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(54) Title: ANTI-CDH17 ANTIGEN-BINDING PROTEINS AND USES THEREOF

(57) Abstract: The present application provides antigen-binding proteins (e.g., antibodies such as single-domain antibodies) that specifically bind cadherin 17 (CDH17). The application also provides fusion proteins and conjugates comprising the antigen-binding proteins, polynucleotides and recombinant vectors encoding the antigen-binding proteins, as well as host cells and methods for preparing the antigen-binding proteins. The application further provides pharmaceutical compositions comprising the antigen-binding proteins and methods for treating a disease or disorder using the antigen-binding proteins.

ANTI-CDH17 ANTIGEN-BINDING PROTEINS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/693,568, filed September 11, 2024, and U.S. Provisional Application No. 63/544,059, filed October 13, 2023, the disclosure of both of which is herein incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on September 16, 2024, is named 260525_000062_SL.xml and is 1,786,513 bytes in size.

FIELD OF THE INVENTION

[0003] The present application relates to antigen-binding proteins (e.g., antibodies such as single-domain antibodies) that specifically bind cadherin 17 (CDH17), methods for their preparation, and uses thereof.

BACKGROUND OF THE INVENTION

[0004] Cadherin 17 (CDH17) is a calcium-dependent cell adhesion glycoprotein belonging to the 7D cadherin subfamily within the cadherin superfamily which is highly expressed in gastrointestinal (GI) tissues and cancers derived therefrom, including gastric cancer (GC), esophageal cancer, pancreatic cancer (PC), hepatocarcinoma (HCC), cholangiocarcinoma, and colorectal cancer (CRC). No other normal tissue, including liver, shows CDH17 expression. Expression of CDH17 is increased in patients with metastasis and correlates with poor prognosis. CDH17 contains an RGD (Arg-Gly-Asp) motif through which it interacts with integrin $\alpha 2\beta 1$, and this interaction has been associated with especially aggressive forms of cancer during late-stage metastasis. Accordingly, there is a need in the art to develop high-affinity molecules which can efficiently target and specifically bind cadherin 17 (CDH17) expressed in tumor cells while having minimal off-tumor toxicity.

SUMMARY OF THE INVENTION

[0005] As mentioned in the background section above, there is an unmet need in the art to develop high-affinity molecules which can efficiently target and specifically bind cadherin 17 (CDH17) expressed in tumor cells while having minimal off-tumor toxicity. This application provides compositions and methods to address this and other related needs.

[0006] In one aspect, provided herein is an antigen-binding protein that specifically binds cadherin 17 (CDH17), comprising a complementarity determining region 3 (CDR3) comprising an amino acid sequence selected from

a). A(A/L)CLLRFE(S/T)CLEYNRAQY(N/P)Y (SEQ ID NO: 83);

b). AAVR(A/S)GSDWWTTM(R/T)QR(D/H)YD(F/Y) (SEQ ID NO: 85);

c). AARDSR(K/R)GGLFADLN(E/G)YDY (SEQ ID NO: 88);

d). AATG(D/N)(L/S)YRGAYDRP(A/T)EYDY (SEQ ID NO: 90);

e). VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

f). AAQFSLPVDA(S/T)PLRRY(A/Y)(H/Y) (SEQ ID NO: 93);

g). AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

h). AARNGGYDLNDYAY (SEQ ID NO: 44);

i). NAGG(G/P/A)(A/R)(L/R)GY (SEQ ID NO: 98);

j). NVGGQL(K/L/R)GY (SEQ ID NO: 101);

k). NQGG(Q/S)KGY (SEQ ID NO: 104);

l). AADG(L/P)PY(G/S)(D/S)WFGDQFDV (SEQ ID NO: 1633);

m). AFNKWGRLSADL(D/N)DYFR (SEQ ID NO: 1636);

n). N(M/T)HRSY(A/D)I(D/N/R/S)FYDN (SEQ ID NO: 1639); and

o). RRYDDY(D/G)S (SEQ ID NO: 1642).

[0007] In some embodiments, the CDR3 comprises an amino acid sequence selected from ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3); AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8); AARDSRRGGLFADLNEYDY (SEQ ID NO: 13); AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18); AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22); AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25); VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29); AAQFSLPVDASPLRRYYY (SEQ ID NO: 34); AATRKTRRSTVAGTEVDY (SEQ ID NO: 39); AARNGGYDLNDYAY (SEQ ID NO: 44); NAGGGRLGY (SEQ ID NO: 49); NAGGAALGY (SEQ ID NO: 54); NVGGQLLGY (SEQ ID NO: 59); NQGGSKGY (SEQ ID NO: 64); AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113); AADGLPYGDWFGDQFDV (SEQ ID NO: 1609); AFNKWGRLSADLDDYFR (SEQ ID NO: 1612); NMHRSYDISFYDN (SEQ ID NO: 1615); and RRYDDYGS (SEQ ID NO: 1618).

[0008] In some embodiments, an antigen-binding protein described herein further comprises a CDR1 comprising an amino acid sequence selected from

a). GFTLSN(T/Y)N (SEQ ID NO: 81);

b). GSPLDYYA (SEQ ID NO: 6);

c). RL(A/N/T)(F/S)(N/S)(R/S)(S/T)T;

d). GRTFS(E/T)PI (SEQ ID NO: 89);

e). GRTFSSPI (SEQ ID NO: 28);

f). TRTF(D/N)MYA (SEQ ID NO: 91);

g). GRTF(D/S)S(L/Y)(L/V) (SEQ ID NO: 94);

h). GRTDSILN (SEQ ID NO: 42);

i). G(I/M)RFS(S/Q)YA (SEQ ID NO: 96);

j). GIRFS(A/S)YA (SEQ ID NO: 99);

k). GS(I/R)FS(R/S)(W/Y)A (SEQ ID NO: 102);

l). G(G/R)TASEYG (SEQ ID NO: 1631);

m). EQTMTGF(T/W) (SEQ ID NO: 1634);

n). GLRFS(S/N)YA (SEQ ID NO: 1637); and

o). (G/R)GT(F/V)SGYA (SEQ ID NO: 1640)

[0009] In some embodiments, the CDR1 comprises an amino acid sequence selected from GFTLSNYN (SEQ ID NO: 1); GSPLDYYA (SEQ ID NO: 6); RLNFSRTT (SEQ ID NO: 11); GRTFSEPI (SEQ ID NO: 16); GRTFSTPI (SEQ ID NO: 21); GRTFSEPI (SEQ ID NO: 16); GRTFSSPI (SEQ ID NO: 28); TRTFNMYA (SEQ ID NO: 32); GRTFSSYL (SEQ ID NO: 37); GRTDSILN (SEQ ID NO: 42); GIRFSSYA (SEQ ID NO: 47); GMRFSQYA (SEQ ID NO: 52); GIRFSAYA (SEQ ID NO: 57); GSRFSSYA (SEQ ID NO: 62); TRTFDMYA (SEQ ID NO: 637); GGTASEYG (SEQ ID NO: 1607); EQTMTGFW (SEQ ID NO: 1610); GLRFSNYA (SEQ ID NO: 1613); and GGTVSGYA (SEQ ID NO: 1616).

[0010] In some embodiments, an antigen-binding protein described herein further comprises a CDR2 comprising an amino acid sequence selected from

a). (F/I)SRGGRT (SEQ ID NO: 82);

b). ISTSGR(C/S)T (SEQ ID NO: 84);

c). SGW(A/S)R(G/T)RT (SEQ ID NO: 87);

d). LISTGGST (SEQ ID NO: 17);

e). I(N/S)RSG(A/T)NT (SEQ ID NO: 92);

f). ISWN(D/G)RST (SEQ ID NO: 95);

g). ISWFRGET (SEQ ID NO: 43);

h). I(F/T)(I/K/N/S)(D/G)(G/Y)(R/S/T)T;

i). MT(A/N/T)GGMT (SEQ ID NO: 100);

j). IT(N/S)GG(G/R/S)T (SEQ ID NO: 103);

k). ISTSGGVT (SEQ ID NO: 1632);

l). ISASGSRV (SEQ ID NO: 1635);

m). IT(N/K)GG(I/N/S)T (SEQ ID NO: 1638); and

n). INSGGPT (SEQ ID NO: 1641).

[0011] In some embodiments, the CDR2 comprises an amino acid sequence selected from ISRGGRT (SEQ ID NO: 2); ISTSGRCT (SEQ ID NO: 7); SGWARGRT (SEQ ID NO: 12); LISTGGST (SEQ ID NO: 17); ISRSGTNT (SEQ ID NO: 33); ISWNDRST (SEQ ID NO: 38); ISWFRGET (SEQ ID NO: 43); ITSGYRT (SEQ ID NO: 48); IFKDGTT (SEQ ID NO: 53); MTAGGMT (SEQ ID NO: 58); ITSGGRT (SEQ ID NO: 63); INRSGANT (SEQ ID NO: 875); ISTSGGVT (SEQ ID NO: 1608); ISASGSRV (SEQ ID NO: 1611); ITKGGIT (SEQ ID NO: 1614); and INSGGPT (SEQ ID NO: 1617).

[0012] In one aspect, the present application provides an antigen-binding protein that specifically binds cadherin 17 (CDH17), comprising a CDR1 comprising an amino acid sequence selected from SEQ ID Nos: 1, 6, 11, 16, 21, 28, 32, 37, 42, 47, 52, 57, 62, 555-792, 1607, 1610, 1613, 1616, 1692-1720; a CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 2, 7, 12, 17, 33, 38, 43, 48, 53, 58, 63, 793-1030, 1608, 1611, 1614, 1617, 1721-1748; and/or a CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 3, 8, 13, 18, 22, 25, 29, 34, 39, 44, 49, 54, 59, 64, 1031-1268, 1609, 1612, 1615, 1618, 1749-1777.

[0013] In some embodiments, the antigen-binding protein comprises

i). a CDR1 comprising an amino acid sequence of GFTLSNYN (SEQ ID NO: 1), a CDR2 comprising an amino acid sequence of ISRGGRT (SEQ ID NO: 2), and a CDR3 comprising an amino acid sequence of ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3);

ii). a CDR1 comprising an amino acid sequence of GSPLDYYA (SEQ ID NO: 6), a CDR2 comprising an amino acid sequence of ISTSGRCT (SEQ ID NO: 7), and a CDR3 comprising an amino acid sequence of AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8);

iii). a CDR1 comprising an amino acid sequence of RLNFSRTT (SEQ ID NO: 11), a CDR2 comprising an amino acid sequence of SGWARGRT (SEQ ID NO: 12), and a CDR3 comprising an amino acid sequence of AARDSRRGGLFADLNEYDY (SEQ ID NO: 13);

iv). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18);

v). a CDR1 comprising an amino acid sequence of GRTFSTPI (SEQ ID NO: 21), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22);

vi). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25);

vii). a CDR1 comprising an amino acid sequence of GRTFSSPI (SEQ ID NO: 28), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO:17), and a CDR3 comprising an amino acid sequence of VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

viii). a CDR1 comprising an amino acid sequence of TRTFNMYA (SEQ ID NO: 32), a CDR2 comprising an amino acid sequence of ISRSGTNT (SEQ ID NO: 33), and a CDR3 comprising an amino acid sequence of AAQFSLPVDASPLRRYYY (SEQ ID NO: 34);

ix). a CDR1 comprising an amino acid sequence of GRTFSSYL (SEQ ID NO: 37), a CDR2 comprising an amino acid sequence of ISWNDRST (SEQ ID NO: 38), and a CDR3 comprising an amino acid sequence of AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

x). a CDR1 comprising an amino acid sequence of GRTDSILN (SEQ ID NO: 42), a CDR2 comprising an amino acid sequence of ISWFRGET (SEQ ID NO: 43), and a CDR3 comprising an amino acid sequence of AARNGGYDLNDYAY (SEQ ID NO: 44);

xi). a CDR1 comprising an amino acid sequence of GIRFSSYA (SEQ ID NO: 47), a CDR2 comprising an amino acid sequence of ITSGYRT (SEQ ID NO: 48), and a CDR3 comprising an amino acid sequence of NAGGGRLGY (SEQ ID NO: 49);

xii). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54);

xiii). a CDR1 comprising an amino acid sequence of GIRFSAYA (SEQ ID NO: 57), a CDR2 comprising an amino acid sequence of MTAGGMT (SEQ ID NO: 58), and a CDR3 comprising an amino acid sequence of NVGGQLLGY (SEQ ID NO: 59);

xiv). a CDR1 comprising an amino acid sequence of GSRFSSYA (SEQ ID NO: 62), a CDR2 comprising an amino acid sequence of ITSGGRT (SEQ ID NO: 63), and a CDR3 comprising an amino acid sequence of NQGGSKGY (SEQ ID NO: 64);

xv). a CDR1 comprising an amino acid sequence of TRTFDMYA (SEQ ID NO: 637), a CDR2 comprising an amino acid sequence of INRSGANT (SEQ ID NO: 875), and a CDR3 comprising an amino acid sequence of AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113);

xvi). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO:1609);

xvii) a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

xviii) a CDR1 comprising an amino acid sequence of GLRFSNYA (SEQ ID NO: 1613), a CDR2 comprising an amino acid sequence of ITKGGIT (SEQ ID NO: 1614), and a CDR3 comprising an amino acid sequence of NMHRSYDISFYDN (SEQ ID NO: 1615); or

xix). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

[0014] In some embodiments, the antigen-binding protein comprises

a). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO: 1609);

b). a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

c). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54); or

d). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

[0015] In some embodiments, the antigen-binding protein is a single-domain antibody.

[0016] In some embodiments, the single-domain antibody is a VHH, a VNAR, or a VH domain.

[0017] In some embodiments, the VHH is a camelid VHH.

[0018] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 105-342, 1619-1622, 1643-1671, and 1778-1806, or an amino acid sequence having at least 75% identity thereto.

[0019] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 187, and 1619-1622,or an amino acid sequence having at least 75% identity thereto.

[0020] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 55, 1619, 1620, and 1622, or an amino acid sequence having at least 75% identity thereto.

[0021] In some embodiments, the VHH is a humanized VHH.

[0022] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 343-554, 1623-1626, and 1672-1691, or an amino acid sequence having at least 75% identity thereto.

[0023] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 421, and 1623-1626, or an amino acid sequence having at least 75% identity thereto.

[0024] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 56, 1623, 1624, and 1626, or an amino acid sequence having at least 75% identity thereto.

[0025] In some embodiments, the antigen-binding protein binds to human CDH17.

[0026] In some embodiments, the antigen-binding protein binds to human CDH17 with a K_D of about 2.2×10^{-7} M or less.

[0027] In some embodiments, the antigen-binding protein binds to human CDH17 with a K_D of about 1.5×10^{-7} M or less.

[0028] In some embodiments, the antigen-binding protein binds to cyno CDH17.

[0029] In some embodiments, the antigen-binding protein binds to cyno CDH17 with a K_D of about 2×10^{-8} M or less.

[0030] In some embodiments, the antigen-binding protein binds to mouse CDH17.

[0031] In some embodiments, the antigen-binding protein binds to the extracellular cadherin domain 6 (EC6) and/or extracellular cadherin domain 7 (EC7) of human CDH17.

[0032] In some embodiments, the antigen-binding protein binds to an extracellular region C-terminal to the tripeptide motif, RGD, in EC6 of human CDH17.

[0033] In some embodiments, the antigen-binding protein binds to the extracellular cadherin domain 1 (EC1) of human CDH17.

[0034] In some embodiments, the antigen-binding protein comprises one or more modifications that reduce binding of said antigen-binding protein by pre-existing antibodies found in human blood or serum.

[0035] In another aspect, provided herein is a fusion protein that specifically binds CDH17, comprising one or more of any of various antigen-binding proteins described herein.

[0036] In some embodiments, the fusion protein comprises three or more said antigen-binding proteins.

[0037] In some embodiments, the one or more antigen-binding proteins bind to the same epitope on CDH17.

[0038] In some embodiments, the one or more antigen-binding proteins bind to different epitopes on CDH17.

[0039] In some embodiments, the one or more antigen-binding proteins are one or more single-domain antibodies.

[0040] In some embodiments, one or more single-domain antibodies are one or more VHHs.

[0041] In some embodiments, the fusion protein described herein further comprises an immunoglobulin Fc region.

[0042] In some embodiments, the immunoglobulin Fc region is an Fc region of a human immunoglobulin. In some embodiments, the immunoglobulin Fc region is an Fc region of human IgG1, IgG2, IgG3 or IgG4, or a variant thereof.

[0043] In some embodiments, the immunoglobulin Fc region is an Fc region of human IgG1, or a variant thereof.

[0044] In some embodiments, the Fc region of human IgG1 comprises one or more mutations selected from Leu234Ala (L234A), Leu234Gly (L234G), Leu234Ser (L234S), Leu234Thr (L234T), Leu234Ala (L234A), Leu235Ala (L235A), Leu235Glu (L235E), Leu235Ser (L235S), Leu235Thr (L235T), Leu235Val (L235V), Leu235Gln (L235Q), Gly236Arg (G236R), Met252Tyr (M252Y), Ser254Thr (S254T), Thr256Glu (T256E), Asp265Asn (D265N), Asp265Ala (D265A), Asp270Asn (D270N), Ser298Asn (S298N), Asn297Ala (N297A), Pro329Ala (P329A), Pro239Gly (P329G), Asn325Glu (N325E) and/or Ala327Ser (A327S) according to EU numbering.

[0045] In some embodiments, the Fc region of human IgG1 comprises a set of mutations selected from

1). L234A and L235A;

2). L234A, L235A, and P329A;

3). D265A, N297A and P329A;

4). L234A, L235A, and G237A;

5). L234G, L235S, and G236R;

6). L234S, L235T, and G236R;

7). L234S, L235V, and G236R;

8). L234T, L235Q, and G236R;

9). L234T, L235T, and G236R;

10). L234A, L235A, and P329G; and

11). M252Y, S254T, and T256E.

[0046] In some embodiments, the immunoglobulin Fc region is an Fc region of human IgG4, or a variant thereof.

[0047] In some embodiments, the Fc region of human IgG4 comprises one or more mutations selected from Ser228Pro (S228P), Leu235Glu (L235E), Leu235Ala (L235A), Phe234Ala (F234A), and/or Pro329Gly (P329G) according to EU numbering.

[0048] In some embodiments, the Fc region of human IgG4 comprises a set of mutations selected from

1). S228P and L235E;

2). S228P and L235A;

3). S228P, F234A, and L235E;

4). S228P, F234A, and L235A; and

5). P329G, S228P, and L235E.

[0049] In some embodiments, a fusion protein described herein further comprises a moiety that binds to serum albumin.

[0050] In another aspect, provided herein is a conjugate comprising an antigen-binding protein described herein or a fusion protein described herein, wherein the antigen-binding protein or fusion protein is conjugated to a second moiety.

[0051] In some embodiments, the second moiety is selected from a detectable label, a drug, a toxin, a radionuclide, an enzyme, an immunomodulatory agent, a cytokine, a cytotoxic agent, a chemotherapeutic agent, a diagnostic agent, or a combination thereof.

[0052] In another aspect, provided herein is a polynucleotide molecule encoding an antigen-binding protein described herein or a fusion protein described herein.

[0053] In some embodiments, a polynucleotide molecule described herein comprises the nucleotide sequence of any one of SEQ ID NOs: 67-80, 1269-1506, 1627-1630, and 1807-1835, or a nucleotide sequence having at least 70% identity thereto.

[0054] In some embodiments, a polynucleotide molecule described herein comprises the nucleotide sequence of any one of SEQ ID NOs: 67-80, 1351, and 1627-1630, or a nucleotide sequence having at least 70% identity thereto.

[0055] In another aspect, provided herein is a recombinant vector comprising a polynucleotide molecule described herein.

[0056] In another aspect, provided herein is a host cell comprising a polynucleotide molecule described herein, or a recombinant vector described herein.

[0057] In another aspect, provided herein is a kit comprising an antigen-binding protein described herein, a fusion protein described herein, a conjugate described herein, a polynucleotide molecule described herein, or a recombinant vector described herein, and optionally, instructions and/or packaging for the same.

[0058] In another aspect, provided herein is a pharmaceutical composition comprising an antigen-binding protein described herein, a fusion protein described herein, a conjugate described herein, a polynucleotide molecule described herein, or a recombinant vector described herein, and a pharmaceutically acceptable carrier and/or excipient.

[0059] In another aspect, provided herein is a method for preparing an antigen-binding protein or a fusion protein that specifically binds CDH17, comprising the steps of:

(a) culturing a host cell described herein in a culture medium under conditions suitable for expression of the antigen-binding protein or fusion protein, and

(b) isolating the antigen-binding protein or fusion protein from the host cell and/or culture medium.

[0060] In another aspect, provided herein is a method for killing a cell expressing CDH17 comprising contacting the cell with an antigen-binding protein described herein, a fusion protein described herein, or a conjugate described herein.

[0061] In some embodiments, said contacting occurs *in vitro*.

[0062] In some embodiments, said contacting occurs *in vivo*.

[0063] In some embodiments, the method further comprises administering the antigen-binding protein, the fusion protein, or the conjugate into a subject in need thereof.

[0064] In some embodiments, the cell expressing CDH17 is a cell of a cancer.

[0065] In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is selected from colorectal cancer, familial GIST, familial pancreatic cancer, gastrointestinal stromal tumor (GIST), hereditary diffuse gastric cancer, hereditary pancreatitis, neuroendocrine tumor of the gastrointestinal tract, neuroendocrine tumor of the pancreas, peritoneal cancer, pancreatic cancer, small bowel cancer, and stomach cancer. In some embodiments, the cancer is gastrointestinal cancer. In some embodiments, the gastrointestinal cancer is colorectal cancer, gastric cancer, esophageal cancer, or pancreatic cancer.

[0066] In some embodiments, the method further comprises contacting the cell with one or more additional therapeutic agents.

[0067] In another aspect, provided herein is a method of treating or preventing a cancer in a subject in need thereof, said method comprising administering to the subject an antigen-binding protein described herein, a fusion protein described herein, or a conjugate described herein.

[0068] In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is selected from colorectal cancer, familial GIST, familial pancreatic cancer, gastrointestinal stromal tumor (GIST), hereditary diffuse gastric cancer, hereditary pancreatitis, neuroendocrine tumor of the gastrointestinal tract, neuroendocrine tumor of the pancreas, peritoneal cancer, pancreatic cancer, small bowel cancer, and stomach cancer. In some embodiments, the cancer is gastrointestinal cancer. In some embodiments, the gastrointestinal cancer is colorectal cancer, gastric cancer, esophageal cancer, or pancreatic cancer.

[0069] In some embodiments, the method further comprises administering one or more additional therapeutic agents.

[0070] In some embodiments, one or more additional therapeutic agents are selected from a chemotherapeutic agent, a vascular endothelial growth factor (VEGF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor , or an apoptosis-inducing agent, an immunotherapeutic agent, or a combination thereof.

[0071] In some embodiments, the chemotherapeutic agent is selected from bleomycin, carboplatin, chlorambucil, cisplatin, colchicine, cyclophosphamide, daunorubicin, doxorubicin or liposomal doxorubicin, mitomycin C, actinomycin, diethylstilbestrol, etoposide, 5-fluorouracil, floxuridine, melphalan, methotrexate, mitomycin, 6-mercaptopurine, teniposide, 6-thioguanine, vincristine and vinblastine, leflunomide, tamoxifen, interferon α-2b, glutamic acid, plicamycin, mercaptopurine, 6-thioguanine, carmustine, BCNU, limousine, CCNU, cytosine arabinose, estramustine, hydroxyurea, procarbazine, busulfan, medroxyprogesterone, estramustine phosphate sodium, ethenyl estradiol,

estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, testolactone, melphalan, chlorambucil, mechlorethamine, thiourea, bethamethasone sodium phosphate, dicarbazine, asparagine, mitotane, vincristine sulfate, vinblastine sulfate, FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) or FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan), and a combination thereof.

[0072] In some embodiments, the VEGF inhibitor is bevacizumab, ramucirumab, regorafenib, ziv-aflibercept, or a combination thereof.

[0073] In some embodiments, the EGFR inhibitor is selected from cetuximab and/or panitumumab.

[0074] In some embodiments, the apoptosis-inducing agent is a B-cell lymphoma 2 (BCL2) inhibitor, a BCL-extra large (BCL-XL) inhibitor, or an inhibitor of apoptosis proteins (IAP) inhibitor, or a combination thereof.

[0075] In some embodiments, the immunotherapeutic agent is an anti-CTLA4 agent, anti-PD1 agent, anti-PD-L1 agent, anti-LAG3 agent, or anti-TIM3 agent, or a combination thereof.

[0076] In some embodiments, the subject is a mammal. In some embodiments, the mammal is human.

BRIEF DESCRIPTION OF DRAWINGS

[0077] **Figure 1** depicts an exemplary immune library construction and general panning strategy for discovery of CDH17 binders.

[0078] **Figure 2** shows sample selection for next generation sequencing (NGS) throughout the phage display process. For the three initial libraries, 6 CDH17 samples of the first panning round, and 12 CDH17 samples of the second panning round were sequenced with 20 million, 2 million, and 2 million reads, respectively. Comparison of V-body enrichment from the initial library to the first and second round of panning enabled the identification of potential V-body candidates.

[0079] **Figure 3** shows a schematic diagram of an exemplary NGS workflow. Following phage display, the VHH region of the phage elutions was polymerase chain reaction (PCR) amplified, unique and sample-specific barcodes were fused, and NGS was performed with the Illumina NovaSeq platform from Genewiz. The raw data were demultiplexed, and then processed by the Pipebio NGS analysis pipeline. Forward and reverse sequence pairs were merged via overlapping regions and the VHHs, including CDRs, were annotated. Based on CDR3 identity, V-body sequences were clustered, allowing for a detailed analysis of V-body enrichment during phage display, sequence diversity, CDR3 length distribution and cluster abundance. Based on these analyses, up to about 500 candidates were selected for DNA synthesis by Twist and further characterization.

[0080] **Figure 4** shows a schematic domain representation and structure prediction of CDH17. Amino acid positions are indicated for the extracellular, transmembrane, and intracellular domains. Extracellular cadherin (EC) repeats are shown positioned superior to the membrane. N-glycans and calcium-binding sites are shown as stars and black dots, respectively. The structure prediction of CDH17 was downloaded from alphafold.ebi.ac.uk/. Information about the amino acid position and domain organization were extracted from Uniport.

[0081] **Figures 5A-5E** illustrate on-cell binding data. **Figure 5A** illustrates on-cell binding of anti-CDH17 V-body monomers to GP2d cell line. **Figure 5B** illustrates on-cell binding of anti-CDH17 V-body monomers to Colo205 cell line. **Figure 5C** illustrates on-cell binding of anti-CDH17 V-body monomers to DLD-1 cell line. **Figure 5D** illustrates on-cell binding of anti-CDH17 V-body monomers to T84 cell line. **Figure 5E** illustrates on-cell binding of anti-CDH17 V-body monomers to HCT-15 cell line.

[0082] **Figure 6** shows a schematic diagram of an exemplary experimental setup for determination of epitope binning. Figure discloses "HHHHHH" as SEQ ID NO: 1838.

[0083] **Figure 7** shows epitope binning of the V-bodies.

[0084] **Figure 8** shows a summary of fluorescence activated cell sorting (FACS) domain mapping.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0085] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. For purposes of interpreting this specification, the following description of terms will apply and whenever appropriate, terms used in the singular will also include the plural and *vice versa*. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that any description of terms set forth conflicts with any document incorporated herein by reference, the description of term set forth below shall control.

[0086] As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 5%. For example, as used herein, the expression "about 100" includes 95 and 105 and all values in between (e.g., 96, 97, 98, 99, etc.).

[0087] The term "antigen" encompasses any agent (e.g., protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleotide, portions thereof, or combinations thereof) that may be specifically bound by the products of specific humoral or cellular immunity, such as an antibody molecule or T-cell receptor. In

various embodiments of the present disclosure, the antigen described herein is CDH17, including human, cynomolgus (cyno), and/or mouse CDH17.

[0088] The term "epitope" can refer to an antigenic determinant on the surface of an antigen to which an antibody molecule binds. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects (e.g., agnostic or antagonistic effects). Epitopes may be either conformational or linear. A conformational epitope is formed by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is formed by adjacent amino acid residues in a polypeptide chain. In some cases, an epitope may include non-peptidic moieties on the antigen, such as saccharides, phosphoryl groups, or sulfonyl groups.

[0089] The term "antigen-binding protein" refers in its broadest sense to a protein that specifically binds an antigen (e.g., CDH17). In certain embodiments, an antigen-binding protein is an antibody or an antigen-binding fragment of an antibody, such as a human antibody, a humanized antibody; a camelid antibody; a chimeric antibody; a recombinant antibody; a heavy chain antibody; a single-domain antibody (e.g., VHH); a single chain antibody (e.g., single chain fragment variable (scFv)); a diabody; a triabody; a tetrabody; a Fab fragment; a F(ab') 2 fragment; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; or an IgG4 antibody, and fragments thereof. The term "antigen-binding protein" also encompasses, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen-binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. In addition, peptide antibody mimetics can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components (e.g., fibronectin type III domain (FN3)) as a scaffold.

[0090] The term “antibody” and “immunoglobulin” or “Ig” are used interchangeably herein, and is used in the broadest sense and encompasses, for example, individual monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full length or intact monoclonal antibodies), antibody compositions with polyepitopic or monoepitopic specificity, polyclonal antibodies, monovalent antibodies, multivalent antibodies, multispecific antibodies (e.g., bispecific antibodies), single-domain antibodies (e.g., VHH), single chain antibodies, intrabodies, anti-idiotypic (anti-Id) antibodies, and antigen-binding fragments of antibodies, as described below. An antibody can be human, humanized, camelized, recombinantly produced, chimeric, synthetic, affinity de-matured and/or affinity matured as

well as an antibody from other species, for example mouse, camel, llama, rabbit, etc. In specific embodiments, the specific target antigen that can be bound by an antibody provided herein includes a CDH17 polypeptide, CDH17 fragment or CDH17 epitope. An "antigen-binding fragment" generally refers a portion of an antibody heavy and/or light chain polypeptide that retains some or all of the binding activity of the antibody from which the fragment was derived. Non-limiting examples of antigen-binding fragments include single-domain antibody (e.g., VHH), single-chain Fvs (scFv), Fab fragments, F(ab') fragments, F(ab)2 fragments, F(ab')2 fragments, disulfide-linked Fvs (sdFv), Fd fragments, Fv fragments, diabody, triabody, tetrabody and minibody, or a chemically modified derivative thereof. In particular, antibodies provided herein include immunoglobulin molecules and molecules that contain immunologically active portion(s) of an immunoglobulin molecule, for example, one or more complementarity determining regions (CDRs) of an antibody that binds to CDH17. Such antibody fragments can be found described in, for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York (1989); Myers (ed.), Molec. Biology and Biotechnology: A Comprehensive Desk Reference, New York: VCH Publisher, Inc.; Huston et al., Cell Biophysics, 22:189-224 (1993); Plückthun and Skerra, Meth. Enzymol., 178:497-515 (1989) and in Day, E.D., Advanced Immunochemistry, Second Ed., Wiley-Liss, Inc., New York, N.Y. (1990). The antibodies provided herein can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule.

[0091] The term "single-domain antibody" or "sdAb" as used herein, refers to an antibody or antibody fragment containing a single antibody variable domain that is able to bind to a specific antigen alone, without the requirement of another antibody variable domain. The complementarity determining regions (CDRs) of a single-domain antibody are part of a single antibody variable domain. Examples of single-domain antibodies include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional four-chain antibodies, engineered antibodies, variable domains derived from the aforementioned antibodies, and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, shark, goat, rabbit, and/or bovine. In some embodiments, a single domain antibody as used herein is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. For clarity reasons, the variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH to distinguish it from the conventional VH of four-chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in Camelidae species, e.g., camel, llama, dromedary, alpaca and guanaco.

Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain, which are also within the scope of the invention. For example, cartilaginous fishes such as sharks can produce immunoglobulin-like structures known as VNAR. In some embodiments, a single-domain antibody may be obtained from a Camelidae VH domain. In some embodiments, a single-domain antibody may be obtained from human VH by camelization. See Saerens et al., Current Opinion in Pharmacology, 2008, 8:600-608, the disclosure of which being incorporated by reference, for review of single-domain antibodies.

[0092] The term "specifically binds" as used herein means that an antigen-binding protein forms a complex with a target antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by a dissociation constant (K_D) of about $1x10^{-6}$ M or less (e.g., less than 10^{-6} M, less than $5x10^{-7}$ M, less than 10^{-7} M, less than $5x10^{-8}$ M, less than 10^{-8} M, less than $5x10^{-9}$ M, less than 10^{-9} M, or less than 10^{-10} M). Methods for determining the binding affinity of an antigen-binding protein, e.g., an antibody or an antibody fragment, to a target antigen are well known in the art and include, e.g., surface plasmon resonance (e.g., BIACORE® assays), bio-layer interferometry, ligand binding assays (e.g., enzyme-linked immunosorbent assay (ELISA)), equilibrium dialysis, fluorescent-activated cell sorting (FACS), or flow cytometry-based binding assays and the like. Specific binding to a particular target antigen from a certain species does not exclude that the antigen-binding protein can also specifically bind to the analogous target from a different species. For example, specific binding to human CDH17 does not exclude that the antigen-binding protein can also specifically bind to CDH17 from cynomolgus monkeys ("cyno") or mice.

[0093] The term "isolated" when used in the context of antigen-binding proteins (e.g., antibodies, such as single-domain antibodies), polypeptides, polynucleotides, and vectors, means the antigen-binding proteins (e.g., antibodies, such as single-domain antibodies), polypeptides, polynucleotides and vectors are at least partially free of other biological molecules from the cells or cell culture from which they are produced. Such biological molecules include nucleic acids, proteins, other antibodies or antigen-binding fragments, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated antigen-binding protein may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof. Generally, the term "isolated" is not intended to refer to a complete absence of such biological molecules (e.g., minor or insignificant amounts of impurity may remain) or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the antigen-binding proteins (e.g., antibodies, such as single-domain antibodies).

[0094] The term “operably linked” as used herein can refer to a functional relationship between two or more regions of a polypeptide chain in which the two or more regions are linked so as to produce a functional polypeptide.

[0095] As used herein, the term “variant”, “derivative” or “derived from” in the context of proteins or polypeptides (e.g., antigen-binding proteins or domains thereof) refer to: (a) a polypeptide that has at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% sequence identity to the polypeptide it is a variant or derivative of; (b) a polypeptide encoded by a nucleotide sequence that has at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% sequence identity to a nucleotide sequence encoding the polypeptide it is a variant or derivative of; (c) a polypeptide that contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid mutations (i.e., additions, deletions and/or substitutions) relative to the polypeptide it is a variant or derivative of; (d) a polypeptide encoded by nucleic acids can hybridize under high, moderate or typical stringency hybridization conditions to nucleic acids encoding the polypeptide it is a variant or derivative of; (e) a polypeptide encoded by a nucleotide sequence that can hybridize under high, moderate or typical stringency hybridization conditions to a nucleotide sequence encoding a fragment of the polypeptide, it is a variant or derivative of, of at least 20 contiguous amino acids, at least 30 contiguous amino acids, at least 40 contiguous amino acids, at least 50 contiguous amino acids, at least 75 contiguous amino acids, at least 100 contiguous amino acids, at least 125 contiguous amino acids, or at least 150 contiguous amino acids; or (f) a fragment of the polypeptide it is a variant or derivative of. The terms also encompass a fusion protein or polypeptide comprising the polypeptide it is a variant or derivative of.

[0096] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0097] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence

identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. *See, e.g.*, Pearson (1994) Methods Mol. Biol. 24: 307-331, herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate, and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-1445, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0098] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as Gap and Bestfit which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild-type protein and a mutein thereof. *See, e.g.*, GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) supra). Another preferred algorithm when comparing a sequence of the disclosure to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. *See, e.g.*, Altschul *et al.* (1990) J. Mol. Biol.

215:403-410 and Altschul *et al.* (1997) Nucleic Acids Res. 25:3389-402, each herein incorporated by reference.

[0099] The terms "enhance" or "promote," or "increase," or "expand," or "improve" refer generally to the ability of a composition contemplated herein to produce, elicit, or cause a greater physiological response (i.e., downstream effects) compared to the response caused by either vehicle or a control molecule/composition. A measurable physiological response may include an increase in immune cell expansion, activation, effector function, persistence, and/or an increase in tumor cell death killing ability, among others apparent from the understanding in the art and the description herein. In certain embodiments, an "increased" or "enhanced" amount can be a "statistically significant" amount, and may include an increase that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (e.g., 500, 1000 times) (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.) the response produced by vehicle or a control composition.

[0100] The terms "decrease" or "lower," or "lessen," or "reduce," or "abate" refer generally to the ability of composition contemplated herein to produce, elicit, or cause a lesser physiological response (i.e., downstream effects) compared to the response caused by either vehicle or a control molecule/composition. In certain embodiments, a "decrease" or "reduced" amount can be a "statistically significant" amount, and may include a decrease that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (e.g., 500, 1000 times) (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.) the response (reference response) produced by vehicle or a control composition.

[0101] The terms "treat" or "treatment" of a state, disorder or condition include: (1) preventing, delaying, or reducing the incidence and/or likelihood of the appearance of at least one clinical or sub-clinical symptom of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition, but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; or (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof or at least one clinical or sub-clinical symptom thereof; or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or sub-clinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0102] The terms "effective amount" or "therapeutically effective amount" refer to a quantity and/or concentration of a composition containing an active ingredient (e.g., anti-CDH17 antigen-binding protein) that when administered into a patient either alone (i.e., as a monotherapy) or in combination

with additional therapeutic agents, yields a significant decrease in disease progression as, for example, by ameliorating or eliminating symptoms and/or the cause of the disease. An effective amount may be an amount that relieves, lessens, or alleviates at least one symptom or biological response or effect associated with a disease or disorder, prevents progression of the disease or disorder, or improves physical functioning of the patient. A therapeutically effective amount of a composition containing an active agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the active agent to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the active agent are outweighed by the therapeutically beneficial effects. A therapeutically effective amount may be delivered in one or more administrations. A therapeutically effective amount refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic and/or prophylactic result.

