as an amount, a temporal duration, and the like, is meant to encompass variati ons of ±20%or in some instances ±10%or in some instances ±5%or in so me instances ±1%or in some instances ±0.1%from the specified value, as such variations are appropriate to perform the disclosed methods.

[0266] The term "vector" includes shuttle and expression vectors. Typically, a vector could be a plasmid construct that also include an origin of replication (e.g., the Col E1 o rigin of replication) and a selectable marker (e.g., ampicillin or tetracycline resis tance) , for replication and selection, respectively, of the plasmids in bacteria. An "expression vector" refers to a vector that contains the necessary control sequences or regulatory elements for expression of the antibodies including antibody fragment of the present disclosure, in bacterial or eukaryotic cells.

[0267] The term “mono-specific antibody” as used herein refers to an antibody having one s ingle specificity to one antigen or a fragment thereof (such as human CDH17 or any of its seven ECDs) . The term “multi-specific antibody” as used herein refers to an anti body having two or more specificities to one or more antigens or to different epitope s of the same antigen. The term multi-specific antibody may be a bi-specific or tri-specific antibody. For example, a bi-specific antibody may comprise a f irst specificity to a first antigen (e.g., CDH17) and a second specificity to a secon d antigen (e.g., a tumor associated antigen or tumor specific antigen) different from

the first antigen. For example, a bi-specific antibody may comprise a first specificity to a first epitope (e.g., ECD3 of CDH17) of an antigen and a second specificity to a second different epitope (e.g., ECD4 of CDH17) of the same antigen. For example, a bi-specific antibody may comprise a first specificity to a first epitope (e.g., a first fragment of ECD4 of CDH17) of an antigen and a second specificity to a second epitope (e.g., a second different fragment of ECD4 of CDH17) of the same antigen.

[0268] As used herein, the term "monoclonal antibody" refers to an antibody from a group of substantially uniform antibodies, i.e., antibodies that make up the group are identical except for a small number of possible natural mutations. A monoclonal antibody has high specificity for one determinant (epitope) of an antigen, while a comparative polyclonal antibody contains different antibodies for different determinants (epitopes) . In addition to specificity, the monoclonal antibody has the advantage of being free from contamination by other antibodies during synthesis. In the context of the present disclosure, a monoclonal antibody also specifically includes a chimeric antibody, i.e., a portion of a heavy chain and/or a light chain is the same as or homologous to a type, a class, or a subclass of antibodies, while the rest is the same as or homologous to another type, another class, or another subclass of antibodies, provided the antibody has required bioactivity. The chimeric antibody available in the disclosure includes an antibody containing a variable region antigen binding sequence from a rodent (e.g., a rat or a mouse) and a human constant region sequence.

[0269] Antibodies Binding to CDH17

[0270] In one aspect, provided is an antibody binding to CDH17 and an antigen binding fragment of the antibody, wherein the antibody or the antigen binding fragment thereof specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166.

[0271] In some embodiments, the antibody binding to CDH17 specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127. In some embodiments, the antibody binding to CDH17 specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 128. In some embodiments, the antibody binding to CDH17 specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 166.

[0272] In some embodiments, the antibody binding to CDH17 specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and SEQ ID NO: 128. In these embodiments, the polypeptide is a fusion of the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and the polypeptide having an amino acid sequence shown

in SEQ ID NO: 128. Preferably, the fusion contains from N terminus to C terminus the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 an d the polypeptide having an amino acid sequence shown in SEQ ID NO: 128.

[0273] In some embodiments, the antibody or the antigen binding fragment th ereof specifically binding to a polypeptide having an amino acid sequence shown in SE Q ID NO: 127 and/or 128 or in SEQ ID NO: 166 has competitive binding activity with the polypeptide having an amino acid sequence shown i n SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%, at lea st 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at l east 99%sequence identity to each thereof, and a light chain variable region having a n amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at leas t 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0274] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 1, and a light chain variable region h aving an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2.

[0275] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 3, and a light chain variable region h

aving an amino acid sequence shown in SEQ ID NO: 4 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 4.

[0276] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 6.

[0277] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 29.

[0278] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 21, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 31 or an amino ac

id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 31.

[0279] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 23, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 33 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 33.

[0280] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0281] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 25, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0282] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 27, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0283] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 43.

[0284] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80% , at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino ac id sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 9 6%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 45.

[0285] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque

nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 47.

[0286] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 176.

[0287] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 166, wherein the anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 172, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 172.

[0288] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes

with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence sho wn in SEQ ID NO: 8 or an amino acid sequence having at least 80%, at least 85%, at le ast 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%seque nce identity to SEQ ID NO: 8;

[0289] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence sho wn in SEQ ID NO: 10 or an amino acid sequence having at least 80%, a t least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at lea st 98%, or at least 99%sequence identity to SEQ ID NO: 10.

[0290] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co mprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 11, and a light chain having an amino acid sequence s hown in SEQ ID NO: 12 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 12.

[0291] In one embodiment, the antibody or the antigen binding fragment ther eof specifically binding to a polypeptide having an amino acid seque nce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody co

mprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 30.

[0292] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 22, and a light chain having an amino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 32.

[0293] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 24, and a light chain having an amino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 34.

[0294] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80

%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 36.

[0295] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 36.

[0296] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 28, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 36.

[0297] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 38 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence s

hown in SEQ ID NO: 44 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 44.

[0298] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 46.

[0299] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 48.

[0300] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequence having at least 8

0%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 177.

[0301] In one embodiment, the antibody or the antigen binding fragment thereof specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 competes with an anti-CDH17 antibody for binding a polypeptide having an amino acid sequence shown in SEQ ID NO: 166, wherein the anti-CDH17 antibody comprises a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 173.

[0302] In some embodiments, the antibody specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 may be a mono-specific antibody, a multi-specific antibody (e.g., a bispecific antibody or a tri-specific antibody) , an intact antibody, a human antibody, a humanized antibody or a chimeric antibody. In preferable embodiments, the antibody specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 may be a human antibody or a humanized antibody. In some embodiments, the antibody specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 may be a monoclonal antibody.

[0303] In some embodiments, the antibody specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 may be an antibody that possesses an ability to internalize that permits cellular uptake. In some embodiments, the antibody specifically binding to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 may be an antibody that possesses an ability to internalize that permits uptake by a cancer cell, e.g., a pancreatic cancer cell, a gastric cancer cell, a colorectal cancer cell, cholangiocarcinoma cancer cell, a liver cancer cell, a neuroendocrine cancer cell, or an esophageal adenocarcinoma cell.

[0304] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 o

f a heavy chain variable region having an amino acid sequence selected from a group c onsisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/ or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 wh ich are same as the LCDR1, LCDR2, and LCDR3 of a light chain variabl e region having an amino acid sequence selected from a group consist ing of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176.

[0305] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCD R1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 o f a heavy chain variable region having an amino acid sequence selected from a group c onsisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/ or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 wh ich are same as the LCDR1, LCDR2, and LCDR3 of a light chain variabl e region having an amino acid sequence selected from a group consist ing of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176; wherein the HCDR 1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined according to an y one of CDR definition schemes selected from a group consisting of IMGT, Kabat, Contact, Chothia, Martin, PyIgClassify, and any combination thereof.

[0306] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCD R1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 o f a heavy chain variable region having an amino acid sequence selected from a group c onsisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/ or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 wh ich are same as the LCDR1, LCDR2, and LCDR3 of a light chain variabl e region having an amino acid sequence selected from a group consist ing of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176; wherein the HCDR 1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined according to an y one of CDR definition schemes selected from a group consisting of IMGT, Kabat, Contact, Chothia, and any combination thereof.

[0307] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCD R1, HCDR2, and HCDR3 having amino acid sequences selected from a gro up consisting of:

[0308] SEQ ID NO: 49, 50, and 51, respectively;

[0309] SEQ ID NO: 68, 69, and 70, respectively;

[0310] SEQ ID NO: 87, 88, and 89, respectively;

[0311] SEQ ID NO: 109, 50, and 51, respectively;

[0312] SEQ ID NO: 49, 50, and 113, respectively;

[0313] SEQ ID NO: 49, 50, and 116, respectively;

[0314] SEQ ID NO: 178, 179, and 180, respectively; and

[0315] SEQ ID NO: 191, 192, and 193, respectively;

[0316] according to IMGT definition scheme; or a group consisting of:

[0317] SEQ ID NO: 55, 56, and 57, respectively;

[0318] SEQ ID NO: 74, 75, and 76, respectively;

[0319] SEQ ID NO: 93, 94, and 95, respectively;

[0320] SEQ ID NO: 55, 106, and 57, respectively;

[0321] SEQ ID NO: 110, 111, and 57, respectively;

[0322] SEQ ID NO: 55, 106, and 114, respectively;

[0323] SEQ ID NO: 55, 106, and 117, respectively;

[0324] SEQ ID NO: 182, 183, and 184, respectively; and

[0325] SEQ ID NO: 197, 198, and 199, respectively;

[0326] according to Kabat definition scheme; or a group consisting of:

[0327] SEQ ID NO: 60, 61, and 57, respectively;

[0328] SEQ ID NO: 79, 80, and 76, respectively;

[0329] SEQ ID NO: 98, 99, and 95, respectively;

[0330] SEQ ID NO: 60, 61, and 114, respectively;

[0331] SEQ ID NO: 60, 61, and 117, respectively;

[0332] SEQ ID NO: 185, 186, and 184, respectively; and

[0333] SEQ ID NO: 202, 203, and 199, respectively;

[0334] according to Chothia definition scheme; or a group consisting of:

[0335] SEQ ID NO: 62, 63, and 64, respectively;

[0336] SEQ ID NO: 81, 82, and 83, respectively;

[0337] SEQ ID NO: 100, 101, and 102, respectively;

[0338] SEQ ID NO: 62, 107, and 64, respectively;

[0339] SEQ ID NO: 62, 108, and 57, respectively;

[0340] SEQ ID NO: 112, 108, and 64, respectively;

[0341] SEQ ID NO: 62, 107, and 115, respectively;

[0342] SEQ ID NO: 62, 107, and 118, respectively;

[0343] SEQ ID NO: 81, 123, and 83, respectively;

[0344] SEQ ID NO: 187, 188, and 189, respectively; and

[0345] SEQ ID NO: 204, 205, and 206, respectively;

[0346] according to Contact definition scheme.

[0347] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0348] SEQ ID NO: 52, 53, and 54, respectively;

[0349] SEQ ID NO: 71, 72, and 73, respectively;

[0350] SEQ ID NO: 90, 91, and 92, respectively;

[0351] SEQ ID NO: 52, 53, and 181, respectively; and

[0352] SEQ ID NO: 194, 195, and 196, respectively;

[0353] according to IMGT definition scheme; or a group consisting of:

[0354] SEQ ID NO: 58, 59, and 54, respectively;

[0355] SEQ ID NO: 77, 78, and 73, respectively;

[0356] SEQ ID NO: 96, 97, and 92, respectively;

[0357] SEQ ID NO: 58, 120, and 54, respectively;

[0358] SEQ ID NO: 58, 59, and 181, respectively; and

[0359] SEQ ID NO: 200, 201, and 196, respectively;

[0360] according to Kabat definition scheme; or a group consisting of:

[0361] SEQ ID NO: 65, 66, and 67, respectively;

[0362] SEQ ID NO: 84, 85, and 86, respectively;

[0363] SEQ ID NO: 103, 104, and 105, respectively;

[0364] SEQ ID NO: 65, 119, and 67, respectively;

[0365] SEQ ID NO: 65, 121, and 67, respectively;

[0366] SEQ ID NO: 65, 122, and 67, respectively;

[0367] SEQ ID NO: 65, 66, and 190, respectively; and

[0368] SEQ ID NO: 207, 208, and 209, respectively;

[0369] according to Contact definition scheme.

[0370] In some embodiments, provided is an antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 having amino acid sequences selected from a group consisting of:

[0371] SEQ ID NO: 49, 50, and 51, respectively;

[0372] SEQ ID NO: 68, 69, and 70, respectively;

[0373] SEQ ID NO: 87, 88, and 89, respectively;

[0374] SEQ ID NO: 109, 50, and 51, respectively;

[0375] SEQ ID NO: 49, 50, and 113, respectively;

[0376] SEQ ID NO: 49, 50, and 116, respectively;

[0377] SEQ ID NO: 178, 179, and 180, respectively; and

[0378] SEQ ID NO: 191, 192, and 193, respectively;

[0379] according to IMGT definition scheme; or a group consisting of:

[0380] SEQ ID NO: 55, 56, and 57, respectively;

[0381] SEQ ID NO: 74, 75, and 76, respectively;

[0382] SEQ ID NO: 93, 94, and 95, respectively;

[0383] SEQ ID NO: 55, 106, and 57, respectively;

[0384] SEQ ID NO: 110, 111, and 57, respectively;

[0385] SEQ ID NO: 55, 106, and 114, respectively;

[0386] SEQ ID NO: 55, 106, and 117, respectively;

[0387] SEQ ID NO: 182, 183, and 184, respectively; and

[0388] SEQ ID NO: 197, 198, and 199, respectively;

[0389] according to Kabat definition scheme; or a group consisting of:

[0390] SEQ ID NO: 60, 61, and 57, respectively;

[0391] SEQ ID NO: 79, 80, and 76, respectively;

[0392] SEQ ID NO: 98, 99, and 95, respectively;

[0393] SEQ ID NO: 60, 61, and 114, respectively;

[0394] SEQ ID NO: 60, 61, and 117, respectively;

[0395] SEQ ID NO: 185, 186, and 184, respectively; and

[0396] SEQ ID NO: 202, 203, and 199, respectively;

[0397] according to Chothia definition scheme; or a group consisting of:

[0398] SEQ ID NO: 62, 63, and 64, respectively;

[0399] SEQ ID NO: 81, 82, and 83, respectively;

[0400] SEQ ID NO: 100, 101, and 102, respectively;

[0401] SEQ ID NO: 62, 107, and 64, respectively;

[0402] SEQ ID NO: 62, 108, and 57, respectively;

[0403] SEQ ID NO: 112, 108, and 64, respectively;

[0404] SEQ ID NO: 62, 107, and 115, respectively;

[0405] SEQ ID NO: 62, 107, and 118, respectively;

[0406] SEQ ID NO: 81, 123, and 83, respectively;

[0407] SEQ ID NO: 187, 188, and 189, respectively; and

[0408] SEQ ID NO: 204, 205, and 206, respectively;

[0409] according to Contact definition scheme;

[0410] and a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0411] SEQ ID NO: 52, 53, and 54, respectively;

[0412] SEQ ID NO: 71, 72, and 73, respectively;

[0413] SEQ ID NO: 90, 91, and 92, respectively;

[0414] SEQ ID NO: 52, 53, and 181, respectively; and

[0415] SEQ ID NO: 194, 195, and 196, respectively;

[0416] according to IMGT definition scheme; or a group consisting of:

[0417] SEQ ID NO: 58, 59, and 54, respectively;

[0418] SEQ ID NO: 77, 78, and 73, respectively;

[0419] SEQ ID NO: 96, 97, and 92, respectively;

[0420] SEQ ID NO: 58, 120, and 54, respectively;

[0421] SEQ ID NO: 58, 59, and 181, respectively; and

[0422] SEQ ID NO: 200, 201, and 196, respectively;

[0423] according to Kabat definition scheme; or a group consisting of:

[0424] SEQ ID NO: 65, 66, and 67, respectively;

[0425] SEQ ID NO: 84, 85, and 86, respectively;

[0426] SEQ ID NO: 103, 104, and 105, respectively;

[0427] SEQ ID NO: 65, 119, and 67, respectively;

[0428] SEQ ID NO: 65, 121, and 67, respectively;

[0429] SEQ ID NO: 65, 122, and 67, respectively;

[0430] SEQ ID NO: 65, 66, and 190, respectively; and

[0431] SEQ ID NO: 207, 208, and 209, respectively;

[0432] according to Contact definition scheme.

[0433] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 having amino acid sequences selected from a group consisting of:

[0434] SEQ ID NO: 49, 50, and 51, respectively;

[0435] SEQ ID NO: 68, 69, and 70, respectively;

[0436] SEQ ID NO: 87, 88, and 89, respectively;

[0437] SEQ ID NO: 109, 50, and 51, respectively;

[0438] SEQ ID NO: 49, 50, and 113, respectively;

[0439] SEQ ID NO: 49, 50, and 116, respectively;

[0440] SEQ ID NO: 178, 179, and 180, respectively; and

[0441] SEQ ID NO: 191, 192, and 193, respectively;

[0442] and a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0443] SEQ ID NO: 52, 53, and 54, respectively;

[0444] SEQ ID NO: 71, 72, and 73, respectively;

[0445] SEQ ID NO: 90, 91, and 92, respectively;

[0446] SEQ ID NO: 52, 53, and 181, respectively; and

[0447] SEQ ID NO: 194, 195, and 196, respectively;

[0448] according to IMGT definition scheme.

[0449] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 having amino a cid sequences selected from a group consisting of:

[0450] SEQ ID NO: 55, 56, and 57, respectively;

[0451] SEQ ID NO: 74, 75, and 76, respectively;

[0452] SEQ ID NO: 93, 94, and 95, respectively;

[0453] SEQ ID NO: 55, 106, and 57, respectively;

[0454] SEQ ID NO: 110, 111, and 57, respectively;

[0455] SEQ ID NO: 55, 106, and 114, respectively;

[0456] SEQ ID NO: 55, 106, and 117, respectively;

[0457] SEQ ID NO: 182, 183, and 184, respectively; and

[0458] SEQ ID NO: 197, 198, and 199, respectively;

[0459] and a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0460] SEQ ID NO: 58, 59, and 54, respectively;

[0461] SEQ ID NO: 77, 78, and 73, respectively;

[0462] SEQ ID NO: 96, 97, and 92, respectively;

[0463] SEQ ID NO: 58, 120, and 54, respectively;

[0464] SEQ ID NO: 58, 59, and 181, respectively; and

[0465] SEQ ID NO: 200, 201, and 196, respectively;

[0466] according to Kabat definition scheme.

[0467] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 having amino a cid sequences selected from a group consisting of:

[0468] SEQ ID NO: 60, 61, and 57, respectively;

[0469] SEQ ID NO: 79, 80, and 76, respectively;

[0470] SEQ ID NO: 98, 99, and 95, respectively;

[0471] SEQ ID NO: 60, 61, and 114, respectively;

[0472] SEQ ID NO: 60, 61, and 117, respectively;

[0473] SEQ ID NO: 185, 186, and 184, respectively; and

[0474] SEQ ID NO: 202, 203, and 199, respectively;

[0475] and a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0476] SEQ ID NO: 58, 59, and 54, respectively;

[0477] SEQ ID NO: 77, 78, and 73, respectively;

[0478] SEQ ID NO: 96, 97, and 92, respectively;

[0479] SEQ ID NO: 58, 120, and 54, respectively;

[0480] SEQ ID NO: 58, 59, and 181, respectively; and

[0481] SEQ ID NO: 200, 201, and 196, respectively;

[0482] according to Chothia definition scheme.

[0483] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 having amino acid sequences selected from a group consisting of:

[0484] SEQ ID NO: 62, 63, and 64, respectively;

[0485] SEQ ID NO: 81, 82, and 83, respectively;

[0486] SEQ ID NO: 100, 101, and 102, respectively;

[0487] SEQ ID NO: 62, 107, and 64, respectively;

[0488] SEQ ID NO: 62, 108, and 57, respectively;

[0489] SEQ ID NO: 112, 108, and 64, respectively;

[0490] SEQ ID NO: 62, 107, and 115, respectively;

[0491] SEQ ID NO: 62, 107, and 118, respectively;

[0492] SEQ ID NO: 81, 123, and 83, respectively;

[0493] SEQ ID NO: 187, 188, and 189, respectively; and

[0494] SEQ ID NO: 204, 205, and 206, respectively;

[0495] and a light chain variable region comprising LCDR1, LCDR2, and LCDR3 having amino acid sequences selected from a group consisting of:

[0496] SEQ ID NO: 65, 66, and 67, respectively;

[0497] SEQ ID NO: 84, 85, and 86, respectively;

[0498] SEQ ID NO: 103, 104, and 105, respectively;

[0499] SEQ ID NO: 65, 119, and 67, respectively;

[0500] SEQ ID NO: 65, 121, and 67, respectively;

[0501] SEQ ID NO: 65, 122, and 67, respectively;

[0502] SEQ ID NO: 65, 66, and 190, respectively; and

[0503] SEQ ID NO: 207, 208, and 209, respectively;

[0504] according to Contact definition scheme.

[0505] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0506] SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;

[0507] SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;

[0508] SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;

[0509] SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;

[0510] SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;

[0511] SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;

[0512] SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and

[0513] SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;

[0514] according to IMGT definition scheme.

[0515] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively, acc ording to IMGT definition scheme.

[0516] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively, acc ording to IMGT definition scheme.

[0517] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively, acc ording to IMGT definition scheme.

[0518] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively, according to IMGT definition scheme.

[0519] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp

rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively, according to IMGT definition scheme.

[0520] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein t he HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequ ences shown in SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively, according to IMGT definition scheme.

[0521] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively, according to IMGT definition scheme.

[0522] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively, according to I MGT definition scheme.

[0523] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es selected from a group consisting of:

[0524] SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;

[0525] SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;

[0526] SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;

[0527] SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;

[0528] SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;

[0529] SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;

[0530] SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;

[0531] SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;

[0532] SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and

[0533] SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;

[0534] according to Kabat definition scheme.

[0535] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively, according to Kabat d efinition scheme.

[0536] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively, according to Kabat d efinition scheme.

[0537] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively, according to Kabat d efinition scheme.

[0538] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively, according to Kabat definition scheme.

[0539] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a

mino acid sequences shown in SEQ ID NO: 110, 111, 57, 58, 120, and 5
4, respectively, according to Kabat definition scheme.

[0540] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 55, 106, 57, 58, 120, and 54 , respectively, according to Kabat definition scheme.

[0541] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 55, 106, 114, 58, 120, and 5 4, respectively, according to Kabat definition scheme.

[0542] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 55, 106, 117, 58, 120, and 5 4, respectively, according to Kabat definition scheme.

[0543] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively, according to Kabat definition scheme.

[0544] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein t he HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequ ences shown in SEQ ID NO: 197, 198, 199, 200, 201, and 196, respecti vely, according to Kabat definition scheme.

[0545] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0546] SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;

[0547] SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;

[0548] SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;

[0549] SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively

[0550] SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;

[0551] SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;

[0552] SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and

[0553] SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;

[0554] according to Chothia definition scheme.

[0555] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively, according to Chothia definition scheme.

[0556] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively, according to Chothia definition scheme.

[0557] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively, according to Chothia definition scheme.

[0558] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha

in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively, according to Chothi a definition scheme.

[0559] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein t he HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequ ences shown in SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively , according to Chothia definition scheme.

[0560] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 60, 61, 117, 58, 120, and 54 , respectively, according to Chothia definition scheme.

[0561] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively, according to Chothia definition scheme.

[0562] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectivel y, according to Chothia definition scheme.

[0563] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the

HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0564] SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;

[0565] SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;

[0566] SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;

[0567] SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;

[0568] SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;

[0569] SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;

[0570] SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;

[0571] SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;

[0572] SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;

[0573] SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;

[0574] SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and

[0575] SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;

[0576] according to Contact definition scheme.

[0577] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively, according to Contact definition scheme.

[0578] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively, according to Contact definition scheme.

[0579] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences shown in SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively, according to Contact definition scheme.

[0580] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp

rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 62, 107, 64, 65, 119, and 67 , respectively, according to Contact definition scheme.

[0581] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively, according to Contac t definition scheme.

[0582] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 112, 108, 64, 65, 121, and 6 7, respectively, according to Contact definition scheme.

[0583] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 62, 107, 115, 65, 122, and 6 7, respectively, according to Contact definition scheme.

[0584] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a mino acid sequences shown in SEQ ID NO: 62, 107, 118, 65, 122, and 6 7, respectively, according to Contact definition scheme.

[0585] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain variable region comprising HCDR1, HCDR2, and HCD R3 and a light chain variable region comprising LCDR1, LCDR2, and LC DR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have a

mino acid sequences shown in SEQ ID NO: 62, 107, 64, 65, 122, and 67 , respectively, according to Contact definition scheme.

[0586] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively, according to Contac t definition scheme.

[0587] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively, according to Contact definition scheme.

[0588] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region comprising HCDR1, HCDR2, and HCDR3 and a light ch ain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequenc es shown in SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectivel y, according to Contact definition scheme.

[0589] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid seque nce having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at l east 97%, at least 98%, or at least 99%sequence identity to each thereof, and/or a li ght chain variable region having an amino acid sequence selected from a group consist ing of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid se quence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, a t least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0590] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid seque

nce having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at l east 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0591] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a light cha in variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to each thereof.

[0592] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy cha in variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid seque nce having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at l east 97%, at least 98%, or at least 99%sequence identity to each thereof, and a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid seque nce having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at l east 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0593] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 1 or an amino acid sequence hav ing at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97 %, at least 98%, or at least 99%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 9 5%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2.

[0594] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 3 or an amino acid sequence hav ing at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97 %, at least 98%, or at least 99%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 9 5%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 4.

[0595] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 6.

[0596] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 29.

[0597] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 21, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 31.

[0598] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 23, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least

t 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 33.

[0599] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 19 or an amino acid sequence ha ving at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 9 7%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 19, and a light chai n variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at leas t 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0600] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 25 or an amino acid sequence ha ving at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 9 7%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 25, and a light chai n variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at leas t 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0601] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 27 or an amino acid sequence ha ving at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 9 7%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 27, and a light chai n variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at leas t 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 35.

[0602] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an ami no acid sequence shown in SEQ ID NO: 37 or an amino acid sequence ha ving at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 9 7%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 37, and a light chai

n variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 43.

[0603] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 45.

[0604] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 47.

[0605] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 172.

[0606] In one embodiment, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody is an anti-CDH17 antibody comprises a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence h

aving at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 174, and a light ch ain variable region having an amino acid sequence shown in SEQ ID NO : 176 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 176.

[0607] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody has a heavy chain con stant region and/or a light chain constant region. In some embodiments, provided is a n antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody has a human heavy chain constant regio n and a human light chain constant region. In some embodiments, the antibody specific ally binding to cadherin-17 or an antigen binding fragment thereof comprises a human heavy chain constant region having an amino acid sequence s hown in SEQ ID NO: 124. In some embodiments, the antibody specifical ly binding to cadherin-17 or an antigen binding fragment thereof comprises a human light chain constant region having an amino acid sequence s hown in SEQ ID NO: 125. In some embodiments, provided is an antibody spec ifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a human heavy chain constant region having an amino acid sequence shown in SEQ ID NO: 124 and a human light chain constant region having an amino acid sequence shown in SEQ ID NO: 125.

[0608] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid se quence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, a t least 97%, at least 98%, or at least 99%sequence identity to each thereof; and/ or a light chain having an amino acid sequence selected from a group con sisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino a cid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0609] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comp rises a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid se quence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, a t least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0610] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a light chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0611] In some embodiments, provided is an antibody specifically binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof; and a light chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0612] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 8.

[0613] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 10.

[0614] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 11, and a light chain having an amino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l

east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 12.

[0615] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2 0, and a light chain having an amino acid sequence shown in SEQ ID N O: 30 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 30.

[0616] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2 2, and a light chain having an amino acid sequence shown in SEQ ID N O: 32 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 32.

[0617] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2 4, and a light chain having an amino acid sequence shown in SEQ ID N O: 34 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 34.

[0618] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2 0, and a light chain having an amino acid sequence shown in SEQ ID N O: 36 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 36.

[0619] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2

6, and a light chain having an amino acid sequence shown in SEQ ID N O: 36 or an amino acid sequence having at least 80%, at least 85%, at lea st 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequen ce identity to SEQ ID NO: 36.

[0620] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 2 8, and a light chain having an amino acid sequence shown in SEQ ID N O: 36 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 36.

[0621] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 38 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 3 8, and a light chain having an amino acid sequence shown in SEQ ID N O: 44 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 44.

[0622] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 4 0, and a light chain having an amino acid sequence shown in SEQ ID N O: 46 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 46.

[0623] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an ami no acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at le ast 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 4 2, and a light chain having an amino acid sequence shown in SEQ ID N O: 48 or an amino acid sequence having at least 80%, at least 85%, at least 90%, at l east 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 48.

[0624] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an am

ino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at l east 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%, at least 85%, at least 90%, a t least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identi ty to SEQ ID NO: 173.

[0625] In one embodiment, provided is an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an am ino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at l east 96%, at least 97%, at least 98%, or at least 99%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequence having at least 80%, at least 85%, at least 90%, a t least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identi ty to SEQ ID NO: 177.

[0626] In some embodiments, the antibody specifically binding to CDH17 may be a mono-specific antibody, a multi-specific antibody (e.g., a bispecific antibody or a tri-specific antibody) , an intact antibody, a human antibody, a humaniz ed antibody or a chimeric antibody. In preferable embodiments, the antibody specifica lly binding CDH17 may be a human antibody or a humanized antibody. I n some embodiments, the antibody specifically binding to CDH17 may b e a monoclonal antibody.

[0627] In some embodiments, the antibody specifically binding to CDH17 may be an antibody that possesses an ability to internalize that permits cellular uptake. In some embodiments, the antibody specifically binding to CDH17 may be an antibody that possesses an ability to internalize that permits uptake by a can cer cell, e.g., a pancreatic cancer cell, a gastric cancer cell, a colorectal cancer cell, cholangiocarcinoma cancer cell, a liver cancer cell, a neuroendocrine cancer ce ll, or an esophageal adenocarcinoma cell.

[0628] In any of the embodiments disclosed herein, the antigen binding fragment is selected from a group consisting of Fab, Fab', Fv, F (ab') $_2$, scFv, di-scFv and dAb, pre ferably Fab or scFv.

[0629] Immunoconjugates

[0630] Another aspect of the disclosure relates to an immunoconjugate, a ph armaceutically acceptable salt thereof, or a solvate thereof, comprising the antibody or an antigen binding fragment thereof according to the "Antibodies Binding to CDH17" section described above, and an active agent or m oiety conjugated to the antibody or an antigen binding fragment thereof.

[0631] In some embodiments, and the active moiety can comprise a drug moiety and/or a label.

[0632] In some embodiments, the drug moiety is selected from the group consisting of a cytotoxic agent, a cytokine, a nucleic acid, a nucleic acid-associated molecule, a radionuclide, a chemokine, an immuno (co) -stimulatory molecule, an immunosuppressive molecule, a death ligand, an apoptosis-inducing protein, a kinase, a prodrug-converting enzyme, a RNase, an agonistic antibody or antibody fragment, an antagonistic antibody or antibody fragment, a growth factor, a hormone, a coagulation factor, a fibrinolytic protein, peptides mimicking these, and fragments, fusion proteins and derivatives thereof.

[0633] In some embodiments, the label is selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent, and a metal ion.

[0634] In some embodiments, the cytotoxic agent comprises a microtubule disrupting drug and/or a DNA-damaging agent.

[0635] In some embodiments, the cytotoxic agent can be selected from: Paclitaxel; cytochalasin B; short bacteriocin D; ethidium bromide; emetine; mitomycin; etoposide; onychothioside; thienoside; vincristine; colchicine; doxorubicin; erythromycin; dihydroxycarbamycin dione; microtubulin inhibitors; mitoxantrone; actinomycin D; 1-dehydrotestosterone; glucocorticoids; procaine; bupivacaine; lidocaine ; propranolol; puromycin; kallikrein or its analogs or derivatives; antimetabolites; alkylating agents; antibiotics; antimitotic agents; diphtheria toxin and related molecules and their active fragments and heterodimeric molecules, ricin toxin, cholera toxin, shiga-like toxin, LT toxin, C3 toxin, shiga toxin, pertussis toxin, tetanus toxin, soybean Bowman-Birk protease inhibitor, Pseudomonas exotoxin, alorin, fucoside, capsidin, gelanin, phaseolus toxin chain A, capsidin chain A, alpha-bromotoxin, oleuropein, staphylin protein, American commercial protein, bitter melon inhibitor, jatropha toxin, croton toxin, soapwort inhibitor, white tree toxin, mitogellin, limiting trichothecene, phenomycin and enoxycin Toxins; Ribonuclease (RNase) ; DNase I, staphylococcal endotoxin A; American commercial land antiviral protein; diphtheria toxin; and Pseudomonas endotoxin.

[0636] In some embodiments, the microtubulin inhibitor can be medensin I or an analogue or derivative thereof; the antimetabolite is aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, fludarabine, 5-fluorouracil, dacarbazine, hydroxyurea, asparaginase, gemcitabine or cladribine; the alkylating agent is azacitidine, thiophan, azacitidine benzoate, melphalan, carazacitidine (BSNU) , lomustine (CCNU) , cyclophosphamide, leucovorin, dibromomannan, streptozotocin, dacarbazine (DTIC) , procarbazine, mitomycin C, cis-molybdenum, carbomolybdenum, duocarmycin A, duocarmycin SA, rachamycin (CC-1065) or analogue

s or derivatives thereof; the antibiotics being bleomycin, adriamycin, idarubicin (or mitomycin, mitoxantrone, puccamycin, antrixin (AMC)) ; the antimitotic agent is monomethyl auristatin E or F; the diphtheria toxin-related molecule is diphtheria A chain; the ricin toxin is ricin A or deglycosylated ricin A chain toxin; the shiga-like toxin is SLT I, SLT II and SLT IIV; the American commercial protein is PAPI, PAPII and PAP S.

[0637] In some embodiments, the radionuclide comprises: At^{211}, I^{131}, I^{125}, I^{123}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212}, Tc^{99}, S^{35}, F^{19}, N^{15}, C^{14}, C^{13} or H^3, optionally the radionuclide can be conjugated to the antibody via a chelating agent.

[0638] In some embodiments, the cytokine comprises: IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-18, IL-23, IL-24, IL-27, IL-28a, IL-28b, IL-29, KGF IFNα, IFNβ, IFNγ, GM-CSF, CD40L, Flt3 ligand, stem cell factor, anisidine or TNFα.

[0639] Anti-CDH17 Antibody Drug Conjugate

[0640] An exemplary immunoconjugate of the present disclosure is an antibody-drug conjugate, and the active agent is a drug moiety, wherein the antibody drug conjugate has a formula of Ab- (L- (D) m) n, wherein Ab is the antibody or an antigen binding fragment thereof as described herein; L is a linker; D is the drug moiety; m is an integer from 1 to 8; and n is any number from 1 to 10.

[0641] The anti-CDH17 antibody of present application can be conjugated to a drug via a linker structure moiety to prepare an anti-CDH17 antibody drug conjugate. The drug is not particularly limited as long as it has a substituent or a partial structure that can be connected to a linker structure. The anti-CDH17 antibody drug conjugate can be used for various purposes according to the conjugated drug. Examples of such a drug can include substances having antitumor activity, substances effective for blood diseases, substances effective for autoimmune diseases, anti-inflammatory substances, antimicrobial substances, antifungal substances, antiparasitic substances, antiviral substances, and anti-anesthetic substances.