[0103] The terms "individual", "subject" and "patient" are used interchangeably herein to refer to an animal; for example a mammal. The terms include human and veterinary subjects. In some embodiments, methods of treating mammals, including, but not limited to, humans, rodents, simians, felines, canines, equines, bovines, porcines, ovines, caprines, mammalian laboratory animals, mammalian farm animals, mammalian sport animals, and mammalian pets, are provided. The subject can be male or female and can be any suitable age, including infant, juvenile, adolescent, adult, and geriatric subjects. In some embodiments, a subject can be a subject in need of treatment for a disease or disorder. In particular embodiments, the subject is a human.

Anti-CDH17 Antigen-binding Proteins

[0104] The present disclosure provides antigen-binding proteins (e.g., antibodies, such as single-domain antibodies) that bind to cadherin 17 (CDH17).

[0105] Cadherin 17 (CDH17) is a calcium-dependent cell adhesion glycoprotein belonging to the 7D cadherin subfamily within the cadherin superfamily. It consists of seven extracellular cadherin (EC) repeats with a total length of 764 amino acids, a single transmembrane helix and a very short intracellular domain of only 23 amino acids, lacking binding sites for interactions with the cytoskeleton proteins such as catenins. CDH17 is predicted to harbor eight N-glycans located throughout all ECs except for EC1, with several of them confirmed experimentally. Between the linkers of each EC domain (except for EC2 and EC3) CDH17 exhibits the typical canonical calcium binding motif that coordinates three calcium ions, which were shown to contribute to the rigidity of the protein.

[0106] Similar to other cadherins, CDH17 contributes to cell adhesion via trans-interaction with cadherins of neighboring cells. However, instead of dimerizing via EC1 and EC2, it was shown that in CDH17 EC2 of one chain interacts with EC4 of a second chain. Further it was suggested that additional EC domains may be involved in the dimerization.

[0107] In addition, it was reported that CDH17 comprises an RGD (Arg-Gly-Asp) tripeptide motif in EC6, through which the protein interacts with integrin $\alpha 2\beta 1$. This CDH17 $\alpha 2\beta 1$ interaction was associated with aggressive forms of cancer during late-stage metastasis. The soluble form of CDH17 was reported to contain the RGD motif suggesting proteolytic cleavage C-terminal of EC6 or even more proximal to the membrane.

[0108] In some embodiments, antigen-binding proteins that specifically bind to cadherin 17 (CDH17) described herein can act as an anchor and/or a guide to a target cancer cell, while avoiding impact on CDH17 biology. Since CDH17 is not expressed on normal adult hepatocytes, CDH17 can be used as a targeting antigen so as to avoid liver toxicity that has plagued various therapeutic molecules aimed at targeting cancer. An anti-CDH17 antigen-binding protein of the present disclosure can target membrane proximal epitopes of CDH17 in order to not impair its dimerization. In some embodiments, membrane proximal targeting of can avoid binding to potentially shed CDH17 thus retaining targeting to tumor cells. In some embodiments, binding of the anti-CDH17 antigen-binding proteins of the present disclosure to the integrin binding tripeptide RGD motif in extracellular cadherin domain 6 (EC6) of human CDH17 can be avoided.

[0109] In various embodiment, anti-CDH17 antigen-binding proteins described herein can specifically bind to CDH17 from human, cyno and/or mouse.

[0110] In some embodiments, a human CDH17 is encoded by a CDH17 gene (NCBI Gene ID 1015; AA Sequence: >sp|Q12864|CAD17_HUMAN Cadherin-17 OS=*Homo sapiens* OX=9606 GN=CDH17 PE=1 SV=3) and has the amino acid sequence

MILQAHLHSLCLLMLYLATGYGQEGKFSGPLKPMTFSIYEGQEPSQIIFQFKANPPAVTFELTGETDNIFVIEREGLLYYNR
ALDRETRSTHNLQVAALDANGIIVEGPVPITIKVKDINDNRPTFLQSKYEGSVRQNSRPGKPFLYVNATDLDDPATPNGQ
LYYQIVIQLPMINNVMYFQINNKTGAISLTREGSQELNPAKNPSYNLVISVKDMGGQSENSFSDTTSVDIIVTENIWKAP
KPVEMVENSTDPHPIKITQVRWNDPGAQYSLVDKEKLPRFPFSIDQEGDIYVTQPLDREEKDAYVFYAVAKDEYGKPLS
YPLEIHVKVKDINDNPPTCPSPVTVFEVQENERLGNSIGTLTAHDRDEENTANSFLNYRIVEQTPKLPMDGLFLIQTYAG
MLQLAKQSLKKQDTPQYNLTIEVSDKDFKTLCFVQINVIDINDQIPIFEKSDYGNLTLAEDTNIGSTILTIQATDADEPFTGS
SKILYHIIKGDSEGRLGVDTDPHTNTGYVIIKKPLDFETAAVSNIVFKAENPEPLVFGVKYNASSFAKFTLIVTDVNEAPQFS
QHVFQAKVSEDVAIGTKVGNVTAKDPEGLDISYSLRGDTRGWLKIDHVTGEIFSVAPLDREAGSPYRVQVVATEVGGSS

LSSVSEFHLILMDVNDNPPRLAKDYTGLFFCHPLSAPGSLIFEATDDDQHLFRGPHFTFSLGSGSLQNDWEVSKINGTHA
RLSTRHTEFEEREYVVLIRINDGGRPPLEGIVSLPVTFCSCVEGSCFRPAGHQTGIPTVGMAVGILLTTLLVIGIILAVVFIRIK
KDKGKDNVESAQASEVKPLRS (UniProtKB Accession No. Q12864) (SEQ ID NO: 1604).

[0111] In some embodiments, a cyno CDH17 is encoded by a CDH17 gene (NCBI Gene ID 102129651; AA Sequence: >tr|A0A2K5X8I8|A0A2K5X8I8_MACFA Cadherin 17 OS=*Macaca fascicularis* OX=9541 GN=CDH17 PE=4 SV=2) and has the amino acid sequence
MLHSYCANKLLEGTTLKVLRISYLVIEPVKILSEIGDLLQIPQLCFFPYSLICCFFPQFKANPPAVTFELTGETDNIFKIEQEGLL
YYTKALDRETRSTHNLQVAALDANGAIVEGPVPITIEVKDVNDNRPTFLQSKYEGSVRQNSRPGKPFLYVNATDLDDPA
TPNGQLSYQIVIQLPMINNVMYFQINNKTGGISLTREGSQELNPAKNPSYNLVISVKDMGGQSENSFSDTTSVDIIVTEN
IWKAPEPVEMVENSTDPHPIKITQVRWNDPGAQYSLVDKEKLPRFPFSIDQEGDIYVTQPLDREEKDAYVFYAVAKDEY
GKPLSYPLEIHVKVQDINDNPPTCPSPVTVFEVQENERLGNSIGALTAHDSDEENTANSLLNYRIVEQTPKLPMDGLFLIQ
TYAGMLQLAKQSLKKQDTPQYNLTIEVSDKDFKTLCFVQINVIDINDQIPIFEKSDYGNLTLAEDTNVGSTILTIQATDADE
PFTGSSKILYHVIKGDSEGRLGVDTDPHTNTGYVIIKKPLDFETAAISNIVFKAENPEPLVFGVTYNASSFAKFTLFVTDVNE
APEFSQYVFQAKVSEDVAIGTKVGNVTAKDPEGLDISYSLRGDTRGWLKIDHVTGEIFSVAPLDREAGSPYRVQVVATEV
GGSSLSSVSQFHLILTDVNDNPPRLAKDYMDLYFCHPLSAPGSLIFEATDDDQHLFRGPHFTFSIASESLQNDWQVSKIN
GTHARLSTRHTDFEEKEYVVSIRINDGGRPPLESTVSLTVTFCSCGEDGCFRPAGHQPGIPTVGMAVGILLTTLLVIGIILA
VVFIRMKTDKGKDNVESAQASEVKPLRS (UniProtKB Accession No. A0A2K5X8I8) (SEQ ID NO: 1605).

[0112] In some embodiments, a mouse CDH17 is encoded by a Cdh17 gene (NCBI Gene ID 12557; AA Sequence: >sp|Q9R100|CAD17_MOUSE Cadherin-17 OS=*Mus musculus* OX=10090 GN=Cdh17 PE=1 SV=1) and has the amino acid sequence
MVSAQLHFLCLLTLYLTCGYGEEGKFSGPLKPMTFSIFEGQEPSQVIFQFKTNPPAVTFELTGETDGIFKIEKDGLLYHTRA
LDRETRAVHHLQLAALDSHGAIVDGPVPITIEVKDINDNRPTFLQSKYEGSVRQNSRPGKPFMYVNATDLDDPATPNG
QLFYQIVIQLPQINDVMYFQIDSKTGAISLTPEGSQELDPVKNPSYNLVVSVKDMGGQSENSFSDTTYVDISIRENIWKA
PEPVEIRENSTDPHPIKITQVQWNDPGAQYSLVNKEKLSPFPFSIDQEGNIYVTQALDREEKNSHVFFATAKDENGKPLA
YPLEIYVKVIDINDNPPTCLSPVTVFEVQENEPLGNSIGIFEAHDMDEANNINSILKYKLVDQTPKVPSDGLFLIGEYEGKV
QLSKQSLKKQDSPQYNLSIEVSDVDFKTLCYIQVNVIDINDQIPIFETSNYGSKTLSEDTAIGSTILIIQATDADEPFTGSSKIL
YKIVQGDTEGRLEVVTDPTTNAGYVKIKKPLDFETQPVSSIVFQAENPEPLVKGIEYNASSFASFELIVTDVNEVPVFPQRI
FQANVSEDAAVGSRVGNVTARDPEGLTVSYSLKGNMRGWLKIDSVTGEIFSAAPLDRETESVYRVQVVATEVGGSSLSS
TADFHLVLTDVNDNPPRLAKDYTGLFFCHPLSAPGSLIFEVTDDDQQSLRRPKFTFALGREGLQSDWEVSKINGTHARLS
TRHTRFEEQVYNIPIRINDGGQPPMEGTVFLPVTFCQCVEGSCFRPAGRQDGIPTVGMAVGILLTTFLVIGIILAVVFIRM
RKDKVENPQSPENKPLRS (UniProtKB Accession No. Q9R100) (SEQ ID NO: 1606).

[0113] In some embodiments, antigen-binding proteins of the present disclosure bind to human CDH17. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of less than about 1×10^{-6} M, for example, less than about 5×10^{-7} M, less than about 3×10^{-7} M, less than about 1×10^{-7} M, less than about 8×10^{-8} M, less than about 5×10^{-8} M, less than about 3×10^{-8} M, less than about 1×10^{-8} M, less than about 8×10^{-9} M, less than about 5×10^{-9} M, less than about 3×10^{-9} M, or less than about 1×10^{-9} M, or about 1×10^{-10} to 1×10^{-9} M, 1×10^{-10} to 5×10^{-9} M, about 1×10^{-10} to 1×10^{-8} M, about 1×10^{-10} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-8} M, about 1×10^{-9} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-7} M, or about 1×10^{-8} to 1×10^{-7} M.

[0114] In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of less than about 3×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of less than about 2.2×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of less than about 1×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of about 1×10^{-10} to 5×10^{-8} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of less than about 160 nM, 150 nM, 140 nM, 130 nM, 120 nM, 110 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 25 nM, 20 nM, 15 nM (e.g., about 12 nM, 11 nM, 10 nM, 9nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2nM, or 1 nM, or less).

[0115] In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of about 1.54×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of about 1.37×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of about 6.2×10^{-8} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to human CDH17 with a K_D of about 3.2×10^{-8} M.

[0116] In some embodiments, antigen-binding proteins of the present disclosure bind to cynomolgus monkey ("cyno") CDH17. In some embodiments, antigen-binding proteins (e.g., antibodies such as

single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of less than about 1×10^{-6} M, for example, less than about 5×10^{-7} M, less than about 3×10^{-7} M, less than about 1×10^{-7} M, less than about 8×10^{-8} M, less than about 5×10^{-8} M, less than about 3×10^{-8} M, less than about 2×10^{-8} M, less than about 1×10^{-8} M, less than about 8×10^{-9} M, less than about 5×10^{-9} M, less than about 3×10^{-9} M, or less than about 1×10^{-9} M, or about 1×10^{-10} to 1×10^{-9} M, 1×10^{-10} to 5×10^{-9} M, about 1×10^{-10} to 1×10^{-8} M, about 1×10^{-10} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-8} M, about 1×10^{-9} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-7} M, about 1×10^{-9} to 2×10^{-7} M, about 1×10^{-9} to 5×10^{-7} M, about 1×10^{-8} to 1×10^{-7} M, about 1×10^{-8} to 2×10^{-7} M, about 1×10^{-8} to 5×10^{-7} M, or about 1×10^{-8} to 1×10^{-6} M.

[0117] In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of about 1.1 x 10^{-8} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of about 1 x 10^{-8} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of about 9.7 x 10^{-9} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of about 5.8 x 10^{-9} M.

[0118] In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of less than about 3×10^{-7} M. In some embodiments, antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may bind to cyno CDH17 with a K_D of about 1×10^{-9} to 1×10^{-7} M.

[0119] In some embodiments, antigen-binding proteins of the present disclosure do not bind to cyno CDH17.

[0120] In some embodiments, antigen-binding proteins of the present disclosure bind to mouse CDH17. In some embodiments, antigen-binding proteins of the present disclosure may bind to mouse CDH17 with a K_D of less than about 1×10^{-6} M, for example, less than about 5×10^{-7} M, less than about 3×10^{-7} M, less than about 1×10^{-7} M, less than about 8×10^{-8} M, less than about 5×10^{-8} M, less than about 3×10^{-8} M, less than about 1×10^{-8} M, less than about 8×10^{-9} M, less than about 5×10^{-9} M, less than about 3×10^{-9} M, or less than about 1×10^{-9} M, or about 1×10^{-10} to 1×10^{-9} M, 1×10^{-10} to 5×10^{-9} M, about 1×10^{-10} to 1×10^{-8} M, about 1×10^{-10} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-8} M, about 1×10^{-9} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-7} M, about 1×10^{-9} to 2×10^{-7} M, about 1×10^{-9} to 5×10^{-7} M, about 1×10^{-8} to 1×10^{-7} M, about 1×10^{-8} to 2×10^{-7} M, about 1×10^{-8} to 5×10^{-7} M, or about 1×10^{-8} to 1×10^{-6} M. In some embodiments, antigen-binding proteins of the present disclosure may bind to mouse CDH17 with a K_D of less than about 2×10^{-7}

M (e.g., about 160 nM, 120 nM, 115 nM, 110 nM, 100 nM, 95 nM, 90 nM, 75 nM, 50 nM, 45 nM, 30 nM, 20 nM, or less).

[0121] In some embodiments, antigen-binding proteins of the present disclosure may bind to mouse CDH17 with a K_D of about $1x10^{-6}$ M. In some embodiments, antigen-binding proteins of the present disclosure may bind to mouse CDH17 with a K_D of about $7x10^{-8}$ M. In some embodiments, antigen-binding proteins of the present disclosure may bind to mouse CDH17 with a K_D of about $5.2x10^{-8}$ M.

[0122] In some embodiments, antigen-binding proteins of the present disclosure do not bind to mouse CDH17.

[0123] In some embodiments, antigen-binding proteins of the present disclosure bind to rat CDH17. In some embodiments, antigen-binding proteins of the present disclosure may bind to rat CDH17 with a K_D of less than about 1×10^{-6} M, for example, less than about 5×10^{-7} M, less than about 3×10^{-7} M, less than about 1×10^{-7} M, less than about 8×10^{-8} M, less than about 5×10^{-8} M, less than about 3×10^{-8} M, less than about 1×10^{-8} M, less than about 8×10^{-9} M, less than about 5×10^{-9} M, less than about 3×10^{-9} M, or less than about 1×10^{-9} M, or about 1×10^{-10} to 1×10^{-9} M, 1×10^{-10} to 5×10^{-9} M, about 1×10^{-10} to 1×10^{-8} M, about 1×10^{-10} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-8} M, about 1×10^{-9} to 5×10^{-8} M, about 1×10^{-9} to 1×10^{-7} M, about 1×10^{-9} to 2×10^{-7} M, about 1×10^{-9} to 5×10^{-7} M, about 1×10^{-8} to 1×10^{-7} M, about 1×10^{-8} to 2×10^{-7} M, about 1×10^{-8} to 5×10^{-7} M, or about 1×10^{-8} to 1×10^{-6} M. In some embodiments, antigen-binding proteins of the present disclosure do not bind to rat CDH17.

[0124] In some embodiments, anti-CDH17 antigen-binding proteins described herein do not block dimerization of CDH17. In some embodiments, anti-CDH17 antigen-binding proteins described herein do not impact CDH17 biological functions. In some embodiments, anti-CDH17 antigen-binding proteins described herein do not bind to shed CDH17 thus retaining targeting to tumor cells.

[0125] In some embodiments, anti-CDH17 antigen-binding proteins described herein do not bind to the integrin binding RGD (Arg-Gly-Asp) motif in extracellular cadherin domain 6 (EC6) of human CDH17.

[0126] In some embodiments, anti-CDH17 antigen-binding proteins described herein bind to the extracellular cadherin domain 6 (EC6) and/or extracellular cadherin domain 7 (EC7) of human CDH17.

[0127] In some embodiments, anti-CDH17 antigen-binding proteins described herein bind to an extracellular region C-terminal to the RGD motif in EC6 of human CDH17.

[0128] In some embodiments, anti-CDH17 antigen-binding proteins described herein bind to the extracellular cadherin domain 1 (EC1) of human CDH17.

[0129] Binding affinity of a molecular interaction between two molecules can be measured via various techniques, such as surface plasmon resonance (SPR), bio-layer interferometry (BLI), enzyme-linked

immunosorbent assay (ELISA), equilibrium dialysis, fluorescent-activated cell sorting (FACS), flow cytometry binding assays, or isothermal titration calorimetry (ITC), and the like. Surface plasmon resonance is a biosensor technique that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, where one molecule is immobilized on the biosensor chip and the other molecule is passed over the immobilized molecule under flow conditions (see e.g., Ober et al. 2001, Intern. Immunology 13: 1551-1559). SPR can for example be performed using the BIACORE® system or Carterra LSA system. Another biosensor technique that can be used to determine affinities of biomolecular interactions is bio-layer interferometry (BLI) (see e.g., Abdiche et al. 2008, Anal. Biochem. 377: 209-217). Bio-layer Interferometry is a label-free optical technique that analyzes the interference pattern of light reflected from two surfaces: an internal reference layer (reference beam) and a layer of immobilized protein on the biosensor tip (signal beam). A change in the number of molecules bound to the tip of the biosensor causes a shift in the interference pattern, reported as a wavelength shift (nm), the magnitude of which is a direct measure of the number of molecules bound to the biosensor tip surface. Since the interactions can be measured in real-time, association and dissociation rates and affinities can be determined. BLI can for example be performed using the Octet® Systems. Alternatively, affinities can be measured in Kinetic Exclusion Assay (KinExA) (see e.g., Drake et al. 2004, Anal. Biochem., 328: 35-43), which is a solution-based method to measure true equilibrium binding affinity and kinetics of unmodified molecules. Equilibrated solutions of an antibody/antigen complex are passed over a column with beads precoated with antigen (or antibody), allowing the free antibody (or antigen) to bind to the coated molecule. Detection of the antibody (or antigen) thus captured is accomplished with a fluorescently labeled protein binding the antibody (or antigen).

[0130] Antigen-binding proteins of the present disclosure can include an antibody or an antigen-binding fragment of an antibody, such as a human antibody, a humanized antibody; a camelid antibody; a chimeric antibody; a recombinant antibody; a heavy chain antibody; a single-domain antibody (e.g., VHH); a single chain antibody (e.g., single chain fragment variable (scFv)); a diabody; a triabody; a tetrabody; a Fab fragment; a F(ab') 2 fragment; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; or an IgG4 antibody, and fragments thereof.

[0131] In some embodiments, an antigen-binding protein that binds to CDH17 is a single-domain antibody (also termed as "sdAb"). The single-domain antibodies of the present disclosure can be derived from numerous sources, including but not limited to VHHs, VNARs, or VH domains (naturally occurring or engineered VH domains). VHHs can be generated from camelid heavy chain only antibodies and

libraries (e.g., synthetic libraries) thereof. VNARs can be generated from cartilaginous fish heavy chain only antibodies and libraries (e.g., synthetic libraries) thereof. Various methods have been implemented to generate monomeric sdAbs from conventionally heterodimeric VH and VL domains, including interface engineering and selection of specific germline families. In some embodiments, the sdAb of the present invention are human or humanized.

[0132] In some embodiments, a single-domain antibody described herein is a VHH fragment (also known as a nanobody). VHH fragments are also referred to as "V-bodies" in the present disclosure. In some embodiments, the VHH is a camelid VHH, a humanized VHH or a camelized VH. In some embodiments, a single-domain antibody described herein is a VH domain. In some embodiments, a single-domain antibody described herein is a naturally occurring VH domain or engineered VH domain.

[0133] The variable domain of an antigen-binding protein (e.g., antibody such as a single-domain antibody) of the present disclosure comprises at least three complementarity determining regions (CDRs) which determine its binding specificity. Preferably, in a variable domain, the CDRs are distributed between framework regions (FRs). The variable domain typically contains 4 framework regions interspaced by 3 CDR regions, resulting in the following typical antibody variable domain structure: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. CDRs and/or FRs of the single domain antibody of the invention may be fragments or derivatives from a naturally occurring antibody variable domain or may be synthetic.

[0134] Sequence identifiers corresponding to exemplary anti-CDH17 VHH antibodies provided herein are listed in **Table 1-1**. **Table 1-1** sets forth the sequence identifiers of amino acid sequences of the complementarity determining regions (CDR1, CDR2 and CDR3), amino acid and DNA sequences of the full-length camelid VHH antibodies, as well as amino acid sequences of corresponding humanized VHH antibodies. Amino acid sequences of additional exemplary anti-CDH17 VHH antibodies and corresponding humanized VHH antibodies are provided in **Table 1-2.**

Table 1-1. Sequence identifiers for exemplary anti-CDH17 VHH antibodies

Antibody ID	Group	CDR1	CDR2	CDR3	Non-humanized VHH		Humanized VHH
		Amino acid sequence	Amino acid sequence	Amino acid sequence	Amino acid sequence	DNA sequence	Amino acid sequence
ODY-N1061	A	1	2	3	4	67	5
ODY-N1070	B	6	7	8	9	68	10
ODY-N1081	C	11	12	13	14	69	15
ODY-45F5	D	16	17	18	19	70	20
ODY-N1083	D	21	17	22	23	71	24

ODY-N1084	D	16	17	25	26	72	27
ODY-N1090	E	28	17	29	30	73	31
ODY-N1091	F	637	875	1113	187	1351	421
ODY-N1092	F	32	33	34	35	74	36
ODY-N1095	G	37	38	39	40	75	41
ODY-43B5	H	42	43	44	45	76	46
ODY-43E7	I	47	48	49	50	77	51
ODY-44A4	I	52	53	54	55	78	56
ODY-N1242	J	57	58	59	60	79	61
ODY-44A1	K	62	63	64	65	80	66
ODY-N1117	M	1607	1608	1609	1619	1627	1623
ODY-N1129	N	1610	1611	1612	1620	1628	1624
ODY-N1186	O	1613	1614	1615	1621	1629	1625
ODY-N1264	P	1616	1617	1618	1622	1630	1626

Table 1-2. Sequence identifiers for additional exemplary VHH antibodies and humanized VHH antibodies

Group	Non-humanized VHH Amino Acid Sequence	Humanized VHH Amino Acid Sequence
A	4	5
A	105	343
A	106	344
A	107	345
A	108	346
A	109	347
A	110	5
A	111	348
A	112	5
A	113	349
B	114	350
B	9	10
B	115	351
B	116	352
B	117	353
B	118	354
B	119	355
B	120	356
B	121	357
B	122	358
B	123	359
B	124	360
B	125	361
B	126	362

B	127	363
C	14	15
C	128	364
C	129	365
C	130	366
C	131	367
D	23	24
D	19	20
D	132	368
D	133	369
D	134	370
D	135	371
D	136	372
D	137	373
D	138	374
D	139	375
D	140	376
D	141	377
D	142	378
D	143	379
D	144	380
D	26	27
D	145	381
D	146	382
D	147	383
D	148	384
D	149	385
D	150	386
D	151	387
D	152	388
D	153	389
D	154	390
D	155	391
D	156	392
D	157	393
D	158	394
D	159	395
D	160	396
D	161	397
D	162	398
D	163	399
D	164	400
D	165	401
D	166	402
D	167	403
D	168	377

D	169	404
D	170	405
D	171	406
D	172	407
D	173	408
D	174	409
D	175	410
D	176	27
D	177	411
D	178	412
D	179	413
D	180	414
D	181	415
D	182	416
D	183	417
D	184	418
D	185	419
D	186	420
E	30	31
F	187	421
F	35	36
F	188	36
F	189	421
F	190	422
F	191	423
F	192	421
F	193	424
F	194	425
G	40	41
G	195	426
G	196	427
G	197	428
H	45	46
H	198	46
H	199	46
H	200	46
H	201	46
I	202	429
I	203	430
I	204	431
I	205	432
I	206	433
I	207	434
I	208	435
I	209	436
I	210	437

I	211	438
I	212	439
I	213	440
I	214	441
I	50	51
I	215	442
I	216	443
I	217	444
I	218	440
I	219	445
I	220	446
I	221	51
I	222	436
I	223	447
I	224	448
I	225	449
I	226	450
I	227	451
I	228	452
I	229	453
I	230	454
I	231	455
I	232	51
I	233	456
I	234	457
I	235	458
I	236	435
I	237	459
I	238	460
I	239	461
I	240	462
I	241	463
I	242	464
I	243	431
I	244	465
I	245	466
I	246	467
I	247	438
I	248	468
I	249	469
I	250	470
I	55	56
I	251	471
I	252	472
I	253	473
I	254	474

I	255	475
I	256	476
I	257	477
I	258	478
I	259	479
I	260	480
I	261	481
I	262	482
I	263	51
I	264	483
I	265	484
I	266	485
I	267	486
I	268	487
I	269	488
I	270	489
I	271	490
I	272	491
I	273	492
I	274	493
I	275	494
I	276	495
I	277	496
I	278	497
I	279	498
I	280	431
I	281	499
I	282	500
I	283	501
I	284	500
I	285	502
I	286	503
I	287	504
I	288	505
I	289	506
I	290	438
I	291	507
J	60	61
J	292	508
J	293	509
J	294	510
J	295	511
J	296	512
J	297	513
J	298	513
J	299	61

J	300	514
J	301	515
K	302	516
K	303	516
K	304	517
K	305	518
K	306	519
K	307	520
K	308	521
K	309	522
K	310	523
K	311	524
K	312	525
K	313	526
K	314	527
K	315	528
K	316	529
K	317	530
K	318	531
K	319	532
K	320	533
K	321	534
K	322	535
K	323	536
K	324	537
K	325	538
K	65	66
K	326	539
K	327	540
K	328	541
K	329	542
K	330	543
K	331	544
K	332	545
K	333	546
K	334	547
K	335	519
K	336	548
K	337	549
K	338	550
K	339	551
K	340	552
K	341	553
K	342	554
M	1619	1623
M	1643	1672

M	1644	1673
M	1645	1623
N	1620	1624
N	1646	1674
N	1647	1675
O	1648	1676
O	1621	1625
O	1649	1677
O	1650	1678
O	1651	1679
O	1652	1680
O	1653	1678
O	1654	1678
O	1655	1681
O	1656	1680
O	1657	1682
O	1658	1681
O	1659	1683
O	1660	1684
O	1661	1685
O	1662	1686
O	1663	1686
O	1664	1681
O	1665	1682
O	1666	1687
O	1667	1678
O	1668	1688
O	1669	1689
P	1622	1626
P	1670	1690
P	1671	1691

[0135] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) described herein may comprise a complementarity determining region 3 (CDR3) comprising an amino acid sequence selected from

a). A(A/L)CLLRFE(S/T)CLEYNRAQY(N/P)Y (SEQ ID NO: 83);

b). AAVR(A/S)GSDWWTTM(R/T)QR(D/H)YD(F/Y) (SEQ ID NO: 85);

c). AARDSR(K/R)GGLFADLN(E/G)YDY (SEQ ID NO: 88);

d). AATG(D/N)(L/S)YRGAYDRP(A/T)EYDY (SEQ ID NO: 90);

e). VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

f). AAQFSLPVDA(S/T)PLRRY(A/Y)(H/Y) (SEQ ID NO: 93);

g). AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

h). AARNGGYDLNDYAY (SEQ ID NO: 44);

i). NAGG(G/P/A)(A/R)(L/R)GY (SEQ ID NO: 98);

j). NVGGQL(K/L/R)GY (SEQ ID NO: 101);

k). NQGG(Q/S)KGY (SEQ ID NO: 104);

l). AADG(L/P)PY(G/S)(D/S)WFGDQFDV (SEQ ID NO: 1633);

m). AFNKWGRLSADL(D/N)DYFR (SEQ ID NO: 1636);

n). N(M/T)HRSY(A/D)I(D/N/R/S)FYDN (SEQ ID NO: 1639); and

o). RRYDDY(D/G)S (SEQ ID NO: 1642).

[0136] In some embodiments, the CDR3 comprises an amino acid sequence selected from ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3); AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8); AARDSRRGGLFADLNEYDY (SEQ ID NO: 13); AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18); AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22); AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25); VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29); AAQFSLPVDASPLRRYYY (SEQ ID NO: 34); AATRKTRRSTVAGTEVDY (SEQ ID NO: 39); AARNGGYDLNDYAY (SEQ ID NO: 44); NAGGGRLGY (SEQ ID NO: 49); NAGGAALGY (SEQ ID NO: 54); NVGGQLLGY (SEQ ID NO: 59); NQGGSKGY (SEQ ID NO: 64); AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113); AADGLPYGDWFGDQFDV (SEQ ID NO: 1609); AFNKWGRLSADLDDYFR (SEQ ID NO: 1612); NMHRSYDISFYDN (SEQ ID NO: 1615); and RRYDDYGS (SEQ ID NO: 1618).

[0137] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) described herein may further comprise a complementarity determining region 1 (CDR1) comprising an amino acid sequence selected from

a). GFTLSN(T/Y)N (SEQ ID NO: 81);

b). GSPLDYYA (SEQ ID NO: 6);

c). RL(A/N/T)(F/S)(N/S)(R/S)(S/T)T;

d). GRTFS(E/T)PI (SEQ ID NO: 89);

e). GRTFSSPI (SEQ ID NO: 28);

f). TRTF(D/N)MYA (SEQ ID NO: 91);

g). GRTF(D/S)S(L/Y)(L/V) (SEQ ID NO: 94);

h). GRTDSILN (SEQ ID NO: 42);

i). G(I/M)RFS(S/Q)YA (SEQ ID NO: 96);

j). GIRFS(A/S)YA (SEQ ID NO: 99);

k). GS(I/R)FS(R/S)(W/Y)A (SEQ ID NO: 102);

l). G(G/R)TASEYG (SEQ ID NO: 1631);

m). EQTMTGF(T/W) (SEQ ID NO: 1634);

n). GLRFS(S/N)YA (SEQ ID NO: 1637); and

o). (G/R)GT(F/V)SGYA (SEQ ID NO: 1640).

[0138] In some embodiments, the CDR1 comprises an amino acid sequence selected from GFTLSNYN (SEQ ID NO: 1); GSPLDYYA (SEQ ID NO: 6); RLNFSRTT (SEQ ID NO: 11); GRTFSEPI (SEQ ID NO: 16); GRTFSTPI (SEQ ID NO: 21); GRTFSEPI (SEQ ID NO: 16); GRTFSSPI (SEQ ID NO: 28); TRTFNMYA (SEQ ID NO: 32); GRTFSSYL (SEQ ID NO: 37); GRTDSILN (SEQ ID NO: 42); GIRFSSYA (SEQ ID NO: 47); GMRFSQYA (SEQ ID NO: 52); GIRFSAYA (SEQ ID NO: 57); GSRFSSYA (SEQ ID NO: 62); TRTFDMYA (SEQ ID NO: 637); GGTASEYG (SEQ ID NO: 1607); EQTMTGFW (SEQ ID NO: 1610); GLRFSNYA (SEQ ID NO: 1613); and GGTVSGYA (SEQ ID NO: 1616).

[0139] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) described herein may further comprise a complementarity determining region 2 (CDR2) comprising an amino acid sequence selected from

a). (F/I)SRGGRT (SEQ ID NO: 82);

b). ISTSGR(C/S)T (SEQ ID NO: 84);

c). SGW(A/S)R(G/T)RT (SEQ ID NO: 87);

d). LISTGGST (SEQ ID NO: 17);

e). I(N/S)RSG(A/T)NT (SEQ ID NO: 92);

f). ISWN(D/G)RST (SEQ ID NO: 95);

g). ISWFRGET (SEQ ID NO: 43);

h). I(F/T)(I/K/N/S)(D/G)(G/Y)(R/S/T)T;

i). MT(A/N/T)GGMT (SEQ ID NO: 100);

j). IT(N/S)GG(G/R/S)T (SEQ ID NO: 103);

k). ISTSGGVT (SEQ ID NO: 1632);

l). ISASGSRV (SEQ ID NO: 1635);

m). IT(N/K)GG(I/N/S)T (SEQ ID NO: 1638); and

n). INSGGPT (SEQ ID NO: 1641).

[0140] In some embodiments, the CDR2 comprises an amino acid sequence selected from ISRGGRT (SEQ ID NO: 2); ISTSGRCT (SEQ ID NO: 7); SGWARGRT (SEQ ID NO: 12); LISTGGST (SEQ ID NO: 17); ISRSGTNT (SEQ ID NO: 33); ISWNDRST (SEQ ID NO: 38); ISWFRGET (SEQ ID NO: 43); ITSGYRT (SEQ ID NO: 48); IFKDGTT (SEQ ID NO: 53); MTAGGMT (SEQ ID NO: 58); ITSGGRT (SEQ ID NO: 63); INRSGANT (SEQ ID

NO: 875); ISTSGGVT (SEQ ID NO: 1608); ISASGSRV (SEQ ID NO: 1611); ITKGGIT (SEQ ID NO: 1614); and INSGGPT (SEQ ID NO: 1617).

[0141] In some embodiments of any of the above-described antigen-binding proteins, the antigen-binding protein comprises

i). a CDR1 comprising an amino acid sequence of GFTLSN(T/Y)N (SEQ ID NO: 81), a CDR2 comprising an amino acid sequence of (F/I)SRGGRT (SEQ ID NO: 82), and a CDR3 comprising an amino acid sequence of A(A/L)CLLRFE(S/T)CLEYNRAQY(N/P)Y (SEQ ID NO: 83);

ii). a CDR1 comprising an amino acid sequence of GSPLDYYA (SEQ ID NO: 6), a CDR2 comprising an amino acid sequence of ISTSGR(C/S)T (SEQ ID NO: 84), and a CDR3 comprising an amino acid sequence of AAVR(A/S)GSDWWTTM(R/T)QR(D/H)YD(F/Y) (SEQ ID NO: 85);

iii). a CDR1 comprising an amino acid sequence of RL(A/N/T)(F/S)(N/S)(R/S)(S/T)T, a CDR2 comprising an amino acid sequence of SGW(A/S)R(G/T)RT (SEQ ID NO: 87), and a CDR3 comprising an amino acid sequence of AARDSR(K/R)GGLFADLN(E/G)YDY (SEQ ID NO: 88);

iv). a CDR1 comprising an amino acid sequence of GRTFS(E/T)PI (SEQ ID NO: 89), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATG(D/N)(L/S)YRGAYDRP(A/T)EYDY (SEQ ID NO: 90);

v). a CDR1 comprising an amino acid sequence of GRTFSSPI (SEQ ID NO: 28), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

vi). a CDR1 comprising an amino acid sequence of TRTF(D/N)MYA (SEQ ID NO: 91), a CDR2 comprising an amino acid sequence of I(N/S)RSG(A/T)NT (SEQ ID NO: 92), and a CDR3 comprising an amino acid sequence of AAQFSLPVDA(S/T)PLRRY(A/Y)(H/Y) (SEQ ID NO: 93);

vii). a CDR1 comprising an amino acid sequence of GRTF(D/S)S(L/Y)(L/V) (SEQ ID NO: 94), a CDR2 comprising an amino acid sequence of ISWN(D/G)RST (SEQ ID NO: 95), and a CDR3 comprising an amino acid sequence of AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

viii) a CDR1 comprising an amino acid sequence of GRTDSILN (SEQ ID NO: 42), a CDR2 comprising an amino acid sequence of ISWFRGET (SEQ ID NO: 43), and a CDR3 comprising an amino acid sequence of AARNGGYDLNDYAY (SEQ ID NO: 44);

ix). a CDR1 comprising an amino acid sequence of G(I/M)RFS(S/Q)YA (SEQ ID NO: 96), a CDR2 comprising an amino acid sequence of I(F/T)(I/K/N/S)(D/G)(G/Y)(R/S/T)T, and a CDR3 comprising an amino acid sequence of NAGG(G/P/A)(A/R)(L/R)GY (SEQ ID NO: 98);

x). a CDR1 comprising an amino acid sequence of GIRFS(A/S)YA (SEQ ID NO: 99), a CDR2 comprising an amino acid sequence of MT(A/N/T)GGMT (SEQ ID NO: 100), and a CDR3 comprising an amino acid sequence of NVGGQL(K/L/R)GY (SEQ ID NO: 101);

xi). a CDR1 comprising an amino acid sequence of GS(I/R)FS(R/S)(W/Y)A (SEQ ID NO: 102), a CDR2 comprising an amino acid sequence of IT(N/S)GG(G/R/S)T (SEQ ID NO: 103), and a CDR3 comprising an amino acid sequence of NQGG(Q/S)KGY (SEQ ID NO: 104);

xii). a CDR1 comprising an amino acid sequence of G(G/R)TASEYG (SEQ ID NO: 1631), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1632), and a CDR3 comprising an amino acid sequence of AADG(L/P)PY(G/S)(D/S)WFGDQFDV (SEQ ID NO: 1633);

xiii). a CDR1 comprising an amino acid sequence of EQTMTGF(T/W) (SEQ ID NO: 1634), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1635), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADL(D/N)DYFR (SEQ ID NO: 1636);

xiv). a CDR1 comprising an amino acid sequence of GLRFS(S/N)YA (SEQ ID NO: 1637), a CDR2 comprising an amino acid sequence of IT(N/K)GG(I/N/S)T (SEQ ID NO: 1638), and a CDR3 comprising an amino acid sequence of N(M/T)HRSY(A/D)I(D/N/R/S)FYDN (SEQ ID NO: 1639); or

xv). a CDR1 comprising an amino acid sequence of (G/R)GT(F/V)SGYA (SEQ ID NO: 1640), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1641), and a CDR3 comprising an amino acid sequence of RRYDDY(D/G)S (SEQ ID NO: 1642).