[0642] Cytotoxic Agent

[0643] As described above, the drug moiety for an antibody-drug conjugate of the present disclosure can be selected from the group consisting of a cytotoxic agent, a cytokine, a nucleic acid, a nucleic acid-associated molecule, a radionuclide, a chemokine, an immuno (co) -stimulatory molecule, an immunosuppressive molecule, a death ligand, an apoptosis-inducing protein, a kinase, a prodrug-converting enzyme, a RNase, an agonistic antibody or antibody fragment, an antagonistic antibody or antibody fragment, a growth factor, a hormone, a coagulation factor, a fibrinolytic protein, peptides mimicking these, and fragments, fusion proteins and derivatives thereof.

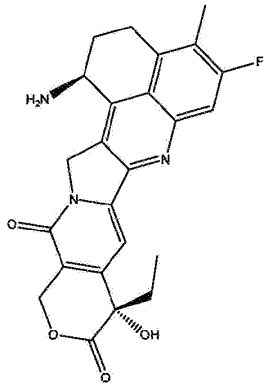
[0644] An example using a cytotoxic agent as a compound to be conjugated in the anti-CDH17 antibody drug conjugate of the present invention will be descr ibed below. The cytotoxic agent is not particularly limited as long as the compound h as an antitumor effect and has a substituent or a partial structure that can be conne cted to a linker structure. Upon cleavage of a part or the whole of the linker in tum or cells, the cytotoxic agent is released so that the cytotoxic agent exhibits an ant itumor effect. As the linker is cleaved at a connecting position with the drug, the c ytotoxic agent is released in its original structure to exert its original antitumor effect.

[0645] In some embodiments, the cytotoxic agent comprises a tubulin inhibitor and/ or a topoisomerase inhibitor. For example, the cytotoxic agent can comprise: m onomethyl auristatin E (MMAE) , monomethyl auristatin F (MMAF) , med ensin I, pyrrolobenzodiazepine (PBD) , camptothecin, nemorubicin, PNU-159682, anthracyclines, betacamycin, perillyl alkaloids, paclitaxel, montelukast, eli nafide, kallikrein, duocarmycin, rachamycin (CC-1065) or an analogue, a derivative or a prodrug thereof.

[0646] In some embodiments, the cytotoxic agent comprises a topoisomerase I inhibitor. For example, the cytotoxic agent can comprise camptothecin (CPT) or a der ivative thereof.

[0647] As a non-restricted example, the camptothecin can comprise camptothecin and c amptothecin derivatives including but not limited to irinotecan, topotecan, lurtoteca n, silatecan, etirinotecan pegol, TAS 103, 9-aminocamptothecin, 7-ethylcamptothecin , 10-hydroxycamptothecin, 9-nitrocamptothecin, 10, 11-methylenedioxycam ptothecin, 9-amino-10, 11-methylenedioxycamptothecin, 9-chloro-10, 11-methylenedioxycamptothecin, 7- (4-methylpiperazinomethylene) -10, 1 1-ethylenedioxy-20 (S) -camptothecin, 7- (4-methylpiperazinomethylene) -10, 1 1-methylenedioxy-20 (S) -camptothecin, and 7- (2-N-isopropylamino) ethyl) - (20S) -camptothecin, and stereoisomers, salts and esters thereof.

[0648] As one example of the cytotoxic agent used in the present invention, exatecan, a camptothecin derivative ((1S, 9S) -1-amino-9-ethyl-5-fluoro-2, 3-dihydro-9-hydroxy-4-methyl-1H, 12H-benzo [de] pyrano [3' , 4' : 6, 7] indolizino [1, 2-b] quinoline-10, 13 (9H, 15H) -dione represented by the following formula) can pre ferably be used.



[0649] Formula 2'

[0650] Exatecan can be easily obtained by, for example, a method described in U.S. Patent Publication No. US2016/0297890 or other known methods , and the amino group at position 1 can be preferably used as a connecting position t o a linker structure.

[0651] Since exatecan has a camptothecin structure, it is known that the equilibrium shifts to a structure with a formed lactone ring (closed ring) in an acidic aqueous medium (e.g., of the order of pH 3) whereas the equilibrium shifts to a structure with an ope ned lactone ring (open ring) in a basic aqueous medium (e.g., of the order of pH 10) . Formula 2' as discussed herein includes a tautomer, mesomer, racemate, enantiomer, or diastereomer thereof, or mixtures thereof, or a pharmaceutically acceptable salt o r a solvate thereof. A drug conjugate into which exatecan residues corresponding to s uch a closed ring structure and/or an open ring structure have been introduced is als o expected to have an equivalent antitumor effect, and it is needless to say that any of such drug conjugate is included within the scope of the present invention.

[0652] Other examples of the cytotoxic agent can include cytotoxic agents described in the l iterature (Pharmacological Reviews, 68, p. 3-19, 2016) . Specific examples ther eof can include doxorubicin, calicheamicin, dolastatin 10, auristatins such as monome thyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) , maytan sinoids such as DM1 and DM4, a pyrrolobenzodiazepine dimer SG2000 (SJG-136) , a camptothecin derivative SN-38, duocarmycins such as CC-1065, amanitin, d aunorubicin, mitomycin C, bleomycin, cyclocytidine, vincristine, vinblastine, methotr exate, platinum-based antitumor agents (cisplatin and derivatives thereof) , and Tax ol and derivatives thereof.

[0653] In the antibody drug conjugate, the number of conjugated drug molecu les per antibody molecule is a key factor having an influence on the efficacy and saf ety thereof. The production of the antibody drug conjugate is carried out by specifyi ng reaction conditions such as the amounts of starting materials and reagents used fo

r reaction, so as to attain a constant number of conjugated drug molecules. Unlike th e chemical reaction of a low-molecular-weight compound, a mixture contain ing different numbers of conjugated drug molecules is usually obtained. The number of conjugated drug molecules per antibody molecule is defined and indicated as an avera ge value, i.e., the average number of conjugated drug molecules. Unless otherwise spe cified, i.e., except in the case of representing an antibody drug conjugate having a specific number of conjugated drug molecules that is included in an antibody drug con jugate mixture having different numbers of conjugated drug molecules , the number of conjugated drug molecules according to the present invention also mea ns an average value as a rule. The number of exatecan molecules conjugated to an anti body molecule is controllable, and as an average number of conjugate d drug molecules per antibody, approximately 1 to 10 exatecan molecu les can be conjugated. The number of exatecan molecules is preferably 2 to 8, 3 to 8, 4 to 8, 5 to 8, 6 to 8 or 7 to 8, more preferably 5 to 8, further preferably 7 to 8, still further preferably 8. It is to be noted that a person skilled in the art can d esign a reaction for conjugating a required number of drug molecules to an antibody m olecule based on the description of Examples of the present application, and can obta in an antibody drug conjugate with a controlled number of conjugated exatecan molecules.

[0654] Linker Structure

[0655] The linker structure which conjugates a drug moiety to the anti-CDH17 antibody in the anti-CDH17 antibody-drug conjugate of the present invention will be des cribed. In the antibody-drug conjugate of the present application, the link er structure which conjugates the anti-CDH17 antibody to the drug is not particularly limited as long as the resulting antibody-drug conjugate can be used. The li nker structure may be appropriately selected and used according to the purpose of use . One example of the linker structure can include a linker described in known literatur e (Pharmacol Rev 68: 3-19, January 2016, Protein Cell DOI 10.1007/s13238-016-0323-0, etc.) .

[0656] Any linker structure given below can preferably be used. It is to be noted that the l eft terminus of the structure is a connecting position to the antibody, and the right terminus thereof is a connecting position to the drug. Furthermore, VA in the linker structures given below represents an amino acid sequence consisting of valine-alanine (VA) linked through peptide bonds, and GGFG in the linker structures given be low represents an amino acid sequence consisting of glycine-glycine-phenylalanine-glycine (GGFG) linked through peptide bonds.

[0657] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-PABC-;

[0658] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-PABC-;

[0659] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-PABC-;

[0660] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-PABC-;

[0661] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-PABC-;

[0662] -CH_2-C (=O) -NH-CH_2CH_2-C (=O) -GGFG-PABC-;

[0663] -C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-PABC-;

[0664] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;

[0665] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0666] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;

[0667] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0668] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-$CH_2CH_2CH_2CH_2$-C (=O) -;

[0669] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2-O-CH_2-C (=O) -;

[0670] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2CH_2-O-CH_2-C (=O) -;

[0671] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0672] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;

[0673] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0674] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;

[0675] -CH_2-C (=O) -NH-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0676] -C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;

[0677] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-PABC-;

[0678] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-PABC-;

[0679] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-PABC-;

[0680] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-PABC-;

[0681] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH2CH2o-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-PABC-;

[0682] -CH_2-C (=O) -NH-CH_2CH_2-C (=O) -VA-PABC-;

[0683] -C (=O) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-PABC-;

[0684] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;

[0685] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;

[0686] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2CH_2-C (=O) -;

[0687] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;

[0688] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-$CH_2CH_2CH_2CH_2CH_2$-C (=O) -;

[0689] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2-O-CH_2-C (=O) -;

[0690] - (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2CH_2-O-CH_2-C (=O) -;

[0691] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;

[0692] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;

[0693] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;

[0694] - (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;

[0695] -CH_2-C (=O) -NH-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -; and

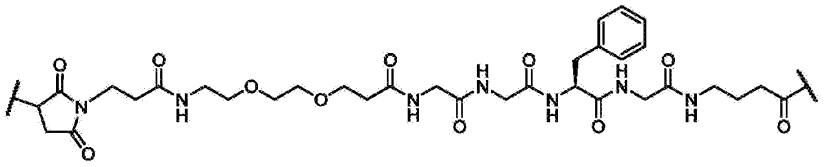
[0696] -C (=O) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -.

[0697] In some embodiments, the spacer comprises self-immolative spacers. For example, t he self-immolative spacer can comprise p-aminobenzoxy carbonyl (PABC) or p-aminobenzyl (PAB) .

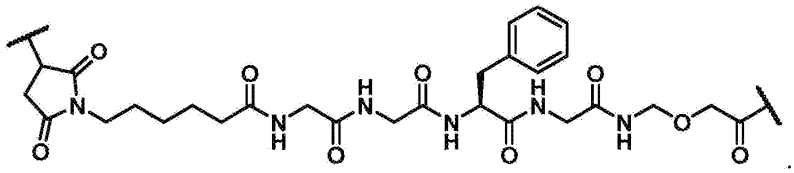
[0698] In some embodiments, the cleavable peptide can be directly spliced to the spacer.

[0699] In some embodiments, the L can comprise: -Val-Cit-PABC-, -Val-Ala-PABC-, -Glu-Val-Cit-PABC-, -Ala-Ala-Asn-PABC-, -Gly-Val-Cit-PABC-, -Gly-Gly-Gly-PABC-, -Gly-Gly-Phe-Gly-PABC-, -Val-Cit-PAB-, -Val-Ala-PAB-, -Glu-Val-Cit-PAB-, -Ala-Ala-Asn-PAB-, -Gly-Val-Cit-PAB-, -Gly-Gly-Gly-PAB-or -Gly-Gly-Phe-Gly-PAB-.

[0700] For example, the L can be selected from the following structure:

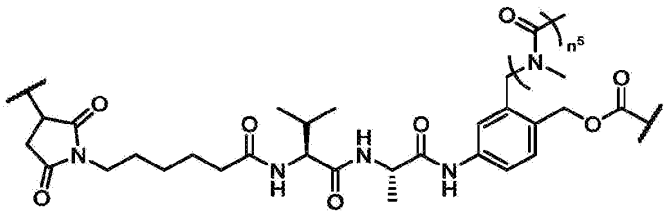


and

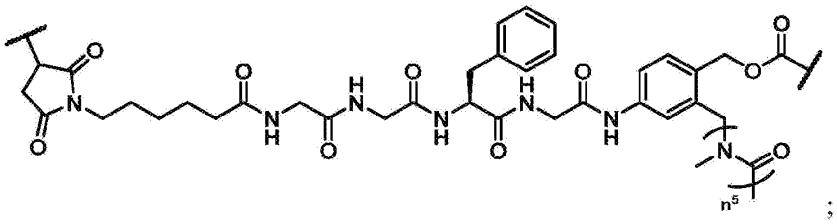


[0701] In some embodiments, the p-aminobenzoxy carbonyl (PABC) or p-aminobenzyl (PAB) comprises a polysarcosine (poly-N-methylglycine) residue.

[0702] In some embodiments, the L is selected from the following structure:



and



;

[0703] wherein n^5 denotes an integer from 0 to 20, optionally the n^5 can denote an in teger from 1 to 15.

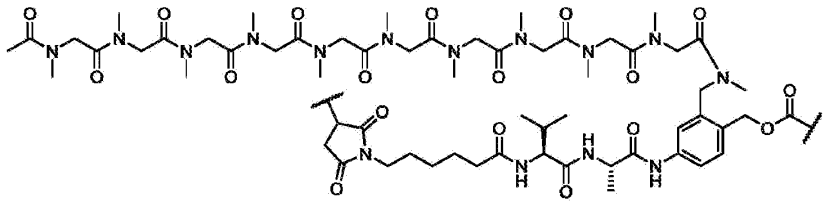
[0704] For example, the n^5 can be 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 , 18, 19 or 20.

[0705] For example, the n^5 can be denote an integer from 1 to 20, 1 to 19, 1 to 18, 1 to 17, 1 to 16, 1 to 15, 1 to 14, 1 to 13, 1 to 12, 1 to 11, 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 20, 2 to 19, 2 to 18, 2 to 17, 2 to 16, 2 to 15, 2 to 14, 2 to 13, 2 to 12, 2 to 11, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6 , 2 to 5, 2 to 4, 2 to 3, 3 to 20, 3 to 19, 3 to 18, 3 to 17, 3 to 16, 3 to 15, 3 to 14, 3 to 13, 3 to 12, 3 to 11, 3 to 10, 3 to 9, 3 to 8, 3 to 7, 3 to 6, 3 to 5, 3 to 4, 4 to 20, 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 4 to 7, 4 to 6, 4 to 5, 5 to 20, 5 to 19, 5 to 18, 5 to 17, 5 to 16, 5 to 15, 5 to 14, 5 to 13, 5 to 12, 5 to 11, 5 to 10, 5 to 9, 5 to 8 , 5 to 7, 5 to 6, 6 to 20, 6 to 19, 6 to 18, 6 to 17, 6 to 16, 6 to 15, 6 to 14, 6 to 13, 6 to 12, 6 to 11, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 20, 7 to 19, 7 to 18, 7 to 17, 7 to 16, 7 to 15, 7 to 14, 7 to 13, 7 to 12, 7 to 11, 7 to 10, 7 to 9, 7 to 8, 8 to 20, 8 to 19, 8 to 18, 8 to 17, 8 to 16, 8 to 15, 8 to 14, 8 to 13, 8 to 12, 8 t o 11, 8 to 10, 8 to 9, 9 to 20, 9 to 19, 9 to 18, 9 to 17, 9 to 16, 9 to 15, 9 to 14,

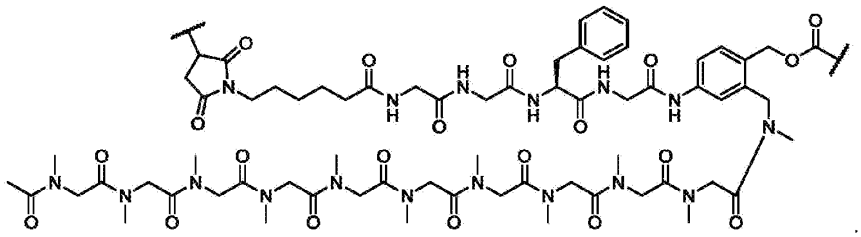
9 to 13, 9 to 12, 9 to 11, 9 to 10, 10 to 20, 10 to 19, 10 to 18, 10 to 17, 10 to 16 , 10 to 15, 10 to 14, 10 to 13, 10 to 12 or 10 to 11.

[0706] For example, the n^5 can be denote an integer from 1 to 7. For example, the n^5 can be denote an integer from 8 to 15.

[0707] For example, the L can be selected from the following structure:



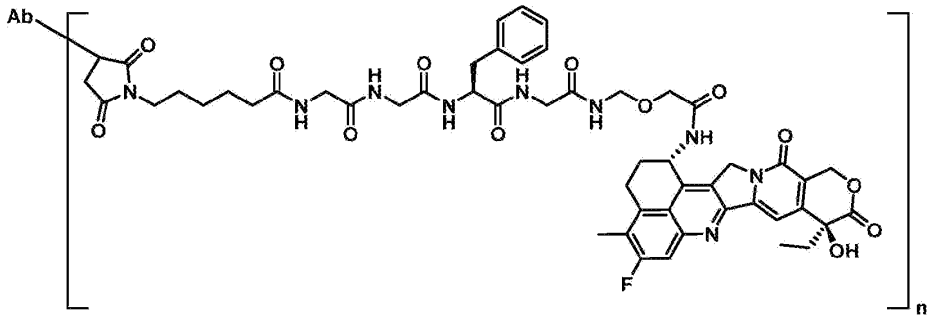
and

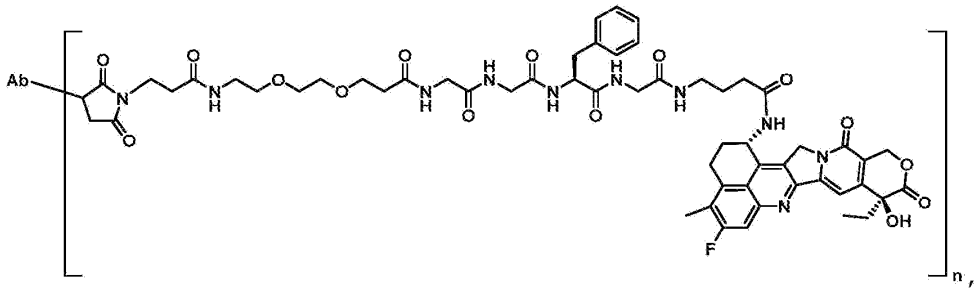


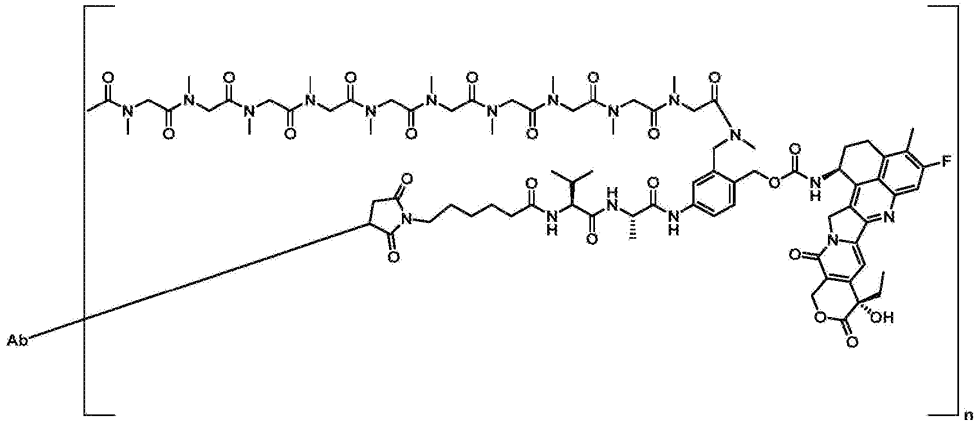
.

[0708] The antibody drug conjugate can be produced by reacting the compound obtainable by a known method (e.g., obtainable by a method described in the patent p ublication literature US2016/297890 (e.g., obtainable by a method described in the pa ragraphs [0336] to [0374])) , with the antibody having a sulfhydryl group. The anti body having a sulfhydryl group can be obtained by a method well know n to a person skilled in the art (Hermanson, G. T, Bioconjugate Techniques, pp. 56-136, pp. 456-493, Academic Press (1996)) .

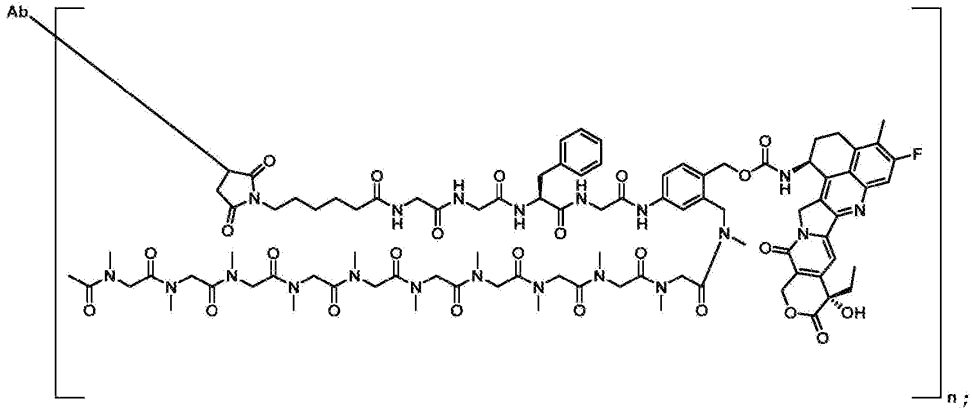
[0709] One specific example of the antibody-drug conjugate of the present inve ntion can include an antibody-drug conjugate having a structure represented by th e following formula:







and



[0710] wherein n can be any number from 1 to 10. For example, the n can be any number from 1 to 9.5, 1 to 9, 1 to 8.5, 1 to 8, 1 to 7.5, 1 to 7, 1 to 6.5, 1 to 6, 1 to 5.5, 1 to 5, 1 to 4.5, 1 to 4, 1 to 3.5, 1 to 3, 1 to 2.5, 1 to 2, 1 to 1.5, 1.5 to 9.5, 1.5 to 9, 1.5 to 8.5, 1.5 to 8, 1.5 to 7.5, 1.5 to 7, 1.5 to 6.5, 1.5 to 6, 1.5 to 5.5, 1.5 to 5, 1.5 to 4.5, 1.5 to 4, 1.5 to 3.5, 1.5 to 3, 1.5 to 2.5, 1.5 to 2, 2 to 9.5, 2 to 9, 2 to 8.5, 2 to 8, 2 to 7.5, 2 to 7, 2 to 6.5, 2 to 6, 2 to 5.5, 2 to 5, 2 to 4.5, 2 to 4, 2 to 3.5, 2 to 3, 2 to 2.5, 2.5 to 9.5, 2.5 to 9, 2.5 to 8.5, 2.5 to 8, 2.5 to 7.5, 2.5 to 7, 2.5 to 6.5, 2.5 to 6, 2.5 to 5.5, 2.5 to 5, 2.5 to 4.5, 2.5 to 4, 2.5 to 3.5, 2.5 to 3, 3 to 9.5, 3 to 9, 3 to 8.5, 3 to 8, 3 to 7.5, 3 to 7, 3 to 6.5, 3 to 6, 3 to 5.5, 3 to 5, 3 to 4.5, 3 to 4, 3 to 3.5, 3.5 to 9.5, 3.5 to 9, 3.5 to 8.5, 3.5 to 8, 3.5 to 7.5, 3.5 to 7, 3.5 to 6.5, 3.5 to 6, 3.5 to 5.5, 3.5 to 5, 3.5 to 4.5, 3.5 to 4, 4 to 9.5, 4 to 9, 4 to 8.5, 4 to 8, 4 to 7.5, 4 to 7, 4 to 6.5, 4 to 6, 4 to 5.5, 4 to 5, 4 to 4.5, 4.5 to 9.5, 4.5 to 9, 4.5 to 8.5, 4.5 to 8, 4.5 to 7.5, 4.5 to 7, 4.5 to 6.5, 4.5 to 6, 4.5 to 5.5, 4.5 to 5, 5 to 9.5, 5 to 9, 5 to 8.5, 5 to 8, 5 to 7.5, 5 to 7, 5 to 6.5, 5 to 6, 5 to 5.5, 5.5 to 9.5, 5.5 to 9, 5.5 to 8.5, 5.5 to 8, 5.5 to 7.5, 5.5 to 7, 5.5 to 6.5, 5.5 to 6, 6 to 9.5, 6 to 9, 6 to 8.5, 6 to 8, 6 to 7.5, 6 to 7, 6 to 6.5, 6.5 to 9.5, 6.5 to 9, 6.5 to 8.5, 6.5 to 8, 6.5 to 7.5, 6.5 to 7, 7 to 9.5, 7 to 9, 7 to 8.5, 7 to 8, 7 to 7.5, 7.5 to 9.5, 7.5 to 9, 7.5 to 8.5, 7.5 to 8, 8 to 9.5, 8 to 9, 8 to 8.5, 8.5 to 9.5, or 8.5 to 9.

[0711] In this context, Ab represents the anti-CDH17 antibody disclosed in the present description, and the antibody is conjugated to the linker-payload via a sulfhydryl group stemming from the antibody. In this context, n has the same meaning as that of the so-called DAR (drug-to-antibody Ratio) , and represents a drug-to-antibody ratio per antibody. Specifically, n represents the number of conjugated drug molecules per antibody molecule, which is a numeric value defined and indicated as an average value, i.e., the average number of conjugated drug molecules. In the present invention, n can be 2 to 8 and is preferably 5 to 8, more preferably 7 to 8, and still more preferably 8, in measurement by common procedure F.

[0712] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody or an antigen binding fragment thereof binding specifically to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166.

[0713] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody having competitive binding activity with the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 against a

n anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and a light chain variable region having an amino acid seq uence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to eac h thereof.

[0714] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, h aving a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moi ety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody having competitive binding activity with the polypeptide having an amino acid sequen ce shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody selected from a group consisting of:

[0715] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 2;

[0716] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 4;

[0717] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence ha ving at least 80%sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;

[0718] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 29 or an amino a cid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[0719] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[0720] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[0721] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0722] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0723] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0724] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

[0725] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;

[0726] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

[0727] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 170, and a light chain variabl

e region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[0728] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[0729] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody having competitive binding activity with the polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody selected from a group consisting of:

[0730] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 8;

[0731] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 10;

[0732] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 11, and a light chain having an amino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 12;

[0733] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 30;

[0734] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 22, and a light chain having an amino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 32;

[0735] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 24, and a light chain having an amino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 34;

[0736] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0737] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0738] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 28, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0739] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 38 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 44;

[0740] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 46;

[0741] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 48;

[0742] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an

amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 173; and

[0743] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 177.

[0744] In any of the anti-CDH17 antibody-drug conjugate described herein, t he heavy chain or the light chain may comprise one or two or more modifications selec ted from the group consisting of posttranslational modifications typified by N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methio nine, addition of a methionine residue to the N-terminus, amidation of a proline r esidue, and conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids at the carboxyl terminus.

[0745] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, h aving a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moi ety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an anti-CDH17 antibody comprising a heavy chain variable region comprising H CDR1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 of a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 which are same as the LCDR1, LCDR2, and LCDR3 of a light chain varia ble region having an amino acid sequence selected from a group consi sting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176.

[0746] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moi ety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an anti-CDH17 antibody comprising a heavy chain variable region comprising H CDR1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 of a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 which are same as the LCDR1, LCDR2, and LCDR3 of a light chain varia ble region having an amino acid sequence selected from a group consi sting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176; wherein the HC

DR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined according to any one of CDR definition schemes selected from a group consisting o f IMGT, Kabat, Contact, Chothia, Martin, PyIgClassify, and any combi nation thereof; preferably, the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, a nd LCDR3 are defined according to any one of CDR definition schemes selected from a group consisting of IMGT, Kabat, Contact, Chothia, a nd any combination thereof.

[0747] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, h aving a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moi ety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody comprising a heavy chain variable region comprising HCDR1, HCDR2, a nd HCDR3 having amino acid sequences selected from a group consisting of:

[0748] SEQ ID NO: 49, 50, and 51, respectively;

[0749] SEQ ID NO: 68, 69, and 70, respectively;

[0750] SEQ ID NO: 87, 88, and 89, respectively;

[0751] SEQ ID NO: 109, 50, and 51, respectively;

[0752] SEQ ID NO: 49, 50, and 113, respectively;

[0753] SEQ ID NO: 49, 50, and 116, respectively;

[0754] SEQ ID NO: 178, 179, and 180, respectively; and

[0755] SEQ ID NO: 191, 192, and 193, respectively

[0756] according to IMGT definition scheme; or a group consisting of:

[0757] SEQ ID NO: 55, 56, and 57, respectively;

[0758] SEQ ID NO: 74, 75, and 76, respectively;

[0759] SEQ ID NO: 93, 94, and 95, respectively;

[0760] SEQ ID NO: 55, 106, and 57, respectively;

[0761] SEQ ID NO: 110, 111, and 57, respectively;

[0762] SEQ ID NO: 55, 106, and 114, respectively;

[0763] SEQ ID NO: 55, 106, and 117, respectively;

[0764] SEQ ID NO: 182, 183, and 184, respectively; and

[0765] SEQ ID NO: 197, 198, and 199, respectively;

[0766] according to Kabat definition scheme; or a group consisting of:

[0767] SEQ ID NO: 60, 61, and 57, respectively;

[0768] SEQ ID NO: 79, 80, and 76, respectively;

[0769] SEQ ID NO: 98, 99, and 95, respectively;

[0770] SEQ ID NO: 60, 61, and 114, respectively;

[0771] SEQ ID NO: 60, 61, and 117, respectively;

[0772] SEQ ID NO: 185, 186, and 184, respectively; and

[0773] SEQ ID NO: 202, 203, and 199, respectively;

[0774] according to Chothia definition scheme; or a group consisting of:

[0775] SEQ ID NO: 62, 63, and 64, respectively;

[0776] SEQ ID NO: 81, 82, and 83, respectively;

[0777] SEQ ID NO: 100, 101, and 102, respectively;

[0778] SEQ ID NO: 62, 107, and 64, respectively;

[0779] SEQ ID NO: 62, 108, and 57, respectively;

[0780] SEQ ID NO: 112, 108, and 64, respectively;

[0781] SEQ ID NO: 62, 107, and 115, respectively;

[0782] SEQ ID NO: 62, 107, and 118, respectively;

[0783] SEQ ID NO: 81, 123, and 83, respectively;

[0784] SEQ ID NO: 187, 188, and 189, respectively; and

[0785] SEQ ID NO: 204, 205, and 206, respectively;

[0786] according to Contact definition scheme;

[0787] and/or a light chain variable region comprising LCDR1, LCDR2, and LC DR3 having amino acid sequences selected from a group consisting of:

[0788] SEQ ID NO: 52, 53, and 54, respectively;

[0789] SEQ ID NO: 71, 72, and 73, respectively;

[0790] SEQ ID NO: 90, 91, and 92, respectively;

[0791] SEQ ID NO: 52, 53, and 181, respectively; and

[0792] SEQ ID NO: 194, 195, and 196, respectively

[0793] according to IMGT definition scheme; or a group consisting of:

[0794] SEQ ID NO: 58, 59, and 54, respectively;

[0795] SEQ ID NO: 77, 78, and 73, respectively;

[0796] SEQ ID NO: 96, 97, and 92, respectively;

[0797] SEQ ID NO: 58, 120, and 54, respectively;

[0798] SEQ ID NO: 58, 59, and 181, respectively; and

[0799] SEQ ID NO: 200, 201, and 196, respectively;

[0800] according to Kabat definition scheme; or a group consisting of:

[0801] SEQ ID NO: 65, 66, and 67, respectively;

[0802] SEQ ID NO: 84, 85, and 86, respectively;

[0803] SEQ ID NO: 103, 104, and 105, respectively;

[0804] SEQ ID NO: 65, 119, and 67, respectively;

[0805] SEQ ID NO: 65, 121, and 67, respectively;

[0806] SEQ ID NO: 65, 122, and 67, respectively;

[0807] SEQ ID NO: 65, 66, and 190, respectively; and

[0808] SEQ ID NO: 207, 208, and 209, respectively;

[0809] according to Contact definition scheme.

[0810] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody comprising a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0811] SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;

[0812] SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;

[0813] SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;

[0814] SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;

[0815] SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;

[0816] SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;

[0817] SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and

[0818] SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;

[0819] according to IMGT definition scheme; or a group consisting of:

[0820] SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;

[0821] SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;

[0822] SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;

[0823] SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;

[0824] SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;

[0825] SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;

[0826] SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;

[0827] SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;

[0828] SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and

[0829] SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;

[0830] according to Kabat definition scheme; or a group consisting of:

[0831] SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;

[0832] SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;

[0833] SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;

[0834] SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively

[0835] SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;

[0836] SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;

[0837] SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and

[0838] SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;

[0839] according to Chothia definition scheme; or a group consisting of:

[0840] SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;

[0841] SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;

[0842] SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;

[0843] SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;

[0844] SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;

[0845] SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;

[0846] SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;

[0847] SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;

[0848] SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;

[0849] SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;

[0850] SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and

[0851] SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;

[0852] according to Contact definition scheme.