[0142] In some embodiments of any of the above-described antigen-binding proteins, the antigen-binding protein comprises

i). a CDR1 comprising an amino acid sequence of GFTLSNYN (SEQ ID NO: 1), a CDR2 comprising an amino acid sequence of ISRGGRT (SEQ ID NO: 2), and a CDR3 comprising an amino acid sequence of ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3);

ii). a CDR1 comprising an amino acid sequence of GSPLDYYA (SEQ ID NO: 6), a CDR2 comprising an amino acid sequence of ISTSGRCT (SEQ ID NO: 7), and a CDR3 comprising an amino acid sequence of AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8);

iii). a CDR1 comprising an amino acid sequence of RLNFSRTT (SEQ ID NO: 11), a CDR2 comprising an amino acid sequence of SGWARGRT (SEQ ID NO: 12), and a CDR3 comprising an amino acid sequence of AARDSRRGGLFADLNEYDY (SEQ ID NO: 13);

iv). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18);

v). a CDR1 comprising an amino acid sequence of GRTFSTPI (SEQ ID NO: 21), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22);

vi). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25);

vii). a CDR1 comprising an amino acid sequence of GRTFSSPI (SEQ ID NO: 28), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO:17), and a CDR3 comprising an amino acid sequence of VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

viii). a CDR1 comprising an amino acid sequence of TRTFNMYA (SEQ ID NO: 32), a CDR2 comprising an amino acid sequence of ISRSGTNT (SEQ ID NO: 33), and a CDR3 comprising an amino acid sequence of AAQFSLPVDASPLRRYYY (SEQ ID NO: 34);

ix). a CDR1 comprising an amino acid sequence of GRTFSSYL (SEQ ID NO: 37), a CDR2 comprising an amino acid sequence of ISWNDRST (SEQ ID NO: 38), and a CDR3 comprising an amino acid sequence of AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

x). a CDR1 comprising an amino acid sequence of GRTDSILN (SEQ ID NO: 42), a CDR2 comprising an amino acid sequence of ISWFRGET (SEQ ID NO: 43), and a CDR3 comprising an amino acid sequence of AARNGGYDLNDYAY (SEQ ID NO: 44);

xi). a CDR1 comprising an amino acid sequence of GIRFSSYA (SEQ ID NO: 47), a CDR2 comprising an amino acid sequence of ITSGYRT (SEQ ID NO: 48), and a CDR3 comprising an amino acid sequence of NAGGGRLGY (SEQ ID NO: 49);

xii). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54);

xiii). a CDR1 comprising an amino acid sequence of GIRFSAYA (SEQ ID NO: 57), a CDR2 comprising an amino acid sequence of MTAGGMT (SEQ ID NO: 58), and a CDR3 comprising an amino acid sequence of NVGGQLLGY (SEQ ID NO: 59);

xiv). a CDR1 comprising an amino acid sequence of GSRFSSYA (SEQ ID NO: 62), a CDR2 comprising an amino acid sequence of ITSGGRT (SEQ ID NO: 63), and a CDR3 comprising an amino acid sequence of NQGGSKGY (SEQ ID NO: 64);

xv). a CDR1 comprising an amino acid sequence of TRTFDMYA (SEQ ID NO: 637), a CDR2 comprising an amino acid sequence of INRSGANT (SEQ ID NO: 875), and a CDR3 comprising an amino acid sequence of AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113);

xvi). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO:1609);

xvii) a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

xviii) a CDR1 comprising an amino acid sequence of GLRFSNYA (SEQ ID NO: 1613), a CDR2 comprising an amino acid sequence of ITKGGIT (SEQ ID NO: 1614), and a CDR3 comprising an amino acid sequence of NMHRSYDISFYDN (SEQ ID NO: 1615); or

xix). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

[0143] In some embodiments, the antigen-binding protein comprises

a). a CDR1 comprising an amino acid sequence of GRTFSSYL (SEQ ID NO: 37), a CDR2 comprising an amino acid sequence of ISWNDRST (SEQ ID NO: 38), and a CDR3 comprising an amino acid sequence of AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

b). a CDR1 comprising an amino acid sequence of RLNFSRTT (SEQ ID NO: 11), a CDR2 comprising an amino acid sequence of SGWARGRT (SEQ ID NO: 12), and a CDR3 comprising an amino acid sequence of AARDSRRGGLFADLNEYDY (SEQ ID NO: 13); or

c). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54).

[0144] In some embodiments, the antigen-binding protein comprises

a). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO: 1609);

b). a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

c). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54); or

d). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

[0145] In some embodiments of any of the above-described antigen-binding proteins, the antigen-binding protein is a single-domain antibody.

[0146] In some embodiments, the single-domain antibody is a VHH, a VNAR, or a VH domain.

[0147] In some embodiments, the VHH is a camelid VHH.

[0148] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 105-342, 1619-1622, 1643-1671, and 1778-1806, or an amino acid sequence having at least 75% identity thereto.

[0149] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 187, and 1619-1622, or an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%,at least 98%, or at least 99% identity thereto.

[0150] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 40, 19, and 55, or an amino acid sequence having at least 75% identity thereto.

[0151] In some embodiments, the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 55, 1619, 1620, and 1622, or an amino acid sequence having at least 75% identity thereto.

[0152] In some embodiments, the VHH is a humanized VHH.

[0153] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66 343-554, 1623-1626, and 1672-1691, or an amino acid sequence having at least 75% identity thereto.

[0154] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 421, and 1623-1626, or an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity thereto.

[0155] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 15, 41, and 56, or an amino acid sequence having at least 75% identity thereto.

[0156] In some embodiments, the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 56, 1623, 1624, and 1626, or an amino acid sequence having at least 75% identity thereto.

[0157] Provided herein are anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) comprising a CDR1 (CDR1) comprising an amino acid sequence selected from any of the CDR1 amino acid sequences listed in **Table 1-1** or **Table 6,** or a similar sequence thereof having at least 70%, at least 80%, at least 90%, or at least 95% sequence identity.

[0158] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) comprises a CDR1 comprising an amino acid sequence selected from SEQ ID NOs: 1, 6, 11, 16, 21, 16, 28, 32, 37, 42, 47, 52, 57, 62, 555-792, 1607, 1610, 1613, 1616, and 1692-1720, or a similar sequence thereof having at least 70%, at least 80%, at least 90%, or at least 95% sequence identity.

[0159] Provided herein are anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) comprising a CDR2 (CDR2) comprising an amino acid sequence selected from any of the CDR2 amino acid sequences listed in **Table 1-1** or **Table 6**, or a similar sequence thereof having at least 70%, at least 80%, at least 90%, or at least 95% sequence identity.

[0160] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) comprises a CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 2, 7, 12, 17, 33, 38, 43, 48, 53, 58, 63, 793-1030, 1608, 1611, 1614, 1617, and 1721-1748, or a similar sequence thereof having at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0161] Provided herein are anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) comprising a CDR3 (CDR3) comprising an amino acid sequence selected from any of the CDR3 amino acid sequences listed in **Table 1-1** or **Table 6**, or a similar sequence thereof having at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0162] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) comprises a CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 3, 8, 13, 18, 22, 25, 29, 34, 39, 44, 49, 54, 59, 64,, 1031-1268, 1609, 1612, 1615, 1618, and 1749-1777, or a similar sequence thereof having at least 70%, at least 80%, at least 90%, at least 95% , at least 98%, or at least 99% sequence identity.

[0163] Provided herein are anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) comprising a set of three CDRs (i.e., CDR1-CDR2-CDR3) contained within any of the

exemplary anti-CDH17 VHH antibodies listed in **Tables 1-1, Table 1-2,** or **Table 6**. In a related embodiment, provided herein are anti-CDH17antigen-binding proteins (e.g., antibodies such as single-domain antibodies) comprising a set of three CDRs (i.e., CDR1-CDR2-CDR3) contained within a VHH amino acid sequence as defined by any of the exemplary anti-CDH17 VHH antibodies listed in **Table 1-1**, **Table 1-2**, or **Table 6**. For example, provided herein are antibodies, or antigen-binding fragments thereof, comprising the set of CDR1-CDR2-CDR3 amino acid sequences contained within a VHH amino acid sequence selected from SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 105-342, 1619-1622, 1643-1671, and 1778-1806.

[0164] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) of the present disclosure can include:

a) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 4;

b) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 9;

c) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 14;

d) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 23

e) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 26;

f) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 30;

g) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 35;

h) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 40;

i) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 45;

j) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 50;

k) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 55;

l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 60;
m) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 65;
l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 187;
l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 1619;
l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 1620;
l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 1621; or
l) a variable domain that comprises a CDR1, CDR2, and CDR3 contained within a VHH comprising the amino acid sequence of SEQ ID NO: 1622.

[0165] In some embodiments, the present disclosure also provides an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) that competes for binding to CDH17 with any one of the exemplary anti-CDH17 VHH antibodies listed in **Table 1-1**, **Table 1-2**, or **Table 6**.

[0166] In some embodiments, the present disclosure also provides an anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) that binds to the same epitope on CDH17 as any one of the exemplary anti-CDH17 VHH antibodies listed in **Table 1-1**, **Table 1-2**, or **Table 6**.

Single-domain antibodies

[0167] A single-domain antibody (e.g., VHH) can be obtained by immunization of dromedaries, camels, llamas, alpacas, or sharks with the desired antigen and subsequent isolation of the mRNA coding for heavy-chain antibodies. Antigens can be purified from natural sources, or in the course of recombinant production. Immunization and/or screening for immunoglobulin sequences can be performed using peptide fragments of such antigens. By reverse transcription and polymerase chain reaction (PCR), a gene library of single-domain antibodies containing several million clones can be produced. Screening techniques such as phage display, yeast display, and ribosome display help to identify the clones binding the antigen. Methods generation of heavy-chain antibody fragments are described in e.g., WO 94/04678; Hamers-Casterman et al. 1993; Muyldermans et al. 2001; and Arbabi Ghahroudi, M. et al. (1997). FEBS Letters 414 (3): 521-526, each of which is incorporated herein by reference in its entirety.

[0168] A different method may use gene libraries from animals that have not been previously immunized. Such naïve libraries usually contain only antibodies with low affinity to the desired antigen, making it necessary to apply affinity maturation by random mutagenesis as an additional step. See e.g., Saerens, D.; et al. (2008). "Single-domain antibodies as building blocks for novel therapeutics". Current Opinion in Pharmacology 8 (5): 600-608.

[0169] Affinity maturation strategies can be categorized as either targeted/rational approaches or untargeted/random approaches. For targeted approaches information about the VHH of interest is needed, such as hot spots for affinity maturation or structural information on the VHH:antigen complex, whereas for untargeted approaches no prior information is needed. Targeted approaches that may be applied for affinity maturation of VHHs include site-directed *in-vitro* mutagenesis and *in-silico*/computational approaches. Common untargeted approaches used for affinity maturation of VHHs include random *in-vitro* mutagenesis, CDR swapping and autonomous hypermutation yeast surface display, with the latter two being novel, emerging and very time efficient techniques. Most of these strategies have in common, that after applying a certain randomization strategy to generate a mutational library, the resulting library can be screened by employing standard display techniques such as yeast, phage or ribosome display to select for the best binders. The choice of the display system is often guided by the library size to be displayed, with yeast display being able to handle library sizes of ~10^7 – 10^9, phage display ~10^8-10^{10} and ribosome display ~10^{12}-10^{13} (Chan and Groves, 2021). Notably, during affinity maturation the number of highly interactive residues such as aromatic amino acids usually increase in the CDR regions. The selected affinity matured clones may be further evaluated by a developability assessment to test for undesired properties, such as unspecific binding to off-targets or VHH instability.

[0170] For targeted *in vitro* mutagenesis, a set of selected residues within the CDRs of a VHH may be mutated (Tiller et al., 2017; Yau et al., 2005). Pre-selection of these residues can be either performed using alanine scanning to identify hot spot residues for mutation or by using structural data of the antigen:VHH complex to identify positions to be mutated. These sites can then be either submitted to saturating mutagenesis to substitute a specific site with all possible amino acids or specific amino acid substitutions yielding several smaller libraries. After mutagenesis binders can be displayed to select the best matured candidate. Usually, several rounds of targeted mutagenesis are performed with separate sub-libraries to obtain combinations of individual mutations that cooperatively result in increased binding affinity.

[0171] Computer-aided/*in silico* methods are often used to guide targeted *in vitro* mutagenesis. Using homology modeling of the target:VHH complex or docking, hotspots for mutations can be identified that are then submitted to *in vitro* mutagenesis (Bert Schepens et al., 2021; Cheng et al., 2019; Inoue et al., 2013; Mahajan et al., 2018). Further, *in silico* methods can search all designed variants in a virtual library (~10^{40} members) in a rather short amount of time to identify a feasible number of promising candidates to be tested experimentally. These techniques can be especially valuable if structural data on the drug-target interaction are available.

[0172] Untargeted/random affinity maturation strategies that can be applied to affinity mature VHHs include random *in vitro* mutagenesis, CDR shuffling/swapping and *in vivo* affinity maturation via yeast display. For random *in vitro* mutagenesis the sequence of either the entire VHH or only the CDRs are mutated randomly (Chen et al., 2021; Ye et al., 2021; Zupancic et al., 2021). The most commonly used technique is error prone PCR employing a DNA polymerase that lacks proof reading activity and PCR conditions that increase the polymerase error rate even further. This technique can be applied without further structural knowledge or information on the importance of residues that contribute to antigen:VHH interaction. The resulting mutational library can then be displayed to select the best matured candidate. This technique may also be combined with NGS sequencing of the display elutions to get an in-depth readout of all obtained candidates, enabling the identification of low abundant but still promising clones (Chen et al., 2021).

[0173] In some embodiments, CDR shuffling or swapping is applied for VHH affinity maturation, such as described in Zupancic et al., 2021. For CDR swapping, enriched libraries can be used as input material for a PCR reaction to individually amplify the CDR of the VHHs. The PCR products can then be mixed and reassembled using overlapping PCR to generate the entire plasmid for further rounds of display to select for the best matured binder. One limitation of this approach is that it can only be used for VHHs comprising the same framework as it is the case for synthetic libraries.

[0174] In some embodiments, *in vivo* affinity maturation via yeast display is applied for VHH affinity maturation, such as described in Wellner et al., 2021. The method is based on an autonomous hypermutation yeast surface display (AHEAD), which imitates somatic hypermutation during VHH selection using engineered yeast strains. The yeast's error prone orthogonal DNA replication system can generate new variants during plasmid replication by randomly introducing mutations. The new variants can then be displayed and selected using yeast surface display to identify the best binders. This enables the production of high affinity clones in very little time (about 2 weeks), which is significantly faster than

classical affinity maturation procedures. The method can be applied using synthetic or immune libraries using unenriched libraries enriched libraries or a subset of preselected clones.

[0175] In case binders with medium affinity are required, as it is the case for the anti-CDH17 V-bodies and the affinity of the identified candidates need to be decreased, very similar techniques can be applied. For example, mutations that are aiming at lowering the affinity can be introduced using the same targeted or untargeted approaches as described for the affinity maturation. The selection afterwards can be adapted accordingly. If larger libraries are generated that need to be screened via a display technique, the selection strategy can be adapted to enrich medium affinity binders while excluding high affinity candidates. This could, for example be a pre-panning in phage display with low antigen concentration to remove all higher affinity candidates, followed by a selection with high antigen concentration to obtain medium affinity VHHs. For library sizes of up to 1000 candidates a kinetic off-rate characterization can be used to get immediate information about the kinetic behavior of the candidates.

[0176] When the most potent clones have been identified, their DNA sequence can be optimized, for example to improve their stability towards enzymes. Another goal is humanization to prevent immunological reactions of the human organism against the antibody. Humanization can be achieved based on the homology between camelid VHH and human VH fragments, which is described in further detail below. Finally, the optimized single-domain antibody can be translated and expressed in suitable organisms such as *E. coli* or *Saccharomyces cerevisiae*.

[0177] Single-domain antibodies can also be derived from conventional antibodies. In some embodiments, single-domain antibodies can be made from conventional murine or human IgG with four chains. The process is similar, comprising gene libraries from immunized or naïve donors and display techniques for identification of the most specific antigens. However, the binding region of a conventional IgG consists of two domains (VH and VL), which tend to dimerize or aggregate because of their lipophilicity. Monomerization can be accomplished by replacing lipophilic by hydrophilic amino acids. (See e.g., Borrebaeck, C. A. K.; Ohlin, M. (2002). "Antibody evolution beyond Nature". Nature Biotechnology 20 (12): 1189-90.) If affinity can be retained after monomerization, the single-domain antibodies can likewise be produced in *E. coli*, *S. cerevisiae* or other suitable organisms.

[0178] A "humanized antibody" refers to a chimeric, genetically engineered, antibody in which the amino acid sequences (typically CDRs) from an antibody (donor antibody), e.g., a camelid antibody, are grafted onto a human antibody (acceptor antibody). Thus, a humanized antibody typically comprises CDRs from a donor antibody and variable region framework and constant regions, when present, from a

human antibody. Accordingly, a "humanized VHH" comprises CDRs that corresponds to the CDRs of a naturally occurring VHH domain (e.g., a camelid VHH), but that has been "humanized". Humanized VHH may be prepared by replacing one or more amino acid residues in the amino acid sequence of the naturally occurring VHH sequence (particularly in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain human antibody. Such humanized VHHs can be obtained in any suitable manner known to a skilled person in the art and thus not strictly limited to methods described herein.

[0179] Humanization of VHHs can achieved using resurfacing or CDR grafting. Resurfacing strategies have been described in e.g., Conrath et al., 2005 J Mol Biol; Kazemi-Lomedasht et al., 2018; Vincke et al., 2009 J Biol Chem, and CDR grafting strategies have been described in e.g., ben Abderrazek et al., 2011; van Faassen et al., 2020 FASEB; Li et al., 2018; Vaneycken et al., 2010; Vincke et al., 2009 J Biol Chem; and Yu et al., 2017, each of which is incorporated herein by reference in its entirety.

[0180] To humanize a camelid VHH using a resurfacing approach, a human germline reference that is most similar to the camelid germline sequence of the selected VHH may be identified. Most of the isolated camelid VHHs in literature belong to the camelid IGHV3 subfamily 2 (Nguyen et al., 2000, EMBO J) with DP-47/VH3-23 from the IGHV3 family commonly used as human reference. The framework of the camelid VHH can then be compared to the human reference sequence. Surface exposed residues are substituted to their human counterpart as it is assumed that their contribution to protein stability is rather low. Buried residues however remain of camelid origin, as they likely contribute to the overall VHH stability. Humanization of framework regions 1, 3 and 4 usually does not impact the physicochemical properties of the VHHs, whereas a general humanization of framework 2 would significantly increase local hydrophobicity. Residues H37, H44, H45 and H47 (Chothia numbering) in framework 2, the so called tetrade or hallmark residues, have a rather hydrophobic nature in human VHs (VGLW) as they are partially buried and involved in VH/VL paring, while in camelid VHHs these residues are partially charged (FERG), which significantly increases VHH solubility and inhibits paring of camelid VL (Soler et al., 2021, Biomolecules, Conrath et al., 2005 J Mol Biol*J*. Further, residues H37 and H47 are known to interact with the CDR-H3 loop in many VHHs, stabilizing its conformation and thereby contributing to antigen binding affinity. In addition, a significant number of VHHs use framework 2 residues H44, H45 and H47 for antigen binding (Zavrtanik et al., 2018*, J Mol Biol*). A full humanization of these residues hence frequently results in reduced solubility or aggregation of the VHHs and a reduced or complete loss of binding affinity for the target antigen (van Faassen et al., 2020, Vincke et al., 2009).

In consequence, all or at least some of these hallmark residues in framework 2 remain of camelid origin when humanizing VHHs.

[0181] Another approach that may be applied to humanize VHHs is CDR grafting. CDRs of the selected VHHs can be transplanted onto a universal VHH framework that has been partially or fully humanized (Saerens et al., 2009 J Biol Chem, Soler et al., 2021, Vincke et al., 2009 J Biol Chem). CDR grafting has been successfully used in some cases but failed for several others, with VHHs frequently losing their potential to bind to the desired antigen and/or becoming structurally instable with a high tendency to aggregate (van Faassen et al., 2020, FASEB). This is mostly attributed to interactions of CDR3 with specific residues in framework 2 that are important for CDR3 conformation, general VHH stability and overall hydrophobicity, which are impaired by this approach. Sometimes camelid backmutations are introduced into the framework to compensate for these effects (van Faassen et al., 2020, FASEB).

[0182] An alternative strategy to mitigate the need of humanizing the selected VHH sequences is to use fully or partially humanized synthetic VHH libraries instead of camelid immune libraries for VHH discovery (Moutel et al. 2016, eLife; McMahon, 2018, NSMB; Zimmermann et al., 2018, eLife). In many of these libraries the hallmark residues are still of camelid origin for reasons discussed above.

[0183] Other suitable humanizing substitutions are described in WO 09/138519 and WO 08/020079, as well as Tables A-3 to A-8 from WO 08/020079 (which are lists showing possible humanizing substitutions), each of which is incorporated herein by reference in its entirety. Non-limiting examples of such humanizing substitutions include Q108L and A14P. Such humanizing substitutions may also be suitably combined with one or more other mutations as described herein (such as with one or more mutations that reduce binding by pre-existing antibodies).

[0184] In some embodiments, humanized VHH sequences still retain the residues that are relevant for protein A binding. In some embodiments, the engineering activities during humanization may be applied to engineer protein A binding properties into a VHH that did previously not interact with protein A (Graille et al., 2000, PNAS).

[0185] Like a "humanized antibody", a "camelized antibody" refers to an antibody having amino acid sequences (typically CDRs) from a donor antibody, e.g., a human antibody, and variable region framework and constant regions, when present, from a camelid antibody. Accordingly, a "camelized VH" comprises an amino acid sequence that corresponds to the amino acid sequence of a naturally occurring VH domain, but that has been "camelized". Camelized VH may be prepared by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring VH domain from a conventional 4-chain antibody by one or more of the amino acid residues that occur at the corresponding position(s)

in a VHH domain of a heavy chain antibody. This can be performed in a manner, for example as described in WO 2008/020079. Such "camelizing" substitutions are usually inserted at amino acid positions that form and/or are present at the VH—VL interface, and/or at the so-called Camelidae hallmark residues, e.g., F37, E44, R45 and F47 (see for example WO 94/04678 and Davies and Riechmann (1994 and 1996)). In one embodiment, the VH sequence that is used as a starting material or starting point for generating or designing the camelized VH is a VH sequence from a mammal, or the VH sequence of a human antibody. However, such camelized VH can be obtained in any suitable manner known to a skilled person in the art and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VH domain as a starting material.

[0186] The amino acid residues of a single-domain antibody can be numbered according to the general numbering for VH domains given by Kabat et al. ("Sequence of proteins of immunological interest", US Public Health Services, NIH Bethesda, Md., Publication No. 91), as applied to VHH domains from Camelids described in Riechmann and Muyldermans, 2000 (J. Immunol. Methods 240 (1-2): 185-195; see for example FIG. 2 of this publication). The total number of amino acid residues in each of the CDRs may vary and may not correspond to the total number of amino acid residues indicated by the Kabat numbering. For example, one or more positions according to the Kabat numbering may not be occupied in the actual sequence, or the actual sequence may contain more amino acid residues than the number allowed for by the Kabat numbering. As a result, the numbering according to Kabat may or may not correspond to the actual numbering of the amino acid residues in the actual sequence. The total number of amino acid residues in a VH domain and a VHH domain is usually in the range of from 110 to 120, often between 112 and 115. However, smaller and longer sequences may also be suitable for the purposes described herein.

[0187] Determination of CDR regions in a single-domain antibody may be accomplished using different methods, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. ("Kabat" numbering scheme); Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme); MacCallum et al., J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745." ("Contact" numbering scheme); Lefranc M P et al., "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp Immunol, 2003 January; 27(1):55-77 ("IMGT" numbering scheme); Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," J Mol Biol, 2001 Jun. 8; 309(3):657-70, ("Aho" numbering scheme); and

Martin et al., "Modeling antibody hypervariable loops: a combined algorithm," PNAS, 1989, 86(23):9268-9272, ("AbM" numbering scheme), each reference cited herein is incorporated by reference in its entirety.

[0188] The boundaries of a given CDR or framework (FR) may vary depending on the scheme used for identification. For example, the Kabat scheme is based on structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, "30a," and deletions appearing in some antibodies. The two schemes place certain insertions and deletions ("indels") at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme. The AbM scheme is a compromise between Kabat and Chothia definitions based on that used by Oxford Molecular's AbM antibody modeling software.

[0189] In some embodiments, CDRs can be defined in accordance with any of the Kabat numbering scheme, the Chothia numbering scheme, a combination of Kabat and Chothia, the AbM numbering scheme, and/or the Contact numbering scheme. A VHH typically comprises three CDRs, designated CDR1, CDR2, and CDR3. **Table 1-3**, below, lists exemplary position boundaries of CDR-H1, CDR-H2, CDR-H3 as identified by Kabat, Chothia, AbM, and Contact schemes, respectively. For CDR-H1, residue numbering is listed using both the Kabat and Chothia numbering schemes. FRs are located between CDRs, for example, with FR-H1 located before CDR-H1, FR-H2 located between CDR-H1 and CDR-H2, FR-H3 located between CDR-H2 and CDR-H3 and so forth. It is noted that because the shown Kabat numbering scheme places insertions at H35A and H35B, the end of the Chothia CDR-H1 loop when numbered using the shown Kabat numbering convention varies between H32 and H34, depending on the length of the loop.

Table 1-3. CDRs definitions according to various numbering schemes.

CDR	Kabat	Chothia	AbM	Contact
CDR-H1 (Kabat Numbering[1])	H31 - H35B	H26 - H32...34	H26 - H35B	H30 - H35B
CDR-H1 (Chothia Numbering[2])	H31 - H35	H26 - H32	H26 - H35	H30 - H35
CDR-H2	H50 - H65	H52 - H56	H50 - H58	H47 - H58
CDR-H3	H95 - H102	H95 - H102	H95 - H102	H93 - H101

[1]Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD;
[2]Al-Lazikani et al., (1997) JMB 273, 927-948

[0190] Thus, unless otherwise specified, a "CDR" or "complementarity determining region," or individual specified CDRs (e.g., CDR-H1, CDR-H2, CDR-H3), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) CDR as defined by any of the above-mentioned schemes. For example, where it is stated that a particular CDR (e.g., a CDR-H3) contains the amino acid sequence of a corresponding CDR in a given VHH amino acid sequence, it is understood that such a CDR has a sequence of the corresponding CDR (e.g., CDR-H3) within the VHH, as defined by any of the above-mentioned schemes. In some embodiments, specific CDR sequences are specified. Exemplary CDR sequences of provided antibodies are described using various numbering schemes (see e.g., **Table 1-3**), although it is understood that a provided antibody can include CDRs as described according to any of the other above-mentioned numbering schemes or other numbering schemes known to a person of ordinary skill in the art.

[0191] In a single-domain antibody sequence of the present disclosure, the framework sequences may be any suitable framework sequences. For example, the framework sequences may be framework sequences derived from a heavy chain variable domain (e.g., a VH sequence or VHH sequence). In some embodiments, the framework sequences are either framework sequences that have been derived from a VHH sequence (in which said framework sequences may optionally have been partially or fully humanized) or are conventional VH sequences (in which said framework sequences may optionally have been partially or fully camelized).

[0192] Antigen-binding fragments (or combinations of fragments) of any of single-domain antibodies described herein, such as fragments that contain one or more CDR sequences, suitably flanked by and/or linked via one or more framework sequences, are also encompassed within the present disclosure.

[0193] It should be noted, however, that the present disclosure is not limited to the origin of the single-domain antibody (or of the nucleotide sequence used to express it), nor to the way that the single-domain antibody or nucleotide sequence is generated or obtained. Thus, an antigen-binding protein of the present disclosure may comprise naturally occurring sequences (from a suitable species), recombinant sequences, or synthetic or semi-synthetic sequences. Similarly, nucleotide sequences encoding antigen-binding proteins of the present disclosure may comprise naturally occurring

nucleotide sequences, recombinant sequences, or synthetic or semi-synthetic sequences (for example, sequences that are prepared by PCR or isolated from a library).

[0194] Anti-CDH17 antigen-binding proteins (e.g., antibodies such single-domain antibodies) of the present disclosure may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy chain variable domains as compared to the exemplary antibody sequences provided herein. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The antigen-binding molecules of the present disclosure may comprise antigen-binding domains which are derived from any of the exemplary amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the VHH domains are mutated back to the residues found in the original germline sequence from which the antigen-binding domain was originally derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antigen-binding domain was originally derived).

[0195] Furthermore, the antigen-binding domains may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antigen-binding domains that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced biological properties (e.g., agonistic

effect), reduced immunogenicity, etc. Antigen-binding proteins comprising one or more antigen-binding domains obtained in this general manner are encompassed within the present disclosure.

[0196] Provided herein are anti-CDH17 antigen-binding proteins comprising variants of any of the VHH and/or CDR amino acid sequences disclosed herein having one or more amino acid substitutions. For example, the present disclosure includes anti-CDH17 antigen-binding proteins having VHH and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, 3 or fewer, 2, or 1 amino acid substitutions relative to any of the VHH and/or CDR amino acid sequences set forth in **Tables 1-1** and **1-2** herein. Amino acid substitutions may be introduced into an antigen-binding protein of interest and the resultant variants can screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or reduced ADCC or CDC.

[0197] Amino acids may be grouped according to common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; (6) aromatic: Trp, Tyr, Phe. In some embodiments, an amino acid substitution is a conservative substitution, meaning exchanging an amino acid with another amino acid of the same class. In some embodiments, amino acid substitutions may also include a non-conservative substitution, meaning exchanging an amino acid with an amino acid of a different class. Other exemplary amino acid substitutions are shown in **Table 2**.

Table 2. Exemplary amino acid substitutions

Original Residue	Exemplary Substitutions
Ala (A)	Val; Leu; Ile
Arg (R)	Lys; Gln; Asn
Asn (N)	Gln; His; Asp, Lys; Arg
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn; Glu
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln; Lys; Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg; Gln; Asn
Met (M)	Leu; Phe; Ile
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Val; Ser

Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe; Thr; Ser
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine

[0198] In some embodiments, single-domain antibodies (e.g., VHH) of the present disclosure may comprise one or more mutations to reduce oxidation levels of oxidation-labile residues such as Met (M). In certain embodiments, it may be desirable to address Met (M) oxidation liability by mutation of a Met (M) residue. In some embodiments, the single-domain antibodies (e.g., VHH) of the present disclosure may comprise one or more mutations (e.g., substitution mutations) of a Met residue to reduce oxidation. As a non-limiting example, a Met residue may be substituted in any of the single-domain antibodies described herein with e.g., Ile (I), Ala (A), or Leu (L), to reduce oxidation.

[0199] In some embodiments, single-domain antibodies (e.g., VHH) of the present disclosure comprise one or more modifications that reduce binding of the single-domain antibodies (e.g., VHH) by pre-existing antibodies found in human blood or serum. In some embodiments, single-domain antibodies (e.g., VHHs) of the present disclosure are modified by mutation of amino acid position 11, for example Leu11Glu (L11E), Leu11Lys (L11K), or Leu11Val (L11V). In one embodiment, a single-domain antibody (e.g., VHH) of the present disclosure may comprise a valine (V) at amino acid position 11 and a leucine (L) at amino acid position 89 (according to Kabat numbering). As another example, a single-domain antibody (e.g., VHH) of the present disclosure may comprise an extension of 1 to 5 (naturally occurring) amino acids, such as a single alanine (A) extension, at the C-terminus of the single-domain antibody (e.g., VHH). The C-terminus of a VHH is normally VTVSS (SEQ ID NO: 1582). In one embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises a lysine (K) or glutamine (Q) at position 110 (according to Kabat numbering). In another embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises a lysine (K) or glutamine (Q) at position 112 (according to Kabat numbering). Accordingly, the C-terminus of a single-domain antibody (e.g., VHH) can be any one of VKVSS (SEQ ID NO: 1583), VQVSS (SEQ ID NO: 1584), VTVKS (SEQ ID NO: 1585), VTVQS (SEQ ID NO: 1586), VKVKS (SEQ ID NO: 1587), VKVQS (SEQ ID NO: 1588), VQVKS (SEQ ID NO: 1589), or VQVQS (SEQ ID NO: 1590). In another embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises a valine (V) at amino acid position 11 and a leucine (L) at amino acid position 89 (according to Kabat numbering), optionally a lysine (K) or glutamine (Q) at position 110 (according to Kabat numbering) and an extension of 1 to 5 (naturally occurring) amino acids, such as a single alanine (A) extension at the C-terminus of the single-domain antibody (e.g., VHH) (such that the C-terminus of the single-domain antibody (e.g., VHH) for example has the sequence VTVSSA (SEQ ID NO: 1591), VKVSSA

(SEQ ID NO: 1592) or VQVSSA (SEQ ID NO: 1593)). In further embodiments, single-domain antibodies (e.g., VHH) of the present disclosure are modified by changes in carboxy-terminal region, for example to a terminal sequence having the sequence GQGTLVTVKPGG (SEQ ID NO: 1594) or GQGTLVTVEPGG (SEQ ID NO: 1595) or modification thereof. Additional modification to reduce binding by pre-existing antibodies in human serum can be found in e.g., WO2012/175741, WO2015/173325, WO2016/150845, WO2011/003622, WO2013/024059; US 11,426,468, US 10,526,397, which are incorporated herein by reference in their entireties.

[0200] In one embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises at the carboxy-terminus starting from position 111 according to Chothia the amino acid sequence VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837). In one embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises at the carboxy-terminus starting from position 111 according to Chothia the amino acid sequence VAGG (SEQ ID NO: 1836). In one embodiment, a single-domain antibody (e.g., VHH) of the present disclosure comprises at the carboxy-terminus starting from position 111 according to Chothia the amino acid sequence VPAG (SEQ ID NO: 1837).

[0201] In some embodiments, a single-domain antibody (e.g., VHH) of the present disclosure comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 5, 9, 10, 14, 15, 19, 20, 23, 24, 26, 27, 30, 31, 35, 36, 40, 41, 45, 46, 50, 51, 55, 56, 60, 61, 65, 66, 105-554, 1619, 1620-1626, and 1778-1806, or a sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity thereto, wherein the amino acid sequence at the carboxy-terminus starting from position 111 according to Chothia comprises VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837).

[0202] In some embodiments, a single-domain antibody (e.g., VHH) of the present disclosure comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 105-342, 1619-1622, and 1643-1671, or a sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, wherein the amino acid sequence at the carboxy-terminus starting from position 111 according to Chothia comprises VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837).

[0203] In some embodiments, a single-domain antibody (e.g., VHH) of the present disclosure comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 187, and 1619-1622, or a sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, wherein the amino acid

sequence at the carboxy-terminus starting from position 111 according to Chothia comprises VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837).

[0204] In some embodiments, a single-domain antibody (e.g., VHH) of the present disclosure comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 343-554, 1623-1626, and 1672-1691, or a sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, wherein the amino acid sequence at the carboxy-terminus starting from position 111 according to Chothia comprises VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837).

[0205] In some embodiments, a single-domain antibody (e.g., VHH) of the present disclosure comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 421, 1623-1626, or a sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% identity thereto, wherein the amino acid sequence at the carboxy-terminus starting from position 111 according to Chothia comprises VAGG (SEQ ID NO: 1836) or VPAG (SEQ ID NO: 1837).

[0206] In some embodiments, single-domain antibodies (e.g., VHH) of the present disclosure are modified to enhance binding to staphylococcal protein A (SpA) or streptococcal protein G (SpG). Binding of SpA and SpG to antibodies or antibody fragments can be useful in the manufacturing process of the antibodies or antibody fragments. The high-affinity interaction of the IgG Fc region with SpA and SpG has been extensively exploited and became the gold standard for monoclonal antibody purification (Björck and Kronvall, 1984). Other non-Fc containing antibody fragments, such as VHHs and Fabs do not have the capacity to bind to SpA or SpG via their Fc regions. However, sequence-dependent interaction with SpA has been demonstrated for these non-Fc containing antibody fragments(Graille et al., 2000; Henry et al., 2016). This characteristic circumvents potential use of affinity tags fused to the drug candidate for affinity chromatography that have the disadvantage as being regarded as a sequence liability, as it may impact protein immunogenicity as well as protein structure and stability and could compromise functionality. The interaction of the single-domain antibodies (e.g., VHH) to SpA relies on an alternative binding mode, with a 1-5 μM affinity, which is comparable to the 0.2 -3 μM measured for VH-SpA interactions (To et al., JBC, 2005; Henry et al., Plos One, 2016).

[0207] In some embodiments, single-domain antibodies (e.g., VHH) of the present disclosure have, or are modified to have a SpA-binding motif. For example, The VHH-SpA interface has been mapped to thirteen residues, which cluster within the framework at the back side of the V-body, distant to the CDRs (Graille et al., 2000, Henry et al., 2016). In the absence of a VHH-SpA co-structure, superposition of a

SpA-Fab crystal structure and a VHH allows for visualizing the binding mode. Based on a structural and functional analysis, the thirteen residues of the VHH-SpA interface have been characterized to be intolerant to substitutions (residues Gly15, Arg19, Tyr59, Gly65, and Arg66), tolerant to specific substitutions (residues Thr/Lys/Arg57, Thr68, Gln81, Asn82a, and Ser82b) or generally tolerant to a variety of substitutions (residues Ser17, Lys64, and Ser70) (all residue positions refer to Kabat numbering) (Henry et al., Plos One, 2016). Thus, a SpA-binding motif included in a single-domain antibody (e.g., VHH) of the present disclosure may include one or more, or all of the thirteen residues.

Alternative protein scaffolds

[0208] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure can adopt an alternative protein scaffold. Such alternative protein scaffold may be a single chain polypeptidic framework, optionally with a reduced size (e.g., less than about 200 amino acids), that contains a highly structured core associated with variable domains of high conformational tolerance allowing insertions, deletions, or other substitutions. Such antigen-binding proteins may be generated by grafting CDRs or variable regions described herein onto a suitable protein scaffold. The structure of alternative scaffolds may vary, but preferably are of human origin for those developed as therapeutics.

[0209] Alternative protein scaffolds of the present disclosure can be based either on a conventional immunoglobulin (Ig) backbone, or are derived from a completely unrelated protein. These variable domains can be modified to create novel binding interfaces toward any targeted antigen. In some embodiments, an alternative protein scaffold of the present disclosure can be derived from Protein A, e.g., the Z-domain thereof (affibodies), ImmE7 (immunity proteins), BPTI/APPI (Kunitz domains), Ras-binding protein AF-6 (PDZ-domains), charybdotoxin (Scorpion toxin), CTLA-4, Min-23 (knottins), lipocalins (anticalins), neokarzinostatin, a fibronectin domain (used in "adnectin"), an ankyrin repeat (AR) domain (used in "DARPins"), avidity multimers (also known as "avimers"), or thioredoxin (Skerra, A., Curr. Opin. Biotechnol. 18:295-304 (2005); Hosse et al., Protein Sci. 15:14-27 (2006); Nicaise et al., Protein Sci. 13:1882-1891 (2004); Nygren and Uhlen, Curr. Opin. Struc. Biol. 7:463-469 (1997), all of which are hereby incorporated by reference in their entirety).

[0210] Anticalins are a suitable type of non-Ig based alternative scaffolds for use in the antigen-binding molecules of the present disclosure. Anticalins are a class of engineered ligand-binding proteins that are based on the lipocalin scaffold. Lipocalins are a family of proteins that transport small hydrophobic molecules such as steroids, bilins, retinoids, and lipids. Lipocalins have limited sequence homology, but

share a common tertiary structure architecture based on eight antiparallel β-barrels. Lipocalins contain four exposed loops built on the rigid β-barrel structure. Exemplary anticalin proteins that are commonly used are about a size of about 180 amino acids and a mass of about 20 kDa.

[0211] DARPins are another suitable non-Ig based alternative scaffold that can be used in the antigen-binding molecules of the present disclosure. DARPins are genetically engineered antibody mimetic proteins typically exhibiting highly specific and high-affinity target protein binding. They are derived from natural ankyrin repeat (AR) proteins, which usually contain a 33 amino acid protein motif consisting of two α-helices separated by loops, which repeats mediate protein—protein interactions. DARPins can be generated using combinatorial AR libraries constructed based on the 33 amino acid AR motif with seven randomized positions. DARPin libraries can be screened using ribosome display, and library members typically are well produced in *Escherichia coli*, do not aggregate, and display high thermodynamic stability. Preferably, DARPins contain two to four of these motifs flanked by N- and C-terminal capping motifs to shield hydrophobic regions and allow increased solubility.

[0212] The avimer structure can also be used as a protein backbone to generate a suitable non-Ig based alternative scaffold. Avimers typically consist of two or more peptide sequences of 30 to 35 amino acids each, connected by peptide linker. The individual sequences are derived from A-domains of various membrane receptors and have a rigid structure, stabilized by disulfide bridges and calcium. Each A-domain can bind to a certain epitope of the target protein. The combination of domains binding to different epitopes of the same protein increases affinity to this protein, an effect known as avidity.

[0213] Proteins derived from fibronectin III (FN3) domains can also be used to generate a suitable non-Ig based alternative scaffold (also known as "monobody"). For example, the tenth fibronectin type III domain (FN10) of human fibronectin corresponds to a β-sandwich with seven β-strands and three connecting loops showing structural homologies to Ig domains without disulfide bridges. In some cases, the connecting loops of FN10, each about 15 to 21 amino acids in length, can be randomized and the domains displayed on both phage and yeast to select for a scaffold with the desirable properties. Adnectins™ is an exemplary scaffold generated using 10^{th} FN3 domains randomized and displayed in this way. Another exemplary scaffold comprising FN3 domains is a Centyrin™. Centryrins™ contain the consensus sequence of FN3 domains of human Tenascin C (TNC), which is found in the extracellular matrix of various tissues. Centyrin™ scaffolds have loops that have structural homology to antibody variable domains (i.e., CDR1, CDR2 and CDR3), and are small (about 10 kDa), simple, and highly stable single domain proteins that do not contain cysteine, disulfides or glycosylated residues. Centyrin™ possess excellent biophysical properties such as stability to heat, pH, denaturant and organic solvents,

reversible unfolding and monodispersity. Another recent exemplary FN3-based scaffold that can be used in the present disclosure is fluctuation-regulated affinity proteins (FLAPs), as described in See et al., 2020. Biotechnology Journal 15(12):e2000078, which is incorporated herein by reference in its entirety.

Fusion Proteins and Conjugates

[0214] In one aspect, provided herein are fusion proteins and conjugates comprising at least one anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) linked, directly or indirectly, to one or more additional domains or moieties. The at least one anti-CDH17 antigen-binding protein can specifically bind CDH17. In some embodiments, the fusion protein or conjugate of the present disclosure comprises a single polypeptide. In other embodiments, the fusion protein or conjugate of the present disclosure comprises more than one polypeptide. In some embodiments, the fusion protein or conjugate of the present disclosure comprises two polypeptides.

[0215] In some embodiments, the fusion protein or conjugate of the present disclosure comprises at least one anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) described herein. In some embodiments, the fusion protein or conjugate is multivalent. For example, the fusion protein or conjugate of the present disclosure may be at least bivalent, but can also be e.g., trivalent, tetravalent, pentavalent, hexavalent, etc. The terms "bivalent", "trivalent", "tetravalent", "pentavalent", or "hexavalent" all fall under the term "multivalent" and indicate the presence of two, three, four, five or six binding units (e.g., VHHs), respectively.

[0216] In certain embodiments, the fusion protein or conjugate is multispecific. For example, in some cases, the one or more additional domain or moieties may be one or more additional binding domain that binds to one or more further antigen or protein. The fusion protein or conjugate of the present disclosure may be, for example, bispecific, trispecific, tetraspecific, pentaspecific, etc. The terms "bispecific", "trispecific", "tetraspecific", "pentaspecific", etc., all fall under the term "multispecific" and refer to binding to two, three, four, five, etc., different target molecules, respectively.

[0217] In some embodiments, a fusion protein or conjugate of the present disclosure comprises one or more of an anti-CDH17 antigen-binding protein described herein. In some embodiments, a fusion protein or conjugate of the present disclosure comprises two or more of an anti-CDH17 antigen-binding protein described herein. In some embodiments, a fusion protein or conjugate of the present disclosure comprises three or more of an anti-CDH17 antigen-binding protein described herein. In some embodiments, a fusion protein or conjugate of the present disclosure comprises four or more of an anti-

CDH17 antigen-binding protein described herein. In some embodiments, a fusion protein or conjugate of the present disclosure comprises one, two, three, four, five, six, seven, eight, nine, or ten, or more of an anti-CDH17 antigen-binding protein described herein.

[0218] In some embodiments, the one or more antigen-binding proteins can bind to the same epitope on CDH17. In some embodiments, the one or more antigen-binding proteins can bind to different epitopes on CDH17.

[0219] In various embodiments, the one or more antigen-binding proteins can be one or more single-domain antibodies disclosed herein, for example, one or more VHHs disclosed herein.

[0220] When two or more anti-CDH17 antigen-binding proteins are included in a fusion protein or conjugate, the two or more anti-CDH17 antigen-binding proteins may comprise the same sequence or may comprise different sequences. In such embodiments, the two or more anti-CDH17 antigen-binding proteins may bind to the same epitope on CDH17 or different epitopes on CDH17. For example, a fusion protein or conjugate of the present disclosure may be biparatopic, e.g., if two VHHs bind two different epitopes on CDH17.

Fusion or Conjugation to Fc regions

[0221] In some embodiments, a fusion protein or conjugate of the present disclosure comprises at least one anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody) provided herein operably linked to an immunoglobulin Fc region. An immunoglobulin Fc region may be linked indirectly or directly to the at least one anti-CDH17 antigen-binding protein (e.g., antibody such as a single-domain antibody). In some embodiments, a fusion protein or conjugate of the present disclosure comprises one, two, three, four, five, six or more anti-CDH17 antigen-binding proteins provided herein operably linked to an Fc region.

[0222] An "Fc region" as used herein refers to a portion of a heavy chain constant region comprising CH2 and CH3. In some embodiments, an Fc region comprises a hinge, CH2, and CH3. In various embodiments, when an Fc region comprises a hinge, the hinge can mediate dimerization between two Fc-containing polypeptides. An Fc region included in a fusion protein or conjugate may be an Fc region from any species, or derived from any species, including, but not limited to, human, mouse, rat, monkey (e.g., cyno), camel, llama, shark, goat, rabbit, and/or bovine. In various embodiments, an Fc region included in a fusion protein or conjugate of the present disclosure is a human immunoglobulin Fc region, or is derived from a human immunoglobulin Fc region. In some embodiments, the immunoglobulin Fc region is of IgG, IgE, IgM, IgD, IgA or IgY isotype. In some embodiments, the immunoglobulin Fc region is

an IgG isotype, such as IgG1, IgG2, IgG3, or IgG4 subclass, or a variant thereof. The immunoglobulin Fc region may comprise a variant or fragment of a native IgG Fc region.

[0223] In some embodiments, an Fc region included in a fusion protein or conjugate described herein may be a murine (e.g., a mouse or a rat) immunoglobulin Fc region, or derived from a murine immunoglobulin Fc region. In some embodiments, an Fc region included in a fusion protein or conjugate described herein may be a cyno immunoglobulin Fc region, or derived from a cyno immunoglobulin Fc region.

[0224] A native Fc region typically possesses an effector function, including but not limited to, Fc receptor binding; Clq binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (for example B-cell receptor); and B-cell activation, etc. Such effector functions generally require the Fc region to be combined with a binding domain (for example, an antibody variable domain) and can be assessed using various assays.

[0225] In some embodiments, a fusion protein or conjugate of the present disclosure can comprise a dimer of Fc regions. In some embodiments, an Fc region mediates dimerization of the CDH17-binding units at physiological conditions, such as when expressed from a cell, such that a dimer is formed that doubles the number of CDH17 binding units. For example, a fusion polypeptide comprising one VHH domain that binds CDH17 and an Fc region is monovalent as a monomer, but the Fc region can mediate dimerization; as a result, the fusion protein is bivalent (i.e., having two anti-CDH17 VHH domains per molecule). Similarly, in some embodiments, two anti-CDH17 VHH domains (2x) are fused to an IgG Fc region and as a result of dimerization, the fusion protein is tetravalent (i.e., having four anti-CDH17 VHH domains per molecule). In some embodiments, three anti-CDH17 VHH domain (3×) are fused to an IgG Fc region and as a result of dimerization, the fusion protein is hexavalent (i.e., having six anti-CDH17 VHH domains per molecule).

[0226] In some embodiments, a fusion protein or conjugate of the present disclosure may comprise two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)n-Linker-Fc, wherein n can be any integral number (e.g., 1, 2, 3, 4, 5, etc). When n≥2, each anti-CDH17 VHH may be optionally operably linked to another anti-CDH17 VHH via a linker.

[0227] In some embodiments, a fusion protein or conjugate of the present disclosure may comprise two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)n-Linker-Fc-(anti-CDH17 VHH)m, wherein n and m can independently be any integral number (e.g., 1, 2, 3,

4, 5, etc). When n≥2 or m≥2, each anti-CDH17 VHH may be optionally operably linked to another anti-CDH17 VHH via a linker.

[0228] In some embodiments, a fusion protein or conjugate of the present disclosure is bivalent. In some embodiments, the bivalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-Fc.

[0229] In some embodiments, a fusion protein or conjugate of the present disclosure is tetravalent. In some embodiments, the tetravalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-(anti-CDH17 VHH)-Linker-Fc. In some embodiments, the tetravalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-Fc-Linker-(anti-CDH17 VHH). The multiple linkers used in the fusion protein are not necessarily the same.

[0230] In some embodiments, a fusion protein or conjugate of the disclosure is hexavalent. In some embodiments, the hexavalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-(anti-CDH17 VHH)-Linker-(anti-CDH17 VHH)-Linker-Fc. In some embodiments, the hexavalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-(anti-CDH17 VHH)-Linker-Fc-linker-(anti-CDH17 VHH). In some embodiments, the hexavalent fusion protein or conjugate of the disclosure comprises two polypeptide chains, each polypeptide chain having the following structure: (anti-CDH17 VHH)-Linker-Fc-Linker-(anti-CDH17 VHH)-Linker-(anti-CDH17 VHH). The multiple linkers used in the fusion protein are not necessarily the same.

[0231] In some embodiments, the CH3 domain of the Fc region can be used as homodimerization domain, such that the resulting fusion protein may be formed from two identical polypeptides. In other cases, the CH3 dimer interface region of the Fc region can be mutated to enable heterodimerization. For example, a heterodimerization domain can be incorporated into the fusion protein such that the construct is a heterodimeric fusion protein.

[0232] When a dimer of Fc regions is used in a fusion protein or conjugate of the present disclosure, the first and second Fc regions may be of the same IgG isotype such as, e.g., IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second Fc regions may be of different IgG isotypes such as, e.g., IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[0233] In some embodiments, the Fc region included in a fusion protein or conjugate of the present disclosure can be mutated or modified. In some embodiments, the mutations include one or more amino acid substitutions to reduce an effector function of the Fc region. Various examples of mutations to Fc regions to alter, such as reduce, effector function are known, including any as described below. In general, the numbering of the residues in an immunoglobulin heavy chain or portion thereof, such as an Fc region, is according to the EU index as in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991).

[0234] In some embodiments, the human IgG Fc region is modified to alter antibody-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC). Non-limiting examples of amino acid modifications that can alter ADCC and/or CDC are described in Alegre et al, 1992 J Immunol, 148: 3461-3468; Idusogie et al., 2001 J Immunol, 166(4): 2571-5; Shields et al., 2001 JBC, 276(9): 6591-6604; Lazar et al., 2006 PNAS, 103(11): 4005-4010; Stavenhagen et al., 2007 Cancer Res, 67(18): 8882-8890; Natsume et al., 2008 Cancer Res, 68(10): 3863-72; Stavenhagen et al., 2008 Advan. Enzyme Regul., 48: 152-164; Moore et al., 2010 mAbs, 2(2): 181-189; and Kaneko and Niwa, 2011 Biodrugs, 25(1):1-11, each of which is incorporated herein by reference in its entirety.

[0235] In some embodiments, an Fc region included in a fusion protein or conjugate of the present disclosure exhibits reduced effector functions (such as CDC and ADCC). Various *in vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the fusion protein construct and/or cleaved components thereof lack FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC are NK cells which express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest are described in e.g., US 5,500,362; US 5,821,337; Hellstrom. et al., Proc. Nat'l Acad. Sci. USA 83:7059-7063 (1986); and Hellstrom et al., Proc. Nat'l Acad. Sci. USA 82:1499-1502 (1985); Bruggemann. et al., J. Exp. Med. 166:1351-1361 (1987). Alternatively, non-radioactive assay methods may be employed, such as ACTI™ non-radioactive cytotoxicity assay for flow cytometry or CytoTox96™ non-radioactive cytotoxicity assay. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in an animal model such as that disclosed in Clynes et al. Proc. Nat'l Acad. Sci. USA 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the fusion protein construct or cleaved components thereof is unable to bind C1q and hence lacks CDC activity (see, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO

2005/100402). To assess complement activation, a CDC assay may be performed (see, e.g., Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996); Cragg, M. S. et al., Blood 101:1045-1052 (2003); and Cragg, M. S. and M. J. Glennie, Blood 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half-life determinations can also be performed using methods known in the art (see, e.g., Petkova, S. B. et al., Int'l. Immunol. 18(12):1759-1769 (2006)).

[0236] Examples of mutations that enhance ADCC include modification at Ser239 and Ile332, for example Ser239Asp and Ile332Glu (S239D, 1332E). Examples of mutations that enhance CDC include modifications at Lys326 and Glu333. In some embodiments, the Fc region is modified at one or both of these positions, for example Lys326Ala and/or Glu333Ala (K326A and E333A) using the Kabat numbering system.

[0237] In some embodiments, the Fc region of the fusion protein is altered at one or more of the following positions to reduce Fc receptor binding: Leu234Ala (L234A), Leu234Gly (L234G), Leu234Ser (L234S), Leu234Thr (L234T), Leu234Ala (L234A), Leu235Ala (L235A), Leu235Glu (L235E), Leu235Ser (L235S), Leu235Thr (L235T), Leu235Val (L235V), Leu235Gln (L235Q), Gly236Arg (G236R), Met252Tyr (M252Y), Ser254Thr (S254T), Thr256Glu (T256E), Asp265Asn (D265N), Asp265Ala (D265A), Asp270Asn (D270N), Ser298Asn (S298N), Asn297Ala (N297A), Pro329Ala (P329A), Pro239Gly (P329G), Asn325Glu (N325E) and/or Ala327Ser (A327S), according to EU numbering . In some embodiments, modifications within the Fc region reduce binding to Fc-receptor-gamma receptors (FcγRs) while have minimal impact on binding to the neonatal Fc receptor (FcRn).

[0238] In some embodiments, the human IgG1 Fc region is modified at amino acid Asn297 (Kabat Numbering) to prevent glycosylation of the fusion protein, e.g., Asn297Ala (N297A) or Asn297Asp (N297D). In some embodiments, the Fc region of the fusion protein is modified at amino acid Leu235 (Kabat Numbering) to alter Fc receptor interactions, e.g., Leu235Glu (L235E) or Leu235Ala (L235A). In some embodiments, the Fc region of the fusion protein is modified at amino acid Leu234 (Kabat Numbering) to alter Fc receptor interactions, e.g., Leu234Ala (L234A). In some embodiments, the Fc region of the fusion protein is modified at amino acid Leu234 (Kabat Numbering) to alter Fc receptor interactions, e.g., Leu235Glu (L235E). In some embodiments, the Fc region of the fusion protein is altered at both amino acids 234 and 235, e.g., Leu234Ala and Leu235Ala (L234A/L235A) or Leu234Val and Leu235Ala (L234V/L235A). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 297, e.g., Leu234Ala, Leu235Ala, Asn297Ala (L234A/L235A/N297A). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 329, e.g., Leu234Ala, Leu235Ala, Pro239Ala (L234A/L235A/P329A). In some embodiments, the Fc region of

the fusion protein is modified at amino acid Asp265 (Kabat Numbering) to alter Fc receptor interactions, e.g Asp265Ala (D265A). In some embodiments, the Fc region of the fusion protein is modified at amino acid Pro329 (Kabat Numbering) to alter Fc receptor interactions, e.g., Pro329Ala (P329A) or Pro329Gly (P329G). In some embodiments, the Fc region of the fusion protein is altered at both amino acids 265 and 329, e.g., Asp265Ala and Pro329Ala (D265A/P329A) or Asp265Ala and Pro329Gly (D265A/P329G). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 265, e.g., Leu234Ala, Leu235Ala, Asp265Ala (L234A/L235A/D265A). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 329, e.g., Leu234Ala, Leu235Ala, Pro329Gly (L234A/L235A/P329G). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, 265 and 329, e.g., Leu234Ala, Leu235Ala, Asp265Ala, Pro329Gly (L234A/L235A/D265A/P329G).

[0239] In some embodiments, the Fc region of the fusion protein is altered at Gly235 to reduce Fc receptor binding. For example, wherein Gly235 is deleted from the fusion protein. In some embodiments, the human IgG1 Fc region is modified at amino acid Gly236 to enhance the interaction with CD32A, e.g., Gly236Ala (G236A). In some embodiments, the human IgG1 Fc region lacks Lys447 (EU index of Kabat et al 1991 Sequences of Proteins of Immunological Interest).

[0240] In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 236, e.g., Leu234Gly, Leu235Ser, Gly236Arg (L234G/L235S/G236R). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 236, e.g., Leu234Ser, Leu235Thr, Gly236Arg (L234S/L235T/G236R). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 236, e.g., Leu234Ser, Leu235Val, Gly236Arg (L234S/L235V/G236R). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 236, e.g., Leu234Thr, Leu235Gln, Gly236Arg (L234T/L235Q/G236R). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 234, 235, and 236, e.g., Leu234Thr, Leu235Thr, Gly236Arg (L234T/L235T/G236R). In some embodiments, the Fc region of the fusion protein fusion protein is altered at amino acids at 234, 235, and 329, e.g., Leu234Thr, Leu235Thr, Pro329Gly (L234A/L235A/P329G). In some embodiments, the Fc region of the fusion protein is altered at amino acids at 252, 254, and 256, e.g., Met252Tyr, Ser254Thr, Thr256Glu (M252Y/S254T/T256E).

[0241] In some embodiments, the Fc region of the fusion protein is lacking an amino acid at one or more of the following positions to reduce Fc receptor binding: Glu233 (E233), Leu234 (L234), or Leu235 (L235). In some embodiments, the Fc region of the fusion protein is lacking an amino acid at one or more of the following positions Glu233 (E233), Leu234 (L234), or Leu235 (L235) and is modified at one

or more of the Asp265 (D265), Asn297 (N297), or Pro329 (P329) to reduce Fc receptor binding. For example, an Fc region included in a CDH17 binding polypeptide is derived from a human Fc domain, and comprises a three amino acid deletion in the lower hinge corresponding to IgG1 E233, L234, and L235. In some embodiments, such Fc polypeptides do not engage FcγRs and thus are referred to as "effector silent" or "effector null." For example, Fc deletion of these three amino acids reduces the complement protein C1q binding. In some embodiments, a polypeptide with an Fc region with Fc deletion of these three amino acids retains binding to FcRn and therefore has extended half-life and transcytosis associated with FcRn mediated recycling.

[0242] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234A, L235A (also known as "LALA" variant) (mutations bolded in the sequence below)

DKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1568)

[0243] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234A, L235A, and P329A (also known as "LALAPA" variant) (mutations bolded in the sequence below)

DKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**A**APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1569)

[0244] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 D265A, N297A and P329A (also known as "DANAPA" variant) (mutations bolded in the sequence below)

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV**A**VSHEDPEVKFNWYVDGVEVHNAKTKPREEQY**A**ST YRVVSVLTVLHQDWLNGKEYKCKVSNKAL**A**APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1570)

[0245] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234A, L235A, and G237A (also known as "LALAGA" variant) (mutations bolded in the sequence below)

DKTHTCPPCPAPE**AA**G**A**PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1571)

[0246] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234G/L235S/G236R (mutations bolded in the sequence below)

DKTHTCPPCPAPE**GSR**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1596)

[0247] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234S/L235T/G236R (mutations bolded in the sequence below)
DKTHTCPPCPAPE**STR**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1597)

[0248] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234S/L235V/G236R (mutations bolded in the sequence below)

DKTHTCPPCPAPE**SVR**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1598)

[0249] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234T/L235Q/G236R (mutations bolded in the sequence below)

DKTHTCPPCPAPE**TQR**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1599)

[0250] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234T/L235T/G236R (mutations bolded in the sequence below)

DKTHTCPPCPAPE**TTR**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1600)

[0251] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 L234A/L235A/P329G (mutations bolded in the sequence below)

DKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**G**APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1601)

[0252] In one embodiment, the immunoglobulin Fc region of the multispecific antigen-binding protein is a variant of human IgG1 Fc region, having an amino acid sequence:

IgG1 M252Y/S254T/T256E (mutations bolded in the sequence below)

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTL**YIT**R**E**PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 1602)

[0253] In some embodiments, the human IgG Fc region is modified to enhance FcRn binding. Examples of Fc mutations that enhance binding to FcRn are Met252Tyr, Ser254Thr, Thr256Glu (M252Y, S254T, T256E, respectively) (Kabat numbering, Dall'Acqua et al 2006, J. Biol Chem Vol. 281(33) 23514-23524), Met428Leu and Asn434Ser (M428L, N434S) (Zalevsky et al 2010 Nature Biotech, Vol. 28(2) 157-159), Met252Ile, Thr256Asp, Met428Leu (M252I, T256D, M428L, respectively) (EU index of Kabat et al 1991 Sequences of Proteins of Immunological Interest), Asn434Ala (N434A), Asn434Trp (N434W), Thr256Asp, Thr307Gln (T256D/T307Q), Thr256Asp, Thr307Trp (T256D/T307W), Met252Tyr, Thr256Asp (M252Y/T256D), Thr307Gln, Gln311Val, Ala378Val (T307Q/Q311V/A378V), Thr256Asp, His286Asp, Thr307Arg, Gln311Val, Ala378Val (T256D/H286D/T307R/Q311V/A378V), or Leu309Asp, Gln311His, Asn434Ser (L309D/Q311H/N434S) (see, Ko et al., BioDrugs (2021) 35:147–157).

[0254] In some embodiments, the Fc region lacks or has reduced fucose attached to the N-linked glycan-chain at N297. There are numerous ways to prevent fucosylation, including but not limited to production in a FUT8 deficient cell line; addition inhibitors to the mammalian cell culture media, for example Castanospermine; and metabolic engineering of the production cell line.

[0255] In some embodiments, the Fc domain included in a fusion protein or conjugate of the present disclosure is derived from a human Fc domain and comprises mutations M252Y and M428V. In some embodiments, the mutated or modified Fc polypeptide includes the following mutations: M252Y and

M428L using the Kabat numbering system. In some embodiments, such mutations enhance binding to FcRn at the acidic pH of the endosome (near 6.5), while losing detectable binding at neutral pH (about 7.2), allowing for enhanced FcRn mediated recycling and extended half-life.

[0256] In some embodiments, the Fc domain included in a fusion protein or conjugate is derived from a human Fc domain and comprises mutations to induce heterodimerization. In some embodiments, such mutations include those referred to as "knob" and "hole" mutations. For example, having an amino acid modification within the CH3 domain at Thr366, which when replaced with a bulkier amino acid, e.g., Try (T366W), is able to preferentially pair with a second CH3 domain having amino acid modifications to less bulky amino acids at positions Thr366, Leu368, and Tyr407, e.g., Ser, Ala and Val, respectively (T366S/L368A/Y407V). In some embodiments, the "knob" Fc domain comprises the mutation T366W. In some embodiments, the "hole" Fc domain comprises mutations T366S, L368A, and Y407V. Heterodimerization via CH3 modifications can be further stabilized by the introduction of a disulfide bond, for example by changing Ser354 to Cys (S354C) and Y349 to Cys (Y349C) on opposite CH3 domains (Reviewed in Carter, 2001 Journal of Immunological Methods, 248: 7-15). In some embodiments, Fc domains used for heterodimerization comprise additional mutations, such as the mutation S354C on a first member of a heterodimeric Fc pair that forms an asymmetric disulfide with a corresponding mutation Y349C on the second member of a heterodimeric Fc pair. In some embodiments, one member of a heterodimeric Fc pair comprises the modification H435R or H435K to prevent protein A binding while maintaining FcRn binding. In some embodiments, one member of a heterodimeric Fc pair comprises the modification H435R or H435K, while the second member of the heterodimeric Fc pair is not modified at H435. In various embodiments, the hole Fc domain comprises the modification H435R or H435K (referred to as "hole-R" in some instances when the modification is H435R), while the knob Fc domain does not. In some instances, the hole-R mutation improves purification of the heterodimer over homodimeric hole Fc domains that may be present.

[0257] In some embodiments, the human IgG Fc region is modified to prevent dimerization. In these embodiments, the fusion proteins of the present disclosure are monomeric. For example, modification at residue Thr366 to a charged residue, e.g. Thr366Lys, Thr366Arg, Thr366Asp, or Thr366Glu (T366K, T366R, T366D, or T366E, respectively), prevents CH3-CH3 dimerization.

[0258] In some embodiments, the immunoglobulin Fc region of the fusion protein is of human IgG3 isotype, or a variant thereof. In one embodiment, the IgG3 Fc region is modified at amino acid Asn297 (Kabat Numbering) to prevent to glycosylation of the antibody, e.g., Asn297Ala (N297A) or Asn297Asp (N297D). In some embodiments, the human IgG3 Fc region is modified at amino acid 435 to extend the

half-life, e.g., Arg435His (R435H). In some embodiments, the human IgG3 Fc region lacks Lys447 (EU index of Kabat et al 1991).

[0259] In some embodiments, the immunoglobulin Fc region of the fusion protein is of human IgG4 isotype, or a variant thereof.

[0260] As a non-limiting example, an immunoglobulin Fc region of human IgG4 isotype may have an amino acid sequence:

ESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1603)

[0261] In some embodiments, the immunoglobulin Fc region of human IgG4 isotype may comprise the amino acid sequence set forth in SEQ ID NO: 1603, or a similar sequence thereof having at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0262] In some embodiments, the human IgG4 Fc region comprises one or more mutations selected from, e.g., Ser228Pro (S228P), Leu235Glu (L235E), Leu235Ala (L235A), Phe234Ala (F234A), and/or Pro329Gly (P329G) according to EU numbering.

[0263] In some embodiments, the IgG4 Fc region of the fusion protein is altered at amino acids at 228 and 235, e.g., Ser228Pro, Leu235Glu or Leu235Ala (S228P/L235E or S228P/L235A). In some embodiments, the IgG4 Fc region of the fusion protein is altered at amino acids at 228, 234 and 235, e.g., Ser228Pro, Phe234Ala, Leu235Glu or Leu235Ala (S228P/F234A/L235E or S228P/F234A/L235A). In some embodiments, the IgG4 Fc region of the fusion protein is altered at amino acids at 228, 235, and 329, e.g., Ser228Pro, Leu235Glu and P329G (S228P/L235E/P329G).

[0264] In one embodiment, the human IgG4 Fc region is modified at amino acid 235 to alter Fc receptor interactions, e.g., Leu235Glu (L235E). In some embodiments, the human IgG4 Fc region is modified at amino acid Asn297 (Kabat Numbering) to prevent to glycosylation of the antibody, e.g., Asn297Ala (N297A) or Asn297Asp (N297D). In some embodiments, the human IgG4 Fc region lacks Lys447 (EU index of Kabat et al 1991).

[0265] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG4 Fc region, having an amino acid sequence:

IgG4 S228P, L235E (mutations bolded in the sequence below)
ESKYGPPCP**P**CPAPEF**E**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1572)

[0266] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG4 Fc region, having an amino acid sequence:

IgG4 S228P, L235A (mutations bolded in the sequence below)
ESKYGPPCP**P**CPAPEF**A**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1573)

[0267] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG4 Fc region, having an amino acid sequence:

IgG4 S228P, F234A, L235E (mutations bolded in the sequence below)
ESKYGPPCP**P**CPAPE**AE**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1574)

[0268] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG4 Fc region, having an amino acid sequence:

IgG4 S228P, F234A, L235A (mutations bolded in the sequence below)
ESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1575)

[0269] In one embodiment, the immunoglobulin Fc region of the fusion protein is a variant of human IgG4 Fc region, having an amino acid sequence:

IgG4 P329G, S228P, L235E (mutations bolded in the sequence below)
ESKYGPPCP**P**CPAPEF**E**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL**G**SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 1576)

[0270] Additional IgG4 heavy chain modifications suitable for use in the fusion proteins or conjugates of the present disclosure include those described in Tables 1 and 2 of Dumet et al., mAbs, 11:8, 1341-1350, which is incorporated herein by reference in its entirety.

[0271] In some embodiments, the fusion protein or conjugate contains an immunoglobulin hinge region. In some embodiments, the hinge region serves as a linker to connect one or more CDH17 binding units (e.g., VHHs) to the Fc region. In other embodiments, the fusion protein can comprise a linker in addition to the hinge region to connect the one or more CDH17 binding units (e.g., VHHs) to the Fc

region. The hinge region can be selected from any of the human IgG subclasses. For example, the fusion protein may contain a modified IgG1 hinge having the sequence of EPKSSDKTHTCPPC (SEQ ID NO: 1577), wherein the Cys220 that typically forms a disulfide bond with the C-terminal cysteine of the light chain is mutated to serine, e.g., Cys220Ser (C220S). In other embodiments, the fusion protein contains a truncated hinge having a sequence DKTHTCPPC (SEQ ID NO: 1578).

[0272] In some embodiments, the fusion protein or conjugate has a modified hinge from IgG4, which is modified to prevent or reduce strand exchange, e.g., Ser228Pro (S228P), having the sequence ESKYGPPCPPC (SEQ ID NO: 1579).

[0273] In alternative embodiments, a fusion protein or conjugate of the present disclosure may comprise sequences other than an Fc region to achieve multimerization (e.g., dimerization). For example, an amino acid sequence containing at least one cysteine residue may be included to facilitate dimerization of two polypeptides by formation of a disulfide bond between the two polypeptides. In some embodiments, such multimerizing domain may comprise one or more cysteine residues, or a short cysteine-containing peptide. Other multimerizing domains include peptides or polypeptides comprising or consisting of a leucine zipper, a helix-loop motif, or a coiled-coil motif.

[0274] Fc mutations suitable for use in the fusion proteins disclosed herein are also discussed in, e.g., Wilkinson et al., Fc-engineered antibodies with immune effector functions completely abolished. PLoS One. 2021; WO2021234402A2; US 8,969,526; EP3692065B1; and US 7,083,784, each of which is incorporated herein by reference.

Fusion or Conjugation to Half-Life Extension Moieties

[0275] In some embodiments, a fusion protein or conjugate of the present disclosure may comprise one or more other moieties which provide the fusion protein or conjugate with increased (in vivo) half-life. In vivo half-life extension means, that the fusion protein or conjugate has an increased half-life in a mammal, such as a human subject, after administration.

[0276] Non-limiting examples of half-life extension moieties suitable for use in the present disclosure include polyethylene glycol (PEG) molecules, serum proteins or fragments thereof, binding units that can bind to serum proteins, an Fc portion, and small proteins or peptides that can bind to serum proteins.

[0277] In some embodiments, a fusion protein or conjugate of the present disclosure may comprise a binding moiety that can bind to serum albumin, such as human serum albumin, or a serum immunoglobulin, such as IgG. In one embodiment, a fusion protein or conjugate of the present

disclosure may comprise a binding moiety that can bind to human serum albumin. In one embodiment, the binding moiety is a single-domain antibody (e.g., VHH).

[0278] For example and without limitation, albumin binders that are described in, e.g., WO 04/041865, WO 06/122787, WO2012/175400, WO 2012/175741, WO2015/173325, WO2017/080850, WO2017/085172, WO2018/104444, WO2018/134235, WO2018/134234, each of which is incorporated herein by reference is its entirety, can be used in the fusion protein or conjugate of the present disclosure.

Fusion or Conjugation to Other Moieties

[0279] Anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) provided herein may be operably linked, directly or indirectly, to a second moiety, such as but not limited to, a detectable label, a drug, a toxin, a radionuclide, an enzyme, an immunomodulatory agent, a cytokine, a cytotoxic agent, a small molecule drug, a chemotherapeutic agent, a therapeutic agent, a diagnostic agent, or a combination thereof.

[0280] In some embodiments, a conjugate of the present disclosure comprises a label, which can generate a detectable signal. Such conjugates can be used for research or diagnostic purposes, such as for the *in vivo* detection of cancer. Preferably, the label is capable of producing, either directly or indirectly, a detectable signal. For example, the label may be radio-opaque or a radioisotope (such as 3H, 14C, 32P, 35S, 123I, 125I, 131I); a fluorescent (fluorophore) or chemiluminescent (chromophore) compound (such as fluorescein isothiocyanate, rhodamine or luciferin); an enzyme (such as β-galactosidase, alkaline phosphatase, or horseradish peroxidase); an imaging agent; or a metal ion. In some embodiments, the label is a radioactive atom for scintigraphic studies, for example 99Tc or 123I, or a spin label for nuclear magnetic resonance (NMR) imaging, such as zirconium-89, iodine-123, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron. Zirconium-89 may also be complexed to various metal chelating agents and conjugated to antibodies, e.g., for PET imaging (WO 2011/056983).

[0281] Anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may be conjugated to another moiety, such as an epitope tag, e.g., for the purpose of purification or detection. Examples of such molecules that are useful in protein purification include those that present structural epitopes capable of being recognized by a second molecule. This is commonly employed in protein purification by affinity chromatography, in which a molecule is immobilized on a solid support and exposed to a heterogeneous mixture containing a target protein

conjugated to a molecule capable of binding the immobilized compound. Non-limiting examples of epitope tag molecules that can be conjugated to anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure, e.g., for the purposes of molecular recognition include a poly-histidine tag (His-tag), a myc-tag, human influenza hemagglutinin (HA) tag, a FLAG-tag, maltose-binding protein, glutathione-S-transferase, biotin, and streptavidin. Conjugates containing the epitopes presented by these molecules are capable of being recognized by complementary molecules such as maltose, glutathione, a nickel-containing complex, an anti-FLAG antibody, an anti-myc antibody, an anti-HA antibody, streptavidin, or biotin, respectively. For example, one can purify an anti-CDH17 antigen-binding protein of the present disclosure that has been conjugated to an epitope tag from a complex mixture of other proteins and biomolecules (e.g., DNA, RNA, carbohydrates, phospholipids, etc) by treating the mixture with a solid phase resin containing a complementary molecule that can selectively recognize and bind the epitope tag of the CDH17 antibody or fragment thereof. Examples of solid phase resins include agarose beads, which are compatible with purifications in aqueous solution.

[0282] In some embodiments, a conjugate of the present disclosure may comprise one or more anti-CDH17 VHH domains described herein conjugated to a therapeutic agent, which can be cytotoxic, cytostatic or otherwise provides some therapeutic benefit. In some embodiments, the cytotoxic agent is a drug, a chemotherapeutic agent, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (e.g., a radioconjugate). Such conjugates may be applicable to, e.g., the treatment or prevention of a cancer. In some embodiments, antibody drug conjugates described herein may allow targeted delivery of a drug moiety to a target tissue (e.g., tumors).