[0853] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein Ab is an antibody comprising a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected from a group consisting of:

[0854] SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;

[0855] SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;

[0856] SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;

[0857] SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;

[0858] SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;

[0859] SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;

[0860] SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and

[0861] SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;

[0862] according to IMGT definition scheme; or a group consisting of:

[0863] SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;

[0864] SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;

[0865] SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;

[0866] SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;

[0867] SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;

[0868] SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;

[0869] SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;

[0870] SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;

[0871] SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and

[0872] SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;

[0873] according to Kabat definition scheme; or a group consisting of:

[0874] SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;

[0875] SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;

[0876] SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;

[0877] SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively

[0878] SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;

[0879] SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;

[0880] SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and

[0881] SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;

[0882] according to Chothia definition scheme; or a group consisting of:

[0883] SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;

[0884] SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;

[0885] SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;

[0886] SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;

[0887] SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;

[0888] SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;

[0889] SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;

[0890] SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;

[0891] SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;

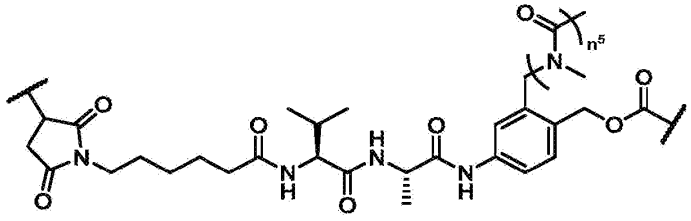
[0892] SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;

[0893] SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and

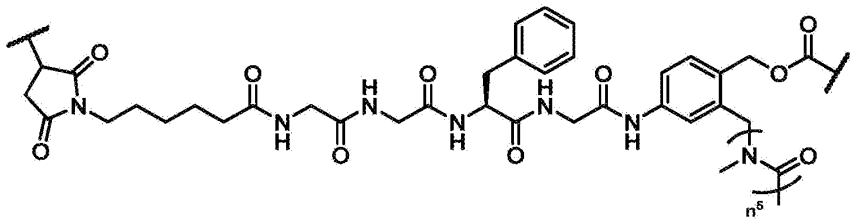
[0894] SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;

[0895] according to Contact definition scheme;

[0896] L is a linker comprising -Val-Cit-PABC-, -Val-Ala-PABC-, -Glu-Val-Cit-PABC-, -Ala-Ala-Asn-PABC-, -Gly-Val-Cit-PABC-, -Gly-Gly-Gly-PABC-, -Gly-Gly-Phe-Gly-PABC-, -Val-Cit-PAB-, -Val-Ala-PAB-, -Glu-Val-Cit-PAB-, -Ala-Ala-Asn-PAB-, -Gly-Val-Cit-PAB-, -Gly-Gly-Gly-PAB-or -Gly-Gly-Phe-Gly-PAB-; preferably, L is selected from the following structures:

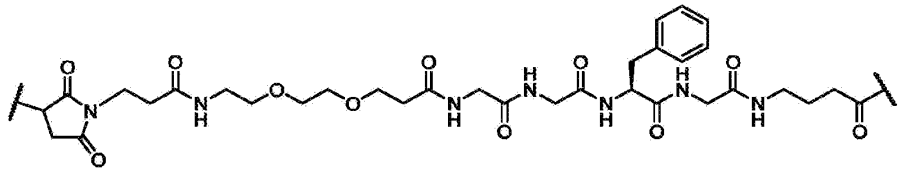


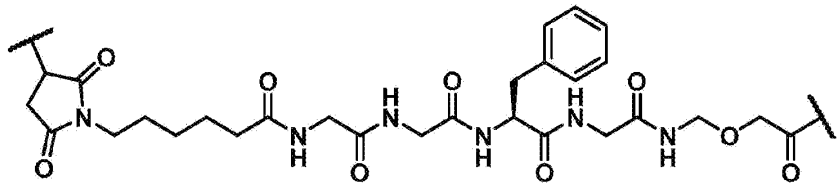
and

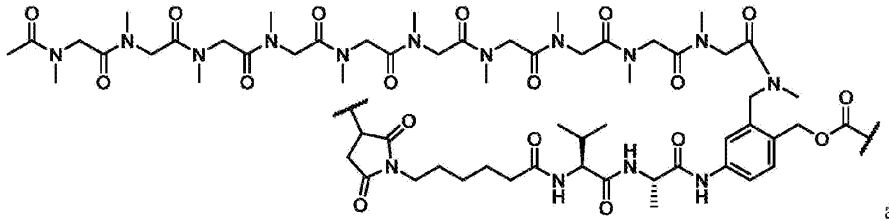


;

[0897] wherein n^5 denotes an integer from 0 to 20, preferably 1 to 15; and even more preferably, L is selected from the following structures:

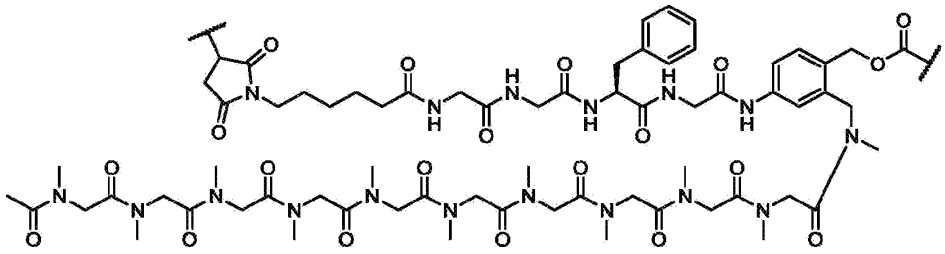
[0898] ,

,



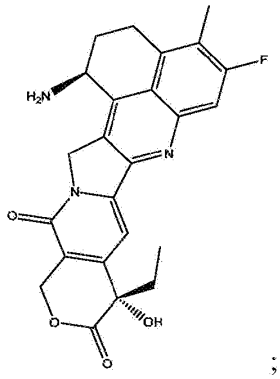
and

in each structur

;

, the wavy line to the left represents linkage site to the Ab moiety, and the wavy li ne to the right represents linkage site to the D moiety;

[0899] D is the drug moiety, wherein the drug moiety is a cytotoxic agent which is preferabl y a microtubule disrupting drug such as a tubulin inhibitor, or a DNA damaging agent such as a topoisomerase inhibitor including a topoisomerase I inhibitor such as campt othecin or a derivative thereof; preferably, the cytotoxic agent has a structure of



;

[0900] m is an integer from 1 to 8; and

[0901] n is any number from 1 to 10.

[0902] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody comprising a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and/or a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to each thereof.

[0903] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody selected from a group consisting of:

[0904] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 2;

[0905] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 4;

[0906] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 5, and a light chain variable region

having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;

[0907] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[0908] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[0909] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[0910] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0911] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0912] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0913] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

[0914] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;

[0915] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47

[0916] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[0917] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[0918] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody comprising a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and/or a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to each thereof.

[0919] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein Ab is an antibody selected from a group consisting of:

[0920] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 2;

[0921] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 4;

[0922] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80% sequence identity to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 6;

[0923] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 29 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[0924] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[0925] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[0926] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0927] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0928] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable regi

on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[0929] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

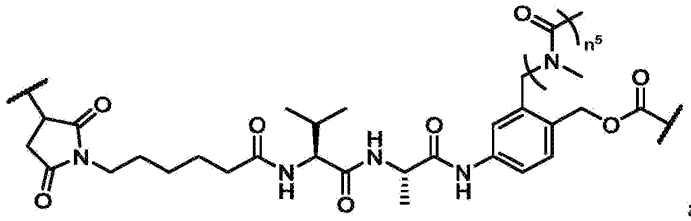
[0930] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45; and

[0931] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

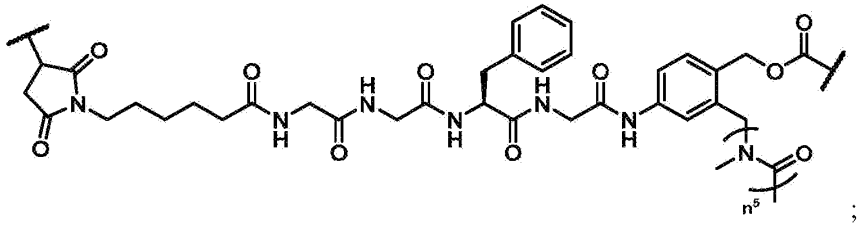
[0932] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[0933] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176;

[0934] L is a linker comprising -Val-Cit-PABC-, -Val-Ala-PABC-, -Glu-Val-Cit-PABC-, -Ala-Ala-Asn-PABC-, -Gly-Val-Cit-PABC-, -Gly-Gly-Gly-PABC-, -Gly-Gly-Phe-Gly-PABC-, -Val-Cit-PAB-, -Val-Ala-PAB-, -Glu-Val-Cit-PAB-, -Ala-Ala-Asn-PAB-, -Gly-Val-Cit-PAB-, -Gly-Gly-Gly-PAB-or -Gly-Gly-Phe-Gly-PAB-; preferably, L is selected from the following structures:



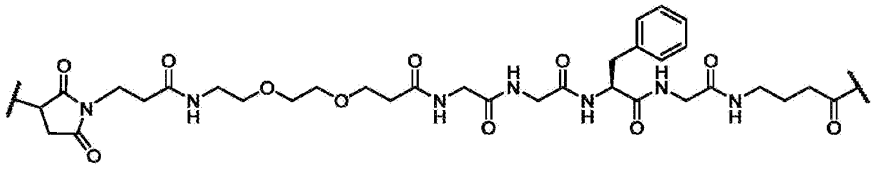
and



;

[0935] wherein n^5 denotes an integer from 0 to 20, preferably 1 to 15; and even more preferably, L is selected from the following structures:

[0936]



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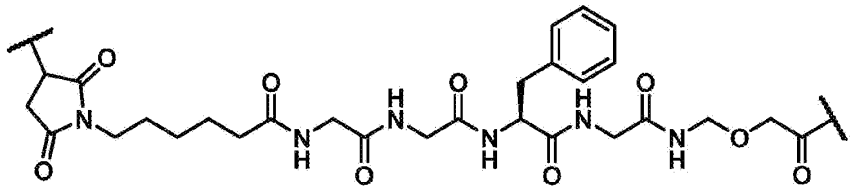

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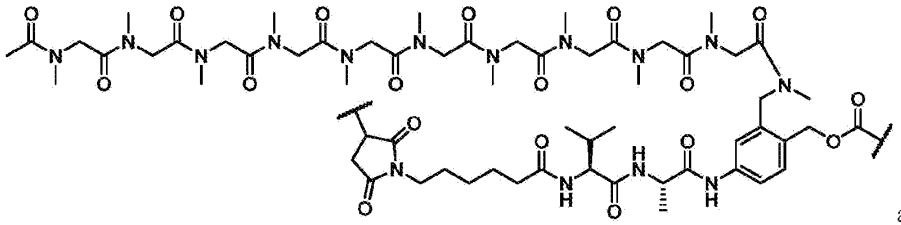
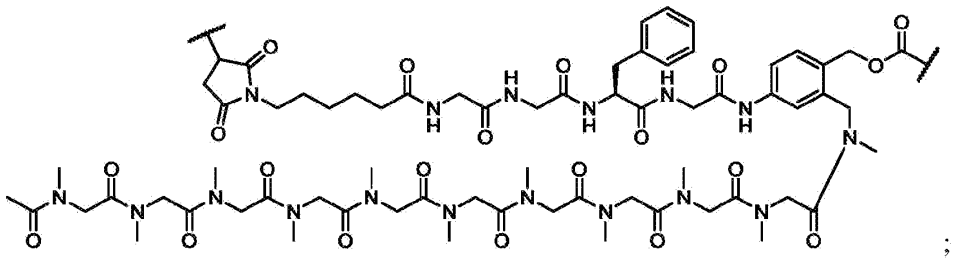


and

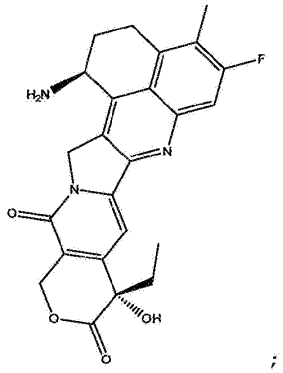
in each structur



;

, the wavy line to the left represents linkage site to the Ab moiety, and the wavy li ne to the right represents linkage site to the D moiety;

[0937] D is the drug moiety, wherein the drug moiety is a cytotoxic agent which is preferably a microtubule disrupting drug such as a tubulin inhibitor, or a DNA damaging agent such as a topoisomerase inhibitor including a topoisomerase I inhibitor such as camptothecin or a derivative thereof; preferably, the cytotoxic agent has a structure of



;

[0938] m is an integer from 1 to 8; and

[0939] n is any number from 1 to 10.

[0940] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody comprising a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof; and/or a light chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[0941] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, having a formula of Ab- (L- (D) m) n, wherein L is a linker; D is the drug moiety; m is an integer from 1 to 8; n is any number from 1 to 10; and Ab is an antibody selected from a group consisting of:

[0942] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 8;

[0943] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 10;

[0944] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 11, and a light chain having an amino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 12;

[0945] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 30;

[0946] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 22, and a light chain having an amino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 32;

[0947] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 24, and a light chain having an amino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 34;

[0948] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0949] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

[0950] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 28, and a light chain having an am

ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0951] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 38 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 38, and a light chain having an am ino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 44;

[0952] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 40 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 40, and a light chain having an am ino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 46;

[0953] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 42 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 42, and a light chain having an am ino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 48;

[0954] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 173; and

[0955] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequenc e having at least 80%sequence identity to SEQ ID NO: 177.

[0956] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate, h aving a formula of Ab- (L- (D) m) n, wherein Ab is an antibody selected from a group consisting of:

[0957] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 7 or an amino acid sequence having at least 80 %sequence identity to SEQ ID NO: 7, and a light chain having an amin o acid sequence shown in SEQ ID NO: 8 or an amino acid sequence havi ng at least 80%sequence identity to SEQ ID NO: 8;

[0958] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 9 or an amino acid sequence having at least 80 %sequence identity to SEQ ID NO: 9, and a light chain having an amin

o acid sequence shown in SEQ ID NO: 10 or an amino acid sequence hav ing at least 80%sequence identity to SEQ ID NO: 10;

[0959] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 11 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 11, and a light chain having an am ino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 12;

[0960] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 20 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 20, and a light chain having an am ino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 30;

[0961] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 22 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 22, and a light chain having an am ino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence havin g at least 80%sequence identity to SEQ ID NO: 32;

[0962] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 24 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 24, and a light chain having an am ino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 34;

[0963] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 20 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 20, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0964] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 26 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 26, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0965] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 28 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 28, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[0966] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 38 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 44;

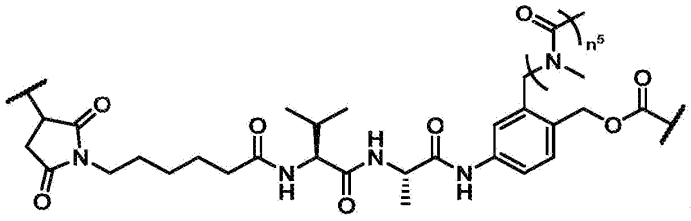
[0967] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 46;

[0968] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 48;

[0969] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 173; and

[0970] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 177;

[0971] L is a linker comprising -Val-Cit-PABC-, -Val-Ala-PABC-, -Glu-Val-Cit-PABC-, -Ala-Ala-Asn-PABC-, -Gly-Val-Cit-PABC-, -Gly-Gly-Gly-PABC-, -Gly-Gly-Phe-Gly-PABC-, -Val-Cit-PAB-, -Val-Ala-PAB-, -Glu-Val-Cit-PAB-, -Ala-Ala-Asn-PAB-, -Gly-Val-Cit-PAB-, -Gly-Gly-Gly-PAB-or -Gly-Gly-Phe-Gly-PAB-; preferably, L is selected from the following structures:



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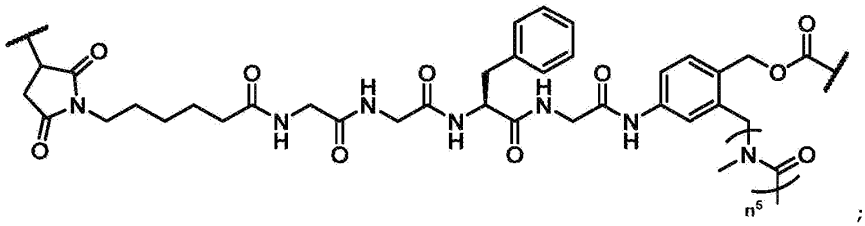
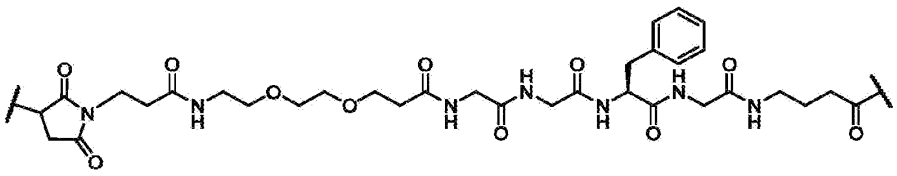


;

[0972] wherein n^5 denotes an integer from 0 to 20, preferably 1 to 15; and even more preferably, L is selected from the following structures:

[0973]



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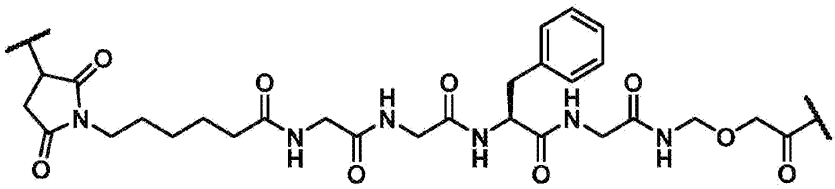

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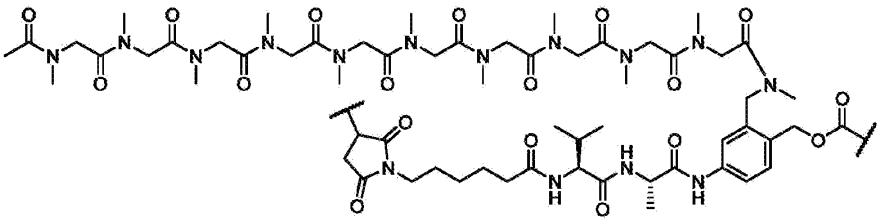
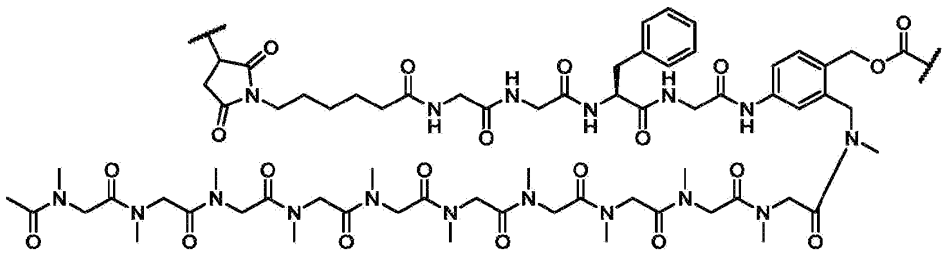


and

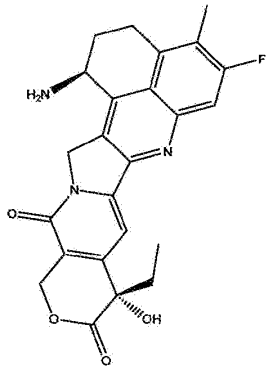


in each structur

;

, the wavy line to the left represents linkage site to the Ab moiety, and the wavy line to the right represents linkage site to the D moiety;

[0974] D is the drug moiety, wherein the drug moiety is a cytotoxic agent which is preferably a microtubule disrupting drug such as a tubulin inhibitor, or a DNA damaging agent such as a topoisomerase inhibitor including a topoisomerase I inhibitor such as camptothecin or a derivative thereof; preferably, the cytotoxic agent has a structure of

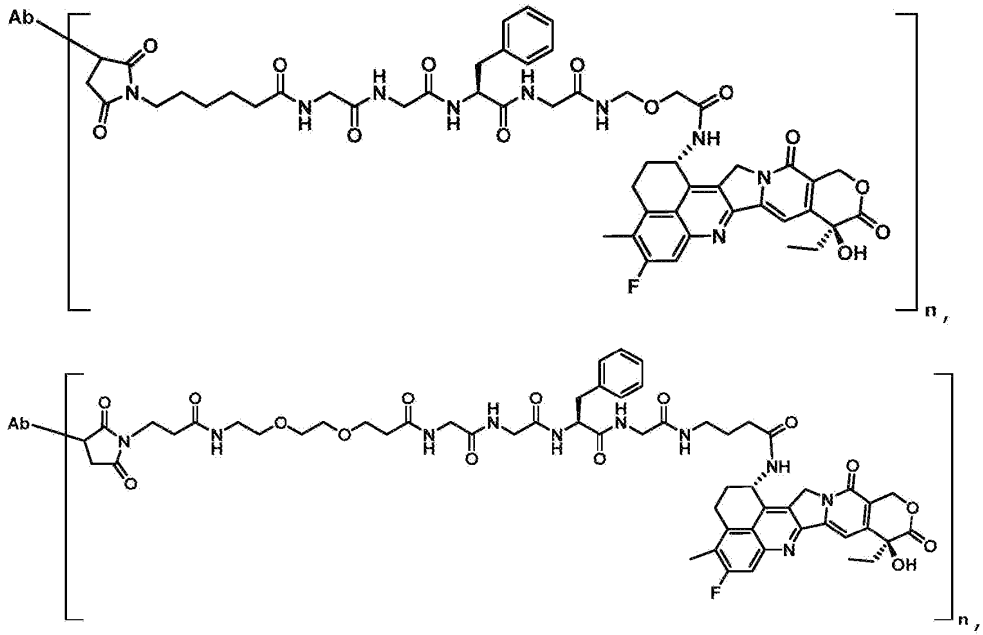


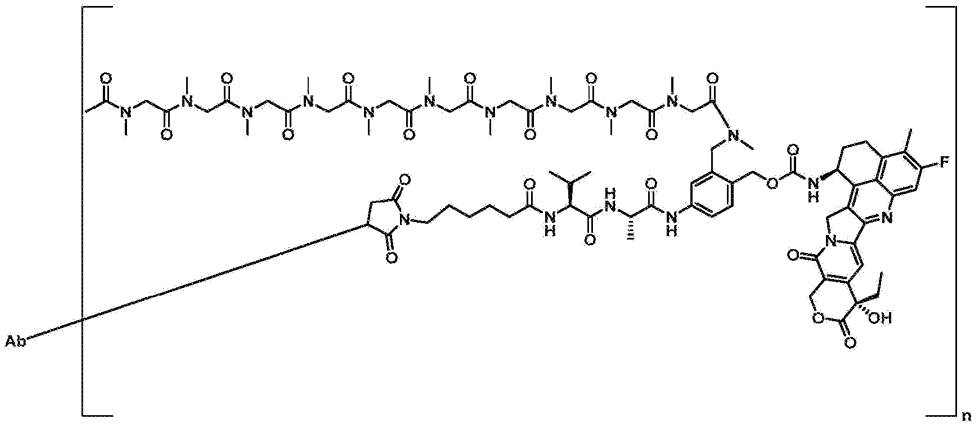
;

[0975] m is an integer from 1 to 8; and

[0976] n is any number from 1 to 10.

[0977] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate having a structure represented by the following formula:





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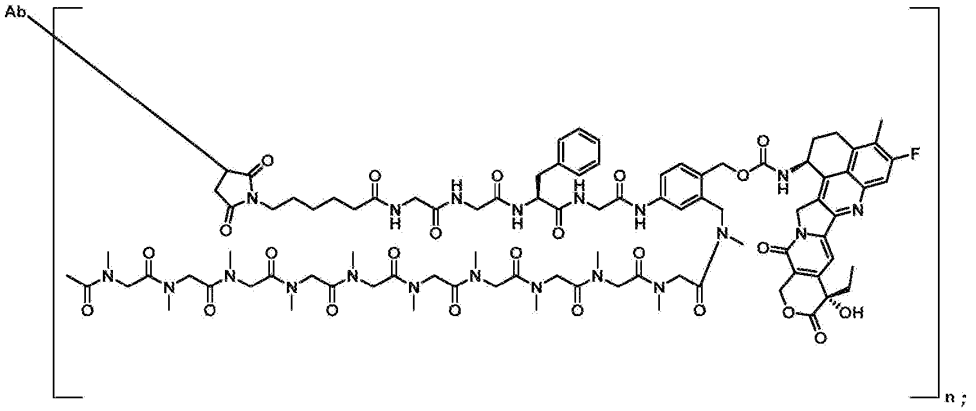
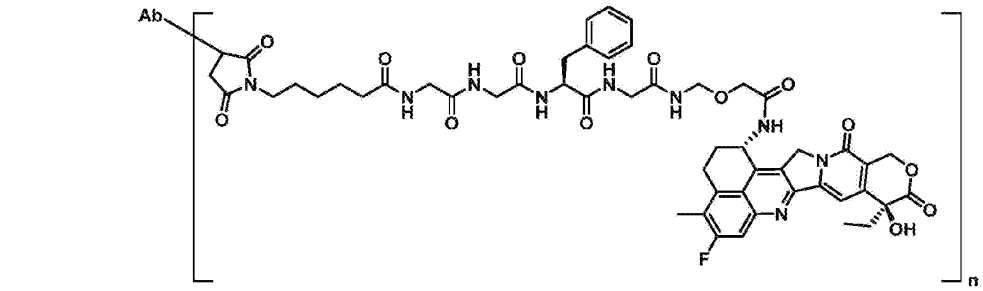


[0978] wherein n can be any number from 1 to 10; and

[0979] wherein Ab is an anti-CDH17 antibody comprising a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 of a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 which are same as the LCDR1, LCDR2, and LCDR3 of a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176; preferably, the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 are defined according to any one of CDR definition schemes selected from a group consisting of IMGT, Kabat, Contact, Chothia, Martin, PyIgClassify, and any combination thereof.

[0980] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate having a structure represented by the following formula:



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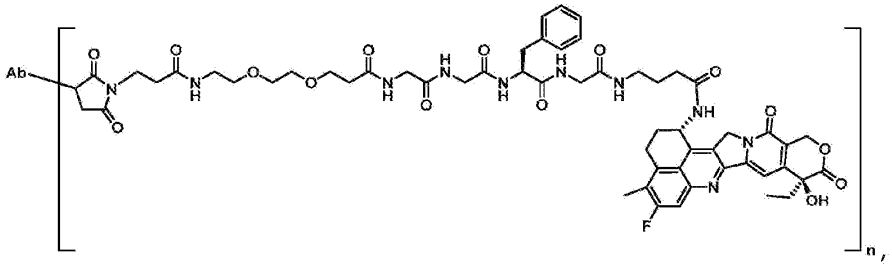

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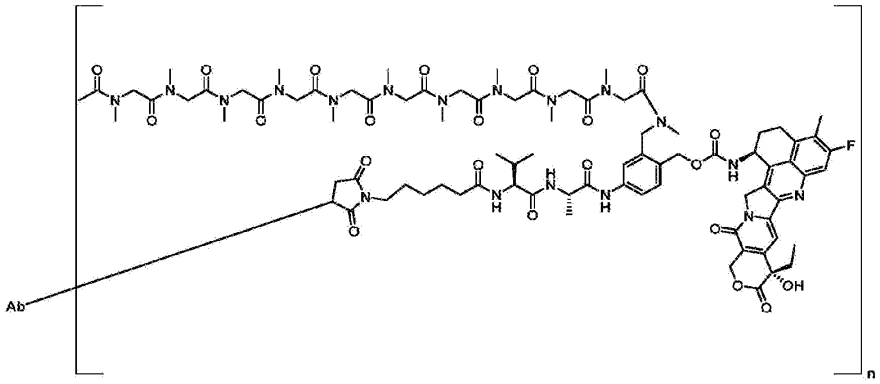

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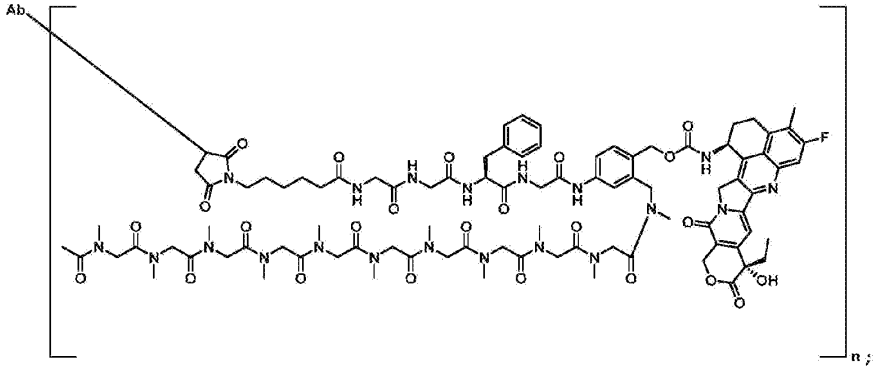


;

[0981] wherein n can be any number from 1 to 10; and

[0982] wherein Ab is an anti-CDH17 antibody comprising a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 and a light chain variable r

egion comprising LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 have amino acid sequences selected fr om a group consisting of:

[0983] SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;

[0984] SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;

[0985] SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;

[0986] SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;

[0987] SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;

[0988] SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;

[0989] SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and

[0990] SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;

[0991] according to IMGT definition scheme; or a group consisting of:

[0992] SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;

[0993] SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;

[0994] SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;

[0995] SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;

[0996] SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;

[0997] SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;

[0998] SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;

[0999] SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;

[1000] SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and

[1001] SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;

[1002] according to Kabat definition scheme; or a group consisting of:

[1003] SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;

[1004] SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;

[1005] SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;

[1006] SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively

[1007] SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;

[1008] SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;

[1009] SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and

[1010] SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;

[1011] according to Chothia definition scheme; or a group consisting of:

[1012] SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;

[1013] SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;

[1014] SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;

[1015] SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;

[1016] SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;

[1017] SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;

[1018] SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;

[1019] SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;

[1020] SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;

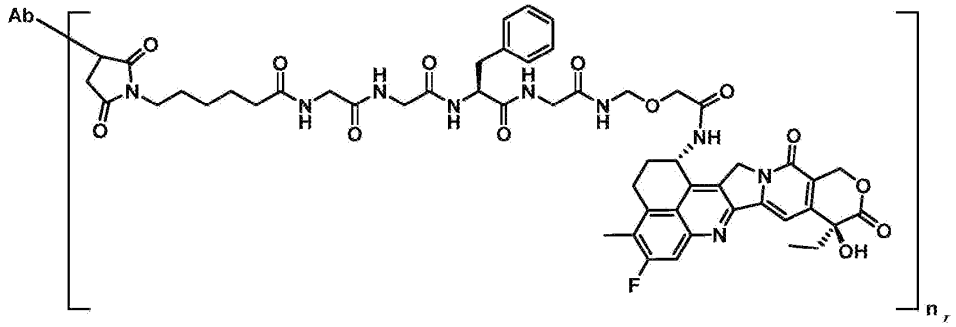
[1021] SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;

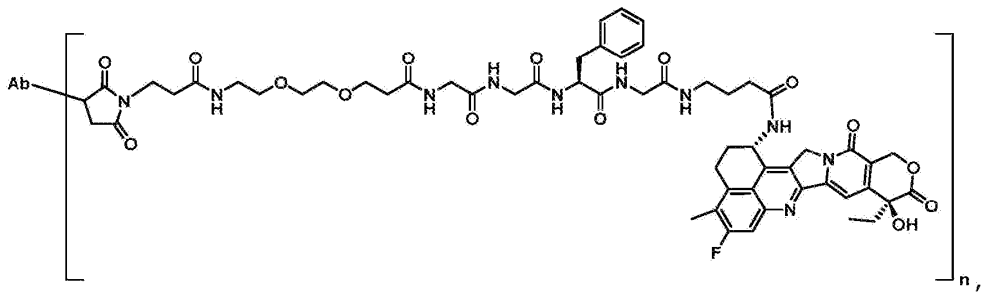
[1022] SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and

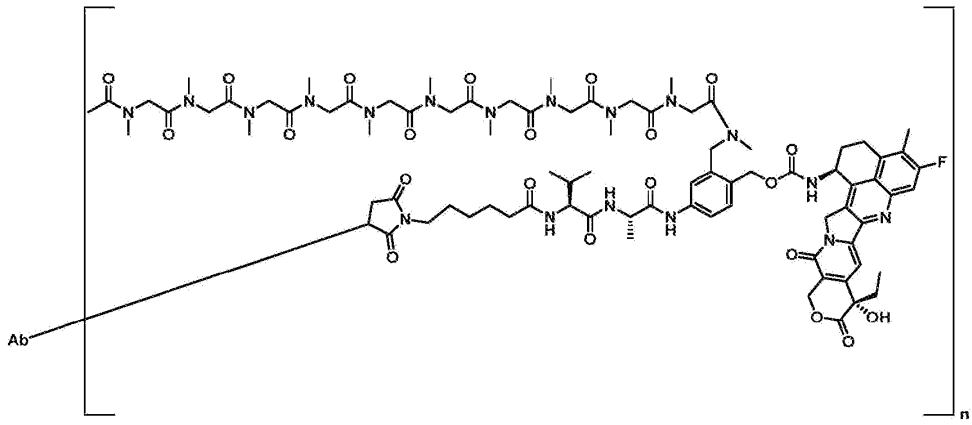
[1023] SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;

[1024] according to Contact definition scheme.

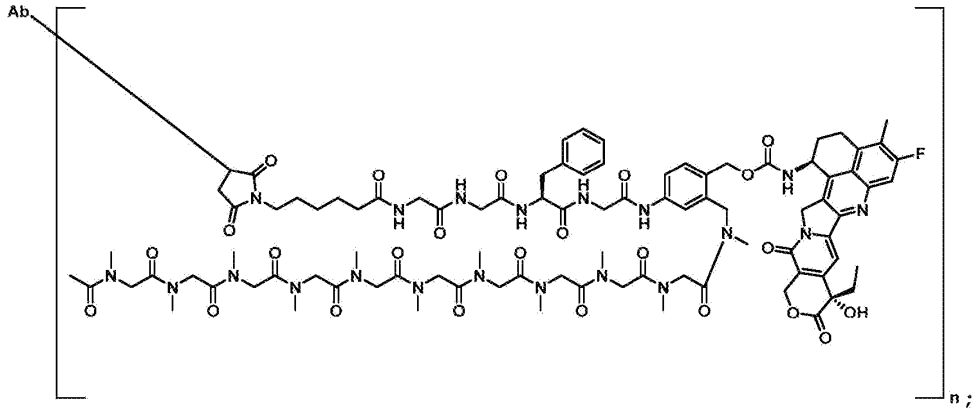
[1025] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate having a structure represented by the following formula:







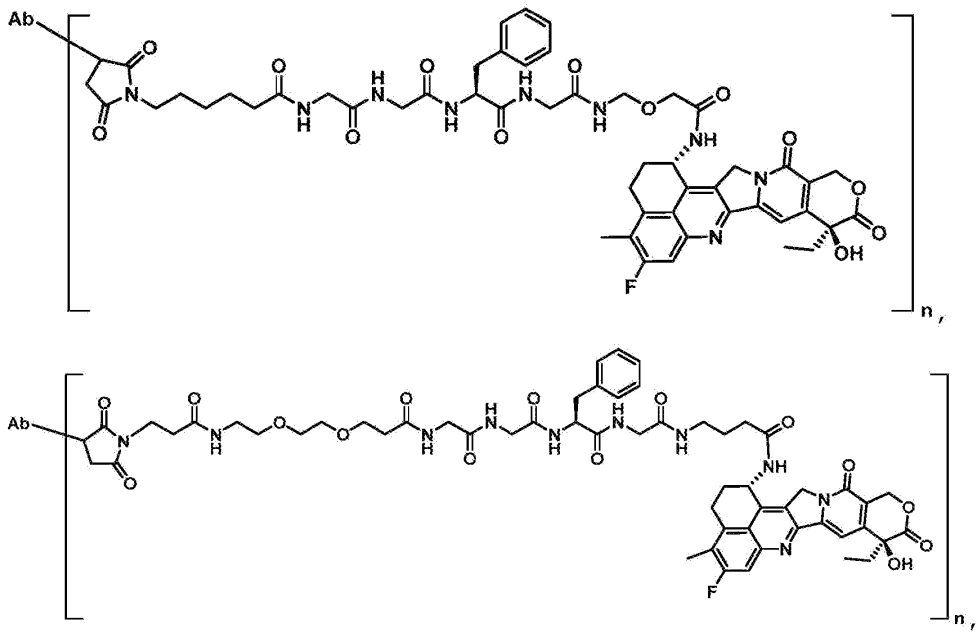
and

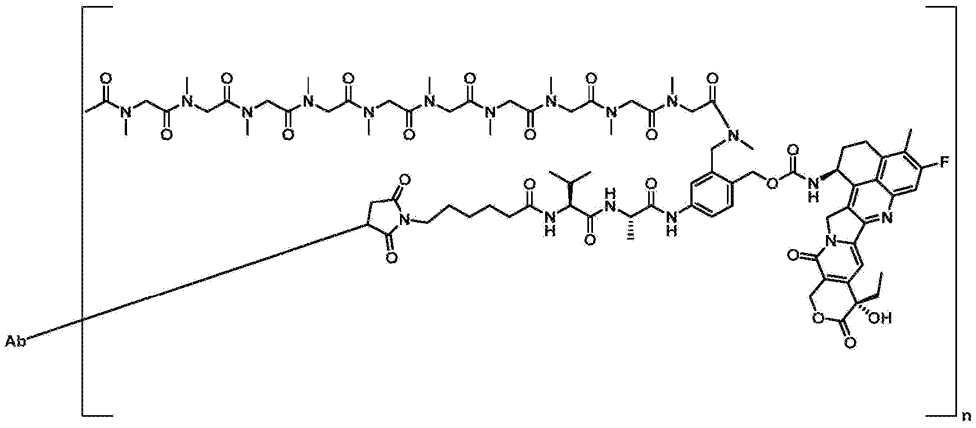


[1026] wherein n can be any number from 1 to 10; and

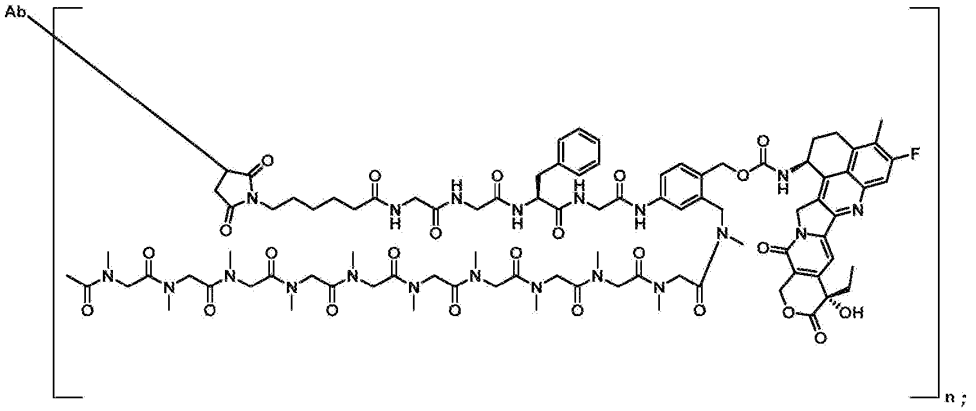
[1027] wherein Ab is an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and/or a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to each thereof.