[0283] In some embodiments, a conjugate of the present disclosure comprises a toxin. In some embodiments, the toxin includes, for example, bacterial toxins such as diphtheria toxin, plant toxins such as ricin, small molecule toxins such as geldanamycin (Mandler et al., J. Nat. Cancer Inst. 92(19):1573-1581 (2000); Mandler et al., Bioorganic & Med. Chem. Letters 10:1025-1028 (2000); Mandler et al., Bioconjugate Chem. 13:786-791 (2002)), maytansinoids (EP 1391213; Liu et al., Proc. Natl. Acad. Sci. USA 93:8618-8623 (1996)), and calicheamicin (Lode et al., Cancer Res. 58:2928 (1998); Hinman et al., Cancer Res. 53:3336-3342 (1993)). The toxins may exert their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition. Examples of other therapeutic agents that can be conjugated to an anti-CDH17 antigen-binding protein of the present disclosure are described herein (see "Treatment Methods and Other Uses" section).

[0284] In some embodiments, anti-CDH17 antigen-binding proteins (e.g., antibodies such as single-domain antibodies) of the present disclosure may be fused or conjugated to one or more moieties that facilitate delivery to the central nervous system (CNS)/brain. The moiety that can facilitate delivery of an anti-CDH17 antigen-binding protein to the central nervous system (CNS)/brain can be for example, a peptide, a polypeptide, small molecule, a lipid, or a synthetic polymer. Various approaches to deliver single-domain antibodies into the brain are described in Pothin et al., Pharmaceutics 2020, 12(10), 937, which is incorporated herein by reference in its entirety.

[0285] As a non-limiting example, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) of the present disclosure may be fused or conjugated to a moiety (e.g., an antibody) that binds to the transferrin receptor (TfR) or insulin receptor. The transferrin receptor (TfR) is highly expressed by brain capillary endothelial cells (BCECs) forming the blood-brain barrier (BBB) and has been utilized as a target for brain drug delivery. Monoclonal antibodies binding to the TfR, such as clone Ri7, have been shown to internalize into BCECs *in vivo*. As another example, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) of the present disclosure may be conjugated to hydrophobic fatty acid moieties, such as C18 fatty acid (stearic acid), C16 fatty acid (palmitic acid) or C8 fatty acid (octanoic acid) moieties; or amphiphilic block copolymer moieties, such as poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (pluronics or poloxamers) or poly(2-oxasolines). Various fatty acid moieties and block copolymer moieties that can be utilized for brain delivery of proteins are described in, e.g., Yi and Kabanov, J Drug Target. 2013; 21(10): 940–955, which is incorporated herein by reference in its entirety.

[0286] Example methods for attaching a moiety, such as a label, to a binding protein include those described in Hunter, et al., Nature 144:945 (1962); David, et al., Biochemistry 13:1014 (1974); Pain, et al., J. Immunol. Meth. 40:219 (1981); Nygren, J. Histochem. and Cytochem. 30:407 (1982); Wensel and Meares, Elsevier, N.Y. (1983); and Colcher et al., Meth. Enzymol., 121 :802-16 (1986). Additional suitable methods for preparing the conjugates of the present disclosure include those described in, e.g., WO 2009/067800, WO 2011/133886, and US2014322129, incorporated by reference herein in their entirety.

[0287] In some embodiments, the attachment between an anti-CDH17 antigen-binding protein and a second moiety can be covalent or non-covalent, e.g., via a biotin-streptavidin non-covalent interaction. In some embodiments, a second moiety can be attached to an anti-CDH17 antigen-binding protein using any of various molecular biological or chemical conjugation and linkage methods known in the art and described below. In some embodiments, linkers such as peptide linkers, cleavable linkers, non-cleavable

linkers or linkers that aid in the conjugation reaction, can be used to link or conjugate a second moiety to an anti-CDH17 antigen-binding protein described herein.

[0288] In some embodiments, an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) is conjugated to one or more second moieties, e.g., about 1 to about 20 moieties per molecule, optionally via a linker. In some embodiments, the one or more second moieties can be the same or different. The linker may be composed of one or more linker components. For covalent attachment of an antibody and the second moiety, the linker typically has two reactive functional groups, i.e., bivalency in a reactive sense. Bivalent linker reagents which are useful to attach two or more functional or biologically active moieties, such as peptides, nucleic acids, drugs, toxins, antibodies, haptens, and reporter groups have been described in, e.g., Hermanson, G. T. (1996) Bioconjugate Techniques; Academic Press: New York, p 234-242.

[0289] In some embodiments, a linker used in a conjugate of the present disclosure may include 6-maleimidocaproyl ("MC"), maleimidopropanoyl ("MP"), valine-citrulline ("val-cit"), a alanine-phenylalanine ("ala-phe"), p-aminobenzyloxycarbonyl ("PAB"), N-Succinimidyl 4-(2-pyridylthio)pentanoate ("SPP"), N-Succinimidyl 4-(N-maleimidomethyl)cyclohexane-I carboxylate ("SMCC"), or N-Succinimidyl(4-iodo-acetyl)aminobenzoate ("STAB"), or a combination thereof.

[0290] In some embodiments, a linker used in a conjugate of the present disclosure may comprise amino acid residues. Exemplary amino acid linker components include a dipeptide, a tripeptide, a tetrapeptide or a pentapeptide. Exemplary dipeptides include valine-citrulline (vc or val-cit), alanine-phenylalanine (af or ala-phe). Exemplary tripeptides include glycine-valine-citrulline (gly-val-cit) and glycine-glycine-glycine (gly-gly-gly). Amino acid residues used in an amino acid linker component may include naturally occurring amino acids, as well as minor amino acids and non-naturally occurring amino acid analogs, such as citrulline. Amino acid linker components can be designed and optimized in their selectivity for enzymatic cleavage by particular enzymes, for example, a tumor-associated protease, cathepsin B, C and D, or a plasmin protease.

[0291] Conjugates of an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody) and second moiety (e.g., cytotoxic agent) can be made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl substrate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-

ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene).

[0292] Conjugates of the present disclosure can be prepared by a variety of methods. For example, the conjugation method may include: (1) reaction of a nucleophilic group of a VHH domain with a bivalent linker reagent, to form VHH-Linker, via a covalent bond, followed by reaction with a drug moiety; or (2) reaction of a nucleophilic group of a drug moiety with a bivalent linker reagent, to form drug-linker, via a covalent bond, followed by reaction with the nucleophilic group of a VHH domain.

[0293] Nucleophilic groups on proteins including antibodies (e.g., VHH domains), include, but are not limited to: (i) N-terminal amine groups, (ii) side chain amine groups (e.g., lysine), (iii) side chain thiol groups (e.g., cysteine), and (iv) sugar hydroxyl or amino groups where the antibody is glycosylated. Amine, thiol, and hydroxyl groups are nucleophilic and capable of reacting to form covalent bonds with electrophilic groups on linker moieties and linker reagents including: (i) active esters such as NHS esters, HOBt esters, haloformates, and acid halides; (ii) alkyl and benzyl halides such as haloacetamides; (iii) aldehydes, ketones, carboxyl, and maleimide groups. Additional nucleophilic groups can be introduced into proteins (e.g., antibodies such as VHH domains) through the reaction of lysines with 2-iminothiolane (Traut's reagent) resulting in conversion of an amine into a thiol. Reactive thiol groups may be introduced into a protein (e.g., antibody such as a VHH domain) by introducing one, two, three, four, or more cysteine residues.

[0294] Conjugates, such as antibody drug conjugates, may also be produced by modification of an antibody, such as a VHH domain, to introduce electrophilic moieties, which can react with nucleophilic substituents on the linker reagent or drug. The sugars of glycosylated antibodies may be oxidized, e.g., with periodate oxidizing reagents, to form aldehyde or ketone groups which may lead with the amine group of linker reagents or drug moieties. The resulting imine Schiff base groups may form a stable linkage, or may be reduced, e.g., by borohydride reagents to form stable amine linkages. In one embodiment, reaction of the carbohydrate portion of a glycosylated antibody with either galactose oxidase or sodium meta-periodate may yield carbonyl (aldehyde and ketone) groups in the protein that can react with appropriate groups on the drug (Hermanson, Bioconjugate Techniques). In another embodiment, proteins containing N-terminal serine or threonine residues can react with sodium meta-periodate, resulting in production of an aldehyde in place of the first amino acid. Such aldehyde can be reacted with a drug moiety or linker nucleophile.

[0295] Likewise, nucleophilic groups on a drug moiety include, but are not limited to: amine, thiol, hydroxyl, hydrazide, oxime, hydrazine, thiosemicarbazone, hydrazine carboxylate, and arylhydrazide

groups capable of reacting to form covalent bonds with electrophilic groups on linker moieties and linker reagents including: (i) active esters such as NHS esters, HOBi esters, haloformates, and acid halides; (ii) alkyl and benzyl halides such as haloacetamides; (iii) aldehydes, ketones, carboxyl, and maleimide groups.

[0296] Alternatively, a fusion protein containing a VHH domain and cytotoxic agent may be made, e.g., by recombinant DNA techniques or peptide synthesis. A DNA sequence may be engineered to comprise respective regions encoding the two portions of the fusion protein either adjacent to one another or separated by a region encoding a linker peptide which does not impair the desired properties of the fusion protein. The DNA sequence can be then transfected into a host cell that expresses the fusion protein. The fusion protein can be recovered from the cell culture and purified using techniques known in the art.

Linkers

[0297] In some embodiments, the one or more polypeptides of the fusion proteins of the present disclosure are operably linked via peptide linkers. A peptide linker can range from 2 amino acids to 60 or more amino acids, and in certain aspects a peptide linker ranges from 3 amino acids to 50 amino acids, from 4 to 30 amino acids, from 5 to 25 amino acids, from 10 to 25 amino acids, 10 amino acids to 60 amino acids, from 12 amino acids to 20 amino acids, from 20 amino acids to 50 amino acids, or from 25 amino acids to 35 amino acids in length.

[0298] In some embodiments, a peptide linker, e.g., a peptide linker separating two VHH domains or an VHH domain and a heavy chain constant region, is at least 5 amino acids, at least 6 amino acids or at least 7 amino acids in length and optionally is up to 30 amino acids, up to 40 amino acids, up to 50 amino acids or up to 60 amino acids in length.

[0299] In some embodiments, the linker ranges from 5 amino acids to 50 amino acids in length, e.g., ranges from 5 to 50, from 5 to 45, from 5 to 40, from 5 to 35, from 5 to 30, from 5 to 25, or from 5 to 20 amino acids in length. In other embodiments of the foregoing, the linker ranges from 6 amino acids to 50 amino acids in length, e.g., ranges from 6 to 50, from 6 to 45, from 6 to 40, from 6 to 35, from 6 to 30, from 6 to 25, or from 6 to 20 amino acids in length. In yet other embodiments of the foregoing, the linker ranges from 7 amino acids to 50 amino acids in length, e.g., ranges from 7 to 50, from 7 to 45, from 7 to 40, from 7 to 35, from 7 to 30, from 7 to 25, or from 7 to 20 amino acids in length.

[0300] In some embodiments, charged (e.g., charged hydrophilic linkers) and/or flexible linkers are used. Examples of flexible linkers that can be used in the fusion proteins of the disclosure include those

disclosed by Chen et ai, 2013, Adv Drug Deliv Rev. 65(10): 1357-1369 and Klein et a/., 2014, Protein Engineering, Design & Selection 27(10): 325-330. Particularly useful flexible linkers are or comprise repeats of glycines and serines (termed "GS-linker" herein), e.g., a monomer or multimer of G_nS (SEQ ID NO: 1553) or SG_n (SEQ ID NO: 1554), where n is an integer from 1 to 10, e.g., 1 2, 3, 4, 5, 6, or 7, 8, 9 or 10. In one embodiment, the linker is or comprises a monomer or multimer of repeat of G_4S (SEQ ID NO: 1507), e.g., $(GGGGS)_n$ (SEQ ID NO: 1555).

[0301] Polyglycine linkers can suitably be used in the fusion proteins of the disclosure. In some embodiments, a peptide linker used herein comprises two consecutive glycines (2Gly), three consecutive glycines (3Gly), four consecutive glycines (4Gly) (SEQ ID NO: 1556), five consecutive glycines (5Gly) (SEQ ID NO: 1557), six consecutive glycines (6Gly) (SEQ ID NO: 1558), seven consecutive glycines (7Gly) (SEQ ID NO: 1559), eight consecutive glycines (8Gly) (SEQ ID NO: 1560), or nine consecutive glycines (9Gly) (SEQ ID NO: 1561).

[0302] In some embodiments, a GS-linker used herein comprises an amino acid sequence selected from GGSGGS (SEQ ID NO: 1562), i.e., $(GGS)_2$ (SEQ ID NO: 1562); GGSGGSGGS (SEQ ID NO: 1563), i.e., $(GGS)_3$ (SEQ ID NO: 1563); GGSGGSGGSGGS (SEQ ID NO: 1564), i.e., $(GGS)_4$ (SEQ ID NO: 1564); and GGSGGSGGSGGSGGS (SEQ ID NO: 1565), i.e., $(GGS)_5$ (SEQ ID NO: 1565). In some embodiments, the fusion proteins can include a combination of a GS-linker and a glycine linker.

[0303] In one embodiment, two or more VHHs are linked via a GGGGSGGGGSGGGGS (SEQ ID NO: 1508) linker. In one embodiment, two or more VHHs are linked via a GGGGSGGGGS (SEQ ID NO: 1566) linker. In one embodiment, a VHH and an Fc region are linked via a GGGGSESKYGPPCPSCP (SEQ ID NO: 1547) linker. In one embodiment, a VHH and an Fc region are linked via a GGGGS (SEQ ID NO: 1507) linker.

[0304] In some embodiments, the one or more polypeptides of the fusion proteins of the present disclosure are operably linked via a "rigid" peptide linker. Such peptidic linker may comprise a proline-rich peptide. In one embodiment, a rigid peptide linker comprises PAPAPAPAPAPAPAP (SEQ ID NO: 1548). In one embodiment, a rigid peptide linker comprises GGGGSPAPAPAPAPAPAPAP (SEQ ID NO: 1549). In one embodiment, a rigid peptide linker comprises PAPAPAPAPAPAPAPGGGGS (SEQ ID NO: 1550). In one embodiment, a rigid peptide linker comprises GGGGSPAPAPAPAPAPAPAPGGGGS (SEQ ID NO: 1551). In one embodiment, a rigid peptide linker comprises GGGGSPAPAPAPAPAPAPAPGGGS (SEQ ID NO: 1552).

[0305] In one embodiment, a rigid peptide linker comprises A(EAAAK)nA (SEQ ID NO: 1567), where n is any integer, e.g., 1 2, 3, 4, 5, 6, or 7, 8, 9 or 10.

[0306] Other exemplary peptide linkers that can be used in the fusion proteins described herein are shown in **Table 3**.

Table 3. Exemplary Peptide Linker Sequences

Linker	Amino acid sequence	SEQ ID NO
G4S	GGGGS	1507
$(G_4S)_3$	GGGGSGGGGSGGGGS	1508
Linker 3	GGSEGKSSGSGSESKSTGGS	1509
Linker 4	GGGSGGGS	1510
Linker 3	GGGSGGGSGGGS	1511
Linker 4	GGGSGGGSGGGSGGGS	1512
Linker 5	GGGSGGGSGGGSGGGSGGGS	1513
Linker 6	GGGGSGGGGSGGGGSGGGGS	1514
Linker 7	GGGGSGGGGSGGGGSGGGGSGGGGS	1515
Linker 8	IRPRAIGGSKPRVA	1516
Linker 9	GKGGSGKGGSGKGGS	1517
Linker 10	GGKGSGGKGSGGKGS	1518
Linker 11	GGGKSGGGKSGGGKS	1519
Linker 12	GKGKSGKGKSGKGKS	1520
Linker 13	GGGKSGGKGSGKGGS	1521
Linker 14	GKPGSGKPGSGKPGS	1522
Linker 15	GKPGSGKPGSGKPGSGKPGS	1523
Linker 16	GKGKSGKGKSGKGKSGKGKS	1524
Linker 17	STAGDTHLGGEDFD	1525
Linker 18	GEGGSGEGGSGEGGS	1526
Linker 19	GGEGSGGEGSGGEGS	1527
Linker 20	GEGESGEGESGEGES	1528
Linker 21	GGGESGGEGSGEGGS	1529
Linker 22	GEGESGEGESGEGESGEGES	1530
Linker 23	GSTSGSGKPGSGEGSTKG	1531
Linker 24	PRGASKSGSASQTGSAPGS	1532
Linker 25	GTAAAGAGAAGGAAAGAAG	1533
Linker 26	GTSGSSGSGSGGSGSGGGG	1534
Linker 28	GSGS	1535
Linker 29	APAPAPAPAP	1536
Linker 30	APAPAPAPAPAPAPAPAP	1537
Linker 31	AEAAAKEAAAKEAAAAKEAAAAKEAAAAKAAA	1538
Linker 32	IEGRMD	1539
(GGGGS)6 linker	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	1540
(GGGGS)7 linker	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	1541
G1 hinge	EPKSCDKTHTCPPCP	1542
9GS-G1 hinge	GGGGSGGGSEPKSCDKTHTCPPCP	1543
Llama upper long hinge region	EPKTPKPQPAAA	1544

G3 hinge	ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPC PRCPEPKSCDTPPPCPRCP	1545
G4 hinge	ESKYGPPCPSCP	1546
G4S-G4 hinge	GGGGSESKYGPPCPSCP	1547
Proline-linker 1	PAPAPAPAPAPAPAP	1548
Proline-linker 2	GGGGSPAPAPAPAPAPAPAP	1549
Proline-linker 3	PAPAPAPAPAPAPAPGGGGS	1550
Proline-linker 4	GGGGSPAPAPAPAPAPAPAPGGGGS	1551
Proline-linker 5	GGGGSPAPAPAPAPAPAPAPGGGS	1552

Signal Sequences

[0307] In some embodiments, the fusion protein described herein may further comprise a signal sequence at its N-terminus. Signal sequences may be present in the precursor molecule of the fusion protein and may be removed after the protein is secreted from the host cell during production. In some embodiments, the signal sequence is MAVMAPRTLVLLLSGALALTQTWA (SEQ ID NO: 1580) or a fragment or variant thereof. In some embodiments, the signal sequence is MYRMQLLSCIALSLALVTNS (SEQ ID NO: 1581), or a fragment or variant thereof.

Polynucleotide Molecules

[0308] In another aspect, provided herein are polynucleotide molecules encoding the anti-CDH17 antigen-binding proteins (e.g., antibodies including single-domain antibodies) or fusion proteins described herein. Polynucleotide molecules encoding polypeptide portion(s) of a conjugate of the present disclosure are also encompassed within the present disclosure.

[0309] In some embodiments, a polynucleotide molecule of the present disclosure comprises the nucleotide sequence selected from SEQ ID NOs: 67-80, 1269-1506, 1627-1630, and 1807-1835, or a similar sequence thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0310] In some embodiments, a polynucleotide molecule of the present disclosure the nucleotide sequence of any one of SEQ ID NOs: 67-80, 1351, and 1627-1630, or a similar sequence thereof having at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0311] In an embodiment provided herein, a polynucleotide molecule of the present disclosure encodes a humanized VHH amino acid sequence selected from SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 343-554, 1623-1626, and 1672-1691, or a similar sequence thereof having at least

70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0312] In another embodiment provided herein, a polynucleotide molecule of the present disclosure encodes a humanized VHH amino acid sequence selected from SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 421, and 1623-1626, or a similar sequence thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% sequence identity.

[0313] A polynucleotide molecule may be used to transform/transfect a host cell or host organism, e.g., for expression and/or production of a polypeptide. Suitable hosts or host cells for production of an anti-CDH17 polypeptides described herein include any suitable fungal, prokaryotic or eukaryotic cell or cell line or any suitable fungal, prokaryotic or eukaryotic organism. A host or host cell comprising a polynucleotide molecule encoding an anti-CDH17 antigen-binding protein polypeptide or fusion protein described herein is also encompassed by the present disclosure.

[0314] A polynucleotide molecule may be for example DNA, RNA, or a hybrid thereof, and may also comprise (e.g., chemically) modified nucleotides, like locked nucleic acids (LNA) or peptide nucleic acids (PNA). In some embodiments, the polynucleotide is single-stranded. In some embodiments, the polynucleotide is double-stranded. In one embodiment, the polynucleotide is in the form of double-stranded DNA (e.g., plasmid). In some embodiments, the polynucleotide is in the form of a single-stranded RNA (e.g., mRNA).

[0315] Techniques for generating polynucleotides may include, for example but not limited to, automated DNA synthesis; site-directed mutagenesis; combining two or more naturally occurring and/or synthetic sequences (or two or more parts thereof), introduction of mutations that lead to the expression of a truncated expression product; introduction of one or more restriction sites (e.g. to create cassettes and/or regions that may easily be digested and/or ligated using suitable restriction enzymes), and/or the introduction of mutations by means of a PCR reaction using one or more "mismatched" primers. Alternatively, polynucleotides of the present disclosure may be isolated from a suitable natural source. Polynucleotide sequences encoding naturally occurring (poly)peptides can for example be subjected to site-directed mutagenesis, to generate a polynucleotide molecule encoding polypeptide with sequence variation.

Vectors

[0316] Also provided herein are vectors comprising the polynucleotide molecules encoding the anti-CDH17 antigen-binding proteins (e.g., antibodies including single-domain antibodies), fusion proteins, or other relevant polypeptides of the present disclosure. A "vector" as used herein is a vehicle suitable for carrying genetic material into a host cell. A vector can include a nucleic acid vector, such as a plasmid or mRNA, or nucleic acids embedded into a bigger structure, such as a liposome or viral vector.

[0317] A vector can include one or more of the following elements: an origin of replication, one or more regulatory sequences (e.g., promoters, enhancers, terminators) that regulate the expression of a polypeptide of interest, and/or one or more selectable marker genes (such as, for example, antibiotic resistance genes and genes that can be used in colorimetric assays, for example, β-galactosidase). For DNA-based vectors, this usually includes the presence of elements for transcription (e.g., a promoter and a polyA signal) and translation (e.g., Kozak sequence). In some embodiments, the vector is an expression vector, i.e. a vector suitable for expressing an encoded polypeptide or construct under suitable conditions in a host cell.

[0318] To express an anti-CDH17 antigen-binding protein or fusion protein (or fragments thereof) of the present disclosure, polynucleotides encoding partial or full-length polypeptide chains, e.g., obtained as described above (e.g., VHH, VHH-Fc), can be inserted into expression vectors such that the genes are operatively linked to one or more transcriptional and translational control sequences. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. Polynucleotides encoding the two or more polypeptide chains (when present and differ from one another) of an anti-CDH17 antigen-binding protein or fusion protein of the present disclosure can be inserted into separate vectors, or, optionally, incorporated into the same expression vector.

[0319] In addition to polynucleotides encoding the polypeptide chain(s) of an anti-CDH17 antigen-binding protein or fusion protein, the recombinant expression vectors of the invention may include regulatory sequences that control the expression of genes encoding the polypeptide chain(s) in a host cell. The design of the expression vector, including the selection of regulatory sequences, may depend on the choice of the host cell to be transformed and/or the desired level of protein expression. For example, suitable regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV), Simian Virus 40 (SV40), adenovirus, (e.g., the adenovirus major late promoter (AdMLP)) and polyoma. Additional examples of viral regulatory elements, and sequences

thereof, include those described in, e.g., U.S. Pat. Nos. 5, 168,062; 4,510,245; and 4,968,615; the disclosures of each of which are incorporated herein by reference.

[0320] Recombinant expression vectors of the present disclosure may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. A selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., US4,399,216; US 4,634,665; and US 5,179,017; the disclosure of each of which is incorporated herein by reference in its entirety). For example, typically the selectable marker gene confers resistance to antibiotics, such as ampicillin, chloramphenicol, kanamycin, or nourseothricin, or cytotoxic drugs, such as G418, puromycin, blasticidin, hygromycin or methotrexate, to a host cell into which the vector has been introduced. Suitable selectable marker genes can include the dihydrofolate reductase (DHFR) gene (for use in DHFR deficient host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

[0321] Vectors of the present disclosure may further include sequence elements that enhance the rate of translation of these genes or improve the stability or nuclear export of the mRNA that results from gene transcription. These sequence elements include, e.g., 5′ and 3′ untranslated regions, an internal ribosomal entry site (IRES), and polyadenylation signal site in order to direct efficient transcription of the gene carried on the expression vector.

[0322] Viral vectors can be used for the efficient delivery of exogenous genes into the genome of a cell (e.g., a eukaryotic or prokaryotic cell). Viral vectors are particularly useful for gene delivery because the polynucleotides contained within such genomes are typically incorporated into the genome of a target cell by generalized or specialized transduction. These processes occur as part of the natural viral replication cycle, and do not require added proteins or reagents to induce gene integration. Examples of suitable viral vectors include a retrovirus, adenovirus (e.g., Ad5, Ad26, Ad34, Ad35, and Ad48), parvovirus (e.g., adeno-associated viruses (AAV) such as AAV2, AAV8, AAV9), negative strand RNA viruses such as orthomyxovirus (e.g., influenza virus), rhabdovirus (e.g., rabies and vesicular stomatitis virus), paramyxovirus (e.g. measles and Sendai), positive strand RNA viruses, such as picornavirus and alphavirus, and double-stranded DNA viruses including adenovirus, herpes virus (e.g., Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus), baculovirus, coronavirus, and poxvirus (e.g., vaccinia, modified vaccinia Ankara (MVA), fowlpox and canarypox). Other viruses useful for delivering polynucleotides encoding polypeptides of the present disclosure include, for example Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, and hepatitis virus. Examples of retroviruses include, but are not limited to, avian leukosis-sarcoma, mammalian C-type, B-type viruses, D-type

viruses, HTLV-BLV group, lentivirus, spumavirus (Coffin, J. M.1996. Fundamental Virology, DMKDN Fields, PM Howley, ed. (Philadelphia, Lippincott-Raven Publishers): 763-843., the disclosure of which is incorporated herein by reference). Other examples of viral genomes useful in the compositions and methods of the present disclosure include murine leukemia viruses, murine sarcoma viruses, mouse mammary tumor virus, bovine leukemia virus, feline sarcoma virus, feline leukemia virus, avian leukemia virus, human T-cell leukemia virus, baboon endogenous virus, Gibbon ape leukemia virus, Mason Pfizer monkey virus, simian immunodeficiency virus, simian sarcoma virus, Rous sarcoma virus, and lentiviruses.

Host Cells

[0323] In one aspect, the present disclosure also provides host cells or host organisms that comprise the polynucleotides or vectors encoding the anti-CDH17 antigen-binding proteins (e.g., antibodies including single-domain antibodies), fusion proteins, or other relevant polypeptides described herein. Suitable host cells or host organisms can be any suitable fungal, prokaryotic or eukaryotic cell or cell line or any suitable fungal, prokaryotic or eukaryotic organism. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. Host cells can also include cells transfected *in vivo* with a polynucleotide(s) or vector provided herein.

[0324] Exemplary eukaryotic cells include mammalian cells, such as primate or non-primate animal cells; fungal cells, such as yeast (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris*); plant cells; and insect cells. Non-limiting exemplary mammalian cells include, but are not limited to, NSO cells, PER.C6® cells (Crucell), COS cells, SP2/0 cells, and 293 and CHO cells, and their derivatives, such as 293-6E, CHO-DG44, CHO-K1, CHO-S, and CHO-DS cells. Exemplary prokaryotic cells include bacterial cells such as *Escherichia coli.*

Preparation Methods

[0325] The present disclosure also provides methods of producing the anti-CDH17 antigen-binding proteins (e.g., antibodies including single-domain antibodies), fusion proteins, or conjugates described herein.

[0326] In some embodiments, a method may comprise transforming/transfecting a host cell or host organism with a polynucleotide encoding an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), fusion protein, or other relevant polypeptide(s) described herein, expressing

the anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), fusion protein, or other relevant polypeptide(s) in the host, optionally followed by one or more isolation and/or purification steps.

[0327] When recombinant expression vectors encoding one or more polypeptide(s) of an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), fusion protein, or conjugate of the present disclosure are introduced into mammalian host cells, the host cells are cultured for a period of time sufficient to allow for expression of the protein(s) or polypeptide(s) in the host cells or secretion of the protein(s) or polypeptide(s) into the culture medium in which the host cells are grown. Protein(s) or polypeptide(s) can be recovered from the culture medium using standard protein purification methods. Host cells can also be used to produce portions of intact antibodies, such as VHH domains.

[0328] Once a protein or polypeptide of the present disclosure has been produced by recombinant expression, it can be purified by any method known in the art for purification of a protein or polypeptide, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for CDH17 after Protein A or Protein G selection, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the proteins or polypeptides of the present disclosure can be fused to heterologous polypeptide sequences described herein (e.g., His-tag) or otherwise known in the art to facilitate purification or to produce therapeutic conjugates below). Once isolated, a protein or polypeptide of the present disclosure can, if desired, be further purified, e.g., by high performance liquid chromatography, or by gel filtration chromatography, such as on a Superdex™ column.

Pharmaceutical Compositions and Formulations

[0329] The present disclosure also provides a composition comprising anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), fusion protein, or conjugate of the present technology, at least one polynucleotide molecule encoding the same, at least one vector comprising such a polynucleotide molecule, or at least one host cell comprising the polynucleotide molecule or vector. The composition may be a pharmaceutical composition. The composition may further comprise at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally comprise one or more further pharmaceutically active polypeptides and/or compounds.

[0330] As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are

described in the most recent edition of Remington's Pharmaceutical Sciences, which is incorporated herein by reference. Suitable examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. Supplementary active compounds can also be incorporated into the compositions.

[0331] Examples of suitable formulations include, but are not limited to, solutions, suspensions, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™, Life Technologies, Carlsbad, CA), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Phdomain Sci Technol 52:238-311.

[0332] A pharmaceutical composition of the present disclosure may be formulated according to its intended route of administration. Examples of suitable routes of administration include, e.g., intravenous, subcutaneous, intratumoral, oral (e.g., buccal, sublingual), intranasal, inhalation, intraocular, intramuscular, intradermal, transdermal (i.e., topical), intraperitoneal, transmucosal, vaginal, and rectal administration, or injection to the CNS/brain (e.g., intraspinal, intracerebral, or intrathecal administration). Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; fixed oils; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as phosphates, acetates, or citrates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of plastic or glass.

[0333] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include, for example, physiological saline, bacteriostatic water, Cremophor EL®, or phosphate buffered saline (PBS). The composition is preferably sterile and has a proper fluidity. In most embodiments, the composition is stable under the conditions of manufacture and storage and can be preserved against the contaminating

action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, e.g., water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the contamination by microorganisms can be achieved by the inclusion of various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0334] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients described above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and/or freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0335] Oral compositions may include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, capsules, or liquid forms. Formulation in tablet and liquid forms may be used for protease insensitive VHHs. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0336] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0337] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0338] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0339] For brain delivery, compounds of the present disclosure may be formulated to facilitate crossing of the blood-brain barrier. For example, anti-CDH17 antigen-binding proteins (e.g., antibody such as single-domain antibody), fusion proteins, or conjugates of the present disclosure may be encapsulated into brain targeted liposomes, lipid nanoparticles, lipid microparticles, or lipid microcapsules for brain delivery. Example liposomes delivery systems are described in Pothin et al., Pharmaceutics 2020, 12(10), 937, which is incorporated herein by reference in its entirety.

[0340] In some embodiments, the active compounds are prepared with carriers that can protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in US 4,522,811, which is incorporated herein by reference in its entirety.

[0341] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure is dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0342] The pharmaceutical compositions (or components thereof) can be included in a kit, container, pack, or dispenser together with instructions for administration. These pharmaceutical compositions can be included in diagnostic kits with instructions for use.

[0343] Pharmaceutical compositions are administered in an amount effective for treatment or prophylaxis of the specific indication. The therapeutically effective amount is typically dependent on the weight of the subject being treated, the physical or health condition of the subject, the extensiveness of the condition to be treated, or the age of the subject being treated. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 50 μg/kg body weight to about 50 mg/kg body weight per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 100 μg/kg body weight to about 50 mg/kg body weight per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 100 μg/kg body weight to about 20 mg/kg body weight per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering a pharmaceutical composition of the present disclosure may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (*e.g.*, Mordenti *et al.*, 1991, *Phdomainaceut. Res. 8*:1351).

[0344] In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 10 mg to about 1,000 mg per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 20 mg to about 500 mg per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 20 mg to about 300 mg per dose. In some embodiments, the pharmaceutical composition may be administered in an amount in the range of about 20 mg to about 200 mg per dose.

[0345] In some embodiments wherein the antigen-binding proteins of the present disclosure are administered as a viral vector (e.g., an AAV), dose ranges and frequency of administration of the viral vector described herein can vary depending on the nature of the viral vector, and the medical condition, as well as parameters of a specific patient and the route of administration used. In some embodiments, viral vector compositions can be administered to a subject at a dose ranging from about 1×10^5 plaque forming units (pfu) to about 1×10^{15} pfu, depending on mode of administration, the route of administration, the nature of the disease and condition of the subject. In some cases, the viral vector

compositions can be administered at a dose ranging from about 1×10^{8} pfu to about 1×10^{15} pfu, or from about 1×10^{10} pfu to about 1×10^{15} pfu, or from about 1×10^{8} pfu to about 1×10^{12} pfu. A more accurate dose can also depend on the subject in which it is being administered. For example, a lower dose may be required if the subject is juvenile, and a higher dose may be required if the subject is an adult human subject. In certain embodiments, a more accurate dose can depend on the weight of the subject. In certain embodiments, for example, a juvenile human subject can receive from about 1×10^{8} pfu to about 1×10^{10} pfu, while an adult human subject can receive a dose from about 1×10^{10} pfu to about 1×10^{12} pfu.

[0346] Various delivery systems are known and can be used to administer the pharmaceutical composition of the disclosure, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, intraocular, epidural, intraspinal, intracerebral, intrathecal and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0347] A pharmaceutical composition of the present disclosure can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present disclosure. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0348] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target,

thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0349] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous, intramuscular, intratumoral, intraperitoneal, intraspinal, intracerebral, and intrathecal injections, drip infusions, etc. In one embodiment, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0001] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the antigen-binding proteins described herein may be about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, the antigen-binding proteins described herein may be contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

[0350] The pharmaceutical composition may be administered as needed to a subject. In some embodiments, an effective dose of the pharmaceutical composition is administered to a subject one or more times. In various embodiments, an effective dose of the pharmaceutical composition is administered to the subject once a month, less than once a month, such as, for example, every two months, every three months, or every six months. In other embodiments, an effective dose of the pharmaceutical composition is administered more than once a month, such as, for example, every two weeks, every week, twice per week, three times per week, daily, or multiple times per day. An effective dose of the pharmaceutical composition is administered to the subject at least once. In some embodiments, the effective dose of the pharmaceutical composition may be administered multiple times, including for periods of at least a month, at least six months, or at least a year. In some

embodiments, the pharmaceutical composition is administered to a subject as needed to alleviate one or more symptoms of a condition.

[0351] In some embodiments, a pharmaceutical composition of the present disclosure may be administered to a subject at levels lower than that required to achieve the desired therapeutic effect and the dosage may be gradually increased until the desired effect is achieved. Alternatively, a pharmaceutical composition of the present disclosure may be administered at a high dose and subsequently administered progressively lower doses until a therapeutic effect is achieved. In general, a suitable daily dose of an antigen-binding protein of the invention is an amount of the antibody which is the lowest dose effective to produce a therapeutic effect.

[0352] Pharmaceutical compositions of the present disclosure may optionally include more than one active agent. For example, compositions of the present disclosure may contain an anti-CDH17 antigen-binding protein conjugated to, admixed with, or administered separately from another pharmaceutically active molecule, e.g., a chemotherapeutic agent, a vascular endothelial growth factor (VEGF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, or an apoptosis-inducing agent, an immunotherapeutic agent, or a combination thereof. For instance, an anti-CDH17 antigen-binding protein may be admixed with one or more additional active agents, such as a chemotherapeutic agent, a vascular endothelial growth factor (VEGF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, or an apoptosis-inducing agent, an immunotherapeutic agent, or a combination thereof, to treat a cancer described herein. Alternatively, pharmaceutical compositions of the present disclosure may be formulated for co-administration or sequential administration with one or more additional active agents that can be used to induce cell death. Examples of additional active agents that can be used to induce cell death and that can be conjugated to, admixed with, or administered separately from an anti-CDH17 antigen-binding protein of the present disclosure include cytotoxic agents, e.g., those described herein.

Treatment Methods and Other Uses

[0353] In one aspect, provided herein is a method of using anti-CDH17 antigen-binding proteins, fusion proteins, and/or conjugates of the present disclosure to induce cell death in a cell (e.g., a cancer cell) and/or a population of cells expressing CDH17.

[0354] In various embodiments of the above methods, the methods may comprise contacting the cells and/or population of cells with an anti-CDH17 antigen-binding protein, fusion protein and/or conjugate described herein. The cells and/or population of cells may comprise cancer cells. The cancer cells may

comprise a solid tumor. The methods may be carried out *in vitro* or *in vivo*. When such methods are carried out *in vivo*, the methods can further comprise administering the anti-CDH17 antigen-binding protein, fusion protein or conjugate described herein into a subject in need thereof. In some embodiments, the subject may be a mammal (e.g., a human).

[0355] In some embodiments, anti-CDH17 antigen-binding proteins, fusion proteins or conjugates of the present disclosure may be capable of inducing cell death in between 1% and 100% cells of a population treated cells (e.g., cancer cells) (e.g., about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%), as measured, e.g., by fluorescence activated cell sorting (FACS) analysis.

[0356] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure are capable of interacting with and promoting signal transduction events mediated by CDH17. Anti-CDH17 antigen-binding proteins of the present disclosure may be able to induce conformational changes within CDH17 that lead, e.g., to receptor trimerization. This spatial configuration has been shown to render CDH17 active for apoptosis signal transduction.

[0357] In another aspect, anti-CDH17 antigen-binding proteins (e.g., antibody such as single-domain antibody), fusion proteins, conjugates, polynucleotide molecules, vectors, and/or host cells described herein, or pharmaceutical compositions thereof, are useful for the (prophylactic or therapeutic) treatment of a wide array of diseases or disorders. Accordingly, the present technology provides an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), a fusion protein, a conjugate, a polynucleotide molecule, a vector, or a host cell for use as a medicament. Also provided is a (prophylactic and/or therapeutic) method of treating a disease or disorder, wherein said method comprises administering, to a subject in need thereof, a pharmaceutically active amount of an anti-CDH17 antigen-binding protein (e.g., antibody such as single-domain antibody), a fusion protein, a conjugate, a polynucleotide molecule, a vector, or a host cell described herein.

[0358] In some embodiments, the compositions and methods described herein are used to treat and/or prevent a cancer. In some embodiments, the cancer can be a solid cancer.

[0359] Non-limiting examples of cancers which may be treated and/or prevented using the compositions and methods described herein include colorectal cancer, familial GIST, familial pancreatic cancer, gastrointestinal stromal tumor (GIST), hereditary diffuse gastric cancer, hereditary pancreatitis, neuroendocrine tumor of the gastrointestinal tract, neuroendocrine tumor of the pancreas, and peritoneal cancer, pancreatic cancer, small bowel cancer, stomach cancer.

[0360] In some embodiments, the cancer may be gastrointestinal cancer. In some embodiments, the gastrointestinal cancer is colorectal cancer, gastric cancer, esophageal cancer, or pancreatic cancer.

[0361] In some embodiments, patients receiving an anti-CDH17 treatment of the present disclosure can be monitored for their responsiveness to the treatment. For example, a physician may monitor the response of a mammalian subject (e.g., a human) to treatment with anti-CDH17 antigen-binding proteins of the present disclosure by analyzing cancer cell death within a particular patient. For example, a composition of the present disclosure may be capable of inducing cancer cell death by e.g., about 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100%.

[0362] Anti-CDH17 antigen-binding proteins described herein may be administered as a monotherapy or in combination with one or more additional therapeutic agents.

[0363] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure may also be admixed, conjugated, or administered with, or administered separately from, another therapeutic agent.

[0364] Non-limiting examples of additional therapeutic agents which can be administered in combination with the anti-CDH17 antigen-binding proteins described herein include a chemotherapeutic agent, a vascular endothelial growth factor (VEGF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an apoptosis-inducing agent, an immunotherapeutic agent, or a combination thereof.

[0365] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure can be admixed with, co-administered with, or administered separately from a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent may be administered prior to administration of the anti-CDH17 antigen-binding protein. In some embodiments, the chemotherapeutic agent may be used in a process of chemosensitization and the chemotherapeutic agent, when administered in combination with the anti-CDH17 antigen-binding protein (e.g., co-administered, or separately administered such as prior to the anti-CDH17 antigen-binding protein), can sensitize a cancer cell, or a population thereof (e.g., in a subject in need thereof such as a human), for the administration of the anti-CDH17 antigen-binding protein. In some embodiments, the sensitization of the cancer cell, or population thereof, can render the cancer cell, or population thereof, more sensitive to the anti-CDH17 antigen-binding protein. In some embodiments, the administration of the chemotherapeutic agent in combination with the anti-CDH17 antigen-binding protein does not affect the efficacy of the anti-CDH17 antigen-binding protein. In some embodiments, the administration of the chemotherapeutic agent in combination with the anti-CDH17 antigen-binding protein enhances the efficacy of the anti-CDH17 antigen-binding protein.

[0366] Examples of chemotherapeutic agents include bleomycin, carboplatin, chlorambucil, cisplatin, colchicine, cyclophosphamide, daunorubicin, doxorubicin or liposomal doxorubicin, mitomycin C, actinomycin, diethylstilbestrol, daunorubicin, etoposide, 5-fluorouracil, floxuridine, melphalan, methotrexate, mitomycin, 6-mercaptopurine, teniposide, 6-thioguanine, vincristine and vinblastine, leflunomide, actinomycin, tamoxifen, interferon α-2b, glutamic acid, plicamycin, 6-mercaptopurine, 6-thioguanine, carmustine, BCNU, limousine, CCNU, cytosine arabinoside, estramustine, hydroxyurea, procarbazine, busulfan, medroxyprogesterone, estramustine phosphate sodium, ethenyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, testolactone, melphalan, chlorambucil, mechlorethamine, thiourea, betamethasone sodium phosphate, dicarbazine, asparagine, mitotane, vincristine sulfate, vinblastine sulfate, FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) or FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan), and a combination thereof.

[0367] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure can be admixed with, co-administered with, or administered separately from a VEGF inhibitor. In some embodiments, the VEGF inhibitor can be, e.g., bevacizumab, ramucirumab, regorafenib, ziv-aflibercept.

[0368] some embodiments, anti-CDH17 antigen-binding protein of the present disclosure can be admixed with, co-administered with, or administered separately from an EGFR inhibitor. Non-limiting examples of EGFR inhibitors are cetuximab and/or panitumumab.

[0369] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure can be admixed with, co-administered with, or administered separately from an apoptosis-inducing agent such as, but not limited to, a B-cell lymphoma 2 (BCL2) inhibitor, a BCL-extra large (BCL-XL) inhibitor, or an inhibitor of apoptosis proteins (IAP) inhibitor, or a combination thereof. In some embodiments, pharmaceutical compositions of the invention may be formulated for co-administration or sequential administration with one or more additional active agents that can be used to induce cell death or inhibit proliferation of a cell. Examples of additional active agents that can be used to inhibit cell proliferation and that can be conjugated to, admixed with, or administered separately from an anti-CDH17 antigen-binding protein of the present disclosure include cytotoxic agents, e.g., those described herein.

[0370] Exemplary cytotoxic agents that can be conjugated to, admixed with, or administered separately from anti-CDH17 antigen-binding protein of the present disclosure include, but not limited to, 13-cis retinoic acid, 14-hydroxy-retro-retinol, 2-chloro-2'-deoxyadenosine, 2-Chloro-2'-arabino-fluoro-2'-deoxyadenosine, 2-chlorodeoxyadenosine, 2-chlorodeoxyadenosine (2-Cda), 2'-deoxycoformycin, 3-methyl TTNEB, 6-mercaptopurine, 6-thioguanine, 9-aminocamptothecin, 9-cis retinoic acid, aclarubicin,

acodazole hydrochloride, acronine, adozelesin, adozelesin, adriamycin, aldesleukin, all-trans retinoic acid, all-trans retinol, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, amsacrine, anastrozole, anisomycin, anthramycin, acivicin, asparaginase, asperlin, azacitidine, azacitidine, azetepa, azotomycin, AZQ, batimastat, benzodepa, bicalutamide, Bis (platinum), bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, busulfan, cactinomycin, calusterone, camptothecin, caracemide, carbetimer, carboplatin, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, CEP-751, chlorambucil, chlorambucil, cirolemycin, cisplatin, cisplatin, cladribine, combretestatin a-4, C1-973, CPT-11, crisnatol mesylate, cyclophosphamide, cyclophosphamide, cytarabine, cytarabine, daca (n-[2-(dimethyl-amino) ethyl] acridine-4-carboxamide), dacarbazine, dactinomycin, Dactinomycin (Actinomycin D), darubicin, daunomycin, Daunomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diacarbazine (DTIC), diaziquone, docetaxel, dolasatins, doxorubicin, Doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, DWA 2114R, edatrexate, eflornithine hydrochloride, ellipticine, elsamitrucin, enloplatin, enpromate, epipropidine, Epirubicin, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, ethiodized oil i 131, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine (2-F-ara-AMP), fludarabine phosphate, fluorodeoxyuridylate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine, gemcitabine hydrochloride, gold ^{198}AU , homocamptothecin, hPRL-G129R, hydroxyurea, hypoxanthine, idarubicin hydrochloride, ifosfamide, ifosfamide, ilmofosine, interferon ɣ-1b, interferon α-2b, interferon α-n1, interferon α-n3, interferon α-2a, interferon β-1a, iproplatin, irinotecan hydrochloride, JM216, JM335, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, linomide, lometrexol sodium, lomustine, losoxantrone, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedepa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitomycin C, mitosper, mitotane, mitoxantrone, mitoxantrone hydrochloride, mitozolomide, mycophenolic acid, N-(2-chloroethyl)-N′ cyclohexyl-N-nitrosourea (CCNU), N-(2-chloroethyl)-N′-(diethyl) ethylphosphonate-N-nitrosourea (fotemustine), N-(2-chloroethyl)-N′-(trans-4-methylcyclohexyl-N-nitrosourea (MeCCNU), N-(4-hydroxyphenyl) retinamide, N,N′-Bis (2-chloroethyl)-N-nitrosourea (BCNU), nitrogen mustard (mechlor ethamine), N-methyl-Nnitrosourea (MNU), nocodazole, nogalamycin;ormaplatin, N-propargyl-5,8-dideazafolic acid, ormaplatin, oxaliplatin, oxisuran, paclitaxel, pegaspargase, peliomycin,

pentamustine, peploycinsulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, pyrazoloacridine, raltitrexed, rhizoxin, rhizoxin d, riboprine, rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, streptozotocin, strontium chloride Sr 89, sulfur mustard, sulofenur, talisomycin, taxane, taxoid, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, temozolomide, teniposide, teniposide 9-amino camptothecin, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, thiotepa, thymitaq, tiazofurin, tirapazamine, tomudex, tomudex, TOP-53, topotecan, topotecan hydrochloride, toremifene citrate, trestolone acetate, trichostatin A, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine, vinblastine sulfate, vincristine, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, or zorubicin hydrochloride.

[0371] Other therapeutic agents that can be conjugated to, admixed with, or administered separately from anti-CDH17 antigen-binding protein of the present disclosure include, but are not limited to, 2' deoxycoformycin (DCF), 1,25 dihydroxyvitamin D3, 5-ethynyluracil, 9-dioxamycin, abiraterone, acylfulvene, adecypenol, ALL-TK antagonists, ambamustine, amidox, amifostine, aminolevulinic acid, amrubicin, anagrelide, andrographolide, angiogenesis inhibitors, antagonist D, antagonist G, antarelix, antiandrogen, prostatic carcinoma, anti-dorsalizing morphogenetic protein-1, antiestrogen, antineoplaston, antisense oligonucleotides, aphidicolin glycinate, apoptosis gene modulators, apoptosis regulators, apurinic acid, ara-CDP-DL-PTBA, argininedeaminase, asulacrine, atamestane, atrimustine, axinastatin 1, axinastatin 2, axinastatin 3, azasetron, azatoxin, azatyrosine, baccatin III derivatives, balanol, BCR/ABL antagonists, benzochlorins, benzoylstaurosporine, beta lactam derivatives, beta-alethine, betaclamycin B, betulinic acid, bFGF inhibitor, bisantrene, bisaziridinylspermine, bisnafide, bistratene A, bleomycin A2, bleomycin B2, breflate, budotitane, buthionine sulfoximine, calcipotriol, calphostin C, camptothecin derivatives (e.g., 10-hydroxy-camptothecin), canarypox IL-2, capecitabine, carboxamide-amino-triazole, carboxyamidotriazole, CaRest M3, CARN 700, cartilage derived inhibitor, casein kinase inhibitors (ICOS), castanospermine, cecropin B, cetrorelix, chlorins, chloroquinoxaline sulfonamide, cicaprost, cis-porphyrin, clomifene analogues, clotrimazole, collismycin A , collismycin B, combretastatin A4, combretastatin analogue, conagenin, crambescidin 816, crisnatol, cryptophycin 8, cryptophycin A derivatives, curacin A, cyclopentanthraquinones, cycloplatam, cypemycin, cytarabine

ocfosfate, cytolytic factor, cytostatin, dacliximab, dehydrodidemnin B, deslorelin, dexifosfamide, dexrazoxane, dexverapamil, didemnin B, didox, diethylnorspermine, dihydro-5-azacytidine, dihydrotaxol, , diphenyl spiromustine, discodermolide, docosanol, dolasetron, doxifluridine, dronabinol, duocarmycin SA, ebselen, ecomustine, edelfosine, edrecolomab, eflornithine, elemene, emitefur, epithilones, epothilones (A, R=H; B, R=Me), epristeride, erythrocyte gene therapy, estramustine analogue, estrogen agonists, estrogen antagonists, etoposide 4′-phosphate (etopofos), exemestane, fadrozole, filgrastim, finasteride, flavopiridol, flezelastine, fluasterone, fludarabine, fluorodaunorunicin hydrochloride, forfenimex, formestane, fostriecin, fotemustine, gadolinium texaphyrin, gallium nitrate, galocitabine, ganirelix, gelatinase inhibitors, glutathione inhibitors, hepsulfam, heregulin, hexamethylene bisacetamide, homoharringtonine (HHT), hypericin, ibandronic acid, idarubicin, idoxifene, idramantone, ifepristone, ilomastat, imidazoacridones, imiquimod, immunostimulant peptides, insulin-like growth factor-1 receptor inhibitor, interferon agonists, interferons, interleukins, iobenguane, iododoxorubicin, ipomeanol, irinotecan, iroplact, irsogladine, isobengazole, isohomohalicondrin B, itasetron, jasplakinolide, kahalalide F, lamellarin-N triacetate, lanreotide, leinamycin, lenograstim, lentinan sulfate, leptolstatin, leukemia inhibiting factor, leukocyte alpha interferon, leuprolide+estrogen+progesterone, leuprorelin, levamisole, liarozole, linear polyamine analogue, lipophilic disaccharide peptide, lipophilic platinum compounds, lissoclinamide 7, lobaplatin, lombricine, lometrexol, lonidamine, lovastatin, loxoribine, lurtotecan, lutetium texaphyrin, lysofylline, lytic peptides, mannostatin A, marimastat, maspin, matrilysin inhibitors, matrix metalloproteinase inhibitors, meterelin, methioninase, metoclopramide, MIF inhibitor, miltefosine, mirimostim, mismatched double stranded RNA, mithracin, mitoguazone, mitolactol, mitomycin analogues, mitonafide, mitotoxin fibroblast growth factor-saporin, mofarotene, molgramostim, monoclonal antibody, human chorionic gonadotrophin, monophosphoryl lipid A+myobacterium cell wall sk, mopidamol, multiple drug resistance gene inhibitor, multiple tumor suppressor 1-based therapy, mustard anticancer agent, mycaperoxide B, mycobacterial cell wall extract, myriaporone, N-acetyldinaline, nafarelin, nagrestip, naloxone+pentazocine, napavin, naphterpin, nartograstim, nedaplatin, nemorubicin, neridronic acid, neutral endopeptidase, nilutamide, nisamycin, nitric oxide modulators, nitroxide antioxidant, nitrullyn, N-substituted benzamides, O6-benzylguanine, octreotide, okicenone, oligonucleotides, onapristone, ondansetron, oracin, oral cytokine inducer, osaterone, oxaliplatin, oxaunomycin, paclitaxel analogues, paclitaxel derivatives, palauamine, palmitoylrhizoxin, pamidronic acid, panaxytriol, panomifene, parabactin, pazelliptine, peldesine, pentosan polysulfate sodium, pentostatin, pentrozole, perflubron, perillyl alcohol, phenazinomycin, phenylacetate,

phosphatase inhibitors, picibanil, pilocarpine hydrochloride, pirarubicin, piritrexim, placetin A, placetin B, plasminogen activator inhibitor, platinum complex, platinum compounds, platinum-triamine complex, podophyllotoxin, propyl bis-acridone, prostaglandin J2, proteasome inhibitors, protein A-based immune modulator, protein kinase C inhibitor, protein kinase C inhibitors, microalgal, protein tyrosine phosphatase inhibitors, purine nucleoside phosphorylase inhibitors, purpurins, pyridoxylated hemoglobin polyoxyethylene conjugate, raf antagonists, ramosetron, ras farnesyl protein transferase inhibitors, ras inhibitors, ras-GAP inhibitor, retelliptine demethylated, rhenium Re 186 etidronate, ribozymes, RII retinamide, rnerbarone, rohitukine, romurtide, roquinimex, rubiginone B 1, ruboxyl, saintopin, SarCNU, sarcophytol A, sargramostim, Sdi 1 mimetics, senescence derived inhibitor 1, sense oligonucleotides, signal transduction inhibitors, signal transduction modulators, single chain antigen-binding protein, sizofiran, sobuzoxane, sodium borocaptate, sodium phenylacetate, solverol, somatomedin binding protein, sonermin, sparfosic acid, spicamycin D, splenopentin, spongistatin 1, squalamine, stem cell inhibitor, stem-cell division inhibitors, stipiamide, stromelysin inhibitors, sulfinosine, superactive vasoactive intestinal peptide antagonist, suradista, suramin, swainsonine, synthetic glycosaminoglycans, tallimustine, tamoxifen methiodide, tauromustine, tazarotene, tellurapyrylium, telomerase inhibitors, tetrachlorodecaoxide, tetrazomine, thaliblastine, thalidomide, thiocoraline, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, thyroid stimulating hormone, tin ethyl etiopurpurin, titanocene dichloride, topsentin, toremifene, totipotent stem cell factor, translation inhibitors, tretinoin, triacetyluridine, triciribine, tropisetron, turosteride, tyrosine kinase inhibitors, tyrphostins, UBC inhibitors, ubenimex, urogenital sinus-derived growth inhibitory factor, urokinase receptor antagonists, variolin B, velaresol, veramine, verdins, vinorelbine, vinxaltine, vitaxin, zanoterone, zilascorb, or zinostatin stimalamer.

[0372] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure may be admixed, conjugated, or administered with, or administered separately from, an anti-inflammatory agent. Exemplary anti-inflammatory agents useful in conjunction with the compositions and methods of the invention include steroids, colchicine, hydroxychloroquine, sulfasalazine, dapsone, methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, sirolimus, everolimus, azathioprine, leflunomide, mycophenolate, inhibitors of IL-1/IL-2/IL-4/IL5/IL-6/IL-13/IL-17/IL-23/TNF/complement/BAFF/interferon/JAK/CD28/IgE/Integrins/T cell costimulation pathway or B-cell depleting agents.

[0373] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure may be admixed, conjugated, or administered with, or administered separately from, an immunotherapy agent.

Exemplary immunotherapy agents useful in conjunction with the compositions and methods of the invention include an anti-CTLA-4 agent, an anti-PD-1 agent, an anti-PD-L1 agent, an anti-PD-L2 agent, a TNFα cross-linking agent, a TRAIL cross-linking agent, an anti-CD27 agent, an anti-CD30 agent, an anti-CD40 agent, an anti-4-1BB agent, an anti-GITR agent, an anti-OX40 agent, an anti-TRAILR1 agent, an anti-CDH17 agent, an anti-TWEAKR agent, an anti-TL1A agent, an anti-LIGHT agent, an anti-BTLA agent, an anti-LAG3 agent, an anti-TIM3 agent, an anti-Siglecs agent, an anti-ICOS ligand agent, an anti-B7-H3 antibody; an anti-B7-H4 agent; an anti-VISTA agent; an anti-TMIGD2 agent; an anti-BTNL2 agent; an anti-CD48 agent; an anti-KIR agent; an anti-LIR agent; an anti-ILT agent; an anti-NKG2D agent; an anti-NKG2A agent; an anti-MICA agent; an anti-MICB agent; an anti-CD244 agent; an anti-CSF1 R agent; an anti-IDO agent; an anti-TGFβ agent; an anti-CD39 agent; an anti-CD73 agent; an anti-CXCR4 agent; an anti-CXCL12 agent; an anti-SIRPA agent; an anti-CD47 agent; an anti-VEGF agent; and an anti-neuropilin agent and, e.g., agents directed toward the immunological targets described in Table 1 of Mahoney et al., Cancer Immunotherapy, 14:561-584 (2015), the disclosure of which is incorporated herein by reference. The immunotherapy agent described herein may be, for example, an antibody, a small molecule, or a chimeric antigen receptor.

[0374] In some embodiments, anti-CDH17 antigen-binding proteins of the present disclosure may be admixed, conjugated, or administered with, or administered separately from, for example, Alymsys (Bevacizumab), Avastin (Bevacizumab), Bevacizumab, Camptosar (Irinotecan Hydrochloride), Capecitabine, Cetuximab, Cyramza (Ramucirumab), Eloxatin (Oxaliplatin), Erbitux (Cetuximab), 5-FU (Fluorouracil Injection), Fluorouracil Injection, Ipilimumab, Irinotecan Hydrochloride, Keytruda (Pembrolizumab), Leucovorin Calcium, Lonsurf (Trifluridine and Tipiracil Hydrochloride), Mvasi (Bevacizumab), Nivolumab, Opdivo (Nivolumab), Oxaliplatin, Panitumumab, Pembrolizumab, Ramucirumab, Regorafenib, Stivarga (Regorafenib), Trifluridine and Tipiracil Hydrochloride, Tucatinib, Tukysa (Tucatinib), Vectibix (Panitumumab), Xeloda (Capecitabine), Yervoy (Ipilimumab), Zaltrap (Ziv-Aflibercept), Zirabev (Bevacizumab), Ziv-Aflibercept, or any combination thereof.

EXAMPLES

[0375] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Example 1. Camelid immunization

[0376] Three juvenile alpacas (*Vicugna pacos*) were immunized by six subcutaneous injections with recombinant human CDH17 using two different adjuvants (complete/incomplete Freund's adjuvant

(CFA/IFA); or Gerbu FAMA) using standard protocols to elicit a humoral immune response that includes the generation of antigen-specific conventional and heavy-chain only antibodies. The immune response was determined by ELISA using sera from day 0 (before immunization), day 28 and day 43.

[0377] In brief, MaxiSorp plates were coated overnight at 4 ˚C with 50 µl of antigen at 2 µg/ml in PBS. The next day, the antigen was removed, plates were washed with PBS and then blocked with 4% milk powder in PBS (MPBS). Next, the wells were incubated with serially diluted sera for 1 hour at room temperature. Bound antibodies in the sera were detected with rabbit-anti-VHH, followed by donkey-anti-rabbit^{HRP}. In between incubations, plates were washed with PBS with 0.05% Tween-20 (PBST) or PBS. Bound HRP-coupled antibodies were detected using o-phenylenediamine dihydrochloride (OPD) with H_2O_2 as substrate and converted substrate was measured at 490nm wavelength.

Example 2. Phage library construction

[0378] Four to ten days after the fourth injection blood samples were collected, and four to six days after the fourth injection a bone marrow sample was aspirated. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood or bone marrow following density gradient purification with Ficoll-PaqueTM Plus. Total RNA was extracted from freshly isolated PBMCs.

[0379] To generate VHH immune libraries, total RNA was reversely transcribed to cDNA using random hexamer primers. Conventional and heavy chain IGH cDNA fragments were amplified by PCR using primers annealing to the IGH leader sequence region and the CH2 region. The resulting amplicons represent the VHH and VH cDNAs, respectively. The VHH fragment was isolated and used as template for a nested PCR to introduce appropriate endonuclease recognition sites for cloning into the pQ81 phagemid in frame with geneIII. Libraries were transformed into electrocompetent E. coli TG1 cells. In total, six libraries were built with 95.5% to 100% VHH insert frequency and maximum library sizes between 4.2x10^8 and 2.4x10^9. Phage for phage display was prepared following standard protocols.

[0380] Binders to human CDH17 were enriched from VHH immune libraries by two rounds of phage display. The general panning strategy is illustrated in **Figure 1** using the panning substrate listed in **Table 4**.

Table 4. Panning substrates

Species	Protein	Modification	Buffer	Cat. #	Lot #	Vendor	MW	N-term. Seq., aa Seq.	Source
Human	CDH17	His-tag	50mM Tris, 100m	11360-H08H	MB15MA1202	Sino	calc. ~87kDa, apparen	Gln23-Met787	HEK293

			M NaCl, 3mM CaCl2, pH 8.0				t 110-115000		

[0381] For the 1st panning round, libraries originating from the 1st harvested blood sample and the 1st harvested bone marrow sample of the same animal had been pooled in equal parts (at the phage level), resulting in 3 pooled input libraries per antigen. Each library had been panned under 4 conditions (2 antigen concentrations and 2 ways of antigen immobilization) resulting in 12 panning reactions. For the 2nd rounds of panning, 6 output samples (enriched libraries) from the first round were chosen and serve as input libraries for the 2nd round. Preferentially, the enriched libraries from the higher panning substrate concentration were chosen to preserve maximum diversity. Pannings of the 2nd round were done with two CDH17 antigen concentrations to result in 12 conditions.

[0382] Phages were produced according to QVQ's standard operating procedures and phage titers were determined to ensure at least 10-fold excess over the maximum diversity of the libraries. Panning substrates were commercially purchased. The panning substrates were immobilized either by direct coating on ELISA plates or by binding of biotinylated antigen on neutravidin-coated ELISA plate. Glycerol stocks were prepared from all outputs and are stored at -80°C.

[0383] Panning outputs were analyzed by random clone picking/PE-ELISA/Sanger sequencing (QVQ) and NGS (Genewiz/PipeBio).

[0384] For random colony picking, rescued outputs of the 1st and 2nd panning rounds were plated out and 460 random single anti-CDH17 clones (equal numbers of colonies from each condition) are picked to create masterplates (96-well format). From the masterplates, expression cultures in deep-well plates were inoculated to produce periplasmic extracts containing monoclonal VHH. Periplasmic extracts were used to determine binding of individual VHHs to human and cynomolgus antigen by ELISA. For conditions where the panning substrate was biotinylated and captured by Neutravidin, background binders were identified by ELISA with Neutravidin. All masterplates had been sequenced by the Sanger method.

[0385] For NGS analysis, minipreps from input libraries and outputs after the 1st and 2nd rounds of panning were prepared, amplified by PCR and sequenced by NGS.

Example 3. Next-generation sequencing

[0386] Following two rounds of panning with the previously mentioned conditions, phages were eluted and corresponding phagemid DNA is extracted. Identification of initial V-body candidates was performed in a parallelized fashion, employing a random colony picking as well as a next generation sequencing (NGS) approach as orthogonal techniques to yield a particularly diverse set of initial candidates. Prior to next generation sequencing techniques, random colony picking was the prevalent method for initial hit identification, which involves transformation of a phagemid pool (from a panning elution) and picking of individual bacterial colonies to isolate single clones. Following this approach, 920 and 460 single colonies were randomly picked from the 18 samples of panning round 2 for CDH17 (**Figure 2**). Then, individual clones were expressed and subject to ELISA screening against the target antigen to select for antigen binding V-bodies, which were further functionally characterized. To mitigate the risk of losing rare binders all panning elutions were also sequenced using next generation sequencing.

[0387] In brief, the entire VHH region first needs to be PCR-amplified from isolated phagemid pools by primers annealing to universal phagemid sequences 5' and 3' of the VHH-encoding region. In a second step, the generated amplicons are fused to sequencing-compatible and sample-specific barcodes. By fusing unique barcodes, it is possible to multiplex hundreds of different samples. An Illumina NovaSeq 6000 with an SP flowcell was employed for sequencing, yielding 250 bp reads from each direction and a total of ~600 million reads. To account for differences in the number of expected unique sequences in the library, and both panning rounds, each library was sequenced with a total of 20 million reads, compared to the first and second round of panning with 2 million reads each. This strategy allows for covering sufficient sequence space in the libraries as well as in the panning elutions, which are expected to have drastically fewer unique sequences compared to the initial libraries. Moreover, spike-in of 30% of a standard PhiX reference genome control into the sequencing reaction helped to provide a technical quality control for assessing sequencing accuracy. The NGS raw data contains multiplexed sequencing reads, which are de-multiplexed based on the sample-specific barcodes. The de-multiplexed data, containing unmerged sequencing reads are then processed by the following strategy, employing an NGS analysis platform of an external service provider. A schematic domain representation and structure prediction of CDH17 is provided in **Figure 4**.

[0388] Based on CDR3 identity, V-body sequences were clustered, allowing for a detailed analysis of V-body enrichment during phage display, sequence diversity, CDR3 length distribution and cluster abundance. 284 V-bodies were identified which can be classified into fifteen distinct clusters, as follows: N1061 (group A), N1070 (group B), N1081 (group C), 45F5-N1083-N1084 (group D), N1090 (group E),

N1091-N1092 (group F), N1095 (group G), 43B5 (group H), 43E7-44A4 (group I), N1242 (group J), and 44A1 (group K), N1117 (group M), N1129 (group N), N1186 (group O), and N1264 (group P). The following **Table 5-1** to **Table 5-33** display the amino acid frequency distribution at each amino acid (AA) position (IMGT) for CDR1, CDR2 and CDR3 for the fifteen clusters. **Table 6** provides the sequence identifiers of amino acid sequences of the complementarity determining regions (CDR1, CDR2 and CDR3), amino acid and DNA sequences of the full-length VHH domain for the identified V-bodies.

Table 5-1 CDR1 amino acid frequency distribution for cluster N1061 (Group A)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	100	0	0	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	100	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	100	0	100
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	0	0	0	90	0	0	0
T	0	0	100	0	10	0	30	0
V	0	0	0	0	0	0	10	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	60	0

Table 5-2 CDR2 amino acid frequency distribution for cluster N1061 (Group A)

	Position						
AA	56	57	58	59	63	64	65
A	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	20	0	0	0	0	0	0
G	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0
I	80	0	0	0	0	0	0
K	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0
R	0	0	100	0	0	100	0
S	0	100	0	0	0	0	0
T	0	0	0	0	0	0	100
V	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0

Table 5-3 CDR3 amino acid frequency distribution for cluster N1061 (Group A)

	Position																			
AA	105	106	107	108	109	110	111	111.1	111.2	111.3	112.4	112.3	112.2	112.1	112	113	114	115	116	117
A	100	40	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
C	0	0	100	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	100	0	0	0	100	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	60	0	100	100	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	40	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	60	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0
R	0	0	0	0	0	100	0	0	0	0	0	0	0	0	100	0	0	0	0	0
S	0	0	0	0	0	0	0	0	40	0	0	0	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	60	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	100	0	100

Table 5-4 CDR1 amino acid frequency distribution for cluster N1070 (Group B)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	0	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	100	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	100	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	100	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	100	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	100	100	0

Table 5-5 CDR2 amino acid frequency distribution for cluster N1070 (Group B)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	0	0	0	6.667	0
C	0	0	0	0	0	0	20	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	0	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	100	0	0
S	0	100	0	100	0	0	60	0
T	0	0	100	0	0	0	13.33	100
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-6 CDR3 amino acid frequency distribution for cluster N1070 (Group B)

	Position																			
AA	105	106	107	108	109	110	111	111.1	111.2	111.3	112.4	112.3	112.2	112.1	112	113	114	115	116	117
A	100	100	0	0	26.67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	6.667	13.33	6.667	6.667	0	6.667	6.667	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	20	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	26.67
G	0	0	0	0	0	93.33	0	0	0	0	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	80	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0
R	0	0	0	93.33	0	0	0	0	0	0	0	0	0	20	0	93.33	0	0	0	0
S	0	0	0	0	60	0	93.33	0	0	0	0	0	0	0	0	6.667	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	100	100	0	80	0	0	0	0	0	0
V	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	93.33	93.33	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	73.33

Table 5-7 CDR1 amino acid frequency distribution for cluster N1081 (Group C)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	20	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	60	0	0	0	0
G	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	100	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	40	0	20	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	100	0	0	0	0	60	0	0
S	0	0	0	40	80	40	40	0
T	0	0	40	0	0	0	60	100
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-8 CDR2 amino acid frequency distribution for cluster N1081 (Group C)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	80	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	100	0	0	0	80	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	100	0	100	0
S	100	0	0	20	0	0	0	0
T	0	0	0	0	0	20	0	100
V	0	0	0	0	0	0	0	0
W	0	0	100	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-9 CDR3 amino acid frequency distribution for cluster N1081 (Group C)

	Position																		
AA	105	106	107	108	109	110	111	111.1	111.2	111.3	112.3	112.2	112.1	112	113	114	115	116	117
A	100	100	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	100	0	0	0	0	0	0	0	0	100	0	0	0	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	0	0	0
F	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	100	100	0	0	0	0	0	0	60	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	60	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	0	100	0	0	0	100	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	100	0	0	100	40	0	0	0	0	0	0	0	0	0	0	0	0
S	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	100

Table 5-10 CDR1 amino acid frequency distribution for cluster 45F5-N1083-N1084 (Group D)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	55.17	0	0
F	0	0	0	98.28	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	100
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	1.724	0	0
P	0	0	0	0	0	0	100	0
Q	0	0	0	0	0	0	0	0
R	0	100	0	0	0	0	0	0
S	0	0	0	0	100	5.172	0	0
T	0	0	100	0	0	37.93	0	0
V	0	0	0	1.724	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-11 CDR2 amino acid frequency distribution for cluster 45F5-N1083-N1084 (Group D)

	Position							
AA	**56**	**57**	**58**	**59**	**62**	**63**	**64**	**65**
A	0	0	0	1.724	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0	0
I	0	100	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	100	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	1.724	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	0	100	8.621	0	0	98.28	0
T	0	0	0	89.66	0	0	0	100
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-12 CDR3 amino acid frequency distribution for cluster 45F5-N1083-N1084 (Group D)

	Position																		
AA	105	106	107	108	109	110	111	111.1	111.2	111.3	112.3	112.2	112.1	112	113	114	115	116	117
A	89.66	96.55	1.724	1.724	0	0	0	0	0	91.38	0	0	0	0	70.69	0	0	1.724	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	70.69	0	6.897	0	0	3.448	1.724	100	0	0	0	1.724	1.724	94.83	1.724
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	96.55	0	0	0
F	0	0	0	0	0	0	3.448	0	0	0	0	0	0	0	0	0	3.448	0	5.172
G	0	0	0	98.28	0	0	0	1.724	100	0	0	0	0	0	0	1.724	0	1.724	0
H	0	0	0	0	0	0	1.724	0	0	0	0	0	0	1.724	0	0	3.448	0	1.724
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	3.448	0	0	0	0	0	0	0	1.724	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	29.31	0	0	0	0	0	0	0	0	0	0	0	0	1.724	0
P	0	0	6.897	0	0	0	0	0	0	0	0	0	0	94.83	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	96.55	0	0	0	0	100	0	0	0	0	0	0
S	0	1.724	0	0	0	94.83	0	1.724	0	1.724	1.724	0	0	1.724	0	0	0	0	3.448
T	5.172	1.724	91.38	0	0	1.724	0	0	0	0	0	0	0	0	29.31	0	0	0	0
V	5.172	0	0	0	0	0	0	0	0	3.448	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	87.93	0	0	0	96.55	0	0	0	0	0	91.38	0	87.93

Table 5-13 CDR1 amino acid frequency distribution for cluster N1090 (Group E)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	100
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	100	0
Q	0	0	0	0	0	0	0	0
R	0	100	0	0	0	0	0	0
S	0	0	0	0	100	100	0	0
T	0	0	100	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-14 CDR2 amino acid frequency distribution for cluster N1090 (Group E)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0	0
I	0	100	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	100	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	0	100	0	0	0	100	0
T	0	0	0	100	0	0	0	100
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-15 CDR3 amino acid frequency distribution for cluster N1090 (Group E)

	Position																		
AA	105	106	107	108	109	110	111	111.1	111.2	111.3	112.3	112.2	112.1	112	113	114	115	116	117
A	0	100	0	0	0	0	0	0	0	100	0	0	0	0	100	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0
F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100
G	0	0	0	100	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	100	0	0	0	0	100	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T	0	0	100	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
V	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0	0	0	100	0	0	0	0	0	100	0	0

Table 5-16 CDR1 amino acid frequency distribution for cluster N1091-N1092 (Group F)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	0	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	33.33	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0
G	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	100	0	0
N	0	0	0	0	55.56	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	100	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0
T	100	0	100	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	11.11	0	100	0

Table 5-17 CDR2 amino acid frequency distribution for cluster N1091-N1092 (Group F)

	Position							
AA	**56**	**57**	**58**	**59**	**62**	**63**	**64**	**65**
A	0	0	0	0	0	33.33	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	0	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	33.33	0	0	0	0	100	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	100	0	0	0	0	0
S	0	66.67	0	100	0	0	0	0
T	0	0	0	0	0	66.67	0	100
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-18 CDR3 amino acid frequency distribution for cluster N1091-N1092 (Group F)

	Position																	
AA	105	106	107	108	109	110	111	111.1	111.2	112.3	112.2	112.1	112	113	114	115	116	117
A	100	100	0	0	0	0	0	0	0	100	0	0	0	0	0	0	33.33	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33.33
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	100	0	0	0	0	0	0	100	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	100	0	0	0	0	100	0	0	0	0	0	0
Q	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0	0	0	0	0	0	100	100	0	0	0
S	0	0	0	0	100	0	0	0	0	0	66.67	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	33.33	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	66.67	66.67

Table 5-19 CDR1 amino acid frequency distribution for cluster N1095 (Group G)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	75	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	75	25
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	100	0	0	0	0	0	0
S	0	0	0	0	25	100	0	0
T	0	0	100	0	0	0	0	0
V	0	0	0	0	0	0	0	75
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	25	0

Table 5-20 CDR2 amino acid frequency distribution for cluster N1095 (Group G)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	25	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	75	0	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	100	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	100	0	0
S	0	100	0	0	0	0	100	0
T	0	0	0	0	0	0	0	100
V	0	0	0	0	0	0	0	0
W	0	0	100	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-21 CDR3 amino acid frequency distribution for cluster N1095 (Group G)

	Position																	
AA	105	106	107	108	109	110	111	111.1	111.2	112.3	112.2	112.1	112	113	114	115	116	117
A	100	100	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0
F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	100	0	0	100	100	0	0	0	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
T	0	0	100	0	0	100	0	0	0	100	0	0	0	100	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	100	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100

Table 5-22 CDR1 amino acid frequency distribution for cluster 43B5 (Group H)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	100	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	100	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	100	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	100
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	100	0	0	0	0	0	0
S	0	0	0	0	100	0	0	0
T	0	0	100	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-23 CDR2 amino acid frequency distribution for cluster 43B5 (Group H)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	100	0
F	0	0	0	100	0	0	0	0
G	0	0	0	0	0	100	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	100	0	0	0
S	0	100	0	0	0	0	0	0
T	0	0	0	0	0	0	0	100
V	0	0	0	0	0	0	0	0
W	0	0	100	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-24 CDR3 amino acid frequency distribution for cluster 43B5 (Group H)