[1028] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate having a structure represented by the following formula:





and



[1029] wherein n can be any number from 1 to 10; and

[1030] wherein Ab is an antibody selected from a group consisting of:

[1031] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 2;

[1032] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 4;

[1033] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 5, and a light chain variable region

having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;

[1034] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80% sequence identity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 29 or an a mino acid sequence having at least 80%sequence identity to SEQ ID NO: 29;

[1035] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 21, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;

[1036] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 23, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;

[1037] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 19, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[1038] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[1039] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

[1040] an anti-CDH17 antibody comprising a heavy chain variable region having an am ino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable regi on having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

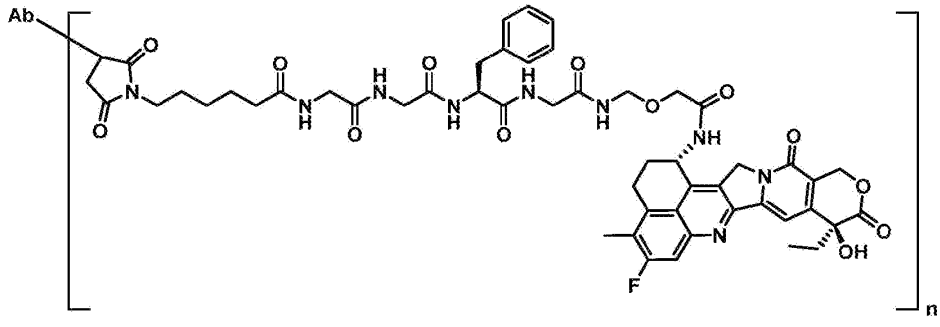
[1041] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;

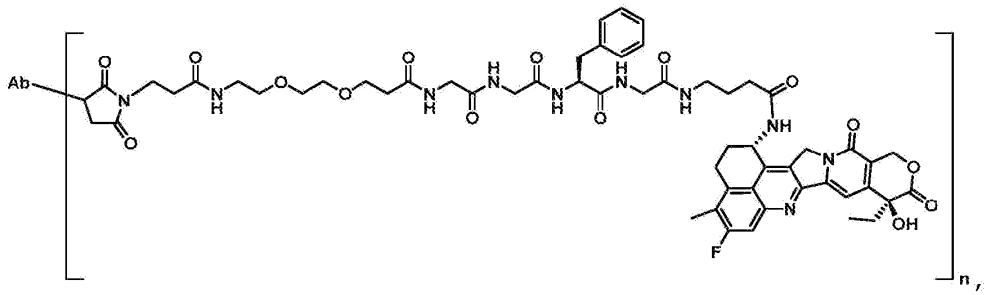
[1042] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

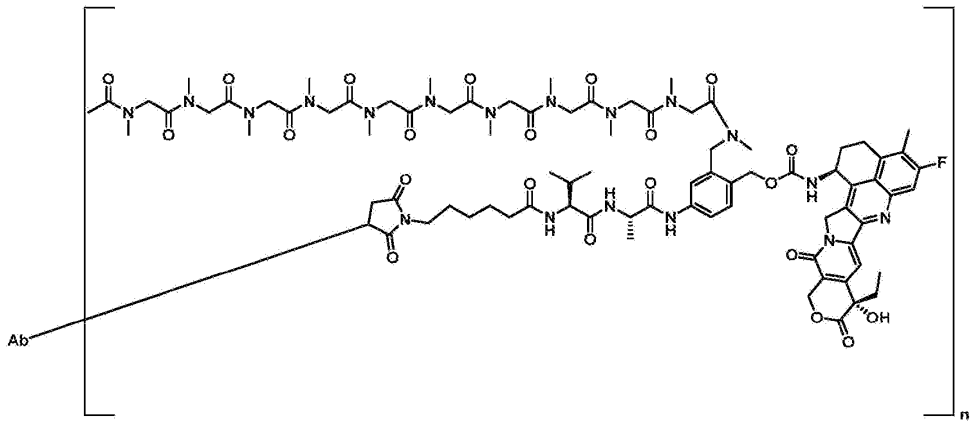
[1043] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

[1044] an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

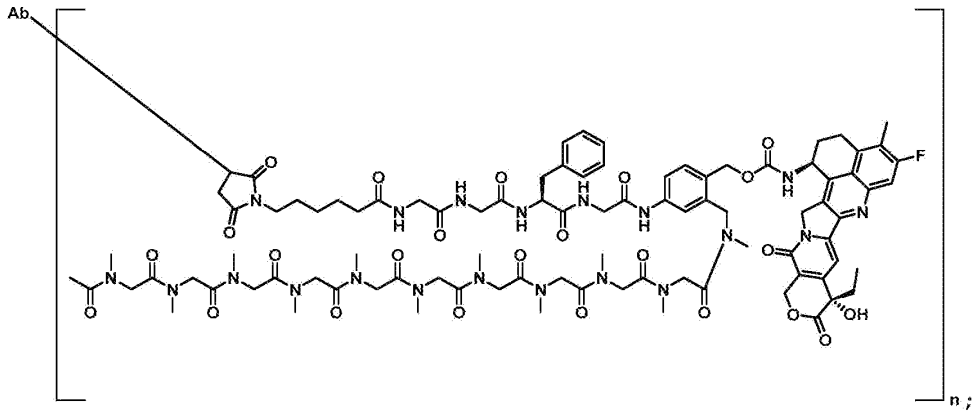
[1045] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate having a structure represented by the following formula:







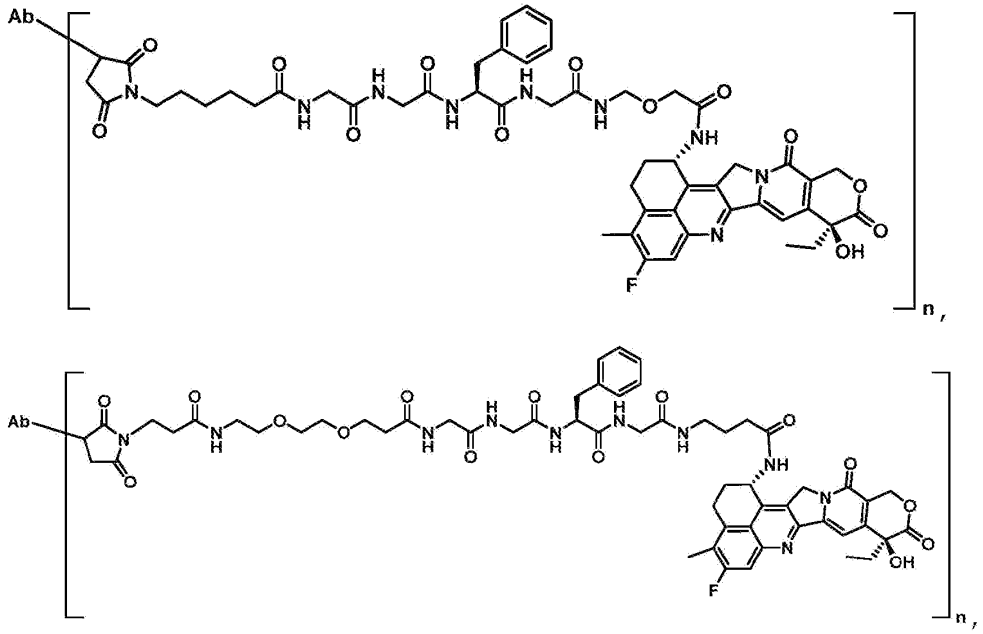
and

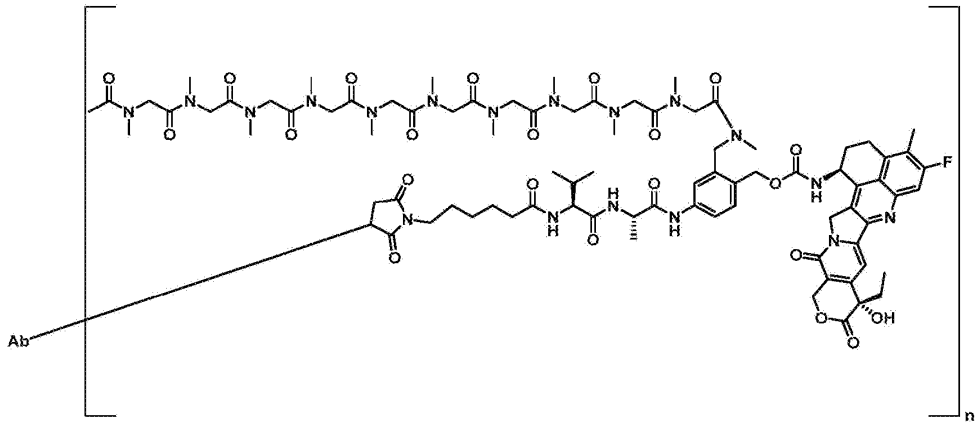


[1046] wherein n can be any number from 1 to 10; and

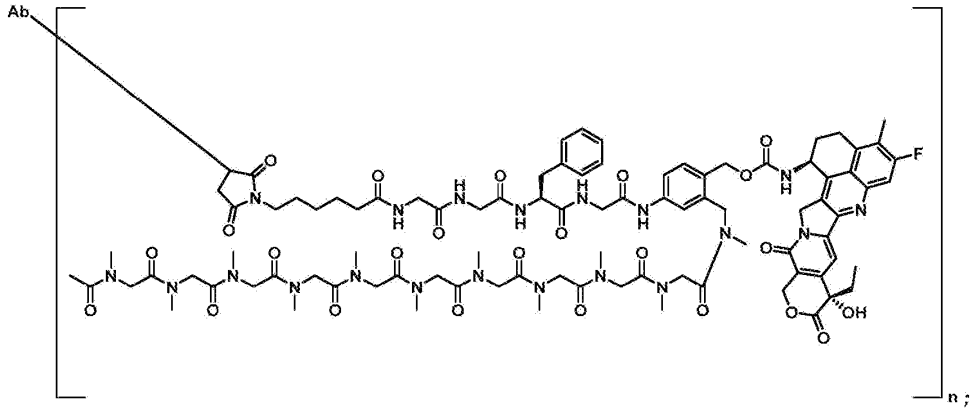
[1047] wherein Ab is an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11 , 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or a t least 99%sequence identity to each thereof; and/or a light chain having an amino ac id sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to each thereof.

[1048] In some embodiments, provided is an anti-CDH17 antibody-drug conjugate ha ving a structure represented by the following formula:





and



[1049] wherein n can be any number from 1 to 10; and

[1050] wherein Ab is an antibody selected from a group consisting of:

[1051] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 8;

[1052] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 10;

[1053] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 11, and a light chain having an am

ino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 12;

[1054] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 20 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 20, and a light chain having an am ino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 30;

[1055] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence id entity to SEQ ID NO: 22, and a light chain having an amino acid sequ ence shown in SEQ ID NO: 32 or an amino acid sequence having at leas t 80%sequence identity to SEQ ID NO: 32;

[1056] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 24 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 24, and a light chain having an am ino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 34;

[1057] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 20 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 20, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[1058] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 26 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 26, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[1059] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 28 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 28, and a light chain having an am ino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 36;

[1060] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequenc e shown in SEQ ID NO: 38 or an amino acid sequence having at least 8 0%sequence identity to SEQ ID NO: 38, and a light chain having an am ino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence h aving at least 80%sequence identity to SEQ ID NO: 44;

[1061] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 40 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 46;

[1062] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 42 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 48;

[1063] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 171 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 173; and

[1064] an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 177.

[1065] Pharmaceutical Compositions

[1066] The present disclosure, in another aspect, provides a pharmaceutical composition comprising an antibody or an antibody-drug conjugate as disclosed herein, and a pharmaceutically acceptable carrier. The compositions are suitable for veterinary or human administration.

[1067] The present compositions can be in any form that allows for the composition to be administered to a patient. For example, the composition can be in the form of a solid, liquid or gas (aerosol) . Typical routes of administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, ocular, intratumor, and intranasal. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In one aspect, the compositions are administered parenterally. In yet another aspect, the compositions are administered intravenously.

[1068] Pharmaceutical compositions can be formulated so as to allow a conjugate to be bioavailable upon administration of the composition to a patient. Compositions can take the form of one or more dosage units, where for example, a tablet can be a single dosage unit, and a container of a conjugate in aerosol form can hold a plurality of dosage units.

[1069] Materials used in preparing the pharmaceutical compositions can be non-toxic in the amounts used. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient (s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of animal (e.g., human) , the particular form of the conjugate, the manner of administration, and the composition employed.

[1070] The pharmaceutically acceptable carrier or vehicle can be particulate, so that the compositions are, for example, in tablet or powder form. The carrier (s) can be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier (s) can be gaseous or particulate, so as to provide an aerosol composition useful in, e.g., inhalatory administration.

[1071] The composition can be in the form of a liquid, e.g., an elixir, syrup, solution, emulsion or suspension. The liquid can be useful for oral administration or for delivery by injection. When intended for oral administration, a composition can comprise one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition for administration by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent can also be included.

[1072] The liquid compositions, whether they are solutions, suspensions or other like form, can also include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or digylcerides which can serve as the solvent or suspending medium, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition can be enclosed in ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material. Physiological saline is an exemplary adjuvant. An injectable composition is preferably sterile.

[1073] The amount of the conjugate that is effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

[1074] The compositions comprise an effective amount of an antibody or a co njugate such that a suitable dosage will be obtained. Typically, this amount is at le ast about 0.01%of an antibody or a conjugate by weight of the compos ition. When intended for oral administration, this amount can be varied to range from about 0.1%to about 80%by weight of the composition. In one aspect, oral compositions can comprise from about 4%to about 50%of the antib ody or the conjugate by weight of the composition. In yet another aspect, present com positions are prepared so that a parenteral dosage unit contains from about 0.01%to a bout 2%by weight of the antibody or the conjugate.

[1075] For intravenous administration, the composition can comprise from ab out 0.01 to about 100 mg of an antibody or a conjugate per kg of the animal's body we ight. In one aspect, the composition can include from about 1 to about 100 mg of an a ntibody or a conjugate per kg of the animal's body weight. In another aspect, the amo unt administered will be in the range from about 0.1 to about 25 mg/kg of body weight of the antibody or the conjugate.

[1076] Generally, the dosage of an antibody or a conjugate administered to a patient is typi cally about 0.01 mg/kg to about 2000 mg/kg of the animal's body weig ht. In one aspect, the dosage administered to a patient is between about 0.01 mg/ kg to about 10 mg/kg of the animal's body weight, in another aspect, the dosage administered to a patient is between about 0.1 mg/kg and about 250 mg/ kg of the animal's body weight, in yet another aspect, the dosage administe red to a patient is between about 0.1 mg/kg and about 20 mg/kg of the animal's body w eight, in yet another aspect the dosage administered is between about 0.1 mg/kg to ab out 10 mg/kg of the animal's body weight, and in yet another aspect, the dosage admin istered is between about 1 mg/kg to about 10 mg/kg of the animal's body weight.

[1077] The antibodies, the conjugates or compositions can be administered b y any convenient route, for example by infusion or bolus injection, by absorption thr ough epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mu cosa, etc.) . Administration can be systemic or local. Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, etc ., and can be used to administer a conjugate or composition. In certain embodiments, more than one antibody, conjugate or composition is administered to a patient.

[1078] In specific embodiments, it can be desirable to administer one or more antibodies, co njugates or compositions locally to the area in need of treatment. This can be achiev ed, for example, and not by way of limitation, by local infusion during surgery; topi cal application, e.g., in conjunction with a wound dressing after surgery; by injecti on; by means of a catheter; by means of a suppository; or by means of an implant, the implant being of a porous, non-porous, or gelatinous material, including membranes

, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a cancer, tumor or neoplastic or pre-neoplastic tissue. In another embodiment, administration can be by direct injection a t the site (or former site) of a manifestation of an autoimmune disease.

[1079] In certain embodiments, it can be desirable to introduce one or more antibody, conjugate or compositions into the central nervous system by any suitable route, including intraventricular and intrathecal injection. Intraventricular injecti on can be facilitated by an intraventricular catheter, for example, attached to a res ervoir, such as an Ommaya reservoir.

[1080] Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fl uorocarbon or synthetic pulmonary surfactant.

[1081] In yet another embodiment, the antibody, conjugate or compositions c an be delivered in a controlled release system, such as but not limited to, a pump or various polymeric materials can be used. In yet another embodiment, a controlled-release system can be placed in proximity of the target of the antibody, conjugate or compositions, e.g., the brain, thus requiring only a fraction of the systemic dose.

[1082] The term “carrier” refers to a diluent, adjuvant or carrier, with which an antibody o r a conjugate is administered. Such pharmaceutical carriers can be liquids, such as w ater and oils, including those of petroleum, animal, vegetable or synthetic origin, s uch as peanut oil, soybean oil, mineral oil, sesame oil and the like. The carriers ca n be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea , and the like. In addition, auxiliary, stabilizing, thickening, lubricating and colo ring agents can be used. In one embodiment, when administered to a patient, the antib ody or the conjugate or compositions and pharmaceutically acceptable carriers are ste rile. Water is an exemplary carrier when the antibodies or conjugates are administere d intravenously. Saline solutions and aqueous dextrose and glycerol solutions can als o be employed as liquid carriers, particularly for injectable solutions. Suitable pha rmaceutical carriers also include carriers such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearat e, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethano l and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[1083] In an embodiment, the conjugates are formulated in accordance with r outine procedures as a pharmaceutical composition adapted for intravenous administrat ion to animals, particularly human beings. Typically, the carriers or vehicles for in travenous administration are sterile isotonic aqueous buffer solutions. Where necessa ry, the compositions can also include a solubilizing agent. Compositions for intraven

ous administration can optionally comprise a local anesthetic such as lignocaine to e ase pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoul e or sachette indicating the quantity of active agent. Where a conjugate is to be adm inistered by infusion, it can be dispensed, for example, with an infusion bottle cont aining sterile pharmaceutical grade water or saline. Where the antibody or the conjug ate is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[1084] The composition can include various materials that modify the physic al form of a solid or liquid dosage unit. For example, the composition can include ma terials that form a coating shell around the active ingredients. The materials that f orm the coating shell are typically inert, and can be selected from, for example, sug ar, shellac, and other enteric coating agents. Alternatively, the active ingredients can be encased in a gelatin capsule.

[1085] The compositions can consist of gaseous dosage units, e.g., it can be in the form of an aerosol. The term aerosol is used to denote a variety of systems ranging from thos e of colloidal nature to systems consisting of pressurized packages. Delivery can be by a liquefied or compressed gas or by a suitable pump system that dispenses the acti ve ingredients.

[1086] Whether in solid, liquid or gaseous form, the present compositions can include a phar macological agent used in the treatment of cancer.

[1087] Uses and Therapies

[1088] The antibodies and conjugates are useful for inhibiting the multiplication of a tumor cell or cancer cell, causing apoptosis in a tumor or cancer cell, or for treating ca ncer in a patient. The antibodies and the conjugates can be used accordingly in a var iety of settings for the treatment of animal cancers. The antibodies and conjugates c an be used to deliver a drug or drug unit to a tumor cell or cancer cell. Without bei ng bound by theory, in one embodiment, the antibody or the antibody moiety of the conjugate disclosed herein binds to or associates with CDH17 antigen ex pressed on, or associated with, the cell surface of a cancer cell or a tumor cell. In the case of a conjugate, the conjugate can be taken up inside a tumor cell or cancer cell through receptor-mediated endocytosis. Once inside the cell, one or more specific peptide sequences within the linker moiety are hydrolytically cleaved b y one or more tumor-cell or cancer-cell-associated proteases, resulting in release of a cytotoxic drug or a drug-linker compound. The released cyto toxic drug or drug-linker compound is then free to migrate within the cell and induce c ytotoxic or cytostatic activities. In an alternative embodiment, the cytotoxic drug o

r drug-linker compound is cleaved from the conjugate outside the tumor cell or cancer cell, and the cytotoxic drug or drug-linker compound subsequently penet rates the cell.

[1089] The present disclosure, in a further aspect, provides a method for treating or preven ting cancer in a subject, comprising administering to the subject an effective amount of an antibody or an antibody-drug conjugate disclosed herein.

[1090] The cancer may be a solid cancer or a hematologic malignancy, positive for CDH17 antigen. A “hematologic malignancy” , also known as a blood cancer, is a cancer that originates in blood-forming tissue, such as the bone marrow or other cells of the immune system. Hematologic malignancies include, without limitation, leukemias (such as acute myeloid leukemia (ANIL) , acute promyelocytic leukemia, acute lymphoblastic leukemia (ALL) , acute mixed lineage leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia (CLL) , hairy, cell leukemia and large granular lymphocytic leukemia) , myelodysplastic syndrome (MDS) , myeloproliferative disorders (polycythemia vera, essential thrombocytosis, primary myelofibrosis and chronic myeloid leukemia) , lymphomas, multiple myeloma, MGUS and similar disorders, Hodgkin’s lymphoma, non-Hodgkin lymphoma (NHL) , primary mediastinal large B-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, transformed follicular lymphoma, splenic marginal zone lymphoma, lymphocytic lymphoma, T-cell lymphoma, and other B-cell malignancies. “Solid cancers” include, without limitation, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon cancer, colorectal cancer, kidney cancer, pancreatic cancer, bone cancer, breast cancer, ovarian cancer, prostate cancer, esophogeal cancer, stomach cancer, oral cancer, nasal cancer, throat cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms'tumor, cervical cancer, uterine cancer, testicular cancer, small cell lung carcinoma, bladder carcinoma, lung cancer, epithelial carcinoma, glioma, glioblastoma multiforme, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealo ma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningiom a, skin cancer, melanoma, neuroblastoma, retinoblastoma. Preferably, the cancers treatable by the present disclosure include pancreatic cancer, gastric c

ancer, colorectal cancer, cholangiocarcinoma cancer, liver cancer, neuroendocrine can cer, and esophageal adenocarcinoma.

[1091] In some embodiments, provided are methods for treating or preventing cancer are provided, including administering to a patient in need thereof a therapeu tically effective amount of an antibody or a conjugate disclosed herein and a chemoth erapeutic agent. In one embodiment, the chemotherapeutic agent is that with which tre atment of the cancer has not been found to be refractory. In another embodiment, the chemotherapeutic agent is that with which the treatment of cancer has been found to b e refractory. The antibodies or the conjugates can be administered to a patient that has also undergone surgery as treatment for the cancer.

[1092] In a specific embodiment, the antibody or the conjugate is administered concurrently with the chemotherapeutic agent or with radiation therapy. In another specific embodi ment, the chemotherapeutic agent or radiation therapy is administered prior or subseq uent to administration of an antibody or a conjugate, in one aspect at least an hour, five hours, 12 hours, a day, a week, a month, in further aspects several months (e.g ., up to three months) , prior or subsequent to administration of an antibody or a co njugate.

[1093] A chemotherapeutic agent can be administered over a series of sessio ns. Suitable chemotherapeutic agents include, but are not limited to, methotrexate, t axol, L-asparaginase, mercaptopurine, thioguanine, hydroxyurea, cytarabine, cyclophosphamide, ifosfamide, nitrosoureas, cisplatin, carboplatin, mitomycin, dacarb azine, procarbizine, topotecan, nitrogen mustards, cytoxan, etoposide, 5-fluorouracil, BCNU, irinotecan, camptothecins, bleomycin, doxorubicin, idarubicin, da unorubicin, dactinomycin, plicamycin, mitoxantrone, asparaginase, vinblastine, vincri stine, vinorelbine, paclitaxel, and docetaxel. With respect to radiation, any radiati on therapy protocol can be used depending upon the type of cancer to be treated. For example, but not by way of limitation, x-ray radiation can be administered; in particular, high-energy megavoltage (radiation of greater that 1 MeV energy) can be used for deep tumors, and electron beam and orthovoltage x-ray radiation can be used for skin cancers. Gamma-ray emitting radioisotopes, such a s radioactive isotopes of radium, cobalt and other elements, can also be administered.

[1094] Additionally, methods of treatment of cancer with an antibody or a c onjugate disclosed herein are provided as an alternative to chemotherapy or radiation therapy where the chemotherapy or the radiation therapy has proven or can prove too toxic, e.g., results in unacceptable or unbearable side effects, for the subject bein g treated. The animal being treated can, optionally, be treated with another cancer t reatment such as surgery, radiation therapy or chemotherapy, depending on which treat ment is found to be acceptable or bearable.

[1095] The antibodies or the conjugates can also be used in an in vitro or ex vivo fashion, such as for the treatment of certain cancers, including, but not limited to leukemias and lymphomas, such treatment involving autologous stem cell transplants. This can involve a multi-step process in which the animal's autologous hematopoietic stem cells are harvested and purged of all cancer cells, the animal's remaining bone-marrow cell population is then eradicated via the administration of a high dose of an antibody or a conjugate with or without accompanying high dose radiation therapy, and the stem cell graft is infused back into the animal. Supportive care is then provided while bone marrow function is restored and the animal recovers.

[1096] Equivalently, the present disclosure also provides an antibody or an antibody-drug conjugate as disclosed herein for use in the treatment of cancer in a subject. Equivalently, the present disclosure also provides use of an antibody or an antibody-drug conjugate as disclosed herein in the manufacturing of a medicament for treatment of cancer in a subject. In both of the equivalent aspects, the cancer is a preferably a CDH17 positive cancer, and more preferably, pancreatic cancer, gastric cancer, colorectal cancer, cholangiocarcinoma cancer, liver cancer, neuroendocrine cancer, or esophageal adenocarcinoma.

[1097] Sequences

SEQ ID NO:	Description	Amino Acid Sequences
1	CL075814 VH	EVQLQQSGPELVKPGASMKISCKASGYSFADYTMNWVKQSHGKN LEWIGLINPYSGGTSYSQNFKGRATLAVDKASSTAYMELLSLTS EDSAVYYCARPNYHGNGYDALDYWGQGTSVTVSS
2	CL075814 VL	DIQMTQSPASLSESVGETVTITCRASGNIHNYLAWYQQKQGKSP QLLVYNAKTLADGVPSRFSGSGSGTQYSLKINSLQPEDFGSYYC QHFWSTPWTFGGGTKLEIK
3	CL075835 VH	EVQLQQSGPDLVKPGASVKISCKASGYSFTDYYMHWMKQSHRKS LEWIGRVNPDNGGTTYSQNFKDKAIITVDKSSRTAYMELRSLTS EDSAVYYCAPGNYDGFAYWGQGTLVTVSA
4	CL075835 VL	DVVLTQSPATLSVTPGDSVSLSCRASQSISNNLHWYHQQSHESP RLLITFASQSISGIPSRFSGSGSGTEFTLSINNVETEDFGMYFC QQSFSWPQTFGGGTKLEIK
5	CL075942 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQPSG KGLEWLTLIYWDDDKRYNPSLESRLTISKDTSRNQVFLKITSVD TADSATYYCARRAFYGHSVYNFAMDYWGQGTSVTVSS
6	CL075942 VL	DIVLTQSPPSLAVSLGQRATISCRASKSVSTSAYSYMHWYQQKP GQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAA TYYCQHSKELPLTFGAGTKLELK
7	Ch814 HC	EVQLQQSGPELVKPGASMKISCKASGYSFADYTMNWVKQSHGKN LEWIGLINPYSGGTSYSQNFKGRATLAVDKASSTAYMELLSLTS EDSAVYYCARPNYHGNGYDALDYWGQGTSVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK

8	Ch814 LC	DIQMTQSPASLSESVGETVTITCRASGNIHNYLAWYQQKQGKSP QLLVYNAKTLADGVPSRFSGSGSGTQYSLKINSLQPEDFGSYYC QHFWSTPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
9	Ch835 HC	EVQLQQSGPDLVKPGASVKISCKASGYSFTDYYMHWMKQSHRKS LEWIGRVNPDNGGTTYSQNFKDKAIITVDKSSRTAYMELRSLTS EDSAVYYCAPGNYDGFAYWGQGTLVTVSAASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
10	Ch835 LC	DVVLTQSPATLSVTPGDSVSLSCRASQSISNNLHWYHQQSHESP RLLITFASQSISGIPSRFSGSGSGTEFTLSINNVETEDFGMYFC QQSFSWPQTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
11	Ch942 HC	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTSGMGVSWIRQPSG KGLEWLTLIYWDDDKRYNPSLESRLTISKDTSRNQVFLKITSVD TADSATYYCARRAFYGHSVYNFAMDYWGQGTSVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK
12	Ch942 LC	DIVLTQSPPSLAVSLGQRATISCRASKSVSTSAYSYMHWYQQKP GQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAA TYYCQHSKELPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
13	Patritumab HC	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKG LEWIGEINHSGSTNYNPSLKSRVTISVETSKNQFSLKLSSVTAA DTAVYYCARDKWTWYFDLWGRGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV

		LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
14	Patritumab LC	DIEMTQSPDSLAVSLGERATINCRSSQSVLYSSSNRNYLAWYQQ NPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCQQYYSTPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
15	Trastuzumab HC	EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKG LEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRA EDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLA PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPG
16	Trastuzumab LC	DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYC QQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
17	Datopotamab HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFTTAGMQWVRQAPGQG LEWMGWINTHSGVPKYAEDFKGRVTISADTSTSTAYLQLSSLKS EDTAVYYCARSGFGSSYWYFDVWGQGTLVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
18	Datopotamab LC	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAP KLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFAVYYC QQHYITPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
19	Hu814-H1 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSS

20	Hu814-H1 HC	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
21	Hu814-H2 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQN LEWIGIINPYSGGTSYSQNFKGRATLTVDKSTSTAYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSS
22	Hu814-H2 HC	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQN LEWIGIINPYSGGTSYSQNFKGRATLTVDKSTSTAYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
23	Hu814-H3 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYYMHWVRQAPGQN LEWIGIINPYSGGTSYAQKFQGRATLTVDKSTSTAYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSS
24	Hu814-H3 HC	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYYMHWVRQAPGQN LEWIGIINPYSGGTSYAQKFQGRATLTVDKSTSTAYMELSSLRS EDTAVYYCARPNYHGNGYDALDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
25	Hu814-H4 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPNYHGQGYDALDYWGQGTLVTVSS
26	Hu814-H4 HC	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS

		EDTAVYYCARPNYHGQGYDALDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
27	Hu814-H5 VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPNYHGNAYDALDYWGQGTLVTVSS
28	Hu814-H5 HC	QVQLVQSGAEVKKPGASVKVSCKASGYSFADYTMNWVRQAPGQG LEWMGIINPYSGGTSYSQNFKGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPNYHGNAYDALDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
29	Hu814-L1 VL	DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAP KLLLYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIK
30	Hu814-L1 LC	DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAP KLLLYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
31	Hu814-L2 VL	DIQMTQSPSSLSESVGDRVTITCRASGNIHNYLAWYQQKPGKSP KLLVYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIK
32	Hu814-L2 LC	DIQMTQSPSSLSESVGDRVTITCRASGNIHNYLAWYQQKPGKSP KLLVYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
33	Hu814-L3 VL	DIQMTQSPSSLSESVGDRVTITCRASGNIHNYLAWYQQKPGKSP KLLVYNAKRLESGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIK
34	Hu814-L3 LC	DIQMTQSPSSLSESVGDRVTITCRASGNIHNYLAWYQQKPGKSP KLLVYNAKRLESGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC

		QHFWSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
35	Hu814-L4 VL	DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAP KLLLYNAKRLESGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIK
36	Hu814-L4 LC	DIQMTQSPSSLSASVGDRVTITCRASGNIHNYLAWYQQKPGKAP KLLLYNAKRLESGVPSRFSGSGSGTDYTLTISSLQPEDFATYYC QHFWSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
37	Hu835-H1 VH	EVQLVQSGPEVVKPGATVKISCKVSGYSFTDYYMHWIRQPHGKS LEWVGRVNPDNGGTTYSQNFKDRFIITVDKSKRTAYMELRSLRS EDTAVYYCAPGNYDGFAYWGQGTLVTVSS
38	Hu835-H1 HC	EVQLVQSGPEVVKPGATVKISCKVSGYSFTDYYMHWIRQPHGKS LEWVGRVNPDNGGTTYSQNFKDRFIITVDKSKRTAYMELRSLRS EDTAVYYCAPGNYDGFAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
39	Hu835-H2 VH	EVQLVQSGAELVKPGASVKISCKASGYSFTDYYMHWVKQAPGKG LEWIGRVNPDNGGTTYSQNFKDRVTITVDKSTDTAYMELSSLRS EDTAVYYCAPGNYDGFAYWGQGTLVTVSS
40	Hu835-H2 HC	EVQLVQSGAELVKPGASVKISCKASGYSFTDYYMHWVKQAPGKG LEWIGRVNPDNGGTTYSQNFKDRVTITVDKSTDTAYMELSSLRS EDTAVYYCAPGNYDGFAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
41	Hu835-H3 VH	EVQLVQSGGGLVKPGASVKISCKASGYSFTDYYMHWVRQAPGKG LEWVGRVNPDNGGTTYSQNFKDRFTITVDKSKNTAYMELNSLRS EDTAVYYCAPGNYDGFAYWGQGTLVTVSS
42	Hu835-H3 HC	EVQLVQSGGGLVKPGASVKISCKASGYSFTDYYMHWVRQAPGKG LEWVGRVNPDNGGTTYSQNFKDRFTITVDKSKNTAYMELNSLRS

		EDTAVYYCAPGNYDGFAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
43	Hu835-L1 VL	EIVLTQSPATLSVSPGQRVTLSCRASQSISNNLHWYQQRPGQPP RLLITFASQSISGIPARFSGSGSGTEFTLTITRVQSEDFGVYYC QQSFSWPQTFGGGTKLEIK
44	Hu835-L1 LC	EIVLTQSPATLSVSPGQRVTLSCRASQSISNNLHWYQQRPGQPP RLLITFASQSISGIPARFSGSGSGTEFTLTITRVQSEDFGVYYC QQSFSWPQTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
45	Hu835-L2 VL	EIVLTQSPATLSVSPGDRATLSCRASQSISNNLHWYQQKPGQAP RLLITFASQSISGIPSRFSGSGSGTEFTLTISSVQSEDFAVYYC QQSFSWPQTFGGGTKVEIK
46	Hu835-L2 LC	EIVLTQSPATLSVSPGDRATLSCRASQSISNNLHWYQQKPGQAP RLLITFASQSISGIPSRFSGSGSGTEFTLTISSVQSEDFAVYYC QQSFSWPQTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
47	Hu835-L3 VL	EIVLTQSPATLSVSPGDRVTLSCRASQSISNNLHWYQQKPGQAP RLLITFASQSISGIPSRFSGSGSGTEFTLTISSVEPEDFAVYYC QQSFSWPQTFGGGTKVEIK
48	Hu835-L3 LC	EIVLTQSPATLSVSPGDRVTLSCRASQSISNNLHWYQQKPGQAP RLLITFASQSISGIPSRFSGSGSGTEFTLTISSVEPEDFAVYYC QQSFSWPQTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
49	CL075814 VH CDR1 IMGT	GYSFADYT
50	CL075814 VH CDR2 IMGT	INPYSGGT
51	CL075814 VH CDR3 IMGT	ARPNYHGNGYDALDY
52	CL075814 VL CDR1 IMGT	GNIHNY
53	CL075814 VL CDR2 IMGT	NAK

54	CL075814 VL CDR3 IMGT	QHFWSTPWT
55	CL075814 VH CDR1 Kabat	DYTMN
56	CL075814 VH CDR2 Kabat	LINPYSGGTSYSQNFKG
57	CL075814 VH CDR3 Kabat	PNYHGNGYDALDY
58	CL075814 VL CDR1 Kabat	RASGNIHNYLA
59	CL075814 VL CDR2 Kabat	NAKTLAD
54	CL075814 VL CDR3 Kabat	QHFWSTPWT
60	CL075814 VH CDR1 Chothia	GYSFADY
61	CL075814 VH CDR2 Chothia	NPYSGG
57	CL075814 VH CDR3 Chothia	PNYHGNGYDALDY
62	CL075814 VH CDR1 Contact	ADYTMN
63	CL075814 VH CDR2 Contact	WIGLINPYSGGTS
64	CL075814 VH CDR3 Contact	ARPNYHGNGYDALD
65	CL075814 VL CDR1 Contact	HNYLAWY
66	CL075814 VL CDR2 Contact	LLVYNAKTLA
67	CL075814 VL CDR3 Contact	QHFWSTPW
68	CL075835 VH CDR1 IMGT	GYSFTDYY
69	CL075835 VH CDR2 IMGT	VNPDNGGT
70	CL075835 VH CDR3 IMGT	APGNYDGFAY
71	CL075835 VL CDR1 IMGT	QSISNN
72	CL075835 VL CDR2 IMGT	FAS
73	CL075835 VL CDR3 IMGT	QQSFSWPQT

74	CL075835 VH CDR1 Kabat	DYYMH
75	CL075835 VH CDR2 Kabat	RVNPDNGGTTYSQNFKD
76	CL075835 VH CDR3 Kabat	GNYDGFAY
77	CL075835 VL CDR1 Kabat	RASQSISNNLH
78	CL075835 VL CDR2 Kabat	FASQSIS
73	CL075835 VL CDR3 Kabat	QQSFSWPQT
79	CL075835 VH CDR1 Chothia	GYSFTDY
80	CL075835 VH CDR2 Chothia	NPDNGG
76	CL075835 VH CDR3 Chothia	GNYDGFAY
81	CL075835 VH CDR1 Contact	TDYYMH
82	CL075835 VH CDR2 Contact	WIGRVNPDNGGTT
83	CL075835 VH CDR3 Contact	APGNYDGFA
84	CL075835 VL CDR1 Contact	SNNLHWY
85	CL075835 VL CDR2 Contact	LLITFASQSI
86	CL075835 VL CDR3 Contact	QQSFSWPQ
87	CL075942 VH CDR1 IMGT	GFSLSTSGMG
88	CL075942 VH CDR2 IMGT	IYWDDDK
89	CL075942 VH CDR3 IMGT	ARRAFYGHSVYNFAMDY
90	CL075942 VL CDR1 IMGT	KSVSTSAYSY
91	CL075942 VL CDR2 IMGT	LAS
92	CL075942 VL CDR3 IMGT	QHSKELPLT
93	CL075942 VH CDR1 Kabat	TSGMGVS

94	CL075942 VH CDR2 Kabat	LIYWDDDKRYNPSLES
95	CL075942 VH CDR3 Kabat	RAFYGHSVYNFAMDY
96	CL075942 VL CDR1 Kabat	RASKSVSTSAYSYMH
97	CL075942 VL CDR2 Kabat	LASNLES
92	CL075942 VL CDR3 Kabat	QHSKELPLT
98	CL075942 VH CDR1 Chothia	GFSLSTSGM
99	CL075942 VH CDR2 Chothia	YWDDD
95	CL075942 VH CDR3 Chothia	RAFYGHSVYNFAMDY
100	CL075942 VH CDR1 Contact	STSGMGVS
101	CL075942 VH CDR2 Contact	WLTLIYWDDDKR
102	CL075942 VH CDR3 Contact	ARRAFYGHSVYNFAMD
103	CL075942 VL CDR1 Contact	STSAYSYMHWY
104	CL075942 VL CDR2 Contact	LLIYLASNLE
105	CL075942 VL CDR3 Contact	QHSKELPL
55	Hu814-H1 VH CDR1 Kabat	DYTMN
106	Hu814-H1 VH CDR2 Kabat	IINPYSGGTSYSQNFKG
57	Hu814-H1 VH CDR3 Kabat	PNYHGNGYDALDY
62	Hu814-H1 VH CDR1 Contact	ADYTMN
107	Hu814-H1 VH CDR2 Contact	WMGIINPYSGGTS
64	Hu814-H1 VH CDR3 Contact	ARPNYHGNGYDALD
62	Hu814-H2 VH CDR1 Contact	ADYTMN
108	Hu814-H2 VH CDR2 Contact	WIGIINPYSGGTS

57	Hu814-H2 VH CDR3 Contact	PNYHGNGYDALDY
109	Hu814-H3 VH CDR1 IMGT	GYSFADYY
50	Hu814-H3 VH CDR2 IMGT	INPYSGGT
51	Hu814-H3 VH CDR3 IMGT	ARPNYHGNGYDALDY
110	Hu814-H3 VH CDR1 Kabat	DYYMH
111	Hu814-H3 VH CDR2 Kabat	IINPYSGGTSYAQKFQG
57	Hu814-H3 VH CDR3 Kabat	PNYHGNGYDALDY
112	Hu814-H3 VH CDR1 Contact	ADYYMH
108	Hu814-H3 VH CDR2 Contact	WIGIINPYSGGTS
64	Hu814-H3 VH CDR3 Contact	ARPNYHGNGYDALD
49	Hu814 H4 VH CDR1 IMGT	GYSFADYT
50	Hu814 H4 VH CDR2 IMGT	INPYSGGT
113	Hu814 H4 VH CDR3 IMGT	ARPNYHGQGYDALDY
55	Hu814 H4 VH CDR1 Kabat	DYTMN
106	Hu814 H4 VH CDR2 Kabat	IINPYSGGTSYSQNFKG
114	Hu814 H4 VH CDR3 Kabat	PNYHGQGYDALDY
60	Hu814 H4 VH CDR1 Chothia	GYSFADY
61	Hu814 H4 VH CDR2 Chothia	NPYSGG
114	Hu814 H4 VH CDR3 Chothia	PNYHGQGYDALDY
62	Hu814 H4 VH CDR1 Contact	ADYTMN
107	Hu814 H4 VH CDR2 Contact	WMGIINPYSGGTS
115	Hu814 H4 VH CDR3 Contact	ARPNYHGQGYDALD

49	Hu814 H5 VH CDR1 IMGT	GYSFADYT
50	Hu814 H5 VH CDR2 IMGT	INPYSGGT
116	Hu814 H5 VH CDR3 IMGT	ARPNYHGNAYDALDY
55	Hu814 H5 VH CDR1 Kabat	DYTMN
106	Hu814 H5 VH CDR2 Kabat	IINPYSGGTSYSQNFKG
117	Hu814 H5 VH CDR3 Kabat	PNYHGNAYDALDY
60	Hu814 H5 VH CDR1 Chothia	GYSFADY
61	Hu814 H5 VH CDR2 Chothia	NPYSGG
62	Hu814 H5 VH CDR1 Contact	ADYTMN
107	Hu814 H5 VH CDR2 Contact	WMGIINPYSGGTS
118	Hu814 H5 VH CDR3 Contact	ARPNYHGNAYDALD
65	Hu814-L1 VL CDR1 Contact	HNYLAWY
119	Hu814-L1 VL CDR2 Contact	LLLYNAKTLA
67	Hu814-L1 VL CDR3 Contact	QHFWSTPW
58	Hu814-L3 VL CDR1 Kabat	RASGNIHNYLA
120	Hu814-L3 VL CDR2 Kabat	NAKRLES
54	Hu814-L3 VL CDR3 Kabat	QHFWSTPWT
65	Hu814-L3 VL CDR1 Contact	HNYLAWY
121	Hu814-L3 VL CDR2 Contact	LLVYNAKRLE
67	Hu814-L3 VL CDR3 Contact	QHFWSTPW
65	Hu814-L4 VL CDR1 Contact	HNYLAWY

122	Hu814-L4 VL CDR2 Contact	LLLYNAKRLE
67	Hu814-L4 VL CDR3 Contact	QHFWSTPW
81	Hu835-H1 VH CDR1 Contact	TDYYMH
123	Hu835-H1 VH CDR2 Contact	WVGRVNPDNGGTT
83	Hu835-H1 VH CDR3 Contact	APGNYDGFA
124	Heavy Chain Constant Region (CH)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
125	Light Chain Constant Region (CL)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
126	Human Cadherin 17	MILQAHLHSLCLLMLYLATGYGQEGKFSGPLKPMTFSIYEGQEP SQIIFQFKANPPAVTFELTGETDNIFVIEREGLLYYNRALDRET RSTHNLQVAALDANGIIVEGPVPITIKVKDINDNRPTFLQSKYE GSVRQNSRPGKPFLYVNATDLDDPATPNGQLYYQIVIQLPMINN VMYFQINNKTGAISLTREGSQELNPAKNPSYNLVISVKDMGGQS ENSFSDTTSVDIIVTENIWKAPKPVEMVENSTDPHPIKITQVRW NDPGAQYSLVDKEKLPRFPFSIDQEGDIYVTQPLDREEKDAYVF YAVAKDEYGKPLSYPLEIHVKVKDINDNPPTCPSPVTVFEVQEN ERLGNSIGTLTAHDRDEENTANSFLNYRIVEQTPKLPMDGLFLI QTYAGMLQLAKQSLKKQDTPQYNLTIEVSDKDFKTLCFVQINVI DINDQIPIFEKSDYGNLTLAEDTNIGSTILTIQATDADEPFTGS SKILYHIIKGDSEGRLGVDTDPHTNTGYVIIKKPLDFETAAVSN IVFKAENPEPLVFGVKYNASSFAKFTLIVTDVNEAPQFSQHVFQ AKVSEDVAIGTKVGNVTAKDPEGLDISYSLRGDTRGWLKIDHVT GEIFSVAPLDREAGSPYRVQVVATEVGGSSLSSVSEFHLILMDV NDNPPRLAKDYTGLFFCHPLSAPGSLIFEATDDDQHLFRGPHFT FSLGSGSLQNDWEVSKINGTHARLSTRHTEFEEREYVVLIRIND GGRPPLEGIVSLPVTFCSCVEGSCFRPAGHQTGIPTVGMAVGIL LTTLLVIGIILAVVFIRIKKDKGKDNVESAQASEVKPLRS
127	Human Cadherin 17 ECD3	VEMVENSTDPHPIKITQVRWNDPGAQYSLVDKEKLPRFPFSIDQ EGDIYVTQPLDREEKDAYVFYAVAKDEYGKPLSYPLEIHVKVKD INDNPPTC

128	Human Cadherin 17 ECD4	PSPVTVFEVQENERLGNSIGTLTAHDRDEENTANSFLNYRIVEQ TPKLPMDGLFLIQTYAGMLQLAKQSLKKQDTPQYNLTIEVSDKD FKTLCFVQINVIDINDQIPIF
166	Human Cadherin 17 ECD6	SQHVFQAKVSEDVAIGTKVGNVTAKDPEGLDISYSLRGDTRGWL KIDHVTGEIFSVAPLDREAGSPYRVQVVATEVGGSSLSSVSEFH LILMDVNDNPPRL
167	RAb17 HC	EVQLVESGGGLVKPGGSLKLSCAASGFSFSDYYMYWVRQAPEKR LEWVASISFDGTYTYYTDRVKGRFTISRDNAKNNLYLQMSSLKS EDTAMYYCARDRPAWFPYWGQGTLVTVSAASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRW
168	RAb17 LC	DVLMTQIPLSLTVSLGDQASISCRSSQSIVHSNGNTYLEWYLQR PGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDL GVYYCFQGSHVPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
169	Mouse CDH17	MVSAQLHFLCLLTLYLTCGYGEEGKFSGPLKPMTFSIFEGQEPS QVIFQFKTNPPAVTFELTGETDGIFKIEKDGLLYHTRALDRETR AVHHLQLAALDSHGAIVDGPVPITIEVKDINDNRPTFLQSKYEG SVRQNSRPGKPFMYVNATDLDDPATPNGQLFYQIVIQLPQINDV MYFQIDSKTGAISLTPEGSQELDPVKNPSYNLVVSVKDMGGQSE NSFSDTTYVDISIRENIWKAPEPVEIRENSTDPHPIKITQVQWN DPGAQYSLVNKEKLSPFPFSIDQEGNIYVTQALDREEKNSHVFF ATAKDENGKPLAYPLEIYVKVIDINDNPPTCLSPVTVFEVQENE PLGNSIGIFEAHDMDEANNINSILKYKLVDQTPKVPSDGLFLIG EYEGKVQLSKQSLKKQDSPQYNLSIEVSDVDFKTLCYIQVNVID INDQIPIFETSNYGSKTLSEDTAIGSTILIIQATDADEPFTGSS KILYKIVQGDTEGRLEVVTDPTTNAGYVKIKKPLDFETQPVSSI VFQAENPEPLVKGIEYNASSFASFELIVTDVNEVPVFPQRIFQA NVSEDAAVGSRVGNVTARDPEGLTVSYSLKGNMRGWLKIDSVTG EIFSAAPLDRETESVYRVQVVATEVGGSSLSSTADFHLVLTDVN DNPPRLAKDYTGLFFCHPLSAPGSLIFEVTDDDQQSLRRPKFTF ALGREGLQSDWEVSKINGTHARLSTRHTRFEEQVYNIPIRINDG GQPPMEGTVFLPVTFCQCVEGSCFRPAGRQDGIPTVGMAVGILL TTFLVIGIILAVVFIRMRKDKVENPQSPENKPLRS
170	Ch2E21_VH	QVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPGQG LEWIGAIYPGDGDIRYTQQFKDKATLTADKSSSTAYIQLSSLTS EDSAVYYCAKPFGSTYGFVYWGQGTLVTVSA

171	Ch2E21_HC	QVQLQQSGAELARPGASVKLSCKASGYTFTSYWMQWVKQRPGQG LEWIGAIYPGDGDIRYTQQFKDKATLTADKSSSTAYIQLSSLTS EDSAVYYCAKPFGSTYGFVYWGQGTLVTVSAASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRW
172	Ch2E21_VL	DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQGKSP QLLVYNAKTLADGVPSRFSGSGSGTQYSLKINSLQPEDFGNYYC QHFWSSPWTFGGGTKLEIK
173	Ch2E21_LC	DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQGKSP QLLVYNAKTLADGVPSRFSGSGSGTQYSLKINSLQPEDFGNYYC QHFWSSPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
174	Ch2F12_VH	DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGN KLEWMGYITYAGSNNYNPSLKNRISITRDTSKNQFFLKLNSVTT EDTATYFCARDQITTAWFTYWGQGTLVTVSA
175	Ch2F12_HC	DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGN KLEWMGYITYAGSNNYNPSLKNRISITRDTSKNQFFLKLNSVTT EDTATYFCARDQITTAWFTYWGQGTLVTVSAASTKGPSVFPLAP SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRW
176	Ch2F12_VL	QVVLTQSPALMSASPGEKVTMTCSATSSVSYMFWYQQKPRSSPK PWIYLTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPSITFGAGTKLELK
177	Ch2F12_LC	QVVLTQSPALMSASPGEKVTMTCSATSSVSYMFWYQQKPRSSPK PWIYLTSNLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPSITFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
178	Ch2E21 VH CDR1 IMGT	GYTFTSYW
179	Ch2E21 VH CDR2 IMGT	IYPGDGDI

180	Ch2E21 VH CDR3 IMGT	AKPFGSTYGFVY
52	Ch2E21 VL CDR1 IMGT	GNIHNY
53	Ch2E21 VL CDR2 IMGT	NAK
181	Ch2E21 VL CDR3 IMGT	QHFWSSPWT
182	Ch2E21 VH CDR1 Kabat	SYWMQ
183	Ch2E21 VH CDR2 Kabat	AIYPGDGDIRYTQQFKD
184	Ch2E21 VH CDR3 Kabat	PFGSTYGFVY
58	Ch2E21 VL CDR1 Kabat	RASGNIHNYLA
59	Ch2E21 VL CDR2 Kabat	NAKTLAD
181	Ch2E21 VL CDR3 Kabat	QHFWSSPWT
185	Ch2E21 VH CDR1 Chothia	GYTFTSY
186	Ch2E21 VH CDR2 Chothia	YPGDGD
184	Ch2E21 VH CDR3 Chothia	PFGSTYGFVY
187	Ch2E21 VH CDR1 Contact	TSYWMQ
188	Ch2E21 VH CDR2 Contact	WIGAIYPGDGDIR
189	Ch2E21 VH CDR3 Contact	AKPFGSTYGFV
65	Ch2E21 VL CDR1 Contact	HNYLAWY
66	Ch2E21 VL CDR2 Contact	LLVYNAKTLA
190	Ch2E21 VL CDR3 Contact	QHFWSSPW
191	Ch2F12 VH CDR1 IMGT	GYSITSGYY
192	Ch2F12 VH CDR2 IMGT	ITYAGSN
193	Ch2F12 VH CDR3 IMGT	ARDQITTAWFTY

194	Ch2F12 VL CDR1 IMGT	SSVSY
195	Ch2F12 VL CDR2 IMGT	LTS
196	Ch2F12 VL CDR3 IMGT	QQWSSNPSIT
197	Ch2F12 VH CDR1 Kabat	SGYYWN
198	Ch2F12 VH CDR2 Kabat	YITYAGSNNYNPSLKN
199	Ch2F12 VH CDR3 Kabat	DQITTAWFTY
200	Ch2F12 VL CDR1 Kabat	SATSSVSYMF
201	Ch2F12 VL CDR2 Kabat	LTSNLAS
196	Ch2F12 VL CDR3 Kabat	QQWSSNPSIT
202	Ch2F12 VH CDR1 Chothia	GYSITSGY
203	Ch2F12 VH CDR2 Chothia	TYAGS
199	Ch2F12 VH CDR3 Chothia	DQITTAWFTY
204	Ch2F12 VH CDR1 Contact	TSGYYWN
205	Ch2F12 VH CDR2 Contact	WMGYITYAGSNN
206	Ch2F12 VH CDR3 Contact	ARDQITTAWFT
207	Ch2F12 VL CDR1 Contact	SYMFWY
208	Ch2F12 VL CDR2 Contact	PWIYLTSNLA
209	Ch2F12 VL CDR3 Contact	QQWSSNPSI

[1098] Note: where the description relates to CDRs (e.g., SEQ ID NO: 49) , the terms IMGT, Kabat, Chothia, or Contact refer to the different CDR definition sche mes as described in the Definition section.

[1099] Examples

[1100] Example 1 Obtaining Mouse Anti-Human CDH17 Antibody

[1101] 1.1 Immunization of mice

[1102] Recombinant CDH17 protein was obtained from Sino Biological (Cat. No. 11360-H08H.) and was used as the immunogen. 8-12 weeks old Balb/c mice were immunized six times with an intra-muscular injection of the immunogen with adjuvant.

[1103] 1.2 Serum detection and screening

[1104] The immunized mice were subjected to blood collection from the eye orbit, and the serum titers were detected by ELISA (recombinant human CDH17 protein was used as coating antigen) . Serum titer need to be greater than 10K for moving to fusion, otherwise the enhanced immunization was continued.

[1105] 1.3 Fusion and screening

[1106] The whole spleen and 1/2 lymph node were taken and fused with myeloma SP2/0 cell by optimized PEG fusion. The fused cells were plated in four 384-well plates (10^2 to 10^4 cells per well) and cultured in 37℃ with 5%CO_2 . The supernatants from each wells were collected and screened by ELISA to detect the binding of the cell culture supernatant to recombinant human CDH17 protein, and hybridoma cells from the binding-postive wells were transferred to 96-well plates for further culture. After several days of growth, the supernatants from each wells were collected and detected for binding to recombinant human CDH17 protein by ELISA. Positive supernatants were further detected for the binding to serial diluted human CDH17 protein for affinity ranking, and 120 parental clones with the highest affinity were selected for subcloning.

[1107] 1.4 Subcloning and screening

[1108] Subcloning was performed by a limited dilution method and the hybridomas were screened by ELISA. Cells were plated in a 96-well plate and cultured to cover approximately 1/6 bottom of the plate. The binding of the supernatant in each well to the human CDH17 recombinant protein was detected by ELISA, and two wells with high OD values and good cell status were used for the next round of subcloning. After the last round of subcloning, all positive monoclonal hybridomas were immediately expanded. A portion of each hybridoma was frozen for later use, and the other portion was used for ascites preparation.

[1109] 1.5 Ascites preparation and antibody purification

[1110] Monoclonal hybridoma was injected to the abdomen of F1 mice for antibody production. The produced ascites was purified with Protein A/G and the concentration of the antibodies was determined by BCA method.

[1111] Example 2 In Vitro Evaluation of Anti-CDH17 Antibodies

[1112] 2.1 Binding Affinity of Anti-CDH17 antibodies on COLO 205 cell

[1113] The binding EC50 of the anti-CDH17 antibodies on tumor cell were tested as follow. Cell culture of human colon cancer cell line COLO 205 (purchased

from National Collection of Authenticated Cell Cultures) was maintained in vitro as i ndependent monolayer cultures at 37℃ with 5%CO_2. Cells were harvested by incubati ng with 1xPBS containing 1mM EDTA followed by centrifugation at 1000 r. p. m for 5 minutes. The cell was resuspended in cold PBS and a serial dilution of CL075814, CL075835 and CL075942 antibodies were added to the respec tive wells. The cell solutions were mixed, incubated at 4℃ for 45 min and then washed with cold PBS prior to addition of AlexaFluor®488-conjugated AffiniPure Goat Anti-Mouse IgG (H+L) (Jackson Immuno Research LABORATOTIES. INC.) second ary antibody at a dilution of 1: 300. After incubation at 4℃ for 30 min, the cells we re washed with cold PBS, and then subjected to flow cytometry analys is. FIG. 1A shows that CL075814 binds to COLO 205 cell with an EC50 of 0.83 nM, CL075835 binds to COLO 205 cell with an EC50 of 3.82 nM. FIG. 1B shows that CL075942 binds to COLO 205 cell with an EC50 of 4.31 nM.

[1114] 2.2 Anti-CDH17 antibodies specifically recognize CDH17 overexpressed on the s urface of 293T cells

[1115] The plasmid for expression of human CDH17 fused to GFP (pCDNA3.1-h. CDH17-GFP) was obtained from YouBio and transfected into 293T cell and imm unofluorescence staining was performed to determine the binding specificity of anti-CDH17 antibodies CL075814 and CL075835. Briefly, sterile cover slide s were put into six well plates. $5x10^5$ 293T cells were seeded to each we ll and cultured at 37℃ overnight. On the next day, pCNDA3.1-h. CDH17-GFP was transfected into the cells using Lipofectamine LTX &PLUS™ Reagent following the manufacture's protocol. 48 hours after the transfection, successful expression of the fusion protein was confirmed by examine GFP signal under fluorescence microscope. Then, cover slides with the transfected cells were washed with cold PBS, fixed with 4%paraformaldehyde, blocked with blocking solution (PBS containing 10%goat serum) . CL075814, CL075835 were diluted to 20 μg/mL with the blocking solution, added onto the cover slides and incubated at 4℃ overnight. 300 uL of 1: 300 diluted Alexa Fluor 594 AffiniPure Goat Anti-Mouse IgG (H+L) secondary antibody was then added onto each cover slides after washing with cold PBS. The cover slides were further incubated at RT for 1 hour protecting from light. Finally, the cover slides were incubated with 1: 10000 diluted DAPI for 5 minutes and washed four times with PBS then analyzed under fluorescence microscope. The results of immunofluorescence staining with CL075814 was show in FIG. 2. FIG. 2A shows the signal from human CDH17-GFP protein, which indicates the location of expressed CDH17. FIG. 2B shows the signal from CL075814 staining. FIG. 2C shows the DAPI staining of nucleus of the cells. FIG. 2D shows the merged view of FIG. 2A,

FIG. 2B and FIG. 2C. The merged view in FIG. 2D shows that the CL075814 staining co-localized well with h. CDH17-GFP fusion protein, which means that CL075814 specifically binds to human CDH17 expressed on the surface of 293T cell. The results of immunofluorescence staining with CL075835 was show in FIG. 3. FIG. 3A shows the signal from human CDH17-GFP protein, which indicates the location of expressed CDH17. FIG. 3B shows the signal from CL075835 staining. FIG. 3C shows the DAPI staining of nucleus of the cells. FIG. 3D shows the merged view of FIG. 3A, FIG. 3B and FIG. 3C. The merged view in FIG. 3D shows that the CL075835 staining co-localized well with h. CDH17-GFP fusion protein, which means that CL075835 specifically binds to human CDH17 expressed on the surface of 293T cell.

[1116] Example 3 Determination of Nucleotide Sequences of cDNA Encoding the Variable Region of Mouse anti-CDH17 Antibodies

[1117] Individual hybridoma clones of CL075814, CL075835 and CL075942 were cultured in T25 flasks with 10 mL hybridoma cell culture medium (PFHM-II Protein-Free Hybridoma Medium) . Cells were grown at 37℃ until 80%confluent. Culture medium was then removed and cells were twice washed with 1x PBS. 1mL TRIzol reagent was added directly to the flask and cells were lysed by mixi ng with pipette. The cell lysate was then recovered from the T25 flask and total RNA was isolated using standard methods. cDNA was then generated from th e isolated RNA according to the TaKaRa PrimeScript II 1st strand cDN A synthesis kit protocol. Amplification of the hybridoma V-region of the res ultant cDNA was then performed according TaKaRa Premix Taq™ (TaKaRa Taq™ Version 2.0 plus dye) protocol. Primer pairs, as listed in Table 1 below, were used for amplification.

[1118] Table 1. Primers for amplifying nucleic acids encoding anti-CDH17 antibodies

SEQ ID NO:	Primer	Sequence (5' to 3')
129	MuIgV H 5'-A	GGGAATTCATGRASTTSKGGYTMARCTKGRTTT
130	MuIgV H 5'-B	GGGAATTCATGRAATGSASCTGGGTYWTYCTCTT
131	MuIgV H 5'-C1	ACTAGTCGACATGGACTCCAGGCTCAATTTAGTTTTCCT
132	MuIgV H 5'-C2	ACTAGTCGACATGGCTGTCYTRGBGCTGYTCYTCTG
133	MuIgV H 5'-C3	ACTAGTCGACATGGVTTGGSTGTGGAMCTTGCYATTCCT
134	MuIgV H 5'-D1	ACTAGTCGACATGAAATGCAGCTGGRTYATSTTCTT
135	MuIgV H 5'-D2	ACTAGTCGACATGGRCAGRCTTACWTYYTCATTCCT
136	MuIgV H 5'-D3	ACTAGTCGACATGATGGTGTTAAGTCTTCTGTACCT
137	MuIgV H 5'-E1	ACTAGTCGACATGGGATGGAGCTRTATCATSYTCTT
138	MuIgV H 5'-E2	ACTAGTCGACATGAAGWTGTGGBTRAACTGGRT
139	MuIgV H 5'-E3	ACTAGTCGACATGGRATGGASCKKIRTCTTTMTCT
140	MuIgV H 5'-F1	ACTAGTCGACATGAACTTYGGGYTSAGMTTGRTTT
141	MuIgV H 5'-F2	ACTAGTCGACATGTACTTGGGACTGAGCTGTGTAT
142	MuIgV H 5'-F3	ACTAGTCGACATGAGAGTGCTGATTCTTTTGTG
143	MuIgV H 5'-F4	ACTAGTCGACATGGATTTTGGGCTGATTTTTTTTATTG
144	MuIgMV H 3'-1	CCCAAGCTTACGAGGGGGAAGACATTTGGGAA
145	MuIgGV H 3'-2	CCCAAGCTTCCAGGGRCCARKGGATARACIGRTGG
146	MuIgκV L 5'-A	GGGAATTCATGRAGWCACAKWCYCAGGTCTTT
147	MuIgκV L 5'-B	GGGAATTCATGGAGACAGACACACTCCTGCTAT
148	MuIgκV L 5'-C	ACTAGTCGACATGGAGWCAGACACACTSCTGYTATGGGT
149	MuIgκV L 5'-D1	ACTAGTCGACATGAGGRCCCCTGCTCAGWTTYTTGGIWTCTT
150	MuIgκV L 6'-D2	ACTAGTCGACATGGGCWTCAAGATGRAGTCACACAKWYYCWGG
151	MuIgκV L 5'-E1	ACTAGTCGACATGAGTGTGCYCACTCAGGTCCTGGSGTT
152	MuIgκV L 5'-E2	ACTAGTCGACATGTGGGGAYCGKTTTYAMMCTTTTCAATTG
153	MuIgκV L 5'-E3	ACTAGTCGACATGGAAGCCCCAGCTCAGCTTCTCTTCC
154	MuIgκV L 5'-F1	ACTAGTCGACATGAGIMMKTCIMTTCAITTCYTGGG
155	MuIgκV L 5'-F2	ACTAGTCGACATGAKGTHCYCIGCTCAGYTYCTIRG
156	MuIgκV L 5'-F3	ACTAGTCGACATGGTRTCCWCASCTCAGTTCCTTG
157	MuIgκV L 5'-F4	ACTAGTCGACATGTATATATGTTTGTTGTCTATTTCT
158	MuIgκV L 5'-G1	ACTAGTCGACATGAAGTTGCCTGTTAGGCTGTTGGTGCT
159	MuIgκV L 5'-G2	ACTAGTCGACATGGATTTWCARGTGCAGATTWTCAGCTT
160	MuIgκV L 5'-G3	ACTAGTCGACATGGTYCTYATVTCCTTGCTGTTCTGG
161	MuIgκV L 5'-G4	ACTAGTCGACATGGTYCTYATVTTRCTGCTGCTATGG
162	MuIgκV L 3'-1	CCCAAGCTTACTGGATGGTGGGAAGATGGA
163	MuIgλV L 5'-A	GGGAATTCATGGCCTGGAYTYCWCTYWTMYTCT
164	MuIgλV L 3'-1	CCCAAGCTTAGCTCYTCWGWGGAIGGYGGRAA

[1119] PCR products were checked with 1%agarose gel. Positive PCR products were recovered using QIAgen gel extraction kits and subsequently cloned into pGM-T vector using pGM-T ligation kit (TIANGEN, VT202-02) . pGM-T vectors with PC R product insertion were transformed into DH5a competent cells and c ultured on Ampicillin-positive agar plates. Each bacterial clone was sent

for Sanger sequencing using the SP6 primer (5' - ATTTAGGTGACACTATAG-3' , SEQ ID NO. 165) . Obtained sequences were compared for consiste nce to confirm target V_H and V_L sequences, respectively. V_H and V_L sequences were t hen analyzed on the IMGT database (imgt. org) to provide the V-region, Frame and CDR elements of V_H and V_L.

[1120] Example 4 Production and in vitro Evaluation of Chimeric Anti-CDH17 Antibodies

[1121] 4.1 Expression and Purification of The Chimeric Anti-CDH17 Antibodies.

[1122] pcDNA3.1-HC containing the human IgG1 heavy chain constant r egion and pcDNA3.1-LC containing the human IgG1 light chain constant r egion were used as expression vectors. The V_H and V_L of CL075814 were synthesized and cloned into pCDNA3.1-HC and pCDNA3.1-LC, respectively, resulting in Ch814-HC and Ch814-LC. Ch814-HC and Ch814-LC were mixed 1: 1 and transfected into 293F cell using Polyethylenimine 'Max' (MW 40,000) (24765-2, Polysciences, Inv.) as transfection reagent and cultured under 125 r. p. m shakin g at 37°C with 5%CO_2 for 7 days. The supernatant was then harvested and chimeric antibody Ch814 was purified following standard protein A p urification procedure and the concentration of the purified antibody was determined b y UV method. The chimeric antibodies Ch835, Ch942, Ch2E21, and Ch2F1 2 were produced the same way.

[1123] 4.2 Flow Cytomerty Analysis of Binding EC50 of Anti-CDH17 Chimeric An tibodies on Human Pancreatic Cancer Cell line AsPC-1.

[1124] Cell culture of human pancreatic cancer cell line AsPC-1 (purchased from National Collection of Authenticated Cell Cultures) was maintained in vitro as indep endent monolayer cultures at 37°C with 5%CO_2. The binding EC50 of Ch814, Ch835 and Ch942 were determined following the same procedure described in example 2.2. FIG. 4 shows that Ch814 binds to AsPC-1 cell with an EC 50 of 0.74 nM, Ch835 binds to AsPC-1 cell with an EC50 of 2.37 nM, Ch 942 binds to AsPC-1 cell with an EC50 of 1.97 nM.

[1125] Example 5 Production and in vitro Evaluation of Humanized Anti-CDH17 Antibodies

[1126] The mouse Anti-CDH17 antibody CL075814 was humanized by CDR grafti ng (Proc. Nal. Acad. Sci. USA 86, 10029-10033 (1989) . The CDR regions of CL075814 were grafted to the most similar human germ line sequences. Some of the key residues that are important were back mutated based on, for example, the criteria given by Queen et al. (Proc. Nal. Acad. Sci. USA 86, 10029-10033 (1989) .