	Position													
AA	105	106	107	108	109	110	111	112.1	112	113	114	115	116	117
A	100	100	0	0	0	0	0	0	0	0	0	0	100	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	100	0	0	100	0	0	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	100	100	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	100	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	100	0	0	0	0	0	100	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	100	0	0	0	0	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0	0	0	0	100	0	100

Table 5-25 CDR1 amino acid frequency distribution for cluster 43E7-44A4 (Group I)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	14.13	0	97.83
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	10.87	0	0	0
F	0	0	1.087	95.65	0	1.087	0	0
G	100	0	0	0	1.087	0	0	0
H	0	0	0	0	0	1.087	0	0
I	0	88.04	9.783	3.261	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	1.087	0	1.087	0	0	0	0
M	0	10.87	1.087	0	0	0	0	0
N	0	0	9.783	0	0	5.435	0	0
P	0	0	0	0	0	5.435	0	0
Q	0	0	0	0	0	3.261	0	0
R	0	0	77.17	0	4.348	9.783	0	0
S	0	0	0	0	83.7	59.78	0	2.174
T	0	0	0	0	0	0	0	0
V	0	0	1.087	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0

Table 5-26 CDR2 amino acid frequency distribution for cluster 43E7-44A4 (Group I)

	Position						
AA	**56**	**57**	**58**	**59**	**63**	**64**	**65**
A	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0
D	1.087	0	0	7.609	6.522	1.087	0
E	0	0	0	0	0	0	0
F	0	11.96	0	0	0	0	0
G	0	1.087	0	75	51.09	2.174	0
H	4.348	0	0	0	0	0	0
I	82.61	0	16.3	1.087	0	1.087	0
K	0	0	14.13	0	0	4.348	0
L	0	1.087	5.435	0	0	2.174	0
M	7.609	0	0	0	0	0	0
N	4.348	1.087	20.65	3.261	4.348	6.522	0
P	0	0	0	1.087	0	0	0
Q	0	0	0	0	0	0	8.696
R	0	0	0	6.522	0	29.35	1.087
S	0	0	43.48	3.261	0	21.74	0
T	0	79.35	0	2.174	0	10.87	90.22
V	0	0	0	0	0	11.96	0
W	0	0	0	0	0	8.696	0
Y	0	5.435	0	0	38.04	0	0

Table 5-27 CDR3 amino acid frequency distribution for cluster 43E7-44A4 (Group I)

	Position								
AA	**105**	**106**	**107**	**108**	**109**	**114**	**115**	**116**	**117**
A	0	98.91	0	0	8.696	7.609	0	2.174	0
C	0	0	0	0	0	0	0	0	0
D	0	0	0	0	1.087	0	0	0	1.087
E	0	0	0	0	3.261	0	0	0	0
F	0	0	0	0	0	0	2.174	0	1.087
G	0	1.087	100	100	42.39	0	0	97.83	0
H	2.174	0	0	0	4.348	0	0	0	1.087
I	0	0	0	0	0	0	2.174	0	0
K	7.609	0	0	0	0	0	1.087	0	0
L	0	0	0	0	1.087	11.96	71.74	0	0
M	0	0	0	0	4.348	0	0	0	0
N	81.52	0	0	0	1.087	1.087	1.087	0	0
P	0	0	0	0	17.39	2.174	0	0	0
Q	0	0	0	0	0	0	0	0	0
R	0	0	0	0	14.13	70.65	20.65	0	0
S	0	0	0	0	2.174	1.087	0	0	0
T	7.609	0	0	0	0	4.348	0	0	0
V	0	0	0	0	0	1.087	0	0	0
W	0	0	0	0	0	0	1.087	0	0
Y	1.087	0	0	0	0	0	0	0	96.74

Table 5-28 CDR1 amino acid frequency distribution for cluster N1242 (Group J)

	Position							
AA	27	28	29	30	35	36	37	38
A	0	0	0	0	0	27.27	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	100	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	100	0	0	9.091	0	0
S	0	0	0	0	100	63.64	0	0
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0

Table 5-29 CDR2 amino acid frequency distribution for cluster N1242 (Group J)

	Position						
AA	56	57	58	59	63	64	65
A	0	0	27.27	0	0	0	0
C	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0
G	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0
I	9.091	0	9.091	0	0	9.091	0
K	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0
M	90.91	0	0	0	0	90.91	0
N	0	0	18.18	0	0	0	0
P	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0
T	0	100	45.45	0	0	0	100
V	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0

Table 5-30 CDR3 amino acid frequency distribution for cluster N1242 (Group J)

	Position								
AA	**105**	**106**	**107**	**108**	**109**	**114**	**115**	**116**	**117**
A	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	0
E	0	0	0	0	0	9.091	0	0	0
F	0	0	0	0	0	0	0	0	0
G	0	0	100	100	0	0	0	100	0
H	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	36.36	0	0
L	0	0	0	0	0	90.91	27.27	0	0
M	0	0	0	0	0	0	9.091	0	0
N	100	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	90.91	0	0	0	0
R	0	0	0	0	9.091	0	27.27	0	0
S	0	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0
V	0	100	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	100

Table 5-31 CDR1 amino acid frequency distribution for cluster 44A1 (Group K)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	4.762	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	2.381	0	0	0
F	0	0	0	100	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	11.9	38.1	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	4.762	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	61.9	0	2.381	40.48	0	0
S	0	83.33	0	0	95.24	54.76	0	0
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	35.71	0
Y	0	0	0	0	0	0	64.29	0

Table 5-32 CDR2 amino acid frequency distribution for cluster 44A1 (Group K)

	Position						
AA	**56**	**57**	**58**	**59**	**63**	**64**	**65**
A	0	0	0	0	0	11.9	0
C	0	0	0	0	0	0	0
D	0	0	0	0	0	4.762	0
E	0	0	0	0	0	0	0
F	0	7.143	0	0	0	0	0
G	0	0	0	85.71	100	23.81	0
H	0	0	0	0	0	0	0
I	95.24	0	4.762	0	0	7.143	0
K	0	0	0	0	0	0	0
L	4.762	0	0	0	0	7.143	0
M	0	0	0	0	0	0	0
N	0	0	40.48	4.762	0	2.381	0
P	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0
R	0	0	0	0	0	9.524	0
S	0	4.762	54.76	9.524	0	19.05	0
T	0	88.1	0	0	0	14.29	100
V	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0

Table 5-33 CDR3 amino acid frequency distribution for cluster 44A1 (Group K)

	Position							
AA	**105**	**106**	**107**	**108**	**114**	**115**	**116**	**117**
A	0	0	0	0	0	0	2.381	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	2.381	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	2.381	100	100	9.524	0	97.62	0
H	0	7.143	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	85.71	0	0
L	0	4.762	0	0	11.9	0	0	0
M	0	0	0	0	0	0	0	0
N	100	0	0	0	0	0	0	0
P	0	7.143	0	0	7.143	0	0	0
Q	0	71.43	0	0	38.1	7.143	0	0
R	0	0	0	0	4.762	7.143	0	0
S	0	4.762	0	0	21.43	0	0	0
T	0	0	0	0	7.143	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	100

Table 5-34 CDR1 amino acid frequency distribution for cluster ODY-N1117 (Group M)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	100	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	100	0	0
F	0	0	0	0	0	0	0	0
G	100	50	0	0	0	0	0	100
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	50	0	0	0	0	0	0
S	0	0	0	0	100	0	0	0
T	0	0	100	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0

Table 5-35 CDR2 amino acid frequency distribution for cluster ODY-N1117 (Group M)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	100	0	100	0	0	0	0
T	0	0	100	0	0	0	0	100
V	0	0	0	0	0	0	100	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-36 CDR3 amino acid frequency distribution for cluster ODY-N1117 (Group M)

	Position																
AA	105	106	107	108	109	110	111	111.1	111.2	112.2	112.1	112	113	114	115	116	117
A	100	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	100	0	0	0	0	0	75	0	0	0	100	0	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0	0	0	100	0	0	0	100	0	0
G	0	0	0	100	0	0	0	75	0	0	0	100	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	75	0	0	0	0	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	25	100	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0
R	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0	25	25	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100
W	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0

Table 5-37 CDR1 amino acid frequency distribution for cluster ODY-N1129 (Group N)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	100	0	0	0	0	0	0	0
F	0	0	0	0	0	0	100	0
G	0	0	0	0	0	100	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	100	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	100	0	0	0	0	0	0
R	0	0	0	0	0	0	0	0
S	0	0	0	0	0	0	0	0
T	0	0	100	0	100	0	0	33.33
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	66.67
Y	0	0	0	0	0	0	0	0

Table 5-38 CDR2 amino acid frequency distribution for cluster ODY-N1129 (Group N)

	Position							
AA	56	57	58	59	62	63	64	65
A	0	0	100	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	100	0	0	0
H	0	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	100	0
S	0	100	0	100	0	100	0	0
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	100
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0

Table 5-39 CDR3 amino acid frequency distribution for cluster ODY-N1129 (Group N)

	Position																
AA	105	106	107	108	109	110	111	111.1	111.2	112.2	112.1	112	113	114	115	116	117
A	100	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0	0	0	100	0	66.7	100	0	0	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0
G	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
K	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	100	0	0	0	100	0	0	0	0	0
M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
N	0	0	100	0	0	0	0	0	0	0	0	0	33.3	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	100
S	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0
T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
W	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0

Table 5-40 CDR1 amino acid frequency distribution for cluster ODY-N1186 (Group O)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	13	0	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	100	0	0	0	0
G	100	0	0	0	0	0	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	100	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	8.7	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	0	0	100	0	0	13	0	0
S	0	0	0	0	87	78.3	0	0
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0

Table 5-41 CDR2 amino acid frequency distribution for cluster ODY-N1186 (Group O)

	Position						
AA	**56**	**57**	**58**	**59**	**63**	**64**	**65**
A	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0
G	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0
I	100	0	0	0	0	21.74	0
K	0	0	8.696	0	0	0	0
L	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0
N	0	0	91.3	0	0	56.52	0
P	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0
S	0	0	0	0	0	17.39	0
T	0	100	0	0	0	4.348	100
V	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0

Table 5-42 CDR3 amino acid frequency distribution for cluster ODY-N1186 (Group O)

	Position												
AA	105	106	107	108	109	110	111	112	113	114	115	116	117
A	0	0	0	0	13.04	0	60.87	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	30.43	0	30.43	0	0	100	0
E	0	0	0	0	0	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	8.696	0	86.96	0	0	0
G	0	0	0	0	0	0	0	0	4.348	0	0	0	0
H	0	0	100	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	91.3	0	0	0	0	0
K	0	0	0	0	0	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0	0	13.04	0	0	0
M	0	56.52	0	0	0	0	0	0	0	0	0	0	0
N	100	0	0	0	0	0	0	0	17.39	0	0	0	95.65
P	0	0	0	0	0	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	100	0	0	0	0	26.09	0	0	0	0
S	0	0	0	0	86.96	0	0	0	21.74	0	0	0	0
T	0	43.48	0	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	8.696	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	100	0	0	0	0	100	0	4.348

Table 5-43 CDR1 amino acid frequency distribution for cluster ODY-N1264 (Group P)

	Position							
AA	**27**	**28**	**29**	**30**	**35**	**36**	**37**	**38**
A	0	0	0	0	0	0	0	100
C	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0	0
F	0	0	0	33.33	0	0	0	0
G	66.67	100	0	0	0	100	0	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	33.33	0	0	0	0	0	0	0
S	0	0	0	0	100	0	0	0
T	0	0	100	0	0	0	0	0
V	0	0	0	66.67	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	100	0

Table 5-44 CDR2 amino acid frequency distribution for cluster ODY-N1264 (Group P)

	Position						
AA	**56**	**57**	**58**	**59**	**63**	**64**	**65**
A	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0
D	0	0	0	0	0	0	0
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0
G	0	0	0	100	100	0	0
H	0	0	0	0	0	0	0
I	100	0	0	0	0	0	0
K	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0
N	0	100	0	0	0	0	0
P	0	0	0	0	0	100	0
Q	0	0	0	0	0	0	0
R	0	0	0	0	0	0	0
S	0	0	100	0	0	0	0
T	0	0	0	0	0	0	100
V	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0
Y	0	0	0	0	0	0	0

Table 5-45 CDR3 amino acid frequency distribution for ODY-N1264 (Group P)

	Position							
AA	**105**	**106**	**107**	**108**	**114**	**115**	**116**	**117**
A	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0
D	0	0	0	100	100	0	66.67	0
E	0	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	33.33	0
H	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0
K	0	0	0	0	0	0	0	0
L	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
N	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0
Q	0	0	0	0	0	0	0	0
R	100	100	0	0	0	0	0	0
S	0	0	0	0	0	0	0	100
T	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0
Y	0	0	100	0	0	100	0	0

Table 6. Sequence Identifiers of V-bodies identified from panning

Group	CDR1 Amino Acid Sequence	CDR2 Amino Acid Sequence	CDR3 Amino Acid Sequence	VHH Amino Acid Sequence	VHH DNA Sequence
A	1	2	3	4	67
A	555	793	1031	105	1269
A	556	794	1032	106	1270
A	557	795	1033	107	1271
A	558	796	1034	108	1272
A	559	797	1035	109	1273
A	560	798	1036	110	1274
A	561	799	1037	111	1275
A	562	800	1038	112	1276
A	563	801	1039	113	1277
B	564	802	1040	114	1278
B	6	7	8	9	68
B	565	803	1041	115	1279
B	566	804	1042	116	1280
B	567	805	1043	117	1281
B	568	806	1044	118	1282
B	569	807	1045	119	1283
B	570	808	1046	120	1284
B	571	809	1047	121	1285
B	572	810	1048	122	1286
B	573	811	1049	123	1287
B	574	812	1050	124	1288
B	575	813	1051	125	1289
B	576	814	1052	126	1290
B	577	815	1053	127	1291
C	11	12	13	14	69
C	578	816	1054	128	1292
C	579	817	1055	129	1293
C	580	818	1056	130	1294
C	581	819	1057	131	1295
D	21	17	22	23	71
D	16	17	18	19	70
D	582	820	1058	132	1296
D	583	821	1059	133	1297
D	584	822	1060	134	1298
D	585	823	1061	135	1299

D	586	824	1062	136	1300
D	587	825	1063	137	1301
D	588	826	1064	138	1302
D	589	827	1065	139	1303
D	590	828	1066	140	1304
D	591	829	1067	141	1305
D	592	830	1068	142	1306
D	593	831	1069	143	1307
D	594	832	1070	144	1308
D	16	17	25	26	72
D	595	833	1071	145	1309
D	596	834	1072	146	1310
D	597	835	1073	147	1311
D	598	836	1074	148	1312
D	599	837	1075	149	1313
D	600	838	1076	150	1314
D	601	839	1077	151	1315
D	602	840	1078	152	1316
D	603	841	1079	153	1317
D	604	842	1080	154	1318
D	605	843	1081	155	1319
D	606	844	1082	156	1320
D	607	845	1083	157	1321
D	608	846	1084	158	1322
D	609	847	1085	159	1323
D	610	848	1086	160	1324
D	611	849	1087	161	1325
D	612	850	1088	162	1326
D	613	851	1089	163	1327
D	614	852	1090	164	1328
D	615	853	1091	165	1329
D	616	854	1092	166	1330
D	617	855	1093	167	1331
D	618	856	1094	168	1332
D	619	857	1095	169	1333
D	620	858	1096	170	1334
D	621	859	1097	171	1335
D	622	860	1098	172	1336
D	623	861	1099	173	1337
D	624	862	1100	174	1338
D	625	863	1101	175	1339

D	626	864	1102	176	1340
D	627	865	1103	177	1341
D	628	866	1104	178	1342
D	629	867	1105	179	1343
D	630	868	1106	180	1344
D	631	869	1107	181	1345
D	632	870	1108	182	1346
D	633	871	1109	183	1347
D	634	872	1110	184	1348
D	635	873	1111	185	1349
D	636	874	1112	186	1350
E	28	17	29	30	73
F	637	875	1113	187	1351
F	32	33	34	35	74
F	638	876	1114	188	1352
F	639	877	1115	189	1353
F	640	878	1116	190	1354
F	641	879	1117	191	1355
F	642	880	1118	192	1356
F	643	881	1119	193	1357
F	644	882	1120	194	1358
G	37	38	39	40	75
G	645	883	1121	195	1359
G	646	884	1122	196	1360
G	647	885	1123	197	1361
H	42	43	44	45	76
H	648	886	1124	198	1362
H	649	887	1125	199	1363
H	650	888	1126	200	1364
H	651	889	1127	201	1365
I	652	890	1128	202	1366
I	653	891	1129	203	1367
I	654	892	1130	204	1368
I	655	893	1131	205	1369
I	656	894	1132	206	1370
I	657	895	1133	207	1371
I	658	896	1134	208	1372
I	659	897	1135	209	1373
I	660	898	1136	210	1374
I	661	899	1137	211	1375
I	662	900	1138	212	1376

I	663	901	1139	213	1377
I	664	902	1140	214	1378
I	47	48	49	50	77
I	665	903	1141	215	1379
I	666	904	1142	216	1380
I	667	905	1143	217	1381
I	668	906	1144	218	1382
I	669	907	1145	219	1383
I	670	908	1146	220	1384
I	671	909	1147	221	1385
I	672	910	1148	222	1386
I	673	911	1149	223	1387
I	674	912	1150	224	1388
I	675	913	1151	225	1389
I	676	914	1152	226	1390
I	677	915	1153	227	1391
I	678	916	1154	228	1392
I	679	917	1155	229	1393
I	680	918	1156	230	1394
I	681	919	1157	231	1395
I	682	920	1158	232	1396
I	683	921	1159	233	1397
I	684	922	1160	234	1398
I	685	923	1161	235	1399
I	686	924	1162	236	1400
I	687	925	1163	237	1401
I	688	926	1164	238	1402
I	689	927	1165	239	1403
I	690	928	1166	240	1404
I	691	929	1167	241	1405
I	692	930	1168	242	1406
I	693	931	1169	243	1407
I	694	932	1170	244	1408
I	695	933	1171	245	1409
I	696	934	1172	246	1410
I	697	935	1173	247	1411
I	698	936	1174	248	1412
I	699	937	1175	249	1413
I	700	938	1176	250	1414
I	52	53	54	55	78
I	701	939	1177	251	1415

I	702	940	1178	252	1416
I	703	941	1179	253	1417
I	704	942	1180	254	1418
I	705	943	1181	255	1419
I	706	944	1182	256	1420
I	707	945	1183	257	1421
I	708	946	1184	258	1422
I	709	947	1185	259	1423
I	710	948	1186	260	1424
I	711	949	1187	261	1425
I	712	950	1188	262	1426
I	713	951	1189	263	1427
I	714	952	1190	264	1428
I	715	953	1191	265	1429
I	716	954	1192	266	1430
I	717	955	1193	267	1431
I	718	956	1194	268	1432
I	719	957	1195	269	1433
I	720	958	1196	270	1434
I	721	959	1197	271	1435
I	722	960	1198	272	1436
I	723	961	1199	273	1437
I	724	962	1200	274	1438
I	725	963	1201	275	1439
I	726	964	1202	276	1440
I	727	965	1203	277	1441
I	728	966	1204	278	1442
I	729	967	1205	279	1443
I	730	968	1206	280	1444
I	731	969	1207	281	1445
I	732	970	1208	282	1446
I	733	971	1209	283	1447
I	734	972	1210	284	1448
I	735	973	1211	285	1449
I	736	974	1212	286	1450
I	737	975	1213	287	1451
I	738	976	1214	288	1452
I	739	977	1215	289	1453
I	740	978	1216	290	1454
I	741	979	1217	291	1455
J	57	58	59	60	79

J	742	980	1218	292	1456
J	743	981	1219	293	1457
J	744	982	1220	294	1458
J	745	983	1221	295	1459
J	746	984	1222	296	1460
J	747	985	1223	297	1461
J	748	986	1224	298	1462
J	749	987	1225	299	1463
J	750	988	1226	300	1464
J	751	989	1227	301	1465
K	752	990	1228	302	1466
K	753	991	1229	303	1467
K	754	992	1230	304	1468
K	755	993	1231	305	1469
K	756	994	1232	306	1470
K	757	995	1233	307	1471
K	758	996	1234	308	1472
K	759	997	1235	309	1473
K	760	998	1236	310	1474
K	761	999	1237	311	1475
K	762	1000	1238	312	1476
K	763	1001	1239	313	1477
K	764	1002	1240	314	1478
K	765	1003	1241	315	1479
K	766	1004	1242	316	1480
K	767	1005	1243	317	1481
K	768	1006	1244	318	1482
K	769	1007	1245	319	1483
K	770	1008	1246	320	1484
K	771	1009	1247	321	1485
K	772	1010	1248	322	1486
K	773	1011	1249	323	1487
K	774	1012	1250	324	1488
K	775	1013	1251	325	1489
K	62	63	64	65	80
K	776	1014	1252	326	1490
K	777	1015	1253	327	1491
K	778	1016	1254	328	1492
K	779	1017	1255	329	1493
K	780	1018	1256	330	1494
K	781	1019	1257	331	1495

K	782	1020	1258	332	1496
K	783	1021	1259	333	1497
K	784	1022	1260	334	1498
K	785	1023	1261	335	1499
K	786	1024	1262	336	1500
K	787	1025	1263	337	1501
K	788	1026	1264	338	1502
K	789	1027	1265	339	1503
K	790	1028	1266	340	1504
K	791	1029	1267	341	1505
K	792	1030	1268	342	1506
M	1607	1608	1609	1619	1627
M	1692	1721	1749	1778	1807
M	1693	1722	1750	1779	1808
M	1694	1723	1751	1780	1809
N	1610	1611	1612	1620	1628
N	1695	1724	1752	1781	1810
N	1696	1725	1753	1782	1811
O	1697	1726	1754	1783	1812
O	1613	1614	1615	1621	1629
O	1698	1727	1755	1784	1813
O	1699	1728	1756	1785	1814
O	1700	1729	1757	1786	1815
O	1701	1730	1758	1787	1816
O	1702	1731	1759	1788	1817
O	1703	1732	1760	1789	1818
O	1704	1733	1761	1790	1819
O	1705	1734	1762	1791	1820
O	1706	1735	1763	1792	1821
O	1707	1736	1764	1793	1822
O	1708	1737	1765	1794	1823
O	1709	1738	1766	1795	1824
O	1710	1739	1767	1796	1825
O	1711	1740	1768	1797	1826
O	1712	1741	1769	1798	1827
O	1713	1742	1770	1799	1828
O	1714	1743	1771	1800	1829
O	1715	1744	1772	1801	1830
O	1716	1745	1773	1802	1831
O	1717	1746	1774	1803	1832
O	1718	1747	1775	1804	1833

P	1616	1617	1618	1622	1630
P	1719	1748	1776	1805	1834
P	1720	1748	1777	1806	1835

Example 4. Flow cytometry binding

[0389] For generation of data depicted in **Figures 5A-5E**, endogenous expressing cells lines GP2d (DMEM, 10% FBS), Colo205 (RPMI, 10% FBS), DLD-1 (RPMI, 10% FBS), and T84 (DMEM:F12, 5% FBS), and negative cell line HCT-15 (RPMI, 10% FBS) were grown to 80-90% confluency in growth media. Cells were harvested by washing with PBS and dissociated using Accutase then pelleted, resuspended with growth media and counted. 150,000 cells/well were added to a 96-well conical bottom non-TC treated plate. Cells were washed with ice-cold FACS buffer (PBS + 1% FBS) and media aspirated. Purified V-bodies were serially diluted 1:5 at a starting concentration of 1 nM (7 points + 0) with FACS buffer. Periplasmic extracts were diluted 1:5 with FACS buffer. Cells were stained with 50 µL of diluted purified V-body or periplasmic extract for 30 minutes on ice then washed with 150 µL of FACS buffer three times. Cells were then stained with 50 µL of Alexa Fluor 647 AffiniPure Goat Anti-Alpaca IgG, VHH domain (Jackson ImmunoResearch #128-605-230) diluted 1:600 with FACS buffer for 30 minutes on ice. Cells were washed with 150 µL of FACS buffer three times and resuspended with 50 µL of FACS buffer. 10,000 events were acquired on a Symphony A1 flow cytometer.

Example 5. Surface plasmon resonance binding affinities

[0390] Binding affinities of the V-bodies for their respective target was determined by surface plasmon resonance (SPR) using a Carterra LSA instrument. Affinity purified V-bodies were covalently crosslinked onto an LSA HC30M chip using EDC/Sulfo NHS. The interaction with human CHD17 (extracellular domain – human and mouse: His-tagged CDH17; Cyno: Fc-tagged CDH17) was measured under physiological conditions (50 mM HEPES pH 7.4, 150 mM NaCl, 0.1 %(w/v) BSA, 0.05% (v/v) Tween20, 25°C) using 10 different antigen concentrations (2-fold serial dilution, start at 500 nM). Resulting sensorgrams were analyzed and KDs were calculated using Carterra's data analysis software *Kinetics*. Binding affinities are summarized in **Table 7**.

Example 6. Epitope Binning

[0391] Epitope binning of the V-bodies was determined by surface plasmon resonance (SPR) using a Carterra LSA instrument. A schematic diagram depicting the experimental setup of the present Example

is shown in **Figure 6**. V-bodies were tested for competition to the same binding region (epitope) in a pairwise combinatorial manner via a one-on-many format. Affinity purified V-bodies were covalently crosslinked onto an LSA HC30M chip using EDC/Sulfo NHS. For each binning cycle, human CDH17 (extracellular domain) (Acro Biosystems) was injected (170 nM) under physiological conditions (50 mM HEPES pH 7.4, 150 mM NaCl, 0.1 %(w/v) BSA, 0.05% (v/v) Tween20, 25°C) followed by a second V-body (300 nM). Binning cycles were repeated to test all V-body pairs. Resulting sensograms were analyzed and V-bodies that compete for the same epitope were grouped together in bins (**Figure 7** and **Table 7**) using Carterra's data analysis software *Epitope*. Additional binding by the second V-body indicates an unoccupied epitope (non-overlapping epitopes), while no binding indicates epitope blocking (overlapping epitopes).

Example 7. Domain Mapping

[0392] Domain mapping of the V-bodies was performed by surface plasmon resonance (SPR) using a Carterra LSA instrument. V-bodies were tested for binding to individual domains or domain formats of human CDH17 (monomers: EC1, EC2, EC3, EC5, EC6; dimer: EC6-7; trimer: EC5-7). Affinity purified V-bodies were covalently crosslinked onto an LSA HC30M chip using EDC/Sulfo NHS. Human CDH17 domain formats were injected (2-fold serial dilution, start at around 4 μM) under physiological conditions (50 mM HEPES pH 7.4, 150 mM NaCl, 0.1 %(w/v) BSA, 0.05% (v/v) Tween20, 25°C). Resulting sensograms were analyzed using Carterra's data analysis software *Kinetics*.

[0393] Domain mapping of the V-bodies was also performed by fluorescence activated cell sorting (FACS). HEK-293 cells were grown to 80-90% confluency in growth media; EMEM supplemented with 10% FBS. Cells were harvested by washing with PBS and dissociated using TrypLE then pelleted, resuspended with growth media and counted. 4 x 10^6 cells each were seeded into 9 T75 flasks in 15 mL of growth media. Cells were grown overnight at 37°C and 5% CO_2. Cells were transfected with CDH17 full length construct hCDH17-FL, and domain swapped constructs hCDH17_deltaEC1, hCDH17_deltaEC2, hCDH17_deltaEC3, hCDH17_deltaEC4, hCDH17_deltaEC5, hCDH17_deltaEC6, hCDH17_deltaEC7, and no DNA control using X-tremeGENE 9 DNA Transfection Reagent (Sigma cat# 6365787001) at a 3:1 (reagent:DNA) dilution in OptiMEM following manufacturer's protocol. Cells were incubated for 48 hours at 37°C and 5% CO_2. Cells were harvested by washing with PBS and dissociated using Accutase then pelleted, resuspended with growth media and counted. 150,000 cells/well of each transfected cell line was added to a 96-well conical bottom non-TC treated plate. Cells were washed with ice-cold FACS buffer and media aspirated. Purified V-bodies and tool compounds were diluted to 100 nM with FACS

buffer. Cells were stained with 50 µL of diluted V-body or tool compounds for 30 minutes on ice then washed with 150 µL of FACS buffer three times. Cells were then stained with 50 µL of Alexa Fluor 647 AffiniPure Goat Anti-Alpaca IgG, VHH domain (Jackson ImmunoResearch #128-605-230), or appropriate secondary antibody, diluted 1:600 with FACS buffer for 30 minutes on ice. Cells were washed with 150 µL of FACS buffer three times and resuspended with 50 µL of FACS buffer. In-house produced anti-CDH17-APC antibody, anti-FLAG-APC antibody (Miltenyi cat# 130-119-584), and internal irrelevant V-body were used as CDH17 and construct expression controls. 10,000 events were acquired on a Symphony A1 flow cytometer. **Figure 8** shows a summary of FACS domain mapping.

[0394] **Table 7** shows a summary of binding affinities, binning and domain mapping data.

Table 7. Summary of Binning and Domain Mapping Data

Name	K_D [nM] human	K_D [nM] cyno	K_D [nM] mouse	Bin (SPR)	Domain Binding (SPR)	Domain Binding (FACS)
Antigen	**hCDH17-His**	**cCDH17-Fc**	**mCDH17-His**		**hCDH17**	**hCDH17**
ODY-N1092	18	6.6	49	3	EC1	n.d.
ODY-N1084	101	15	>1µM	2	EC6/EC7	EC6/EC7
ODY-44A1	57	-	93	1	EC1	EC1
ODY-N1061	62	-	No binding	3	EC1	EC1
ODY-43E7	41	6.9	47	1	EC1	EC1
ODY-45F5	26	-	No binding	2	EC6/EC7	EC6/EC7
ODY-N1081	215	38	630	3	inconclusive	EC1
ODY-N1242	104	7.3	59	1	EC1	EC1
ODY-43B5	binding	-	No binding	4	EC6/EC7	EC7
ODY-N1083	54	-	No binding	2	EC6/EC7	EC7
ODY-N1095	25	18	No binding	2	inconclusive	inconclusive
ODY-N1090	153	-	No binding	2	EC6/EC7	EC6/EC7
ODY-N1070	binding	-	No binding	5	inconclusive	EC3/EC4
ODY-44A4	32	5.8	>1µM	1	EC1	EC1
ODY-N1091	128	43	No binding	-	EC1	EC1
ODY-N1117	154	9.7	No binding	-	EC1	EC1
ODY-N1129	137	10	52	-	EC1	EC1
ODY-N1186	43	40	290	-	EC1	EC1
ODY-N1264	62	11	70	-	EC1	EC1
Competitor #1				1		EC1

Competitor #2				1		EC1
						- : not tested

* * *

[0395] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[0396] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference in their entirety as if physically present in this specification.

Listing of Sequences

SEQ ID NO: 1 ODY-N1061, Group A, CDR1, amino acid sequence
GFTLSNYN

SEQ ID NO: 2 ODY-N1061, Group A, CDR2, amino acid sequence
ISRGGRT

SEQ ID NO: 3 ODY-N1061, Group A, CDR3, amino acid sequence
ALCLLRFETCLEYNRAQYPY

SEQ ID NO: 4 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREGVSSISRGGRTNYVDSAKGRFTISRDNAKNTVY
LQMNSLKPADSAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 5 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREGVSSISRGGRTNYADSAKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 6 Group B, Consensus CDR1; ODY-N1070, Group B, CDR1, amino acid sequence
GSPLDYYA

SEQ ID NO: 7 ODY-N1070, Group B, CDR2, amino acid sequence
ISTSGRCT

SEQ ID NO: 8 ODY-N1070, Group B, CDR3, amino acid sequence
AAVRSGSDWWTTMTQRHYDF

SEQ ID NO: 9 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDWWTTMTQRHYDFWGQGTQVTVSS

SEQ ID NO: 10 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAAVRSGSDWWTTMTQRHYDFWGQGTQVTVSS

SEQ ID NO: 11 ODY-N1081, Group C, CDR1, amino acid sequence
RLNFSRTT

SEQ ID NO: 12 ODY-N1081, Group C, CDR2, amino acid sequence
SGWARGRT

SEQ ID NO: 13 ODY-N1081, Group C, CDR3, amino acid sequence
AARDSRRGGLFADLNEYDY

SEQ ID NO: 14 ODY-N1081, Group C, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLTLSCATSRLNFSRTTVAWFRQAPGKERDFVAASGWARGRTYYADSLQGRFTISRDNNKN
TVYLQMNSLKLEDTAVYYCAARDSRRGGLFADLNEYDYWGQGTQVTVSS

SEQ ID NO: 15 ODY-N1081, Group C, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCATSRLNFSRTTVAWFRQAPGKERDFVAASGWARGRTYYADSLKGRFTISRDNNKNT
VYLQMNSLRLEDTAVYYCAARDSRRGGLFADLNEYDYWGQGTQVTVSS

SEQ ID NO: 16 ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR1, amino acid sequence
GRTFSEPI

SEQ ID NO: 17 Group D, Consensus CDR2; Group E, Consensus CDR2; ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR2; ODY-N1090, Group E, CDR2, amino acid sequence
LISTGGST

SEQ ID NO: 18 ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR3, amino acid sequence
AATGDSYRGAYDRPAEYDY

SEQ ID NO: 19 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 20 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 21 ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR1, amino acid sequence
GRTFSTPI

SEQ ID NO: 22 ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR3, amino acid sequence
AATGNSYRGAYDRPTEYDY

SEQ ID NO: 23 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 24 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 25 ODY-45F5_ODY-N1083_ODY-N1084, Group D, CDR3, amino acid sequence
AATGDLYRGAYDRPAEYDY

SEQ ID NO: 26 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPGDTAVYYCAATGDLYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 27 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence

EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDLYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 28 Group E, Consensus CDR1; ODY-N1090, Group E, CDR1, amino acid sequence
GRTFSSPI

SEQ ID NO: 29 Group E, Consensus CDR3; ODY-N1090, Group E, CDR3, amino acid sequence
VATGNTYRGAYDRPAEYDF

SEQ ID NO: 30 ODY-N1090, Group E, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSPIAGWFRQHPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNML
YLQMNSLKPEDTAVYYCVATGNTYRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 31 ODY-N1090, Group E, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSSPIAGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCVATGNTYRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 32 ODY-N1091_ODY-N1092, Group F, CDR1, amino acid sequence
TRTFNMYA

SEQ ID NO: 33 ODY-N1091_ODY-N1092, Group F, CDR2, amino acid sequence
ISRSGTNT

SEQ ID NO: 34 ODY-N1091_ODY-N1092, Group F, CDR3, amino acid sequence
AAQFSLPVDASPLRRYYY

SEQ ID NO: 35 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 36 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 37 ODY-N1095, Group G, CDR1, amino acid sequence
GRTFSSYL

SEQ ID NO: 38 ODY-N1095, Group G, CDR2, amino acid sequence
ISWNDRST

SEQ ID NO: 39 Group G, Consensus CDR3; ODY-N1095, Group G, CDR3, amino acid sequence
AATRKTRRSTVAGTEVDY

SEQ ID NO: 40 ODY-N1095, Group G, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYLMGWFRQAPGKEREFVAAISWNDRSTYYADSVKGRFTISRDNAKNT
VYLQMNSLKPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 41 ODY-N1095, Group G, humanized, amino acid sequence

EVQLLESGGGLVQPGGSLRLSCAASGRTFSSYLMGWFRQAPGKEREFVAAISWNDRSTYYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 42 Group H, Consensus CDR1; ODY-43B5, Group H, CDR1, amino acid sequence
GRTDSILN

SEQ ID NO: 43 Group H, Consensus CDR2; ODY-43B5, Group H, CDR2, amino acid sequence
ISWFRGET

SEQ ID NO: 44 Group H, Consensus CDR3; ODY-43B5, Group H, CDR3, amino acid sequence
AARNGGYDLNDYAY

SEQ ID NO: 45 ODY-43B5, Group H, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGRTDSILNMGWFRQAPGKEREIVAAISWFRGETIYTASVKGRFTISRDKSKNTL
YLQMSSLKPEDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 46 ODY-43B5, Group H, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTDSILNMGWFRQAPGKEREIVAAISWFRGETIYADSVKGRFTISRDKSKNTLY
LQMNSLRPEDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 47 ODY-43E7_ODY-44A4, Group I, CDR1, amino acid sequence
GIRFSSYA

SEQ ID NO: 48 ODY-43E7_ODY-44A4, Group I, CDR2, amino acid sequence
ITSGYRT

SEQ ID NO: 49 ODY-43E7_ODY-44A4, Group I, CDR3, amino acid sequence
NAGGGRLGY

SEQ ID NO: 50 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 51 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 52 ODY-43E7_ODY-44A4, Group I, CDR1, amino acid sequence
GMRFSQYA

SEQ ID NO: 53 ODY-43E7_ODY-44A4, Group I, CDR2, amino acid sequence
IFKDGTT

SEQ ID NO: 54 ODY-43E7_ODY-44A4, Group I, CDR3, amino acid sequence
NAGGAALGY

SEQ ID NO: 55 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence

EVQLVESGGGLVQPGGSLRLSCAASGMRFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKN
TLYLQMNSLKPEDTAVYVCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 56 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMRFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKN
TLYLQMNSLRPEDTAVYYCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 57 ODY-N1242, Group J, CDR1, amino acid sequence
GIRFSAYA

SEQ ID NO: 58 ODY-N1242, Group J, CDR2, amino acid sequence
MTAGGMT

SEQ ID NO: 59 ODY-N1242, Group J, CDR3, amino acid sequence
NVGGQLLGY

SEQ ID NO: 60 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSAYAMGWYRRGPGKQRELVANMTAGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLLGYWGQGTQVTVSS

SEQ ID NO: 61 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSAYAMGWYRQAPGKQRELVANMTAGGMTTYADSVKGRFTISRDNDKK
TVYLQMNSLRSEDTAVYYCNVGGQLLGYWGQGTQVTVSS