[1127] Five humanized heavy chain variants were named Hu814-H1, Hu814-H2, Hu814-H3, Hu814-H4, Hu814-H5. The amino acid sequence of the Hu814-H1 heavy chain is shown in SEQ ID NO: 20. The amino acid sequence of the Hu814-H2 heavy chain is shown in SEQ ID NO: 22. The amino acid sequence of the Hu814-H3 heavy chain is shown in SEQ ID NO: 24. The amino acid sequence of the Hu814-H4 heavy chain is shown in SEQ ID NO: 26. The amino acid sequence of the Hu814-H5 heavy chain is shown in SEQ ID NO: 28. Four humanized light chain variants were named Hu814-L1, Hu814-L2, Hu814-L3, Hu814-L4. The amino acid sequence of the Hu814-L1 light chain is shown in SEQ ID NO: 30. The amino acid sequence of the Hu814-L2 light chain is shown in SEQ ID NO: 32. The amino acid sequence of the Hu814-L3 light chain is shown in SEQ ID NO: 34. The amino acid sequence of the Hu814-L4 light chain is shown in SEQ ID NO: 36.

[1128] The DNA sequences encoding the full length Hu814-H1, Hu814-H2, Hu814-H3, Hu814-H4, Hu814-H5, Hu814-L1, Hu814-L2, Hu814-L3, Hu814-L4 amino acid sequences were individually synthesized and constructe d into pcDNA3.1 expression vector. The antibodies Hu814-H1L1, Hu814-H2L2, Hu814-H3L3 and Hu814-H1L4, Hu814-H4L4, Hu814-H5L4 were produce d in 293F cell following the same procedure described in example 4.1.

[1129] The binding EC50 of the humanized antibodies on COLO 205 or SNU-16 tumor cells were tested following the same procedure described in example 2.2. FIG. 5A shows that Hu814-H1L1, Hu814-H2L2 binds to COL O 205 cell with comparable affinity as the chimeric antibody Ch814, while the binding affinity of Hu814-H3L3 is much weaker than other humanized antibodies . FIG. 5B shows that Hu814-H1L4, Hu814-H4L4 and Hu814-H5L4 binds to SNU-16 cell with comparable affinity as the chimeric antibody Ch814.

[1130] The mouse Anti-CDH17 antibody CL075835 was humanized by the same m ethods. Three humanized heavy chain variants were named Hu835-H1, Hu835-H2, and Hu835-H3; and three humanized light chain variants were named Hu835-L1, Hu835-L2, and Hu835-L3. The amino acid sequence of the Hu835-H1 heavy chain is shown in SEQ ID NO: 38. The amino acid sequence of the Hu835-H2 heavy chain is shown in SEQ ID NO: 40. The amino acid sequence of the Hu835-H3 heavy chain is shown in SEQ ID NO: 42. The amino acid sequence of the Hu835-L1 light chain is shown in SEQ ID NO: 44. The amino acid sequence of the Hu835-L2 light chain is shown in SEQ ID NO: 46. The amino acid sequence of the Hu835-L3 light chain is shown in SEQ ID NO: 48. Results are shown in FIG. 6. Hu835-H1L1, Hu835-H2L2 and Hu835-H3L3 binds to human gastric cell l ine AGS with comparable affinity as the chimeric antibody Ch835.

[1131] Example 6 Analysis of Binding Affinity Against Human and Monkey CDH17

[1132] Plasmids encoding human CDH17 fused with GFP (pcDNA3.1-h. CDH17-GFP) and cyno monkey CDH17 fused with GFP (pcDNA3.1-c. CDH17-GFP) were obtained from YouBio. 293F cells were cultured with OPM-293 CD05 medium in an incubator with shaking (125 r.p. m) at 37℃, 5% CO_2. When the cell density reaches $2x10^6$/mL and the viability is greater than 95%, 20 mL of the cells were put into a 125 mL flask, a total of 3 flasks were prepared. pcDNA3.1-h. CDH17-GFP, pcDNA3.1-c. CDH17-GFP, and the empty vector expression GFP only (pcDNA3.1-GFP) were transfected into the 293F cells with PEI max reagent following standard procedure. 48 hours after transfection, the expression of the fusion protein was confirmed by examine the GFP signal under fluorescence microscope. Then Cells were harvested by centrifugation at 1000 r. p. m for 5 minutes. The cells were resuspended in cold PBS and aliquoted into 96 well plates and a serial dilution of Hu814-H1L4 , Hu814-H5L4 were added to the respective wells. The cell solutions were mixed, incubated at 4℃ for 45 min and then washed with cold PBS prior to addition of Anti-Human IgG (Fc specific) -FITC antibody produced in goat (SIGMA, F9512-2ML) secondary antibody at a dilution of 1: 300. After incubation at 4℃, the cells were washed with cold PBS, and then subjected to flow cytometry analysis. FIG. 7 A shows that Hu814-H1L4 binds to 293F-h. CDH17-GFP with an EC50 of 1.97 nM, binds to 293F-c. CDH17-GFP with an EC50 of 2.11 nM, and the antibody does not bind to 293F-vector. FIG. 7B shows that Hu814-H5L4 binds to 293F-h. CDH17-GFP with an EC50 of 3.23 nM, binds to 293F-c. CDH17-GFP with an EC50 of 4.11 nM, and the antibody does not bind to 293F-vector.

[1133] Example 7 In Vitro Stability Assessment of Humanized Anti-CDH17 Antibodies

[1134] Long term stability is critical for antibody-based therapeutics to be successfully developed. Accelerated stability assessment under 40℃ are generally used as a surrogate for long term stability of antibody. So, we evaluated the stability of Hu814-H1L4 and Hu814-H5L4 under 40℃ incubation. Hu814-H1L4 and Hu814-H5L4 were prepared at a concentration of 20 mg/kg in 20 mM Histidine-acetate, 150 mM NaCl, pH 5.5 buffer, and aliquoted into 3 tubes each. One tube of the antibodies were marked as T0 and stored at -80℃, the other tubes of the antibodies were marked as Day14 and Day28 and incubated at 40℃ for 14 days and 28 days, respectively. After incubation, the T0, Day14 and Day 28 samples were subjected to flow cytometry analysis following the procedure described in example 6 to determine the binding affinity of the samples on SNU-16 gastric cancer cell line. In addition, the T0 and Day14 samples were also analyzed by size exclusion chromatography (SEC) , reduced capillary electrophoresis sodium dodecyl sulfate (rCE-SDS) , non-reduced capillary electrophoresis sodium dodecyl su

lfate (nrCE-SDS) , and imaged capillary isoelectric focusing (iCIEF) following s tandard procedure. FIG. 8A shows that Hu814-H1L4 Day14 sample has similar EC50 as that of the T0 sample. However, the binding EC50 of Hu814-H1L4 decreased sl ightly from 2.41 nM to 5.8nM after incubating at 40℃ for 28 days. FI G. 8B shows that no significant change in EC50 was observed even aft er incubating Hu814-H5L4 at 40℃ for 28 days. Table 2 shows that no sign ificant changes in main peaks of SEC, rCE-SDS and nr-CE-SDS were observed for neither Hu814-H1L4 nor Hu814-H5L4 after incubating at 40℃ for 1 4 days. The main peak of iCIEF decreased 17.5%for Hu814-H4L4 after incuba ting at 40℃ for 14 days. The main peak of iCIEF also decreased for Hu814-H5L4 after incubating at 40℃ for 14 days. However, the decrease is lesser than that o f CL07814-H1L4.

[1135] Table 2 Summary of SEC, rCE, nrCE and iCIEF results

		SEC(%)			rCE-SDS(%)		nrCE-SDS(%)			iCIEF(%)		
Antibody	Sample ID	HMW	Main	LMW	Main	LMW	Main	HMW	LMW	Acid	Main	Basic
CL07581_H1L4	T0	0.96	99.04	0	98.1	2	96.3	3.6	0.1	32.5	63.8	3.6
	Day14	0.98	98.09	0.93	97.5	2.5	95.1	4.7	0.2	47.1	46.3	6.6
CL07581_H5L4	T0	1.01	98.99	0	98.6	1.4	96.8	3	0.2	30.4	66.9	2.7
	Day14	0.93	98.09	0.97	98.4	1.6	95.5	4.1	0.4	41.7	54	4.3

[1136] Example 8 Production of Anti-HER3 Antibody Patritumab, Anti-Trop2 Antibody Da topotamab and Anti-CDH17 Reference AntibodyRAb17.

[1137] Patritumab is an antibody recognizing human HER3 protein. The heavy chain sequence (SEQ ID NO: 13) of patritumab was obtained from KEGG DRUG Database. DNA encoding the heavy chain was synthesized and clon ed into pcDNA3.1 vector, resulting in patritumab-HC. The light chain sequence (SEQ ID NO: 14) of patritumab was obtained from KEGG DRUG Database. DNA e ncoding the light chain was synthesized and cloned into pcDNA3.1 vec tor, resulting in patritumab-LC. Patritumab-HC and patritumab-LC were mixed 1: 1 and transfected into 293F cells using PEI reagent and cultured under 125 r.p. m sha king at 37℃ with 5%CO_2 for 7 days. The supernatant was then harvested and patritumab was purified following standard protein A purification procedure and the concentration of the purified antibody was determined by UV method.

[1138] Datopotamab is an antibody recognizing human Trop2 protein. The heavy chain sequence (SEQ ID NO: 17) and light chain sequence (SEQ ID NO: 18) of datopotamab was also obtained from KEGG DRUG Database. Datopotamab was produced following the same procedure as producing patritumab.

[1139] RAb17 is a reference antibody recognizing human CDH17 protein. The heavy chain sequence (HC, SEQ ID NO: 167) and light chain sequence (LC, SEQ ID NO: 168) of RAb17 was obtained from patent US9207242B2. RAb17 was produced following the same procedure as producing patritumab.

[1140] Example 9 Determine the Binding Domain of Anti-Human CDH17 Antibodies

[1141] Hu814-H1L4, Hu835-H1L1, Ch942, Ch2F12, and RAb17 bind to human CDH17, but do not bind to mouse CDH17. Ch2E21 binds to both human CDH17 and mouse CDH17, but the binding on mouse CDH17 is weak comparing with human CDH17. The binding domain of these anti-CDH17 antibodies on human CDH17 were determined by a domain swapping approach. To construct domain swapping plasmids, each of the seven extracellular domains (ECD1, ECD2, ECD3, ECD4, ECD5, ECD6, and ECD7) of human CDH17 were replaced with the corresponding extracellular domain sequences of mouse CDH17, and the constructs were also fused with GFP protein, resulting in pcDNA3.1-ECD1-GFP, pcDNA3.1-ECD2-GFP, pcDNA3.1-ECD3-GFP, pcDNA3.1-ECD4-GFP, pcDNA3.1-ECD5-GFP, pcDNA3.1-ECD6-GFP and pcDNA3.1-ECD7-GFP, respectively. The plasmids were then transfected into 293F following procedure described in example 6.48 hours after transfection, the expression of the fusion protein was confirmed by examine the GFP signal under fluorescence microscope. Then Cells were harvested by centrifugation at 1000 r. p. m for 5 minutes. The cells were resuspended in cold PBS and aliquoted to 96-well plate to $1x10^5$ cells per well. Then 50 ug/mL of Hu814-H1L4, Hu835-H1L1, Ch942, Ch2F12, RAb17, Ch2E21 and human IgG control were added to the respective wells. The cell solutions were mixed, incubated at 4℃ for 45 min and then washed with cold PBS prior to addition of Alexa Fluor®647 AffiniPure Goat Anti-Human IgG, Fcγ fragment specific (Jackson ImmunoResearch LABORATORIES INC., 109-605-190) secondary antibody at a dilution of 1: 300. After incubation at 4℃, the cells were washed with cold PBS, and then subjected to flow cytometry analysis. FIG. 9A shows the histogram graphs of the Hu814-H1L4 domain mapping experiment. The gray line shows the background signal from human IgG control, the black line shows the binding of Hu814-H1L4 to the indicated cells. The binding signal of Hu814-H1L4 diminished only when the ECD4 of human CDH17 was swapped with the ECD4 of mouse CDH17. This result show that Hu814-

H1L4 binds to the ECD4 domain of human CDH17. Similarly, FIG. 9B sho ws that Hu835-H1L1 binds to the ECD3 domain of human CDH17. Simil arly, FIG. 9C shows that Ch942 also binds to the ECD3 domain of huma n CDH17. Similarly, FIG. 9D shows that Ch2F12 binds to the ECD4 doma in of human CDH17. Similarly in FIG. 9E, a partial reduction of bind ing of Ch2E21 on ECD6 was observed, indicating that Ch2E21 binds to the ECD6 domain of human CDH17. Similarly, FIG. 9F shows that RAb17 binds to the ECD2 domain of human CDH17, which is consistent with th e result from patent US9207242B2.

[1142] Example 10 Preparation of linker-payload

[1143] 10.1 Preparation of compound LP-1

[1144] Step 1: Synthesis of intermediate 11-1

[1145] To the solution of compound 11-1A (Mc-Val-Ala-OH, purchased fro m purchased from MedChemExpress Shanghai, 2.4 g, 6.29 mmol) and 11-1B (3.18 g, 6.29 mmol) in the mixture of DCM: MeOH (v: v=2: 1, 90 mL) , EEDQ (1.86 g, 7.55 mmol) was added at room temperature (rt) . The reaction was st irred at rt for 24 hours, solvent was removed in vacuo, the crude residue was further purified by flash chromatography to give compound 11-1 (3.9g, 71%) . LC-MS (ESI, m/z) : 868.49 (M+H) .

[1146] Step 2: Synthesis of intermediate 11-2

[1147] Compound 11-1 (2 g, 2.3 mmol) was dissolved in anhydrous THF (5 0 mL) , hydrogen fluoride-pyridine (4.6 g, 46 mmol) was added under an argon atmosphere at 0°C, and then the reaction mixture was stirred at 0°C for 2 hours. The re action was quenched by addition of water, extracted with DCM (Dichlo romethane) , and the organic phase dried, and concentrated. The residue was purified by silica gel chromatography to afford compound 11-2 (1.1g, 76%) . LC-MS (ESI, m/ z) : 630.31 (M+H) .

[1148] Step 3: Synthesis of intermediate 11-3

[1149] Compound 11-2 (700 mg, 1.11 mmol) was dissolved in anhydrous DMF (N, N-dimethylformamide) (4 mL) , DIPEA (N, N-Diisopropylethylamine) (0.39 ml, 2 .23 mmol) and 4, 4'-dinitrodiphenyl carbonate (406 mg, 1.33 mmol) were added under a argon atmosphere at room temperature, and then the rea ction mixture was stirred at ambient temperature for overnight. The solvent was remov ed by concentration, the product was precipitated from MTBE (methyl tertiary-butyl ether) . The yellow solid was collected by filtration, washed with diethyel eth er, and dried to give compound 11-3, used in next step directly. LC-MS (ESI, m/z) : 7 95.41 (M+H) .

[1150] Step 4: Synthesis of intermediate 11-4

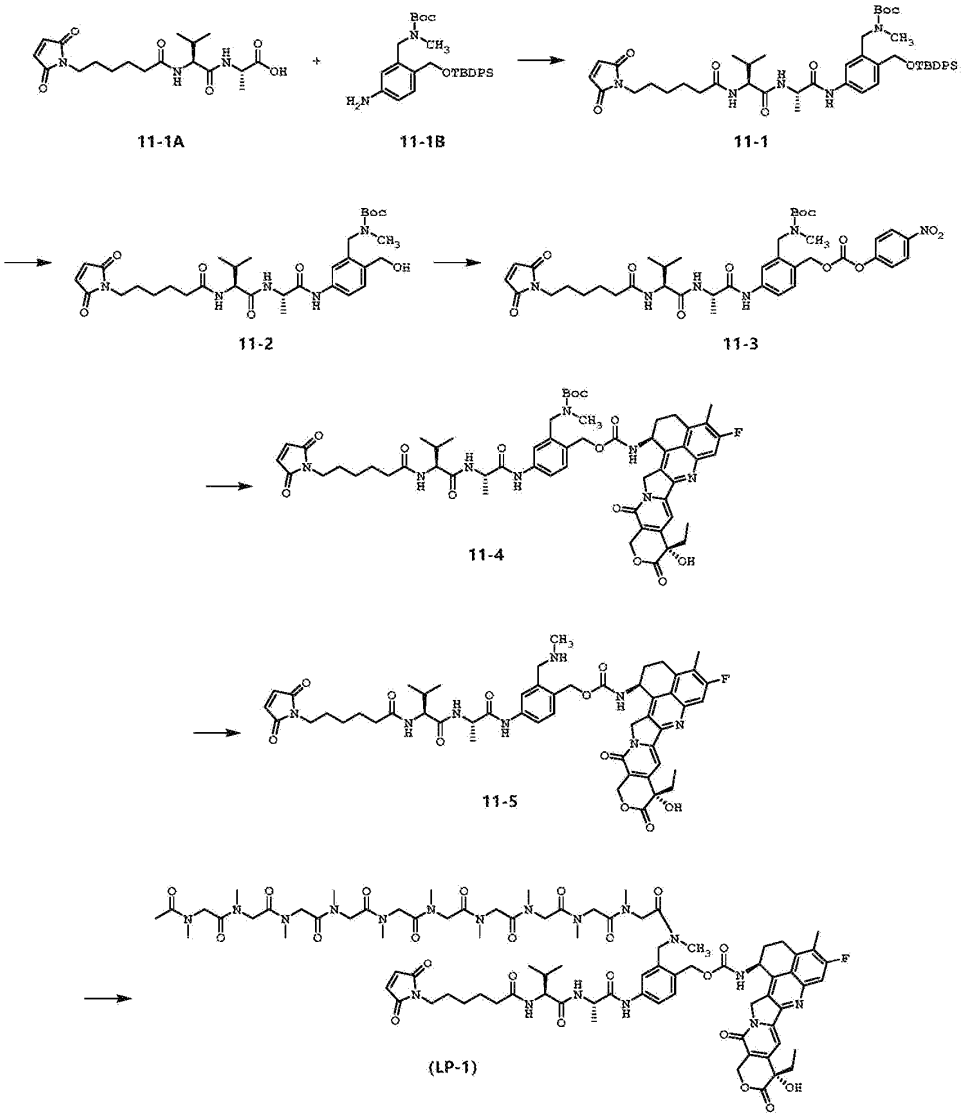
[1151] Compound 11-3 (300 mg, 0.44 mmol) was dissolved in anhydrous DMF (4 mL) , dried pyridine (1 mL) was added, followed by exatecan mesylate (purchased from MedChemExpress Shanghai, 234 mg, 0.44 mmol) and HOBt (1-Hydroxybenzotriazole) (60 mg, 0.44 mmol) . The reaction mixture was stirred at rt under argon overnight. The product was purified by pre-HPLC to afford intermediate 11-4 (230 mg, 48%) . LC-MS (ESI, m/z) : 1091.53 (M+H) .

[1152] Step 5: Synthesis of intermediate 11-5

[1153] Compound 11-4 (200 mg, 0.183 mmol) was dissolved in 1 mL anhydrous DCM, 300 μL TFA was added at 0℃, the reaction mixture was stirred at rt for 30 min, the solvent was removed by concentration, to afford the intermediate 11-5 as TFA (Trifluoroacetate) salt, which is used in next step without further purification. LC-MS (ESI, m/z) : 991.47 (M+H) .

[1154] Step 6: Synthesis of compound LP-1

[1155] Compound 11-5 (120 mg, 0.109 mmol) was dissolved in 1 mL anhydrous DMF, Ac-Sar10-COOH (84 mg, 0.109 mmol) was added, followed by HATU (2- (7-Azabenzotriazol-1-yl) -N, N, N', N'-tetramethyluronium hexafluorophosphate) (50 mg, 0.130 mmol) and DIPEA (38 μL, 0.22 mmol) , the reaction mixture was stirred at rt overnight, the solvent was removed by concentration, the crude product was purified by pre-HPLC to afford compound LP-1 (74 mg, 38%) . LC-MS (ESI, m/z) : 1743.85 (M+H) .



[1156] Example 11 Production of Antibody-Drug Conjugate

[1157] General Method for Producing Antibody-Drug Conjugate

[1158] The antibody that can be used in the antibody-drug conjugate of the present inve ntion is not particularly limited as long as it is an anti-CDH17 antibody ha ving internalization activity or a functional fragment of the antibody.

[1159] The -L1-Lx- (linkers) and -NH-DX (active moieties or payload) are presented for t he purposes of illustrating the exemplary embodiments disclosed herein and not for th e purposes of limiting the same.

[1160] Next, a typical method for producing the antibody-drug conjugate of the present inve ntion will be described. It is to be noted that, in the description below, “compound No. ” shown in each reaction scheme is used to represent a compound. Specifically, ea

ch compound is referred to as a “compound of formula (1) ” , “compound (1) ” , or the like. The same holds true for the other compound Nos.

[1161] The antibody-drug conjugate of this invention in which the anti-CDH17 antibody is connected to the linker structure via a thioether can be produced by reacting an antibody having a sulfhydryl group converted from a disulfide bond by the reduction of the anti-CDH17 antibody, with the compound (2) . This antibody-drug conjugate can be produced by the following method, for example.

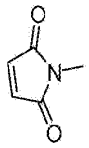
[1162] [Expression 1]

$$L^1\text{-}L^x\text{-(NH-DX)} \xrightarrow{Ab} Ab\text{-}L^1\text{-}L^x\text{-(NH-DX)}$$

(2) (1)

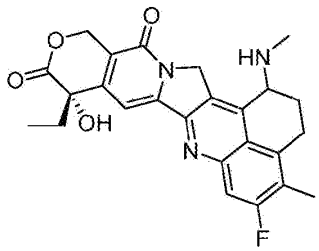
[1163] Wherein Ab represents an antibody with a sulfhydryl group, wherein L^1 has a structure represented by - (Succinimid-3-yl-N) -, and L^1 represents a maleimidyl group represented by the following formula.

[1164] [Formula 1]



[1165] Wherein (NH-DX) can be a structure represented by the following formula.

[1166] [Formula 2]



[1167] $-L^1-L^x-$can be a structure represented by any of the following formulas:

[1168] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -GGFG-PABC-;

[1169] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-PABC-;

[1170] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-PABC-;

[1171] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-PABC-;

[1172] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-PABC-; -CH2-C (=O) -NH-CH2CH2-C (=O) -GGFG-PABC-;

[1173] -C (=O) -CH2CH2CH2CH2CH2CH2-C (=O) -GGFG-PABC-; - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -GGFG-NH-CH2CH2-C (=O) -;

[1174] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1175] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2CH2-C (=O) -;

[1176] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1177] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2CH2CH2-C (=O) -;

[1178] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2-O-CH2-C (=O) -;

[1179] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2CH2-O-CH2-C (=O) -;

[1180] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1181] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-NH-CH2CH2-C (=O) -;

[1182] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1183] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -GGFG-NH-CH2CH2-C (=O) -;

[1184] -CH2-C (=O) -NH-CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1185] -C (=O) -CH2CH2CH2CH2CH2CH2-C (=O) -GGFG-NH-CH2CH2CH2-C (=O) -;

[1186] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -VA-PABC-;

[1187] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-PABC-;

[1188] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-PABC-;

[1189] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-PABC-;

[1190] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2o-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-PABC-;

[1191] -CH2-C (=O) -NH-CH2CH2-C (=O) -VA-PABC-;

[1192] -C (=O) -CH2CH2CH2CH2CH2CH2-C (=O) -VA-PABC-;

[1193] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -VA-NH-CH2CH2-C (=O) -;

[1194] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -;

[1195] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2CH2-C (=O) -;

[1196] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -;

[1197] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2CH2CH2CH2CH2-C (=O) -;

[1198] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2-O-CH2-C (=O) -;

[1199] - (succinimidyl-3-yl-N) -CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2CH2-O-CH2-C (=O) -;

[1200] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -;

[1201] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-NH-CH2CH2-C (=O) -;

[1202] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -;

[1203] - (succinimidyl-3-yl-N) -CH2CH2-C (=O) -NH-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2O-CH2CH2-C (=O) -VA-NH-CH2CH2-C (=O) -;

[1204] -CH2-C (=O) -NH-CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -; and

[1205] -C (=O) -CH2CH2CH2CH2CH2CH2-C (=O) -VA-NH-CH2CH2CH2-C (=O) -.

[1206] In the above-described reaction scheme, the antibody-drug conjugate (1) can be understood as having a structure in which one structure moiety from the drug to the linker terminus is connected to one antibody. However, this description is given for the sake of convenience, and there are actually many cases in which a plurality of the aforementioned structure moieties is connected to one antibody molecule. The same holds true for the explanation of the production method described below.

[1207] The antibody having a sulfhydryl group can be obtained by a method well known to a person skilled in the art (Hermanson, G. T, Bioconjugate Techniques, pp. 56-136, pp. 456-493, Academic Press (1996)) . Examples of the method can include, but are not limited to: Traut's reagent being reacted with the amino group of the antibody; N-succinimidyl S-acetylthioalkanoates being reacted with the amino group of the antibody followed by reaction with hydroxylamine; N-succinimidyl 3- (pyridyldithio) propionate being reacted with the antibody, followed by reaction with a reducing agent; the antibody being reacted with a reducing agent such as dithiothreitol, 2-mercaptoethanol, or tris (2-carboxyethyl) phosphine hydrochloride (TCEP) to reduce the interchain disulfide bond in the antibody, so as to form a sulfhydryl group.

[1208] Specifically, an antibody with interchain disulfide bonds partially or completely reduced can be obtained by using 0.3 to 3 molar equivalents of TCEP as a reducing agent per interchain disulfide bond in the antibody and reacting the reducing agent with the antibody in a buffer solution containing a chelating agent. Examples of the chelating agent can include ethylenediaminetetraacetic acid (EDTA) and diet

hylenetriaminepentaacetic acid (DTPA) . The chelating agent can be used at a concentr ation of 1 mM to 20 mM. A solution of sodium phosphate, sodium borat e, sodium acetate, or the like can be used as the buffer solution.

[1209] It is to be noted that by carrying out an addition reaction of a sulfhydryl group to a drug-linker moiety, the drug-linker moiety can be conjugated by a thioether bond.

[1210] Then, using 2 to 20 molar equivalents of the compound (2) per antibo dy having a sulfhydryl group, the antibody-drug conjugate (1) in which 2 to 8 drug molecules are conjugated per antibody can be produced. Specifically, a solution containing the compound (2) dissolved therein may be added to a buf fer solution containing the antibody having a sulfhydryl group for the reaction. In t his context, a sodium acetate solution, sodium phosphate, sodium borate, or the like can be used as the buffer solution. pH for the reaction is 5 to 9, and more preferabl y, the reaction may be performed near pH 7. An organic solvent such as dimethyl sulfoxide (DMSO) , dimethylformamide (DMF) , dimethylace tamide (DMA) , or N-methyl-2-pyrrolidone (NMP) can be used as a solvent for diss olving the compound (2) . The reaction may be performed by adding th e solution containing the compound (2) dissolved in the organic solvent at 1 to 20%v/ v to a buffer solution containing the antibody having a sulfhydryl group. The reactio n temperature is 0 to 37℃, more preferably 10 to 25℃, and the reaction time is 0.5 to 2 hours. The reaction can be terminated by deactivating the reactivity of unreacted compound (2) with a thiol-containing reagent. The thiol-containing reagen t is, for example, cysteine or N-acetyl-L-cysteine (NAC) . More specifically , the reaction can be terminated by adding 1 to 2 molar equivalents of NAC to the com pound (2) used, and incubating the obtained mixture at room temperature for 10 to 30 minutes.

[1211] Identification of Antibody-Drug Conjugate

[1212] The produced antibody-drug conjugate (1) can be subjected to concentratio n, buffer exchange, purification, and measurement of antibody concentration and the a verage number of conjugated drug molecules per antibody molecule acc ording to common procedures described below, to identify the antibody- drug conjugate (1) .

[1213] Common Procedure A: Concentration of Aqueous Solution of Antibody or Antibody-Drug Conjugate

[1214] To an Amicon Ultra (50,000 MWCO, Millipore Corporation) container, a solution of an antibody or an antibody-drug conjugate was added, and the solution of the antibody or the antibody-drug conjugate was concentrated by centrifugation (centrifugation at 2000 G to 3800 G for 5 to 20 minutes) .

[1215] Common Procedure B: Measurement of Antibody Concentration

[1216] Using a Microplate reader (Multiskan GO, Thermo Fisher Scientific In c.) , measurement of the antibody absorption was carried out according to the method defined by the manufacturer. In this respect, 280 nm absorption coefficient differin g among antibodies (1.3 $mLmg^{-1}$ cm^{-1} to 1.8 $mLmg^{-1}$ cm^{-1}) was used.

[1217] Common Procedure C: Buffer Exchange for Antibody

[1218] Zeba™ Spin Desalting columns (5mL, 40K MWCO, Thermo Scientific™) were equilibrated with a phosphate buffer (50 mM, pH 7.0) (referred to as PBS7.0/ EDTA in the present description) containing sodium chloride (50 mM) an d EDTA (2 mM) according to the method defined by the manufacturer. A n aqueous solution of the antibody was applied in an amount of 2 mL per Zeba™ (5mL) column, and thereafter, a fraction (about 2 mL) was collected by centrifuging the desalting column (centrifugation at 1000 G for 4 minutes) . This fraction can be concentrated by common procedure A. After measurement of the concent ration of the antibody using common procedure B, the antibody concen tration was adjusted to more than 10 mg/mL using PBS7.0/EDTA.

[1219] Common Procedure D: Purification of Antibody-Drug Conjugate

[1220] Zeba™ Spin Desalting columns (5mL, 40K MWCO, Thermo Scientific™) were equilibrated with any available formulation buffer solution such as a histidine-acetate buffer (20 mM histidine, pH 5.5) containing sodium chloride (150 mM) , or a p hosphate buffer (50 mM, pH 7.0) containing sodium chloride (50 mM) . An aqueous reaction solution of the antibody-drug conjugate (approximately 2 mL) was applied to the Zeba™ column (5 mL) , and thereafter, an antibody fracti on (about 2 mL) was collected by centrifuging the desalting column (centrifugation at 1000 G for 4 minutes) . A gel filtration purification process, in which the collecte d fraction was applied again to the Zeba™ desalting column, and elution was carried out with centrifugation, was repeated a total of 2 times to obtain the antib ody-drug conjugate excluding non-conjugated linker-payload and low-molecular-weight compounds (tris (2-carboxyethyl) phosphine hydrochloride (TCEP) , N-acetyl-L-cysteine (NAC) , and dimethyl sulfoxide) .

[1221] Common Procedure E: Measurement of Antibody Concentration in Antibod y-Drug Conjugate and Average Number of Conjugated Drug Molecules Per A ntibody Molecule

[1222] The conjugated drug concentration in the antibody-drug conjugate ca n be calculated by measuring UV absorbance of an aqueous solution of the antibody-drug conjugate at two wavelengths of 280 nm and 370 nm, and thereaft er performing the calculation shown below.

[1223] The total absorbance at any given wavelength is equal to the sum of the absorbance of all light-absorbing chemical species that are present in a system [additivity of absorbance] . Therefore, based on the hypothesis that the molar absorption coefficients of the antibody and the drug do not vary between before and after conjugation between the antibody and the drug, the antibody concentration and the drug concentration in the antibody-drug conjugate are represented by the following equations.

[1224] $A_{280} = A_{D,280} + A_{A,280} = \varepsilon_{D,280}C_D + \varepsilon_{A,280}C_A$ Equation (1)

[1225] $A_{370} = A_{D,370} + A_{A,370} = \varepsilon_{D,370}C_D + \varepsilon_{A,370}C_A$ Equation (2)

[1226] In this context, A_{280} represents the absorbance of an aqueous solution of the antibody-drug conjugate at 280 nm, A_{370} represents the absorbance of an aqueous solution of the antibody-drug conjugate at 370 nm, $A_{A,280}$ represents the absorbance of the antibody at 280 nm, $A_{A,370}$ represents the absorbance of the antibody at 370 nm, $A_{D,280}$ represents the absorbance of a conjugate precursor at 280 nm, $A_{D,370}$ represents the absorbance of a conjugate precursor at 370 nm, $\varepsilon_{A,280}$ represents the molar absorption coefficient of the antibody at 280 nm, $\varepsilon_{A,370}$ represents the molar absorption coefficient of the antibody at 370 nm, $\varepsilon_{D,280}$ represents the molar absorption coefficient of a conjugate precursor at 280 nm, $\varepsilon_{D,370}$ represents the molar absorption coefficient of a conjugate precursor at 370 nm, C_A represents the antibody concentration in the antibody-drug conjugate, and C_D represent the drug concentration in the antibody-drug conjugate.

[1227] In this context, with regard to $\varepsilon_{A,280}$, $\varepsilon_{A,370}$, $\varepsilon_{D,280}$, and $\varepsilon_{D,370}$, preliminarily prepared values (estimated values based on calculation or measurement values obtained by UV measurement of the compound) are used. For example, $\varepsilon_{A,}$ 280 can be estimated from the amino acid sequence of the antibody by a known calculation method (Protein Science, 1995, vol. 4, 2411-2423) . $\varepsilon_{A,370}$ is generally zero. $\varepsilon_{D,280}$ and $\varepsilon_{D,370}$ can be obtained according to Lambert-Beer's law (Absorbance Molar concentration × Molar absorption coefficient × Cell path length) by measuring the absorbance of a solution in which the conjugate precursor used is dissolved at a certain molar concentration. C_A and C_D can be determined by measuring A_{280} and A_{370} of an aqueous solution of the antibody-drug conjugate, and then solving the simultaneous equations (1) and (2) by substitution of these values. Further, by dividing C_D by C_A, the average number of conjugated drug molecules per antibody can be determined.

[1228] Common Procedure F: Measurement of Antibody Aggregation in Antibody-Drug Conjugate

[1229] The aggregation in the antibody-drug conjugate can be determined by size exclusion chromatography (SEC) in high-performance liquid chromatography (HPLC) analysis u sing the following method.

[1230] HPLC system: Agilent 1260 Infinity II HPLC system (Agilent Technologies, Inc.)

[1231] Detector: Ultraviolet absorption spectrometer (measurement wavelength: 280 nm)

[1232] SEC-Column: TOSOH TSKgel G3000SWXL (7.8×300 mm, 5 μm)

[1233] Mobile phase: 200 mmol/L KHPO4, 150 mmol/L NaCl, 15% (v/v) isopropan ol, pH7.0

[1234] Flow rate: 0.75 mL/min

[1235] Isocratic Operation: 18 min

[1236] Column temperature: room temperature

[1237] Sample injection: 50 μg

[1238] Data Analysis

[1239] The SEC chromatogram of quality control (Hu814-H1L4) was shown i n FIG. 10A, it is confirmed that the molecular weight of the main QC product is about 150 kDa and the monomer retention time is around 9.5-10.5 min. Meanwhi le, the retention time of aggregation is earlier than that of monomer.

[1240] Common Procedure G: Comparison of Antibody Hydrophilicity in Antibody-Drug Conjugate

[1241] The Hydrophilicity of the antibody-drug conjugate can be determined b y hydrophobic interaction chromatography (HIC) in high-performance liqui d chromatography (HPLC) analysis using the following method.

[1242] HPLC system: Agilent 1260 Infinity II HPLC system (Agilent Technologies, Inc.)

[1243] Detector: Ultraviolet absorption spectrometer (measurement wavelength: 280 nm)

[1244] HIC-Column: TOSOH TSKgel Butyl-NPR (4.6 mm I.D. × 3.5 cm, 2.5μm)

[1245] Mobile phase A: 1.5 mol/L (NH4) 2SO4, 50 mmol/L KHPO4, pH7.0

[1246] Mobile phase B: 50 mmol/L KHPO4, 25% (v/v) isopropanol, pH7.0

[1247] Isocratic Operation: 25 min or 22 min

[1248] Column temperature: room temperature

[1249] 25 min Gradient program (B %) : 0%-25% (0 min-1 min) , 25% (1 min-3 min) , 25%-80% (3 min-13 min) , 80% (13 min-17 min) , 80%-0% (17 min-17.10 min) , 0% (17.10 min-25 min)

[1250] 22 min Gradient program (B %) : 0% (0 min-2 min) , 0%-100% (2 min-12 min) , 100%-0% (12 min-15.1 min) , 0% (15.1 min-22 min)

[1251] Sample injection: 10 μL

[1252] Data Analysis: The HIC chromatogram of quality control (Hu814-H1L4) was shown in FIG. 10B. Compared with non-conjugated antibody, antibody-drug conjugates exhibit higher hydrophobicity and thus have a larger retention time.

It is confirmed that the shorter the retention time, the better of the sample's hydro philicity.

[1253] The average number of conjugated drug molecules per antibody molecul e in the antibody-drug conjugate is calculated according to the following expression.

[1254] Average number of conjugated drug molecules = DAR0 peak area ratio×0 +DAR2 peak area ratio×2+DAR4 peak area ratio×4+DAR6 peak area ratio× 6+DAR8 peak area ratio×8

[1255] 4.1: Production of Antibody-Drug Conjugate

[1256] 4.1.1 Production of Antibody-Drug Conjugate Ch814-vc-MMAE

[1257] Step 1: Antibody-Drug Conjugate

[1258] Reduction of antibody: Ch814 was adjusted to 31 mg/mL with PBS7.0/ED TA by using common procedures B (using 1.582 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (64.52 uL) , an aqueous solution of 5 mM TCEP (6.34 uL; 2.3 equivalents per anti body molecule) . After confirming that the solution had a pH within 7.0±0.1, the inte rchain disulfide bond in the antibody was reduced by incubating the solution at 37℃ f or 2 hours.

[1259] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4℃ for 10 minutes. Subsequently, a 5 mM solution of vc-MMAE in dimethylacetamide (19.31 uL; 7 equivalents per antibody molecule) was added the reto, and the obtained mixture was incubated at 22℃. for 30 minutes to conjugate the linker-payload to the antibody.

[1260] Purification: The above-described solution was purified by common procedure D described in production method to obtain 0.2 mL of a solution containing the title antibody-drug conjugate "Ch814-vc-MMAE" .

[1261] Characterization: Using common procedure B, procedure F, and procedu re G described in production method, the following characteristic values were obtaine d.

[1262] Antibody concentration: 9.72 mg/mL. The aggregation of the antibody- drug conjugate was measured by common procedure F: 3.31% (FIG. 11A) . Average number of conjugated drug molecules (n) per antibody molec ule was measured by common procedure G: 3.42 (FIG. 11B) .

[1263] 4.1.2 Production of Antibody-Drug Conjugate Ch835-vc-MMAE

[1264] Step 1: Antibody-Drug Conjugate

[1265] Reduction of antibody: Ch835 was adjusted to 5 mg/mL with PBS7.0/EDT A by using common procedures B (using 1.403 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (1.14 mL) ,

an aqueous solution of 5 mM TCEP (18.06 uL; 2.3 equivalents per anti body molecule) . After confirming that the solution had a pH within 7.0±0.1, the inte rchain disulfide bond in the antibody was reduced by incubating the solution at 37°C f or 2 hours.

[1266] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4°C for 10 minutes. Subsequently, a 5 mM solution of vc-MMAE in dimethylacetamide (78.54 uL; 10 equivalents per antibody mol ecule) was added thereto, and the obtained mixture was incubated at 22°C. for 30 minut es to conjugate the linker-payload to the antibody.

[1267] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1.2 mL of a solution containing the title antibody-drug conjugate "Ch835-vc-MMAE" .

[1268] Characterization: Using common procedure B, procedure F, and procedu re G described in production method, the following characteristic values were obtaine d.

[1269] Antibody concentration: 2.40 mg/mL. The aggregation of the antibody-drug conjugate was measured by common procedure F: 1.43% (FIG. 12A) . Average number of conjugated drug molecules (n) per antibody molec ule was measured by common procedure G: 4.16 (FIG. 12B) .

[1270] 4.1.3 Production of Antibody-Drug Conjugate Ch942-vc-MMAE

[1271] Step 1: Antibody-Drug Conjugate

[1272] Reduction of antibody: Ch942 was adjusted to 9 mg/mL with PBS7.0/EDT A by using common procedures B (using 1.42 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (0.18 mL) , an aqueous solution of 5 mM TCEP (5.14 uL; 2.3 equivalents per antib ody molecule) . After confirming that the solution had a pH within 7.0±0.1, the inter chain disulfide bond in the antibody was reduced by incubating the solution at 37°C fo r 2 hours.

[1273] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4°C for 10 minutes. Subsequently, a 5 mM solution of vc-MMAE in dimethylacetamide (15.64 uL; 7 equivalents per antibody molecule) was added the reto, and the obtained mixture was incubated at 22°C. for 30 minutes to conjugate the linker-payload to the antibody.

[1274] Purification: The above-described solution was purified by common procedure D described in production method to obtain 0.2 mL of a solution containing the title antibody-drug conjugate "Ch942-vc-MMAE" .

[1275] Characterization: Using common procedure B and procedure G described in production method, the following characteristic values were obtained.

[1276] Antibody concentration: 7.98 mg/mL. Average number of conjugated dru g molecules (n) per antibody molecule was measured by common procedu re G: 3.28 (FIG. 13) .

[1277] 4.1.4 Production of Antibody-Drug Conjugate Hu814-H1L4-vc-MMAE

[1278] Step 1: Antibody-Drug Conjugate

[1279] Reduction of antibody: Hu814-H1L4 was adjusted to 20 mg/mL with PBS7.0/ EDTA by using common procedures B (using 1.572 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (0.85 mL) , an aqueous solution of 5 mM TCEP (43.61 uL; 1.86 equivalents per ant ibody molecule) . After confirming that the solution had a pH within 7.0±0.1, the int erchain disulfide bond in the antibody was reduced by incubating the solution at 37℃. for 2 hours.

[1280] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4℃ for 10 minutes. Subsequently, a 5 mM solution of vc-MMAE in dimethylacetamide (0.164 mL; 7 equivalents per antibody mole cule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minute s to conjugate the linker-payload to the antibody.

[1281] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1.7 mL of a solution containing the title antibody-drug conjugate “Hu814-H1L4-vc-MMAE” .

[1282] Characterization: Using common procedure B, procedure F, and procedu re G described in production method, the following characteristic values were obtaine d.

[1283] Antibody concentration: 8.59 mg/mL. The aggregation of the antibody-drug conjugate was measured by common procedure F: 4.52% (FIG. 14A) . Average number of conjugated drug molecules (n) per antibody molec ule was measured by common procedure G: 3.22 (FIG. 14B) .

[1284] 4.1.5 Production of Antibody-Drug Conjugate Hu814-H1L4-LP1 (DAR8)

[1285] Step 1: Antibody-Drug Conjugate

[1286] Reduction of antibody: Hu814-H1L4 was adjusted to 9 mg/mL with PBS7.0/ EDTA by using common procedures B (using 1.572 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (0.563 mL) , an aqueous solution of 5 mM TCEP (0.105 mL; 7.0 equivalents per ant ibody molecule) . After confirming that the solution had a pH within 7.0±0.1, the int erchain disulfide bond in the antibody was reduced by incubating the solution at 37℃. for 2 hours.

[1287] Conjugation between antibody and linker-payload: The above-described solution was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of LP1 in dimethylacetamide (0.113 mL; 15 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minutes to conjugate the linker-payload to the antibody.

[1288] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1.5 mL of a solution containing the title antibody-drug conjugate "Hu814-H1L4-LP1 (DAR8)".

[1289] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=6384 and $\varepsilon_{D,370}$ =16180), procedure F and procedure G described in production method, the following characteristic values were obtained.

[1290] Antibody concentration: 7.42 mg/mL, average number of conjugated drug molecules (n) per antibody molecule was measured by common procedure E: 8.65. The aggregation of the antibody-drug conjugate was measured by common procedure G: 2.79%(FIG. 15A). The retention time of the antibody-drug conjugate was measured by common procedure G: 7.511 min (FIG. 15B).

[1291] 4.1.6 Production of Antibody-Drug Conjugate Hu814-H5L4-LP1 (DAR4)

[1292] Step 1: Antibody-Drug Conjugate

[1293] Reduction of antibody: Hu814-H5L4 was adjusted to 13.27 mg/mL with PBS7.0/EDTA by using common procedures B (using 1.572 $mLmg^{-1}$ cm^{-1} as 280 nm absorption coefficient) and C described in production method. To this solution (37.68 uL), an aqueous solution of 5 mM TCEP (1.8 uL; 2.7 equivalents per antibody molecule). After confirming that the solution had a pH within 7.0±0.1, the inter chain disulfide bond in the antibody was reduced by incubating the solution at 37℃. for 2 hours.

[1294] Conjugation between antibody and linker-payload: The above-described solution was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of LP1 in dimethylacetamide (2.33 uL; 7 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minutes to conjugate the linker-payload to the antibody.

[1295] Purification: The above-described solution was purified by common procedure D described in production method to obtain 0.1 mL of a solution containing the title antibody-drug conjugate "Hu814-H5L4-LP1 (DAR4)".

[1296] Characterization: Using common procedure F and procedure G described in production method, the following characteristic values were obtained.

[1297] The aggregation of the antibody-drug conjugate was measured by common procedure G: 0.75% (FIG. 16A). Average number of conjugated dru

g molecules (n) per antibody molecule was measured by common procedu re G: 4.11 (FIG. 16B) .

[1298] 4.1.7 Production of Antibody-Drug Conjugate Patritumab-GGFG-DXd

[1299] Step 1: Antibody-Drug Conjugate

[1300] The DNA and protein sequences of patritumab variable regions were di sclosed in US20190151328A1.

[1301] Reduction of antibody: Patritumab was adjusted to 9.44 mg/mL with PBS7.0/ EDTA by using common procedures B (using 1.77 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (37 uL) , an aqueous solution of 5 mM TCEP (3.27 uL; 7 equivalents per antibody molecule) . After confirming that the solution had a pH within 7.0±0.1, the interchai n disulfide bond in the antibody was reduced by incubating the solution at 37℃. for 2 hours.

[1302] Conjugation between antibody and linker-payload: The above-described solution was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of GGFG-DXd (purchase from DC Chemicals, DC7556) in dimethylacetamide (3.27 uL; 14 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃ for 30 minutes to conjugate the linker-payload to the antibody.

[1303] Purification: The above-described solution was purified by common procedure D described in production method to obtain 0.1 mL of a solution containing the title antibody-drug conjugate Patritumab-GGFG-DXd.

[1304] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=5178 and $\varepsilon_{D,370}$ =20217) , procedure F and procedure G described in production method , the following characteristic values were obtained.

[1305] Antibody concentration: 3.10 mg/mL, average number of conjugated dru g molecules (n) per antibody molecule was measured by common procedu re E: 6.63. The aggregation of the antibody-drug conjugate was measured by com mon procedure F: 2.04%(FIG. 17A) . The retention time of the antibody-drug conjugate was measured by common procedure G: 8.215 min (FIG. 17B) .

[1306] 4.1.8 Production of Antibody-Drug Conjugate Trastuzumab-GGFG-DXd

[1307] Step 1: Antibody-Drug Conjugate

[1308] The sequences of heavy chain and light chain of Trastuzumab are show n in SEQ ID NO: 15 and 16, respectively.

[1309] Reduction of antibody: Trastuzumab was adjusted to 15 mg/mL with PBS7.0/ EDTA by using common procedures B (using 1.48 $mLmg^{-1}$ cm^{-1} as 280 nm absorp tion coefficient) and C described in production method. To this solution (60 uL) , an aqueous solution of 5 mM TCEP (12 uL; 10 equivalents per antibody m

olecule) . After confirming that the solution had a pH within 7.0±0.1, the interchain disulfide bond in the antibody was reduced by incubating the solution at 37℃. for 2 hours.

[1310] Conjugation between antibody and linker-payload: The above-described solution was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of GGFG-DXd (purchase from DC Chemicals, DC7556) in dimethylacetamide (7.2 uL; 12 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃ for 30 minutes to conjugate the linker-payload to the antibody.

[1311] Purification: The above-described solution was purified by common procedure D described in production method to obtain 0.2 mL of a solution containing the title antibody-drug conjugate Trastuzumab-GGFG-DXd.

[1312] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=5178 and $\varepsilon_{D,370}$ =20217) , procedure F and procedure G described in production method , the following characteristic values were obtained.

[1313] Antibody concentration: 5.44 mg/mL, average number of conjugated drug molecules (n) per antibody molecule was measured by common procedure E: 7.01. The aggregation of the antibody-drug conjugate was measured by common procedure F: 0.79%(FIG. 18A) . The retention time of the antibody-drug conjugate was measured by common procedure G: 7.874 min (FIG. 18B) .

[1314] 4.1.8 Production of Antibody-Drug Conjugate Datopotamab-GGFG-DXd

[1315] Step 1: Antibody-Drug Conjugate

[1316] Reduction: The 'Datopotamab-GGFG-DXd' was prepared by the technology of 'WuXiDAR4' which was described in the patent 'WO2020164561A1' . Firstly, Datopotamab was adjusted into 50 mM phosphate buffer, pH 7.0 (no EDTA contained) , and then corresponding volume of mAb, TCEP , $ZnCl_2$ was pipetted to EP and mixed well. The final reaction concentration of mAb was 7 mg/mL. The equivalent of Tcep was 4 and the equivalent of $ZnCl_2$ was 2. The reaction mixture was stirred at 4 ℃ overnight.

[1317] Conjugation: Corresponding volume of GGFG-DXd in dimethylacetamide (purchase from DC Chemicals, DC7556, 10 mM) and DMA was pipetted to reaction system and the reaction was continued at 4 ℃ for 2 hours. The equivalent of linker-payload was 6. Then 4 equivalent cysteine was added to quench the excessive linker-payload at 4 ℃ for 30 min. Subsequently, 4 equivalent EDTA was added to trap Zn^{2+} at RT for 30 min. Finally, 8 equivalent DHAA was added to oxidize the excessive thiol groups at RT for 2 hours.

[1318] Purification: The above-described solution was purified by common procedure D described in production method to obtain a solution containing the title antibody-drug conjugate Datopotamab-GGFG-DXd.

[1319] Characterization: Using common procedure B, procedure F, and procedure G described in production method, the following characteristic values were obtained.

[1320] Antibody concentration: 5.47 mg/mL. The aggregation of the antibody-drug conjugate was measured by common procedure F: 1.83% (FIG. 19A). Average number of conjugated drug molecules (n) per antibody molecule was measured by common procedure G: 4.14 (FIG. 19B).

[1321] 4.1.9 Production of Antibody-Drug Conjugate Human IgG-vc-MMAE

[1322] Step 1: Antibody-Drug Conjugate

[1323] Reduction of antibody: Human IgG (purchase from Solarbio) was adjusted to 15 mg/mL with PBS7.0/EDTA by using common procedures B (using 1.5 $mLmg^{-1}$ cm^{-1} as 280 nm absorption coefficient) and C described in production method. To this solution (0.8 mL), an aqueous solution of 5 mM TCEP (40 uL; 2.5 equivalents per antibody molecule). After confirming that the solution had a pH within 7.0±0.1, the interchain disulfide bond in the antibody was reduced by incubating the solution at 37℃ for 2 hours.

[1324] Conjugation between antibody and linker-payload: The above-described solution was incubated at 4℃ for 10 minutes. Subsequently, a 5 mM solution of vc-MMAE in dimethylacetamide (0.112 mL; 7 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minutes to conjugate the linker-payload to the antibody.

[1325] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1.6 mL of a solution containing the title antibody-drug conjugate “Human IgG-vc-MMAE”.

[1326] Characterization: Using common procedure B, procedure F, and procedure G described in production method, the following characteristic values were obtained.

[1327] Antibody concentration: 9.21 mg/mL. The aggregation of the antibody-drug conjugate was measured by common procedure F: 7.67% (FIG. 20A). The HIC chromatogram of Hu IgG-vc-MMAE was shown in FIG. 20B.

[1328] 4.1.10 Production of Antibody-Drug Conjugate Human IgG-LP1 (DAR8)

[1329] Step 1: Antibody-Drug Conjugate

[1330] Reduction of antibody: Human IgG (purchase from Solarbio) was adjusted to 10 mg/mL with PBS7.0/EDTA by using common procedures B (using 1.35 $mLmg^{-1}$ cm^{-1}

as 280 nm absorption coefficient) and C described in production method. To this solu tion (1.33 mL) , an aqueous solution of 5 mM TCEP (0.267 mL; 10 equi valents per antibody molecule) . After confirming that the solution had a pH within 7 .0±0.1, the interchain disulfide bond in the antibody was reduced by incubating the s olution at 37℃. for 2 hours.

[1331] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of LP1 in dimethylacetamide (0.2 mL; 15 equivalents per antibody mo lecule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minu tes to conjugate the linker-payload to the antibody.

[1332] Purification: The above-described solution was purified by common procedure D described in production method to obtain 2 mL of a solution containing the title a ntibody-drug conjugate “Human IgG-LP1 (DAR8) ” .

[1333] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=6384 and $\varepsilon_{D,370}$ =16180) , procedure G and procedure H described in production method , the following characteristic values were obtained.

[1334] Antibody concentration: 11.08 mg/mL, average number of conjugated dr ug molecules (n) per antibody molecule was measured by common proced ure E: 9.15. The aggregation of the antibody-drug conjugate was measured by com mon procedure G: 4.38%(FIG. 21A) . The retention time of the antibody-drug conjugate was measured by common procedure H: 6.213 min (FIG. 21B) .

[1335] 4.1.11 Production of Antibody-Drug Conjugate Human IgG-LP1 (DAR4)

[1336] Step 1: Antibody-Drug Conjugate

[1337] Reduction of antibody: Human IgG (purchase from Solarbio) was adjusted to 15 mg/ mL with PBS7.0/EDTA by using common procedures B (using 1.35 $mL mg^{-1} cm^{-1}$ as 280 nm absorption coefficient) and C described in production method. To this solu tion (0.8 mL) , an aqueous solution of 5 mM TCEP (0.037 mL; 2.3 equi valents per antibody molecule) . After confirming that the solution had a pH within 7 .0±0.1, the interchain disulfide bond in the antibody was reduced by incubating the s olution at 37℃. for 2 hours.

[1338] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of LP1 in dimethylacetamide (0.056 mL; 15 equivalents per antibody molecule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minutes to conjugate the linker-payload to the antibody.

[1339] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1.2 mL of a solution containing the title antibody-drug conjugate “Human IgG-LP1 (DAR4) ” .

[1340] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=5814 and $\varepsilon_{D,370}$ =14742) , procedure F and procedure G described in production method , the following characteristic values were obtained.

[1341] Antibody concentration: 9.13 mg/mL, average number of conjugated dru g molecules (n) per antibody molecule was measured by common procedu re E: 3.93. The aggregation of the antibody-drug conjugate was measured by com mon procedure G: 5.66%(FIG. 22A) . The HIC chromatogram of Human IgG-LP1 (DAR4) was shown in FIG. 22B.

[1342] 4.1.12 Production of Antibody-Drug Conjugate Human IgG-GGFG-DXd

[1343] Step 1: Antibody-Drug Conjugate

[1344] Reduction of antibody: Human IgG (purchase from Solarbio) was adjusted to 10 mg/ mL with PBS7.0/EDTA by using common procedures B (using 1.35 $mLmg^{-1}$ cm^{-1} as 280 nm absorption coefficient) and C described in production method. To this solu tion (2.45 mL) , an aqueous solution of 5 mM TCEP (0.327 mL; 10 equi valents per antibody molecule) . After confirming that the solution had a pH within 7 .0±0.1, the interchain disulfide bond in the antibody was reduced by incubating the s olution at 37℃. for 2 hours.

[1345] Conjugation between antibody and linker-payload: The above-described solutio n was incubated at 4℃ for 10 minutes. Subsequently, a 10 mM solution of GGFG-DXd in dimethylacetamide (0.294 mL; 18 equivalents per antibody mole cule) was added thereto, and the obtained mixture was incubated at 22℃. for 30 minute s to conjugate the linker-payload to the antibody.

[1346] Purification: The above-described solution was purified by common procedure D described in production method to obtain 1 mL of a solution containing the title a ntibody-drug conjugate “Human IgG-GGFG-DXd” .

[1347] Characterization: Using common procedure E (using $\varepsilon_{D,280}$=5178 and $\varepsilon_{D,370}$ =20217) , procedure G and procedure H described in production method , the following characteristic values were obtained.

[1348] Antibody concentration: 8.20 mg/mL, average number of conjugated dru g molecules (n) per antibody molecule was measured by common procedu re E: 7.08. The aggregation of the antibody-drug conjugate was measured by com mon procedure G: 4.25%(FIG. 23A) . The retention time of the antibody-drug conjugate was measured by common procedure H: 8.222 min (FIG. 23B) .

[1349] Example 12 In Vitro Tumor Growth Inhibition Activities of Chimeric Antibody-Drug Conjugate

[1350] CDH17-positive human gastric cancer cell line SNU-16 (purchased fro m Zhejiang Meisen Cell Technology Co., Ltd.) was maintained in vitr

o as independent monolayer cultures at 37°C in an atmosphere of 5%CO_2. The cells were seeded over a 96 well plate at 5000 cells/100uL/well in culture mediu m, the cells were then cultured overnight. On the next day, each of the conjugates we re added to the cells such that the final concentrations were from 0.01 nM to 100 nM. After culturing for 5 days, media were removed from the cells and the CCK-8 (Cell Counting Kit-8) viability assays were performed according to the manufacturer's instructions. Cell viability was calculated as %of control wells with only tumor cells. FIG. 24 shows concentration-dependent cell growth inhibition a ctivities of Ch814-vc-MMAE, Ch835-vc-MMAE and Ch942-vc-MMAE. The activit y of the chimeric antibody-drug conjugates was stronger than that of isotype c ontrol ADC (IgG-vc-MMAE) , demonstrating target dependent activities.

[1351] In vitro tumor growth inhibition activities of chimeric antibodies conjugated with LP 1 were also tested with similar procedure. Ch814-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F12-LP1 (DAR8) , and RAb17-LP1 (DAR8) were produced following similar procedure as in example 4 .1.5. FIG. 25A shows concentration-dependent cell growth inhibition activities of Ch81 4-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F12-LP1 (DAR8) , and RAb17-LP1 (DAR8) (Anti-CDH17 Reference Antibody-LP1(DAR8)) in CDH17-positive AsPC-1 pancreatic cancer cell line. Ch814-LP1 (DAR8) and Ch2F12-LP1 (DAR8) has comparable activity, and the activit y is slightly stronger than that of Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) . Furt hermore, RAb17-LP1 (DAR8) has the weakest activity among the ADCs tested. FIG. 25B shows concentration-dependent cell growth inhibition a ctivities of Ch814-LP1 (DAR8) , Ch942-LP1 (DAR8) , Ch2E21-LP1 (DAR8) , Ch2F 12-LP1 (DAR8) , and RAb17-LP1 (DAR8) in CDH17-positive SNU5 gas tric cancer cell line. Ch814-LP1 (DAR8) , Ch2F12-LP1 (DAR8) and Ch942-LP1 (DAR8) has comparable activity, and the activity is stronger than that of Ch2E21-LP1 (DAR8) . Again, RAb17-LP1(DAR8) has the weakest activity among the ADCs t ested in this cell line. FIG. 25C shows concentration-dependent cell growth inhibition a ctivities of Ch814-LP1 (DAR8) , Ch942-LP1(DAR8) , Ch2E21-LP1 (DAR8) , Ch2F 12-LP1 (DAR8) , and RAb17-LP1 (DAR8) (Anti-CDH17 Reference Antibody-LP1 (DAR8)) in CDH17-positive SNU16 gastric cancer cell line. Ch814-LP1 (DAR8) and Ch2F12-LP1 (DAR8) has comparable activity, and the activit y is stronger than that of Ch942-LP1 (DAR8) . The activity of Ch942-LP1 (DAR8) is stronger than that of Ch2E21-LP1 (DAR8) . Again, RAb17-LP1 (DAR8) has the weakest activity among the ADCs tested in this cell line.

[1352] Example 13 In Vitro Evaluation of humanized Antibody-Drug Conjugate

[1353] 13.1 Internalization Activity of Antibody-Drug Conjugate

[1354] CDH17-positive human gastric cancer cell lines SNU-5 (purchased from Zhejiang Meisen Cell Technology Co., Ltd.) and SNU-16 (purchased fro m Zhejiang Meisen Cell Technology Co., Ltd.) were maintained in vit ro as independent monolayer cultures at 37℃ in an atmosphere of 5%CO_2 . Cells were harvested by treating with 1xPBS containing 1mM EDTA fo llowed by centrifugation at 1000 rpm for 5 minutes. The cells were r esuspended in cold PBS and 50ug/mL of Hu814-H1L4-vc-MMAE and Hu814-H1L4-LP1 (DAR8) were added. The cell solutions were mixed, incubated at 4 ℃ for 30 min, then the cells were washed with PBS, and then aliquoted into 6 tubes an d incubated at 37℃ for 0, 0.5, 1, 2, 4 and 8 hours. At each time point, one tube was taken out and washed with cold PBS prior to adding anti-human IgG (Fc spe cific) -FITC antibody produced in goat (SIGMA, F9512-2ML) secondary an tibody at a dilution of 1: 300. After incubation at 4℃, the cells were washed with PB S, and then subjected to flow cytometry analysis. The results are shown in FIGS. 25D and 25E. Both Hu814-H1L4-vc-MMAE and Hu814-H1L4-LP1 (DAR8) were i nternalized into SNU16 (FIG. 25D) and SNU-5 (FIG. 25E) cells in a time depen dent manner.

[1355] 13.2 In Vitro Tumor Growth Inhibition Activities of Humanized Antibody-drug Conjugates

[1356] CDH17-positive human gastric cancer cell line SNU-16 (purchased fro m Zhejiang Meisen Cell Technology Co., Ltd.) was maintained in vitr o as independent monolayer cultures at 37℃ in an atmosphere of 5%CO_2 . The cells were seeded over a 96 well plate at 5000 cells/100uL/well in culture medi um and then cultured overnight. On the next day, a serial dilution of each of the hum anized antibody-drug conjugates were added to the cells. After culturing for 5 days, media were removed from the cells and the CCK-8 (Cell Counting Kit-8) viability assays were performed according to the manufacturer's instructions. Cell viability was calculated as %of control wells with only tumor cells. FIG. 26A shows concentration-dependent cell growth inhibition activity of Hu814-H1L4-vc-MMAE. The activity of Hu814-H1L4-vc-MMAE was stronger than that of iso type control ADC (IgG-vc-MMAE) , demonstrating target dependent t umor growth inhibition activity. FIG. 26B shows the concentration-dependent cell gr owth inhibition activities of Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) . The activities of Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) were stronger than that of their corresponding isotype control ADCs IgG-LP1 (DAR8) and IgG-LP1 (DAR4) , demonstrating target dependent tumor g rowth inhibition activity.

[1357] Example 14 In Vivo Antitumor Effect of Antibody-Drug Conjugates

[1358] 14.1 In vivo antitumor effect in SNU-5 gastric cancer xenograft model

[1359] 6 weeks female Balb/c Nude mice were purchased from Shanghai Lingcha ng Biotechnology Co., Ltd.. Human gastric cancer cell line SNU-5 (ATCC) cells we re mixed with Matrigel (Corning, 354234) , then implanted subcutaneously at 10 millio n cells/animal. On day 24 (mean tumor size ~150 mm^3) following impla nting of SNU-5 cells, mice were injected intravenously once with one of the follo wing substances: Vehicle, IgG-vc-MMAE (6 mg/kg) , Hu814-H1L4-vc-MMAE (1.5, 3 and 6 mg/kg) , IgG-LP1 (DAR8) (10 mg/kg) , Hu814-H1L4-LP1 (DAR8) (5 and 10 mg/kg) . Tumor volumes were measured two times per week from the day of treatment initiation by caliper and calculated as follows: T V= (Width*Length) ^{2}/2. The results are shown in FIG. 27. FIG. 27A shows that 3 mg/kg Hu814-H1L4-vc-MMAE decreased tumor growth rate and 6 mg/kg Hu814-H1L4-vc-MMAE caused tumor regression. Notably, both 5 mg/kg and 10 mg/kg Hu814-H1L4-LP1 (DAR8) caused stronger tumor regression than that of 6 mg/kg Hu814-H1L4-vc-MMAE. FIG. 27B shows that the antibody-drug conjugates did not significan tly affect the body weight of the mice.

[1360] 14.2 In vivo antitumor effect in gastric patient derived xenograft model

[1361] LD1-2017-3621200 (LIDE Biotech) is a human gastric cancer patient derived xen ograft model which expresses human HER2 (H-Score=170) , HER3 (H-Score=120) , Trop2 (H-Score=270) and CDH17 (H-Score=60) . Antitumor effects of H ER2-targeting antibody-drug conjugate Trastuzumab-GGFG-DXD, HER3-targeting antibody-drug conjugate Patritumab-GGFG-DXd, Trop2-targeting antibod y-drug conjugate Datopotamab-GGFG-DXd and CDH17-targeting antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) were evaluated in this model. 6-8 weeks Balb/c Nu/Nu mice were purchased from Beijing Vital River La boratory Animal Technology Co., Ltd. Tumors of LD1-2017-361200 were slice d into about 3 mm × 3 mm × 3 mm fragments and implanted subcutaneous ly into the flank of mice. On day 35 (mean tumor size ~173 mm^3) following impla nting, mice were injected intravenous with 10 mg/kg of one of the following substance s: Vehicle, Datopotamab-GGFG-DXd, Patritumab-GGFG-DXd, Trastuzumab-GGFG-DXd, Hu814-H1L4-LP1 (DAR8) . Datopotamab GGFG-DXd was dosed wee kly for three doses (QW*3) , The other antibody-drug conjugates were dosed weekly for two doses (QW*2) . Tumor volumes were measured two times per wee k from day of treatment initiation by Caliper and calculated as follows: TV= (Width*L ength) ^{2}/2. FIG. 28A shows that Patitumab-GGFG-DXd had no tumor growth inhibition activity. Transtuzumab-GGFG-DXd inhibited tumor growth partial ly. Datopotamab-GGFG-DXd showed similar tumor growth inhibition activity

as that of Transtuzumab-GGFG-DXd, although one more dose of Datopotamab-GGFG-DXd was given. Notably, Hu814-H1L4-LP1 (DAR8) showed the strongest tumor growth inhibition activity. FIG. 28B shows that the antibody-drug conjugates did not affect the body weight of the animals. The arrowhead in the figure indicates the time for dosing.

[1362] 14.3 In vivo antitumor effect in AsPC-1 pancreatic cancer xenograft model

[1363] 6 weeks female Balb/c Nude mice were purchased from GemPharmatech Co., Ltd. Human pancreatic cancer cell line AsPC-1 (purchased from Zhejiang Meisen Cell Technology Co., Ltd.) cells were implanted subcutaneously at 5 million cells/animal. On day 6 (mean tumor size ~130mm^3) following implanting of AsPC-1 cells, mice were injected intravenously once with one of the following substances: PBS, 10 mg/kg Hu814-H1L4-LP1 (DAR8) , 10 mg/kg Hu814-H5L4-LP1 (DAR4) . Tumor volumes were measured two times per week from day of treatment initiation by Caliper and calculated as follows: TV= (Width*Length) ^{2}/2. The results are shown in FIG. 29. Both of the CDH17 targeting antibody-drug conjugates caused tumor regression (Fig. 29A) after a single dose administration without affecting mice body weight significantly (FIG. 29B) .

[1364] 14.4 In vivo antitumor effect in colorectal cancer patient derived xenograft model

[1365] 6 weeks female Balb/c Nude mice were purchased from GemPharmatech Co., Ltd. GemPharmatech Co., Ltd. Tumors of PDX28, a human colorectal cancer xenograft model which expresses human CDH17 (H-score=70) , were sliced into about 3 mm × 3 mm × 3 mm fragments and implanted subcutaneously into the flank of mice. On day 15 (mean tumor size ~190mm^3) following implanting, mice were injected intravenous with 10 mg/kg of one of the following substances: IgG-LP1 (DAR8) , Hu814-H1L4-LP1 (DAR8) , IgG-LP1 (DAR4) , Hu814-H5L4-LP1 (DAR4) . Tumor volumes were measured two times per week from the day of treatment initiation by Caliper and calculated as follows: TV= (Width*Length) ^{2}/2. FIG. 30A shows that a single dose of both Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) decreased tumor volume significantly. The tumor volume in Hu814-H5L4-LP1 (DAR4) group rebounded about 20 days after the dosing, while tumor volume in Hu814-H1L4-LP group did not rebound untill the end of the study. FIG. 30B shows that in the two groups receiving the two isotype ADCs, body weight of the mice decreased approximately 15%, indicating that the tumor growth affected the body weight of the mice. In the two groups receiving Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) , no decrease more than 5%of body weight was observed.

[1366] 14.5 In vivo antitumor effect in colorectal cancer patient derived xenograft model

[1367] LD1-2012-362014 (LIDE Biotech) is a human colorectal cancer patient derived xenograft model which expresses human HER3 (H-Score=210) and CDH17 (H-Score=260) . Antitumor effects of HER3-targeting antibody-drug conjugate Patritumab-GGFG-DXd and CDH17-targeting antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) were evaluated in this model. 6-8 weeks Balb/c Nu/Nu mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. Tumors of LD1-2012-362014 were sliced into about 3 mm × 3 mm × 3 mm fragments and implanted subcutaneously into the flank of mice. On day 28 (mean tumor size ~191 mm^3) following implanting, mice were injected intravenous with one of the following substances: Vehicle, IgG-GGFG-DXd (10 mg/kg) , Patritumab-GGFG-DXd (10 mg/kg) , IgG-LP1 (DAR8) (10 mg/kg) , Hu814-H1L4-LP1 (DAR8) (10 mg/kg) . The antibody-drug conjugates were dosed weekly for 3 weeks (QW*3) . Tumor volumes were measured two times per week from day of treatment initiation by Caliper and calculated as follows: TV= (Width*Length) ^{2}/2. FIG. 31A shows that Hu814-H1L4 (DAR8) inhibited tumor growth significantly while Patritumab-GGFG-DXd showed no significant tumor growth inhibition activity. FIG. 31B shows that the antibody-drug conjugates did not affect the body weight of the animals. The arrowhead in the figures indicates the time for dosing.

[1368] 14.6 In vivo antitumor effect in cholangiocarcinoma patient derived xenograft model

[1369] LD1-0060-360976 (LIDE Biotech) is a human cholangiocarcinoma patient derived xenograft model which expresses human CDH17 (H-Score=230) . Antitumor effects of CDH17-targeting antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1(DAR4) were evaluated in this model. 6-8 weeks Balb/c Nu/Nu mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. Tumors of LD1-0060-360976 were sliced into about 3 mm × 3 mm × 3 mm fragments and implanted subcutaneously into the flank of mice. On day 21 (mean tumor size ~192 mm^3) following implanting, mice were injected intravenous with 10 mg/kg of one of the following substances: Vehicle, IgG-LP1 (DAR8) , Hu814-H1L4-LP1 (DAR8) , IgG-LP1 (DAR4) , Hu814-H5L4-LP1 (DAR4) . Tumor volumes were measured two times per week from day of treatment initiation by Caliper and calculated as follows: TV= (Width*Length) ^{2}/2. FIG. 32A shows that a single dose of both Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) inhibited the growth of tumor significantly. FIG. 32B shows that the ADCs did not affect the body weight of the animals.

[1370] 14.7 In vivo antitumor effect in liver cancer patient derived xenograft model

[1371] LD1-0011-360763 (LIDE Biotech) is a human liver cancer patient derived xenograft model which expresses human CDH17 (H-Score=140) . Antitumor effects of CDH17-targeting antibody-drug conjugate Hu814-H1L4-LP1 (DAR8) and Hu814-H5L4-LP1 (DAR4) were evaluated in this model. 6-8 weeks Balb/c mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. Tumors of LD1-0011-360763 were sliced into about 3 mm × 3 mm × 3 mm fragments and implanted subcutaneously into the flank of mice. On day 34 (mean tumor size ~160mm^3) following implanting, mice were injected intravenous with one of the following substances: Vehicle, IgG-LP1 (DAR8) (10 mg/kg) , Hu814-H1L4-LP1 (DAR8) (3 and 10 mg/kg) , IgG-LP1 (DAR4) (10 mg/kg) , Hu814-H5L4-LP1 (DAR4) (3 and 10 mg/kg) . Tumor volumes were measured two times per week from day of treatment initiation by Caliper and calculated as follows: TV= (Width*Length) ^{2}/2. FIG. 33A shows that a single dose of 3 mg/kg or 10 mg/kg Hu814-H1L4-LP1 (DAR8) and 10 mg/kg Hu814-H5L4-LP1 (DAR4) all caused tumor regression. A single dose of 3 mg/kg Hu814-H5L4-LP1 (DAR4) also caused tumor regression, but to a less degree than that of 10 mg/kg Hu814-H5L4-LP1 (DAR4) . FIG. 33B shows that the ADCs did not affect the body weight of the animals.

[1372] Example 15 Detection of CDH17 expression in tissue samples by immunohistochemistry using CL075814 as primary antibody.

[1373] Incubate paraffin sections at 60℃ for 30 minutes, then put in xylene to remove the paraffin. And then put the sections in a graded alcohol series (95%, 75%, 0%) to eliminate xylene and ethanol. Place the sections in 1x antigen retrieval buffer (DAKO: DM828) , and heat for 5 minutes, and then left to cool down to room temperature (RT) . Wash the sections with washing buffer (1xPBS+0.05%Tween20) for 3 times , then incubate in 3%H_2O_2 at RT for 10 minutes and then wash again with washing buffer for 3 times. Block the sections with blocking solution (5%normal goat serum in 1xPBS) at RT for 30 minutes. Dilute CL075814 to 2ug/mL in 1xPBS , then discard the blocking solution from the sections and add 300uL diluted CL075814 on the sections, incubate at RT for 1 hour. Wash the sections with washing buffer for 3 times, then add 300uL of Dako REAL™ EnVision™ /HRP, Rabbit/Mouse (ENV) reagent and incubate at RT for 1 hour. Wash the sections with washing buffer for 3 times, then add 300uL of Dako REAL™ DAB + Chromogen and incubate at RT for 3 minutes. Wash with washing buffer for 1 minutes and then counterstain the sections with Hematoxylin QS. FIG. 34 shows the detection of CDH17 exprssion in gastric cancer (A) , colorectal cancer (B) , pancreatic cancer (C) , esophageal adenocarcinoma (D) , cholangiocarcinoma (E) and

neuroendocrine cancer (F) by immunohistochemistry using CL075814 as primary antibody.

[1374] Example 16 Competition ELISA

[1375] Competition between Ch835 and Ch942, and between Ch814 and Ch2F12 were analyzed with competition ELISA. Ch835, Ch942, Ch2F12 and Ch814 antibodies were biotin-labelled using EZ-Link Sulfo-NHS-Biotin (Thermo, Cat: A39257) reagents following the experimental steps in the instruction manual. The concentrations of the products were determined by the UV method.

[1376] In order to determining whether Ch2F12 competes with Ch814-Biotin, competition ELISA was carried out as per the following steps: Microtiter plates were coated with recombinant Human CDH17-ECD-His protein to capture Ch814-Biotin. Serial dilutions of Ch2F12 and Ch814 were added to the corresponding wells alongside 45.10 ng/mL Ch814-Biotin. After several washing steps, Peroxidase (HRP) -SA was dispensed into the wells and bound to the Ch814-Biotin. A tetramethylbenzidine (TMB) -peroxidase substrate solution was then added to the wells after the final wash. TMB in the substrate solution reacts with the peroxide and in the presence of HRP produces a colorimetric signal that is proportional to the amount of Ch814-Biotin present in the wells. The color development was stopped by addition of HCl and the intensity of the color (optical density, OD) was measured at 450 nm by a plate reader SpectraMaxM3. FIG. 35A shows that Ch814, as a positive control, competes with Ch814-Biotin, indicating that the experiment works properly. Ch2F12 also competes with Ch814-Biotin in this experiment.

[1377] Competition ELISA was performed to determine whether Ch814 competes with Ch2F12-Biotin following similar procedure. FIG. 35B shows that Ch2F12, as a positive control, competes with Ch2F12-Biotin, indicating that the experiment works properly. Ch814 also competes with Ch2F12-Biotin in this experiment.

[1378] Competition ELISA was performed to determine whether Ch942 competes with Ch835-Biotin following similar procedure. FIG. 35C shows that Ch835, as a positive control, competes with Ch835-Biotin, indicating that the experiment works properly. Ch942 also competes with Ch835-Biotin in this experiment.

[1379] Competition ELISA was performed to determine whether Ch835 competes with Ch942-Biotin following similar procedure. FIG. 35D shows that Ch942, as a positive control, competes with Ch942-Biotin, indicating that the experiment works properly. Ch835 at high concentration, showed low degree of competitions with Ch942-Biotin in this experiment.

[1380] When used herein in the context of two or more antibodies, the term "competes with" or "cross-competes with" indicates that the two or more antib

odies compete for binding to CDH17, e.g. compete for CDH17 binding i
n the assay described in Example 16 herein. For some pairs of antibodies, competition
in the assay of Example 16 is only observed when one antibody is coated on the plate
and the other is used to compete, and not vice versa. The term “competes with” when
used herein is also intended to cover such pairs of antibodies.

Claims

[Claim 1] An antibody binding to cadherin-17 or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment thereo f specifically binds to a polypeptide having an amino acid sequence shown in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166.

[Claim 2] The antibody or the antigen binding fragment thereof according to cl aim 1, wherein the antibody has competitive binding activity with th e polypeptide having an amino acid sequence shown i n SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 ag ainst an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an amino acid sequence having at least 80%sequence identity to each thereof, and a light chain variable region having an amino acid seq uence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31 , 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having at least 80%sequence identity to each thereof.

[Claim 3] The antibody or the antigen binding fragment thereof according to cl aim 2, wherein the antibody has competitive binding activity with th e polypeptide having an amino acid sequence shown i n SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 166 against an anti-CDH17 antibody selected from a group consisting of:

(a) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 2 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 2;

(b) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 3 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 3, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 4 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 4;

(c) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 5 or an amino acid sequence having at least 80%sequence identity

to SEQ ID NO: 5, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 6 or an amino aci d sequence having at least 80%sequence identity to SEQ ID NO: 6;
(d) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80% sequence id entity to SEQ ID NO: 19, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 29 or an a mino acid sequence having at least 80%sequence iden tity to SEQ ID NO: 29;
(e) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 21 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 21, and a light chain variable region having an amin o acid sequence shown in SEQ ID NO: 31 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 31;
(f) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 23 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 23, and a light chain variable region having an amin o acid sequence shown in SEQ ID NO: 33 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 33;
(g) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 19 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 19, and a light chain variable region having an amin o acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;
(h) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 25, and a light chain variable region having an amin o acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;
(i) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 27, and a light chain variable region having an amin

o acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;
(j) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;
(k) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45;
(l) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;
(m) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and
(n) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[Claim 4] The antibody or the antigen binding fragment thereof according to claim 2 or 3, wherein the antibody has competitive binding activity with the polypeptide having an amino acid sequence sh

own in SEQ ID NO: 127 and/or 128 or in SEQ ID NO: 1
66 against an anti-CDH17 antibody selected from a group consisting of:
(a) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 7 or an amin
o acid sequence having at least 80%sequence identit
y to SEQ ID NO: 7, and a light chain having an amino acid sequence s
hown in SEQ ID NO: 8 or an amino acid sequence havi
ng at least 80%sequence identity to SEQ ID NO: 8;
(b) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 9 or an amin
o acid sequence having at least 80%sequence identit
y to SEQ ID NO: 9, and a light chain having an amino acid sequence s
hown in SEQ ID NO: 10 or an amino acid sequence hav
ing at least 80%sequence identity to SEQ ID NO: 10;
(c) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 11 or an ami
no acid sequence having at least 80%sequence identity to SEQ ID NO:
11, and a light chain having an amino acid sequence shown in SEQ ID
NO: 12 or an amino acid sequence having at least 80%
sequence identity to SEQ ID NO: 12;
(d) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 20 or an ami
no acid sequence having at least 80%sequence identity to SEQ ID NO:
20, and a light chain having an amino acid sequence shown in SEQ ID
NO: 30 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 30;
(e) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 22 or an ami
no acid sequence having at least 80%sequence identity to SEQ ID NO:
22, and a light chain having an amino acid sequence shown in SEQ ID
NO: 32 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 32;
(f) an anti-CDH17 antibody comprising a heavy chain having an a
mino acid sequence shown in SEQ ID NO: 24 or an ami
no acid sequence having at least 80%sequence identity to SEQ ID NO:
24, and a light chain having an amino acid sequence shown in SEQ ID
NO: 34 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 34;

(g) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 20 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 36;

(h) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 26 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 36;

(i) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 28 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 28, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 36;

(j) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 38 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 44;

(k) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 40 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 46;

(l) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 42 or an amino acid seque nce having at least 80%sequence identity to SEQ ID NO: 42, and a lig ht chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence ide ntity to SEQ ID NO: 48;

(m) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 171 or an am

ino acid sequence having at least 80%sequence identity to SEQ ID NO: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 173; and

(n) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 175 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ ID NO: 177 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 177.

[Claim 5] An antibody specifically binding to cadherin-17, preferably human cadherin-17, or an antigen binding fragment thereof, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 which are same as the HCDR1, HCDR2, and HCDR3 of a heavy chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, and 174, and/or a light chain variable region comprising LCDR1, LCDR2, and LCDR3 which are same as the LCDR1, LCDR2, and LCDR3 of a light chain variable region having an amino acid sequence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 31, 33, 35, 43, 45, 47, 172, and 176.

[Claim 6] The antibody or an antigen binding fragment thereof according to claim 5, wherein the antibody comprises a heavy chain variable region comprising HCDR1, HCDR2, and HCDR3 having amino acid sequences selected from a group consisting of:

SEQ ID NO: 49, 50, and 51, respectively;
SEQ ID NO: 68, 69, and 70, respectively;
SEQ ID NO: 87, 88, and 89, respectively;
SEQ ID NO: 109, 50, and 51, respectively;
SEQ ID NO: 49, 50, and 113, respectively;
SEQ ID NO: 49, 50, and 116, respectively;
SEQ ID NO: 178, 179, and 180, respectively; and
SEQ ID NO: 191, 192, and 193, respectively;

according to IMGT definition scheme; or a group consisting of:

SEQ ID NO: 55, 56, and 57, respectively;
SEQ ID NO: 74, 75, and 76, respectively;
SEQ ID NO: 93, 94, and 95, respectively;

SEQ ID NO: 55, 106, and 57, respectively;
SEQ ID NO: 110, 111, and 57, respectively;
SEQ ID NO: 55, 106, and 114, respectively;
SEQ ID NO: 55, 106, and 117, respectively;
SEQ ID NO: 182, 183, and 184, respectively; and
SEQ ID NO: 197, 198, and 199, respectively;
according to Kabat definition scheme; or a group consisting of:
SEQ ID NO: 60, 61, and 57, respectively;
SEQ ID NO: 79, 80, and 76, respectively;
SEQ ID NO: 98, 99, and 95, respectively;
SEQ ID NO: 60, 61, and 114, respectively;
SEQ ID NO: 60, 61, and 117, respectively;
SEQ ID NO: 185, 186, and 184, respectively; and
SEQ ID NO: 202, 203, and 199, respectively;
according to Chothia definition scheme; or a group consisting of:
SEQ ID NO: 62, 63, and 64, respectively;
SEQ ID NO: 81, 82, and 83, respectively;
SEQ ID NO: 100, 101, and 102, respectively;
SEQ ID NO: 62, 107, and 64, respectively;
SEQ ID NO: 62, 108, and 57, respectively;
SEQ ID NO: 112, 108, and 64, respectively;
SEQ ID NO: 62, 107, and 115, respectively;
SEQ ID NO: 62, 107, and 118, respectively;
SEQ ID NO: 81, 123, and 83, respectively;
SEQ ID NO: 187, 188, and 189, respectively; and
SEQ ID NO: 204, 205, and 206, respectively;
according to Contact definition scheme;
and/or a light chain variable region comprising LCD
R1, LCDR2, and LCDR3 having amino acid sequences se
lected from a group consisting of:
SEQ ID NO: 52, 53, and 54, respectively;
SEQ ID NO: 71, 72, and 73, respectively;
SEQ ID NO: 90, 91, and 92, respectively;
SEQ ID NO: 52, 53, and 181, respectively; and
SEQ ID NO: 194, 195, and 196, respectively;
according to IMGT definition scheme; or a group consisting of:
SEQ ID NO: 58, 59, and 54, respectively;
SEQ ID NO: 77, 78, and 73, respectively;

SEQ ID NO: 96, 97, and 92, respectively;
SEQ ID NO: 58, 120, and 54, respectively;
SEQ ID NO: 58, 59, and 181, respectively; and
SEQ ID NO: 200, 201, and 196, respectively;
according to Kabat definition scheme; or a group consisting of:
SEQ ID NO: 65, 66, and 67, respectively;
SEQ ID NO: 84, 85, and 86, respectively;
SEQ ID NO: 103, 104, and 105, respectively;
SEQ ID NO: 65, 119, and 67, respectively;
SEQ ID NO: 65, 121, and 67, respectively;
SEQ ID NO: 65, 122, and 67, respectively;
SEQ ID NO: 65, 66, and 190, respectively; and
SEQ ID NO: 207, 208, and 209, respectively;
according to Contact definition scheme.

[Claim 7] The antibody or an antigen binding fragment thereof according to cla im 5, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 , and LCDR3 have amino acid sequences selected from a group consisti ng of:
SEQ ID NO: 49, 50, 51, 52, 53, and 54, respectively;
SEQ ID NO: 68, 69, 70, 71, 72, and 73, respectively;
SEQ ID NO: 87, 88, 89, 90, 91, and 92, respectively;
SEQ ID NO: 109, 50, 51, 52, 53, and 54, respectively;
SEQ ID NO: 49, 50, 113, 52, 53, and 54, respectively;
SEQ ID NO: 49, 50, 116, 52, 53, and 54, respectively;
SEQ ID NO: 178, 179, 180, 52, 53, and 181, respectively; and
SEQ ID NO: 191, 192, 193, 194, 195, and 196, respectively;
according to IMGT definition scheme; or a group consisting of:
SEQ ID NO: 55, 56, 57, 58, 59, and 54, respectively;
SEQ ID NO: 74, 75, 76, 77, 78, and 73, respectively;
SEQ ID NO: 93, 94, 95, 96, 97, and 92, respectively;
SEQ ID NO: 55, 106, 57, 58, 59, and 54, respectively;
SEQ ID NO: 110, 111, 57, 58, 120, and 54, respectively;
SEQ ID NO: 55, 106, 57, 58, 120, and 54, respectively;
SEQ ID NO: 55, 106, 114, 58, 120, and 54, respectively;
SEQ ID NO: 55, 106, 117, 58, 120, and 54, respectively;
SEQ ID NO: 182, 183, 184, 58, 59, and 181, respectively; and
SEQ ID NO: 197, 198, 199, 200, 201, and 196, respectively;
according to Kabat definition scheme; or a group consisting of:

SEQ ID NO: 60, 61, 57, 58, 59, and 54, respectively;
SEQ ID NO: 79, 80, 76, 77, 78, and 73, respectively;
SEQ ID NO: 98, 99, 95, 96, 97, and 92, respectively;
SEQ ID NO: 60, 61, 57, 58, 120, and 54, respectively
SEQ ID NO: 60, 61, 114, 58, 120, and 54, respectively;
SEQ ID NO: 60, 61, 117, 58, 120, and 54, respectively;
SEQ ID NO: 185, 186, 184, 58, 59, and 181, respectively; and
SEQ ID NO: 202, 203, 199, 200, 201, and 196, respectively;
according to Chothia definition scheme; or a group consisting of:
SEQ ID NO: 62, 63, 64, 65, 66, and 67, respectively;
SEQ ID NO: 81, 82, 83, 84, 85, and 86, respectively;
SEQ ID NO: 100, 101, 102, 103, 104, and 105, respectively;
SEQ ID NO: 62, 107, 64, 65, 119, and 67, respectively;
SEQ ID NO: 62, 108, 57, 65, 66, and 67, respectively;
SEQ ID NO: 112, 108, 64, 65, 121, and 67, respectively;
SEQ ID NO: 62, 107, 115, 65, 122, and 67, respectively;
SEQ ID NO: 62, 107, 118, 65, 122, and 67, respectively;
SEQ ID NO: 62, 107, 64, 65, 122, and 67, respectively;
SEQ ID NO: 81, 123, 83, 84, 85, and 86, respectively;
SEQ ID NO: 187, 188, 189, 65, 66, and 190, respectively; and
SEQ ID NO: 204, 205, 206, 207, 208, and 209, respectively;
according to Contact definition scheme.

[Claim 8] The antibody or an antigen binding fragment thereof according to cla im 5, wherein the antibody comprises a heavy chain variable region h aving an amino acid sequence selected from a group consisting of SEQ ID NO: 1, 3, 5, 19, 21, 23, 25, 27, 37, 39, 41, 170, 174, and an am ino acid sequence having at least 80%sequence identity to each there of, and/or a light chain variable region having an amino acid se quence selected from a group consisting of SEQ ID NO: 2, 4, 6, 29, 3 1, 33, 35, 43, 45, 47, 172, 176, and an amino acid sequence having a t least 80%sequence identity to each thereof.

[Claim 9] The antibody or an antigen binding fragment thereof according to cla im 8, wherein the antibody is selected from a group consisting of:
(a) an anti-CDH17 antibody comprising a heavy chain variable re gion having an amino acid sequence shown in SEQ ID NO: 1 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 1, and a light chain variable region having an amino

acid sequence shown in SEQ ID NO: 2 or an amino aci
d sequence having at least 80%sequence identity to SEQ ID NO: 2;
(b) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 3 or an amino acid sequence having at least 80%sequence identity
to SEQ ID NO: 3, and a light chain variable region having an amino
acid sequence shown in SEQ ID NO: 4 or an amino aci
d sequence having at least 80%sequence identity to SEQ ID NO: 4;
(c) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 5 or an amino acid sequence having at least 80%sequence identity
to SEQ ID NO: 5, and a light chain variable region having an amino
acid sequence shown in SEQ ID NO: 6 or an amino aci
d sequence having at least 80%sequence identity to SEQ ID NO: 6;
(d) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 19 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 19, and a light chain variable region having an amin
o acid sequence shown in SEQ ID NO: 29 or an amino
acid sequence having at least 80%sequence identity to SEQ ID NO: 29;
(e) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 21 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 21, and a light chain variable region having an amin
o acid sequence shown in SEQ ID NO: 31 or an amino
acid sequence having at least 80%sequence identity to SEQ ID NO: 31;
(f) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 23 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 23, and a light chain variable region having an amin
o acid sequence shown in SEQ ID NO: 33 or an amino
acid sequence having at least 80%sequence identity to
SEQ ID NO: 33;
(g) an anti-CDH17 antibody comprising a heavy chain variable re
gion having an amino acid sequence shown in SEQ ID
NO: 19 or an amino acid sequence having at least 80%sequence identit
y to SEQ ID NO: 19, and a light chain variable region having an amin

o acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

(h) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 25 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 25, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

(i) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 27 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 27, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 35 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 35;

(j) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 37 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 37, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 43 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 43;

(k) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 39 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 39, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 45 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 45; and

(l) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 41 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 41, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 47 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 47;

(m) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 170 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 170, and a light chain variable region having an amino acid sequence shown in SEQ ID NO:

172 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 172; and

(n) an anti-CDH17 antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 174 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 174, and a light chain variable region having an amino acid sequence shown in SEQ ID NO: 176 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 176.

[Claim 10] The antibody or an antigen binding fragment thereof according to claim 5, wherein the antibody comprises a heavy chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 7, 9, 11, 20, 22, 24, 26, 28, 38, 40, 42, 171, 175, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof; and/or a light chain having an amino acid sequence selected from a group consisting of SEQ ID NO: 8, 10, 12, 30, 32, 34, 36, 44, 46, 48, 173, 177, and an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%sequence identity to each thereof.

[Claim 11] The antibody or an antigen binding fragment thereof according to claim 10, wherein the antibody is selected from a group consisting of:

(a) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 7 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 7, and a light chain having an amino acid sequence shown in SEQ ID NO: 8 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 8;

(b) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 9 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 9, and a light chain having an amino acid sequence shown in SEQ ID NO: 10 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 10;

(c) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 11 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO:

11, and a light chain having an amino acid sequence shown in SEQ ID NO: 12 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 12;

(d) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 30 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 30;

(e) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 22 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 22, and a light chain having an amino acid sequence shown in SEQ ID NO: 32 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 32;

(f) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 24 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 24, and a light chain having an amino acid sequence shown in SEQ ID NO: 34 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 34;

(g) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 20 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 20, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

(h) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 26 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 26, and a light chain having an amino acid sequence shown in SEQ ID NO: 36 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 36;

(i) an anti-CDH17 antibody comprising a heavy chain having an amino acid sequence shown in SEQ ID NO: 28 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 28, and a light chain having an amino acid sequence shown in SEQ ID

NO: 36 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 36;

(j) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 38 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 38, and a light chain having an amino acid sequence shown in SEQ ID NO: 44 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 44;

(k) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 40 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 40, and a light chain having an amino acid sequence shown in SEQ ID NO: 46 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 46;

(l) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 42 or an ami no acid sequence having at least 80%sequence identity to SEQ ID NO: 42, and a light chain having an amino acid sequence shown in SEQ ID NO: 48 or an amino acid sequence having at least 80%sequence identit y to SEQ ID NO: 48;

(m) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 171 or an am ino acid sequence having at least 80%sequence identity to SEQ ID N O: 171, and a light chain having an amino acid sequence shown in SEQ ID NO: 173 or an amino acid sequence having at least 80%sequence id entity to SEQ ID NO: 173; and

(n) an anti-CDH17 antibody comprising a heavy chain having an a mino acid sequence shown in SEQ ID NO: 175 or an am ino acid sequence having at least 80%sequence identity to SEQ ID NO: 175, and a light chain having an amino acid sequence shown in SEQ I D NO: 177 or an amino acid sequence having at least 80%sequence identity to SEQ ID NO: 177.

[Claim 12] The antibody or an antigen binding fragment thereof according to any of claims 1 to 11, wherein the antibody is a mono-specific antibody , a multi-specific antibody, an intact antibody, a human anti body, a humanized antibody or a chimeric antibody.

[Claim 13] The antibody or an antigen binding fragment thereof according to any of claims 1 to 12, wherein the antigen binding fragment is selected

from a group consisting of Fab, Fab', Fv, F (ab') $_2$, scFv, di-scFv and dAb.

[Claim 14] An immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, comprising an antibody or an antigen binding fragment thereof according to any of claims 1 to 13, linked to an active agent; wherein the active agent is preferably a drug moiety or a label; wherein the label is preferably selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent, and a metal ion; and wherein the drug moiety is preferably selected from the group consisting of a cytotoxic agent, a cytokine, a nucleic acid, a nucleic acid-associated molecule, a radionuclide, a chemokine, an immuno (co) -stimulatory molecule, an immunosuppressive molecule, a death ligand, an apoptosis-inducing protein, a kinase, a prodrug-converting enzyme, a RNase, an agonistic antibody or antibody fragment, an antagonistic antibody or antibody fragment, a growth factor, a hormone, a coagulation factor, a fibrinolytic protein, peptides mimicking these, and fragments, fusion proteins and derivatives thereof.

[Claim 15] The immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to claim 14, wherein the immunoconjugate is an antibody-drug conjugate, and the active agent is the drug moiety, wherein the antibody drug conjugate has a formula of Ab- (L- (D) m) n, wherein Ab is the antibody or an antigen binding fragment thereof according to any of claims 1 to 11; L is a linker; D is the drug moiety; m is an integer from 1 to 8; and n is any number from 1 to 10.

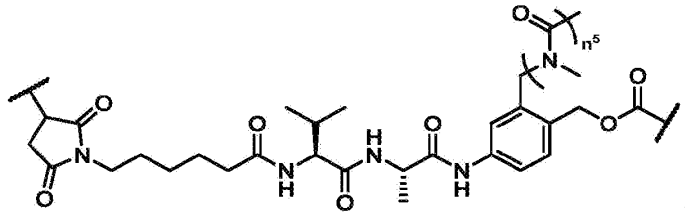
[Claim 16] The immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to claim 15, wherein the L comprises: -Val-Cit-PABC-, -Val-Ala-PABC-, -Glu-Val-Cit-PABC-, -Ala-Ala-Asn-PABC-, -Gly-Val-Cit-PABC-, -Gly-Gly-Gly-PABC-, -Gly- Gly-Phe-Gly-PABC-, -Val-Cit-PAB-, -Val-Ala-PAB-, -Glu-Val-Cit-PAB-, -Ala-Ala-Asn-PAB-, -Gly-Val-Cit-PAB-, -Gly-Gly-Gly-PAB-or -Gly-Gly-Phe-Gly-PAB-; preferably, L is selected from a group consisting of:

- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-PABC-;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-PABC-;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-PABC-;

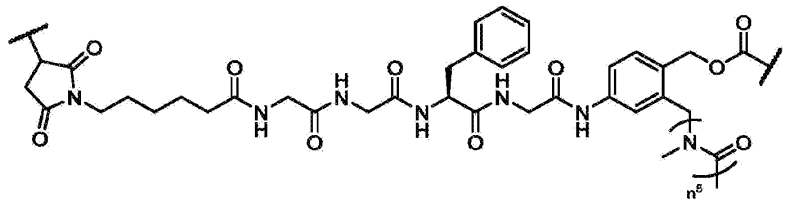
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-PABC-;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-PABC-;
-CH_2-C (=O) -NH-CH_2CH_2-C (=O) -GGFG-PABC-;
-C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-PABC-;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2 CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2 CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2 $CH_2CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2 -O-CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-CH_2 CH_2-O-CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2 O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -GGFG-NH-CH_2CH_2-C (=O) -;
-CH_2-C (=O) -NH-CH_2CH_2-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;
-C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -GGFG-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-PABC-;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-PABC-;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-PABC-;

- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-PABC-;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH2CH2o-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-PABC-;
-CH_2-C (=O) -NH-CH_2CH_2-C (=O) -VA-PABC-;
-C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-PABC-;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-$CH_2CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2-O-CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -$CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-CH_2CH_2-O-CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;
- (succinimidyl-3-yl-N) -CH_2CH_2-C (=O) -NH-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2O-CH_2CH_2-C (=O) -VA-NH-CH_2CH_2-C (=O) -;
-CH_2-C (=O) -NH-CH_2CH_2-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -
; and
-C (=O) -$CH_2CH_2CH_2CH_2CH_2CH_2$-C (=O) -VA-NH-$CH_2CH_2CH_2$-C (=O) -;

more preferably, L is selected from the following structures:

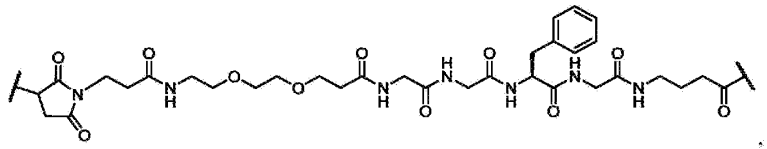


and

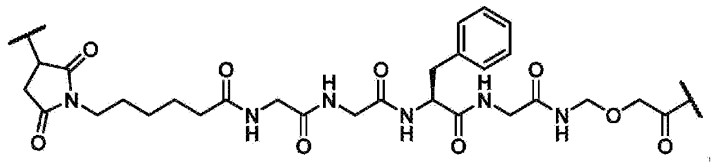


;

wherein n^5 denotes an integer from 0 to 20, preferably 1 to 1
5; and even more preferably, L is selected from the following struct
ures:



,



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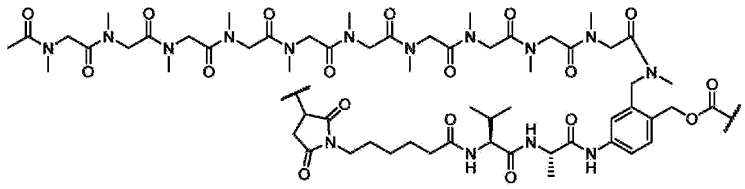
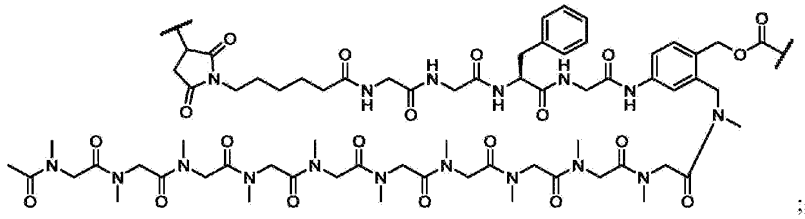


and



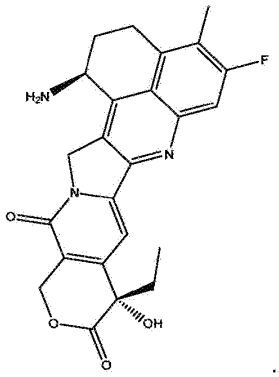
in each structu

;

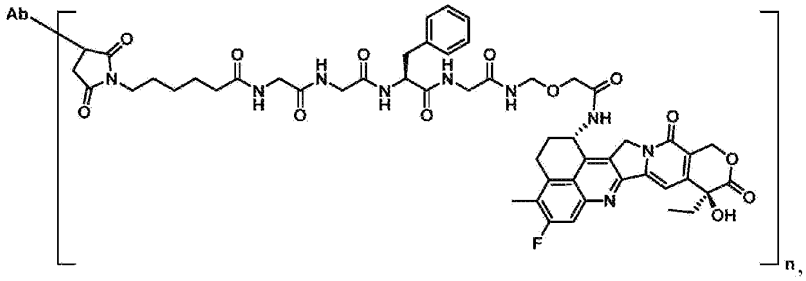
, the wavy line to the left represents linkage site to the Ab moiety
y, and the wavy line to the right represents linkage site to the D moiety.

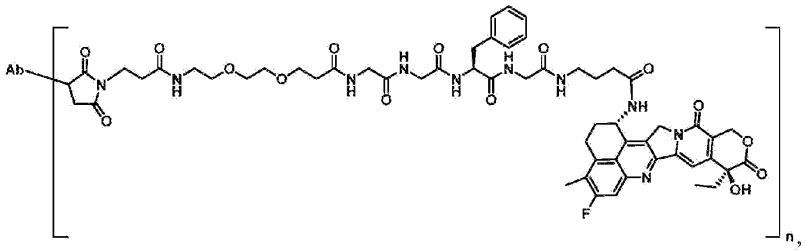
[Claim 17] The immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to claim 15 or 16, wherein the drug moi
ety derives from a cytotoxic agent which is preferably a microtubule

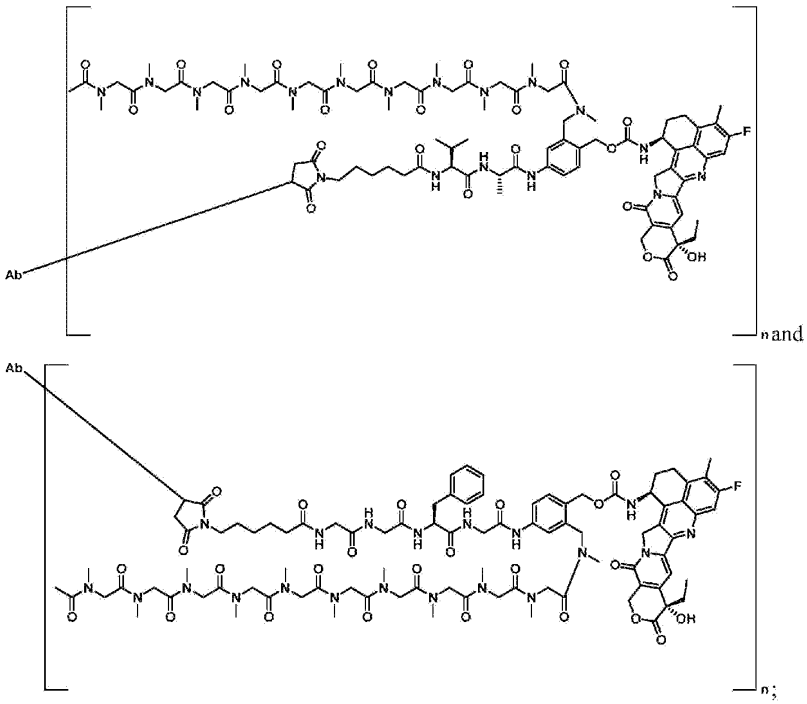
disrupting drug such as a tubulin inhibitor, or a DNA damaging agen t such as a topoisomerase inhibitor including a topoisomerase I inhi bitor such as camptothecin or a derivative thereof; pref erably, the cytotoxic agent has a structure of



[Claim 18] The immunoconjugate, a pharmaceutically acceptable salt thereof, or a solvate thereof, according to claim 17, wherein the antibody drug conjugate is selected from the following structures:







wherein n is any number from 1 to 10, preferably, n is any number fr om 2 to 9.

[Claim 19] A nucleic acid molecule encoding the antibody or an antigen binding fragment thereof according to any of claims 1 to 13.

[Claim 20] An expression vector containing the nucleic acid molecule of claim 19.

[Claim 21] A non-human host cell containing the expression vector of claim 20.

[Claim 22] A pharmaceutical composition comprising the antibody or an antigen b inding fragment thereof according to any of claims 1 to 13, or the i mmunoconjugate, a pharmaceutically acceptable salt thereof, or a sol vate thereof, according to any of claims 14 to 18; and a pharmaceuti cally acceptable carrier.

[Claim 23] Use of the antibody or an antigen binding fragment thereof according to any of claims 1 to 13, or the immunoconjugate, a pharmaceuticall y acceptable salt thereof, or a solvate thereof, according to any of claims 14 to 18 in the preparation of a medicament for the treatmen t of cancer.