SEQ ID NO: 62 ODY-44A1, Group K, CDR1, amino acid sequence
GSRFSSYA

SEQ ID NO: 63 ODY-44A1, Group K, CDR2, amino acid sequence
ITSGGRT

SEQ ID NO: 64 ODY-44A1, Group K, CDR3, amino acid sequence
NQGGSKGY

SEQ ID NO: 65 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYTDSVKGRFTITRDNAKDTV
YLQMNSLKPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 66 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYADSVKGRFTISRDNAKDT
VYLQMNSLRPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 67 ODY-N1061, Group A, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGAGTCTCCTGCGCAGCCTC
TGGATTCACTTTGAGCAATTATAATATAGGGTGGTTCCGCCAGGCCCCAGGGAAGGAGCGTGAAGGGGTCTCATC
CATTAGTAGAGGTGGAAGAACAAACTATGTAGACTCCGCGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGCGGACTCAGCCGTCTATTATTGTGCATTATGTTTATTA
AGATTCGAAACATGTCTCGAATATAACCGCGCGCAATATCCTTACTGGGGTCAGGGGACCCAGGTCACCGTCTCCT
CA

SEQ ID NO: 68 ODY-N1070, Group B, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGACTCTCCTGCGCGGCCTC
CGGAAGCCCTTTGGATTATTATGCCATAGGCTGGTTCCGCCAGGCCCCAGGGAAGGAGCGTGAGGGGGTCTCCTG
TATTAGTACGAGTGGTCGCTGCACAAACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGC
CAGGAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAAGACACAGCCGTTTATTTCTGTGCAGCAGTTCGT
AGTGGTAGTGACTGGTGGACCACAATGACACAGAGACACTATGACTTCTGGGGCCAGGGGACCCAGGTCACCGT
CTCCTCA

SEQ ID NO: 69 ODY-N1081, Group C, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGGCTGGGGGCTCTCTGACACTCTCCTGTGCAACCTCT
AGACTCAACTTCAGTAGAACCACCGTGGCCTGGTTCCGCCAGGCCCCAGGGAAGGAGCGTGACTTTGTCGCAGCA
AGTGGGTGGGCTAGAGGTAGGACATACTATGCAGACTCCCTGCAGGGCCGATTCACCATCTCCAGAGACAACAAC
AAGAACACGGTGTATCTACAAATGAACAGCCTGAAACTTGAGGACACGGCCGTTTATTACTGTGCAGCCCGGGAC
AGCCGGAGGGGGGGACTTTTCGCGGACCTTAACGAATATGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTC
CTCA

SEQ ID NO: 70 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TGGACGCACCTTCAGTGAACCTATCGTGGGCTGGTTCCGCCAGACTCCAGGGAAGGAGCGTGACTTCGTGGCCGC
TCTTATTTCAACTGGTGGTAGTACGAGGTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC
AAGAACACGCTGTATTTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTGTATTATTGTGCGGCAACGGGG
GACTCGTACCGTGGCGCCTATGATCGGCCCGCTGAATATGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCC
TCA

SEQ ID NO: 71 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TGGACGCACCTTCAGTACGCCTATCACGGGCTGGTTCCGCCAGGCTCCAGGGAAGGAGCGTGAGTTTGTGGCCGC
TCTTATTTCAACTGGTGGTAGTACGAGGTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACGACGCC
AAGAACACGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTGTATTATTGTGCGGCAACGGGG
AACTCGTACCGTGGCGCCTATGATCGGCCCACTGAATATGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCC
TCA

SEQ ID NO: 72 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
CGGACGCACCTTCAGTGAACCTATCGTGGGCTGGTTCCGCCAGACTCCAGGGAAGGAGCGTGACTTCGTGGCCGC
TCTTATTTCAACTGGTGGTAGTACGAGGTATGCCGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC
AAGAACACGCTGTATTTGCAAATGAACAGCCTGAAACCTGGGGACACGGCCGTGTATTATTGTGCGGCAACGGGG
GACTTGTACCGTGGCGCCTATGATCGGCCCGCTGAATATGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCC
TCA

SEQ ID NO: 73 ODY-N1090, Group E, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TGGACGCACCTTCAGTAGTCCTATCGCGGGCTGGTTCCGCCAGCATCCAGGGAAGGAGCGTGAGTTTGTGGCCGC
TCTTATTTCAACTGGTGGTAGTACGAGGTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC

AAGAACATGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTGTATTATTGTGTGGCAACGGGG
AACACGTACCGTGGCGCCTATGATCGGCCCGCTGAATATGACTTTTGGGGCCAGGGGACCCAGGTCACCGTCTCC
TCA

SEQ ID NO: 74 ODY-N1091_ODY-N1092, Group F, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TACTCGCACCTTCAATATGTATGCCTTGGGCTGGTTCCGCCAGGCTCCAGGGAAGGAGCGTGAGTTTGTAGCAGCT
ATTAGTCGGAGTGGTACTAACACACCCTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA
ACAACTTACTGTATCTGCGCATGAACAGCCTGGAACCTGAGGACACGGCCGTGTATTATTGTGCGGCACAATTCTC
GCTACCGGTAGACGCGTCCCCCCTTAGACGGTATTACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 75 ODY-N1095, Group G, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TGGACGCACCTTCAGTAGCTATCTCATGGGCTGGTTCCGCCAGGCTCCAGGAAAGGAGCGTGAGTTTGTAGCAGC
TATTAGCTGGAATGATCGTAGCACATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC
AAGAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTTTATTACTGTGCAGCAACCAGA
AAGACTCGAAGGTCGACAGTAGCTGGTACGGAGGTCGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTC
A

SEQ ID NO: 76 ODY-43B5, Group H, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCGCCTGTGCAGCCTC
TGGACGCACCGACAGTATCCTTAACATGGGCTGGTTCCGCCAGGCTCCTGGGAAGGAGCGTGAGATTGTAGCAGC
TATTAGCTGGTTTCGCGGTGAAACTATTTATACAGCATCCGTGAAGGGCCGATTCACCATCTCCAGAGACAAGTCC
AAGAACACGCTGTATCTGCAAATGAGCAGCCTGAAACCTGAGGACACGGCCGTGTATTATTGTGCGGCAAGAAAT
GGCGGCTATGACCTAAATGACTATGCCTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 77 ODY-43E7_ODY-44A4, Group I, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGACTCTCCTGTGCAGCCTC
TGGAATTCGCTTCAGTAGCTATGCCATGGGCTGGTACCGCCAGGCTCCAGGGAAGCAGCGCGAGTTCATCGCACA
AATTACTAGTGGTTATCGCACGAACTATACAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGGCAA
GAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTCTATTTCTGTAATGCAGGGGGGG
GTCGGTTAGGCTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 78 ODY-43E7_ODY-44A4, Group I, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGACTCTCCTGTGCAGCCTC
TGGAATGCGCTTCAGTCAATATGCCATGGGCTGGTACCGCCAGGCTCCAGGGAAGCAGCGCGAGTTGGTCGCAA
ATATCTTTAAAGATGGTACCACAAACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACACGCTGTATCTCCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTCTATGTTTGCAATGCAGGCGGGGC
CGCCCTCGGGTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 79 ODY-N1242, Group J, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGAGGTCTCTGAGACTCTCTTGTACAGCCTCT
GGAATCCGCTTCAGTGCCTATGCCATGGGTTGGTACCGCCGGGGTCCAGGAAAGCAGCGCGAGTTGGTCGCAAAT
ATGACTGCTGGTGGTATGACAACCTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGACAAG
AAGACGGTGTATCTGCAAATGAACAGCCTGAAATCTGAAGACACGGCCGTCTATTACTGTAATGTAGGTGGTCAG
CTCCTGGGCTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 80 ODY-44A1, Group K, non-humanized DNA, nucleotide sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGACTCTCCTGTACATCCTCT
GGAAGCCGATTCAGTAGCTACGCCATGGTCTGGTACCGCCAGGCTCCAGGGAAGCAGCGCGACATGGTCGCATTA
ATTACTAGTGGTGGTCGTACAAACTATACAGACTCCGTGAAGGGCCGATTCACCATCACCAGAGACAACGCCAAG
GACACGGTATATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCGTCTATTACTGCAATCAAGGCGGGAGT
AAGGGCTATTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 105 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSSISRGGRTNYADSVKGRFTISRDNAKNTVY
LQMNSLKPADSAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 106 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSSFSRGGRTNYADSVKGRFTISRDNAKNTV
YLQMNSLKPADSAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 107 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNVNIGWFRQAPGKEREGVSWISRGGRTNYADSVKGRFTISRDNAKNTV
YLQMNSLKPADSAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 108 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLTNYNIGWFRQAPGKEREGVSSISRGGRTNYVDSAKGRFTISRDNAKNTVY
LQMNSLKPADSAVYFCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 109 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREGVSSISRGGRTNYVDSAKGRFTISRDSAKNTVY
LQMNSLKPADSAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 110 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQVPGKEREGVSSISRGGRTNYVDSAKGRFTISRDNAKNTVY
LQMNSLKPADSAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 111 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREEVSSISRGGRTNYVDSAKGRFTISRDNAKNTVY
LQMNSLKPADSAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 112 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREGVSSISRGGRTNYVDSAKGRFTISRDNAKNTVY
LQMSSLKPADSAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 113 ODY-N1061, Group A, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSWFSRGGRTAYADSVKGRFTISRDNAKNT
VYLQMNSLKPADSAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 114 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRCGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 115 ODY-N1070, Group B, non-humanized, amino acid sequence

EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDCWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 116 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSWISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDWWTTMTQRHYDFWGQGTQVTVSS

SEQ ID NO: 117 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGCDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 118 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 119 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVCSGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 120 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSWISTSGRTTNYADSLKGRFTISRDTARNAV
YLQINSLKPEDTAVYFCAAVRAGSDWWTTMRQRDYDYWGQGTQVTVSS

SEQ ID NO: 121 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRTTNYADSLKGRFTISRDTARNAVY
LQINSLKPEDTAVYFCAAVRAGSDWWTTMRQRDYDYCGQGTQVTVSS

SEQ ID NO: 122 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDWWTTMTQRHYDFCGQGTQVTVSS

SEQ ID NO: 123 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSGSDWCTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 124 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRSCSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 125 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRAGSDWWTTMRQRDYDYWGQGTQVTVSS

SEQ ID NO: 126 ODY-N1070, Group B, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNARNTV
YLQMNSLKPEDTAVYFCAAVRCGSDWWTTMTQSHYDFWGQGTQVTVSS

SEQ ID NO: 127 ODY-N1070, Group B, non-humanized, amino acid sequence

EVQLVESGGGLVQPGGSLRLSCAAAGSPLDYYAIGWFRQAPGKEREGVSCISTSGRATNYADSVKGRFTISRDNAGNTV
YLQMNSLKPEDTASYFCAAVRAGSDWWTTMTQRHYDYCGQGTQVTVSS

SEQ ID NO: 128 ODY-N1081, Group C, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLTLSCATSRLNFSRTTVAWFRQAPGKERDFVAASGWARGRTYYADSLQGRFTISRDSNKNT
VYLQMNSLKLEDTAVYYCAARDSRRGGLFADLNEYDYWGQGTQVTVSS

SEQ ID NO: 129 ODY-N1081, Group C, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLTLSCAASRLAFSSSTVAWFRQAPGKEREFVAASGWSRTRTYYADSLQGRFTISRDNNRSTV
FLQTNSLKLEDTAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 130 ODY-N1081, Group C, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLTLSCTASRLTSSSSTMAWFRQAPGKERDFVAASGWARGRTYYADSLQGRFTISRDNTRNT
VYLQMNSLKLEDTAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 131 ODY-N1081, Group C, non-humanized, amino acid sequence
EVQLVESGGGLVQAGDSLTLSCTASRLTSNRTTMAWFRQAPGKERDFVAASGWARGRTYYADSLQGRFTISRDNNKN
TVYLQMNSLKLEDAAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 132 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDLVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 133 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLY
LQMNSLKPEDTAVYYCVATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 134 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAAAGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 135 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAGYDYWGQGTQVTVSS

SEQ ID NO: 136 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSHRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 137 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATADSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 138 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDTAKNTLY
LQMNSLKPEDTAVYYCAATGDSDRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 139 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKLEDTAVYYCVATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 140 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGASDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 141 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPADTAVYYCAATGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 142 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSDRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 143 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPTEYDDWGQGTQVTVSS

SEQ ID NO: 144 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRHAEYDYWGQGTQVTVSS

SEQ ID NO: 145 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEHDYWGQGTQVTVSS

SEQ ID NO: 146 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPTEYDSWGQGTQVTVSS

SEQ ID NO: 147 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence

EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCTATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 148 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGADDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 149 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYSGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 150 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGVYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 151 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISAGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPTEFDYWGQGTQVTVSS

SEQ ID NO: 152 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGVYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 153 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEHDYWGQGTQVTVSS

SEQ ID NO: 154 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSPIVGWFRQHPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNML
YLQMNSLKPEDTAVYYCAATGNSDRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 155 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCATTGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 156 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSPIVGWFRQHPGKEREFVAALISTGGNTRYADSVKGRFTISRDNAKNML
YLQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 157 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCASTGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 158 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRLAEYDYWGQGTQVTVSS

SEQ ID NO: 159 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSFRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 160 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGDYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 161 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEDDYWGQGTQVTVSS

SEQ ID NO: 162 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAAPGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 163 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGDYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 164 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCTATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 165 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYDSWGQGTQVTVSS

SEQ ID NO: 166 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence

EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAAPGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 167 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 168 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPADTAVYYCAATGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 169 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYGYWGQGTQVTVSS

SEQ ID NO: 170 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPTEFDYWGQGTQVTVSS

SEQ ID NO: 171 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYDHWGQGTQVTVSS

SEQ ID NO: 172 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLY
LQMNSLKPEDTAVYYCAAPGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 173 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPADYDYWGQGTQVTVSS

SEQ ID NO: 174 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYNYWGQGTQVTVSS

SEQ ID NO: 175 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGAYDRPAEYAYWGQGTQVTVSS

SEQ ID NO: 176 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDLYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 177 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPADTAVYYCAAPGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 178 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSSPIVGWFRQHPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNML
YLQMNSLKPEDTAVYYCAATGNSFRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 179 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPADTAVYYCAATGDSYRGAYDRSAEYDYWGQGTQVTVSS

SEQ ID NO: 180 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDSYRGSYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 181 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLY
LQMNSLKPEDTAVYYCAATGDSYGGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 182 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCVATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 183 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLY
LQMNSLKPEDTAVYYCTATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 184 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFSEPIVGWFRQTPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGDTYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 185 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence

EVQLVESGGGLVQAGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLKPEDTAVYYCAATGNSDRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 186 ODY-45F5_ODY-N1083_ODY-N1084, Group D, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCKASGRTVSNPIIGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCAATGNSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 187 ODY-N1091, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFDMYALGWFRQAPGKEREFVAAINRSGANTAYADSVKGRFTISRDNANN
LLYLRMNSLEPEDTAVYYCAAQFSLPVDATPLRRYAHWGQGTQVTVSS

SEQ ID NO: 188 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 189 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASTRTFDMYALGWFRQAPGKEREFVAAINRSGANTAYADSVKGRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDATPLRRYAHWGQGTQVTVSS

SEQ ID NO: 190 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFYMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNANNLL
YLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 191 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFNMYALGWFRQAPGKDREFVAAISRSGTNTPYADSVKGRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 192 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFDMYALGWFRQAPGKEREFVAAINRSGANTAYADSVKSRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDATPLRRYAHWGQGTQVTVSS

SEQ ID NO: 193 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDDANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 194 ODY-N1091_ODY-N1092, Group F, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNANNL
LYLRMNSLEPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTRVTVSS

SEQ ID NO: 195 ODY-N1095, Group G, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFDSLVMGWFRQAPGKEREFVAAISWNGRSTYYADSVKGRFTISRDNAKN
TVYLQMNSLKPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 196 ODY-N1095, Group G, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFDSLVMGWFRQAPGKEREFVAAISWNGRSTYYADSVKGRFTISRDNAKN
TMYLQMNSLKPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 197 ODY-N1095, Group G, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGRTFDSLVMGWFRQAPGKGREFVAAISWNGRSTYYADSVKGRFTISRDNAKN
TVYLQMNSLKPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 198 ODY-43B5, Group H, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGRTDSILNMGWFRQAPGKEREIVAAISWFRGETIYTASVKGRFTISRDKSKNTL
YLQMSSLKPGDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 199 ODY-43B5, Group H, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGRTDSILNMGWFRQALGKEREIVAAISWFRGETIYTASVKGRFTISRDKSKNTLY
LQMSSLKPEDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 200 ODY-43B5, Group H, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGRTDSILNMGWFRQVPGKEREIVAAISWFRGETIYTASVKGRFTISRDKSKNTL
YLQMSSLKPEDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 201 ODY-43B5, Group H, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACAASGRTDSILNMGWFRQAPGKEREIVAAISWFRGETIYTASVKGRFTISRDKSKNTLY
LQMSSLKPEDTAVYYCAARNGGYDLNDYAYWGQGTQVTVSS

SEQ ID NO: 202 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGDLVQPGGSLRLSCAASGIRFSNYAVGWFRRAPGKQRELVGMMYISGNTNYADSAKGRFTISRDDAKKTV
YLQMNSLKPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 203 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRRAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKTV
YLQMNSLKPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 204 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 205 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGDLVQPGGSLRLSCAASGIRFSNYAVGWFRRAPGKQRELVGMMYISGNTNYADSVKGRFTISRDDAKKTV
YLQMNSLKPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 206 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 207 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGGLTNYTDSVKGRFTISRDNDKNTVY
LQMNSLKPEDTAVYFCNAGGRRLGYWGQGIQVTVSS

SEQ ID NO: 208 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 209 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 210 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKGT
VYLQMNSLKSEDAAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 211 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFRPYAVGWYRQAPGEQRELVVTHTIRNKTDYADSVKGRFTISRDNAKNMV
YLQMNSLTPEDTAVYYCNAGGPTLGYWGQGTQVTVSS

SEQ ID NO: 212 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRRAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKTV
YLQMNSLKPEDTAVYYCNAGGMSLGYWGQGTQVTVSS

SEQ ID NO: 213 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGLRGYWGRGTQVTVSS

SEQ ID NO: 214 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYWTNYTDSAKGRFTISRDNGKNTV
YLQMNSLKPEDTAVYFCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 215 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCTAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 216 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCHAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 217 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGRRGYWGRGTQVTVSS

SEQ ID NO: 218 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGLRGYWGRGTQVTVSS

SEQ ID NO: 219 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYTESVKGRFTISRDNAKNTVY
LQMNSLKPEDTAVYYCNAGGGLRGYWGRGTQVTVSS

SEQ ID NO: 220 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSAYAMGWYRQAPGKQREFIAQITNGGITSYTDSVKGRFTISRDNDKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 221 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 222 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMTSLKPEDTAVYFCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 223 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCHAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 224 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYPDSVKGRFTISRDNAKNTVY
LQMNSLQPEDTAVYVCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 225 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCEASGIIFEPYSIGWHRQAPGKQRELVANMTSGGSTNYADSVKGRFTISRDNAKNTIY
LQMNSLKPEDTAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 226 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIILRPYAVGWYRQAPGEQRELVVTHTIRNKTDYADFVKGRFTISRDNAKNMV
YLQMNSLTPEDTAVYYCNAGGPTLGYWGQGTQVTVSS

SEQ ID NO: 227 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVATITNGGSTDYADSVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNGGGRLRGYWGQGTQVTVSS

SEQ ID NO: 228 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGLWGYWGRGTQVTVSS

SEQ ID NO: 229 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYTESVKGRFTISRDNAKNTVY
LQMNSLKPEDTAVYYCNAGGPRRGYWGRGTQVTVSS

SEQ ID NO: 230 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGENTVY
LQMNGLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 231 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCVASGIRFSSYAMAWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNDKNTVY
LQMNSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 232 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGENTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 233 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCTAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 234 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCNAGGRRFGYWGQGTQVTVSS

SEQ ID NO: 235 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRIGYWGQGTQVTVSS

SEQ ID NO: 236 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMTSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 237 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYTESVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 238 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGHWGQGTQVTVSS

SEQ ID NO: 239 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRFGYWGQGTQVTVSS

SEQ ID NO: 240 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRIGYWGQGTQVTVSS

SEQ ID NO: 241 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVRNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 242 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRLAYWGQGTQVTVSS

SEQ ID NO: 243 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRRTSGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 244 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGGLTNYTDSVKGRFTISRDNDKNTVY
LQMNSLKPEDTDVYFCNAGGRRLGYWGQGIQVTVSS

SEQ ID NO: 245 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGTLRLSCAASGIRFSFYALGWYRQAPGNQRELVANMTSGGSTSYADSVKGRFTISRDNAKNTV
FLQMNNLKPEDTAVYYCNAGGARLGYWGQGTQVTVSS

SEQ ID NO: 246 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSRYAAGWYRQAPGEKRELVATDTIRGVTNYSDSVKGRFAISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 247 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFRPYAVGWYRQAPGEQRELVVTHTIRNKTDYADSVKGRFTISRDNAKNMV
YLQMNSLTPEDTAVYYCNAGGPTLGYWGQGAQVTVSS

SEQ ID NO: 248 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSAYAMGWYRQAPGKQRELVATIFNSGGTNYADSVKGRFSISRDNAKNTV
YLQMKSLEPEDTAVYYCNAGGGLNGYWGQGTQVTVSS

SEQ ID NO: 249 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKNTL
YLQMNSLKPEDTAVYVCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 250 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKNTL
YLQMNSLKPEDAAVYVCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 251 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRRAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKTV
YLQMNSLKPEDTAVYYCNAGGLRRGYWGQGTQVTVSS

SEQ ID NO: 252 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDDAKNTVYL
QMNSLKPEDTAVYYCNAGGGLRGYWGRGTQVTVSS

SEQ ID NO: 253 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLARPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGLRGYWGRGTQVTVSS

SEQ ID NO: 254 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMLWYRQAPGLERELVAIITNGGSTNYTESVKGRFTISRDNAKNTVYL
QMNSLKPEDTAVYYCNAGGGPRGYWGRGTQVTVSS

SEQ ID NO: 255 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQREFVATITNGGSTDYQDSVKGRFTISRDNAKNTV
YLEMNSLKPEDTAVYYCNAGGRRRGYWGQGTQVTVSS

SEQ ID NO: 256 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFGSYAMGWYRQAPGKQRELVAIITNGGSTNYTESVKGRFTISRDNAKNTLY
LQMNSLKPEDTAVYYCNAGGRRRGYWGRGTQVTVSS

SEQ ID NO: 257 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRDMVAIITNGGSTNYTESVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNAGGHRRGYWGRGTQVTVSS

SEQ ID NO: 258 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYTESVKGRFTISRDNAKNTVL
LQMNSLKPEDTAVYYCNAGGHRRGYWGRGTQVTVSS

SEQ ID NO: 259 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCVASGIRFSSYAMGWHRQAPGKQRELVAIITNGGSTNYTESVKGRFTISRDNAKNTVY
LQMNSLKPEDTAVYYCNAGGHRRGYWGRGTQVTVSS

SEQ ID NO: 260 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCVASGIMFSHYAAGWYRQAPGKERELVVEIFLGGSTNYGDSLKGRATISRDNAKNTV
YLQMTSLKPDDTAVYYCNAGGGAKGYWGQGTQVTVSS

SEQ ID NO: 261 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQREEVAIITNGGSTNYAESVKGRFTISRDNAENTVY
LQMNSLKPEDTAVYYCNAGGPRRGYWGRGTQVTVSS

SEQ ID NO: 262 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITNGGTTNYADSVKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 263 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQALGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGENTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 264 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGDLVQPGGSLRLSCAASGLRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 265 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCYAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 266 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGDWGQGTQVTVSS

SEQ ID NO: 267 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCKAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 268 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRSTISRDNGKNTVY
LQMNSLKPEDTAVYFCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 269 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDTGKNTVY
LQMNSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 270 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRSTISRDNGKNTVY
LQMNSLKPEDTAVYFCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 271 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRSTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 272 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYTDSAKGRFTISRDNDKNTV
YLQMNSLKPEDTAVYFCNAGGRRLGFWGQGTQVTVSS

SEQ ID NO: 273 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYTESVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 274 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGSRLGYWGQGTQVTVSS

SEQ ID NO: 275 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGDRLGYWGQGTQVTVSS

SEQ ID NO: 276 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRSTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGSRLGYWGQGTQVTVSS

SEQ ID NO: 277 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDNGKNTVY
LQMNSLKPEDTAVYFCNAGGGRLAYWGQGTQVTVSS

SEQ ID NO: 278 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYTDSVKGRFTISRDTGKNTVY
LQMNSLKPEDTAVYFCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 279 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYWTNYTDSAKGRFTISRDNGKNTV
YLQMNSLKPEDTAVYFCNAGGHRLGYWGQGTQVTVSS

SEQ ID NO: 280 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCAASGMNFEAYAMMWFRRTPGKQRELVASITKGGVQNYSDSTKGRFTIFRDNAKST
VYLQMNSLKSEDAAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 281 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLTLSCVASGIVFSRYSAGWFRQAPGKQRELVAEIFLGGSTNYTDSLKGRFTISRDNVKNMVY
LQMSSLKPDDTAVYYCNAGGRNLGYWGQGTQVTVSS

SEQ ID NO: 282 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCTASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTVY
LQMNSLQPEDTAVYVCNAGGGALGYWGQGTQVTVSS

SEQ ID NO: 283 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTVY
LQLNSLQPEDTAVYVCNAGGGALGYWGQGTQVTVSS

SEQ ID NO: 284 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTVY
LQMNSLQPEDTAVYVCNAGGGALGYWGQGTQVTVSS

SEQ ID NO: 285 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCTASGIRFSRYAMGWYRQTPGNQRELVVSITSGGNTDYADSAKGRFTISRDNAKNTV
YLAMNSLKPEDTAVYICNAGGNVLGYWGQGTQVTVSS

SEQ ID NO: 286 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGIIFSSYAAGWYRQAPGKKREVVAGITKPGDTNYADSVKGRFAISRDNAKNTVY
LQMNSLKPEDTGVYYCNAGGAPLGYWGQGTQVTVSS

SEQ ID NO: 287 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRISAYAMGWYRQATGKQRELVAQNFLTGTTNYTDSVTGRFTISRDNGENTV
YLQMNSLKPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 288 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRISAYAMGWYRQATGKMRELVAHNLLTGTTNYADSVTGRFTISRDNGENTV
YLQMNSLKPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 289 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSRYAAGWYRQAPGEKRELVATNNIRDVTNYSDSVKGRFAISRDNAKNTVY
LQMNSLKPEDTAVYYCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 290 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFRPYAVGWYRQAPGEQRELVVTHTIRNKTDYADPVKGRFTISRDNAKNMV
YLQMNSLTPEDTAVYYCNAGGPTLGYWGQGTQVTVSS

SEQ ID NO: 291 ODY-43E7_ODY-44A4, Group I, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIFISRYAMGWYRQARGMQRELVALNGLIDGTNYADSVTGRFTMSRDNGENT
VYLQMNSLKPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 292 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSSYAMGWYRQGPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 293 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGSVQPGRSLRLSCTASGIRFSSYAMGWYRQGPGKQRELVANMTIGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYFCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 294 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSSYAMGWYRQGPGKQRDLVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLKGYWGQGTQVTVSS

SEQ ID NO: 295 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSSYAMGWYRQGPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGRLKGYWGQGTQVTVSS

SEQ ID NO: 296 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSRYAMGWYRQGPGKQRDLVASMTNGGMTTYADSVKGRFTISRDNDKK
VVYLQMNSLKSEDTAVYYCNVGGQEMGYWGQGTQVTVSS

SEQ ID NO: 297 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTASGIRFSSYAMGWYRQGPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLKGYWGQGTQVTVSS

SEQ ID NO: 298 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSSYAMGWYRQGPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLKGYWGQGTQVTVSS

SEQ ID NO: 299 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLKLSCTASGIRFSAYAMGWYRRGPGKQRELVANMTAGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLLGYWGQGTQVTVSS

SEQ ID NO: 300 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCTASGIRFSAYAMGWYRRGPGKQRELVASMTAGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLKSEDTAVYYCNVGGQLLGYWGQGTQVTVSS

SEQ ID NO: 301 ODY-N1242, Group J, non-humanized, amino acid sequence
EVQLVESGGGLVQPGRSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVATITNGGITNYTDSVKGRFTISRDNAKNTM
YLQMSNLKPEDTAVYYCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 302 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGDSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMIAFITSGGSTNYTDSVKGRFTISRDNAKSRA
YLQMNSLKPEDTAVYYCNQGGPKGYWGKGTQVTVSS

SEQ ID NO: 303 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMIAFITSGGSTNYTDSVKGRFTISRDNAKSRA
YLQMNSLKPEDTAVYYCNQGGPKGYWGQGTQVTVSS

SEQ ID NO: 304 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCGASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYTDSVKGRFTISRDNAKNTS
NLQMNSLKPEDTAVYYCNEGGLKGYWGQGTQVTVSS

SEQ ID NO: 305 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCGASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYTDSVKGRFTISRDNAKNTS
NLQMNSLKPEDTAVYYCNGGGLKGYWGQGTQVTVSS

SEQ ID NO: 306 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYTDSLKGRFTISRDNAKNT
VYLQMNSLSPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 307 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQPPGKQRELVALITNSGTTNYTDSVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNQGGQRGYWGKGTQVTVSS

SEQ ID NO: 308 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMIAFITSGGSTNYTDSVKGRFTISRDNAKSRA
YLQMNSLKPEDTAVYYCNPGGPKGYWGQGTQVTVSS

SEQ ID NO: 309 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCAASGIRFRAYAMGWYRQAPGKQREMVAFITSGGSTNYADSVKGRFTISRDNAKNT
VYLQMNSLKPEDTDVYYCNSGGLKGYWGQGTQVTVSS

SEQ ID NO: 310 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNT
TYLQMNSLKPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 311 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYTDSVKGRFTITRDNAKDTV
YLQMNSLKPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 312 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYTDSLKGRSTISRDNAKST
VYLQMNSLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 313 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAVGWYRQGPGLQRELVAQLTINGDTTYEDSVKGRFTISRDNAKAMV
YLQMTSLKPEDTAVYYCNLGGSKGYWGQGTQVTVSS

SEQ ID NO: 314 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYTDSVKGRFTISRDNAKKRA
YLQMNSLKPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 315 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYTDSVKGRFTISRDNAKSRA
YLQMNSLKPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 316 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSRFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYTDSVKGRFTISRDNAKSRA
YLQMNSLKPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 317 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYTDSVKGRFTISRDNAKKRA
YLQMNSLKPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 318 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCGASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYTDSVKGRFTISRDNAKNTS
NLQMNSLKPEDTAVYYCNPGGLKGYWGQGTQVTVSS

SEQ ID NO: 319 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNTA
YLQMNSLKPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 320 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNT
TYLQMNSLKPEDTAVYYCNQGGRKGYWGQGTQVTVSS

SEQ ID NO: 321 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNTA
YLQMNSLKPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 322 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNTA
YLQMNSLKPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 323 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNTA
YLQMNSLKPEDTAVYYCNPGGSKGYWGQGTQVTVSS

SEQ ID NO: 324 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLACTSSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYTDSVKGRFTITRDNAKNT
TYLQMNSLKPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 325 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLTCISSGSIFSSYAMVWYRQAPGKQRDMVAWITSGGRTNYTDSVKGRFTITRDNAKNTA
YLQMNSLKPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 326 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCTSSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYTDSVKGRFTITRDNAKDTV
YLQMNSLKPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 327 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYTDSLKGRSTISRDNAKNT
VYLQMNSLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 328 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVAMITNGGTTNYTDSVKGRFAISRDNAKDT
VYLQMNSLKSEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 329 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYTDSLKGRSTISRDNAKST
VYLQMNSLKPEDTAVYYCNQGGQQGYWGKGTQVTVSS

SEQ ID NO: 330 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVAWITNGGITNYTDSLLGRFTISRDNAKNTL
YLQMNSLKPEDTAVYYCNQGGRKGYWGLGTQVTVSS

SEQ ID NO: 331 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAVGWYRQAPGKQRESVATITNGGTTNYTDSVKGRFSISRDNANNTV
YLQMNSLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 332 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYTDSLKGRFTISRDNAKNT
VYLQMNSLSPEDTAVYYCNQGGQQGYWGKGTQVTVSS

SEQ ID NO: 333 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYTDSLKGRFTISRDNAKNT
VYLQMNSLSPEDTAVYYCNQGGQRGYWGKGTQVTVSS

SEQ ID NO: 334 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYTDSLKGRFTISRDNAKNT
VYLQMNSLSPEDTAVYYCNQGGQKAYWGKGTQVTVSS

SEQ ID NO: 335 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYTDSLKGRFTISRDNAKN
TVYLQMNSLSPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 336 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAVGWYRQGPGLQRELVAQLTINGDTTYEDSVKGRFSISRDNAKAMV
YLQMTSLKPEDTAVYYCNLGGSKGYRGQGTQVTVSS

SEQ ID NO: 337 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQAGESLRLSCATSGIRFEAYAMGWYRQAPGKQREMVALITSGGNTNYADSAKGRFTISRDNAKNT
VYLQMNSLKPDDTDVYYCNSGGLKGYWGQGTQVTVSS

SEQ ID NO: 338 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQPPGKQRDLVALITNSGTTNYTDSVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNQGGQRGYWGKGTQVTVSS

SEQ ID NO: 339 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQPPGKQRELVALITNSGTTNYTDSVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 340 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQPPGKQRELVALITNSGTTNYTDSVKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNQGGQQGYWGKGTQVTVSS

SEQ ID NO: 341 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCVSSGSIFSRYAMVWYRQAPGKQRELVAWISNGGITNYTDSLLGRFTISRDNAKNTVY
LQMNNLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 342 ODY-44A1, Group K, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRYAMGWYRQAPEKQRELVAWISNGGITNYTDSLKGRFTISRDNAKNTV
YLQMNSLKPEDTAVYYCNQGGQKGYWGKGTQVTVSS

SEQ ID NO: 343 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSSISRGGRTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 344 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSSFSRGGRTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 345 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNVNIGWFRQAPGKEREGVSWISRGGRTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 346 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLTNYNIGWFRQAPGKEREGVSSISRGGRTNYADSAKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 347 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREGVSSISRGGRTNYADSAKGRFTISRDSAKNTVY
LQMNSLRPEDTAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 348 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNYNIGWFRQAPGKEREEVSSISRGGRTNYADSAKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCALCLLRFETCLEYNRAQYPYWGQGTQVTVSS

SEQ ID NO: 349 ODY-N1061, Group A, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRVSCAASGFTLSNTNIGWFRQAPGKEREGVSWFSRGGRTAYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAACLLRFESCLEYNRAQYNYWGQGTQVTVSS

SEQ ID NO: 350 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRCGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 351 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRSGSDCWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 352 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSWISTSGRSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAAVRSGSDWWTTMTQRHYDFWGQGTQVTVSS

SEQ ID NO: 353 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRSGCDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 354 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAAVRSGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 355 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVCSGSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 356 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSWISTSGRTTNYADSLKGRFTISRDTAKNTV
YLQINSLRPEDTAVYYCAAVRAGSDWWTTMRQRDYDYWGQGTQVTVSS

SEQ ID NO: 357 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRTTNYADSLKGRFTISRDTAKNTVY
LQINSLRPEDTAVYYCAAVRAGSDWWTTMRQRDYDYCGQGTQVTVSS

SEQ ID NO: 358 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRSGSDWWTTMTQRHYDFCGQGTQVTVSS

SEQ ID NO: 359 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRSGSDWCTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 360 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRSCSDWWTTMTQRHYDYWGQGTQVTVSS

SEQ ID NO: 361 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRCTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAAVRAGSDWWTTMRQRDYDYWGQGTQVTVSS

SEQ ID NO: 362 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGSPLDYYAIGWFRQAPGKEREGVSCISTSGRSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCAAVRCGSDWWTTMTQSHYDFWGQGTQVTVSS

SEQ ID NO: 363 ODY-N1070, Group B, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAAAGSPLDYYAIGWFRQAPGKEREGVSCISTSGRATNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCAAVRAGSDWWTTMTQRHYDYCGQGTQVTVSS

SEQ ID NO: 364 ODY-N1081, Group C, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCATSRLNFSRTTVAWFRQAPGKERDFVAASGWARGRTYYADSLKGRFTISRDSNKNT
VYLQMNSLRLEDTAVYYCAARDSRRGGLFADLNEYDYWGQGTQVTVSS

SEQ ID NO: 365 ODY-N1081, Group C, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASRLAFSSSTVAWFRQAPGKEREFVAASGWSRTRTYYADSLKGRFTISRDNNKSTV
YLQTNSLRLEDTAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 366 ODY-N1081, Group C, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASRLTSSSSTMAWFRQAPGKERDFVAASGWARGRTYYADSLKGRFTISRDNTKNT
VYLQMNSLRLEDTAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 367 ODY-N1081, Group C, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASRLTSNRTTMAWFRQAPGKERDFVAASGWARGRTYYADSLKGRFTISRDNNKN
TVYLQMNSLRLEDTAVYYCAARDSRKGGLFADLNGYDYWGQGTQVTVSS

SEQ ID NO: 368 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDLVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGNSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 369 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLYL
QMNSLRPEDTAVYYCVATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 370 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAAAGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 371 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAGYDYWGQGTQVTVSS

SEQ ID NO: 372 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSHRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 373 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATADSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 374 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDTAKNTLY
LQMNSLRPEDTAVYYCAATGDSDRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 375 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRLEDTAVYYCVATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 376 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGASDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 377 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 378 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSDRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 379 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGAYDRPTEYDDWGQGTQVTVSS

SEQ ID NO: 380 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRHAEYDYWGQGTQVTVSS

SEQ ID NO: 381 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLYL
QMNSLRPEDTAVYYCAATGDSYRGAYDRPAEHDYWGQGTQVTVSS

SEQ ID NO: 382 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGAYDRPTEYDSWGQGTQVTVSS

SEQ ID NO: 383 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCTATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 384 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGADDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 385 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYSGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 386 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGVYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 387 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISAGGSTRYADSVKGRFTISRDDAKNTLY
LQMNSLRPEDTAVYYCAATGNSYRGAYDRPTEFDYWGQGTQVTVSS

SEQ ID NO: 388 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGVYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 389 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEHDYWGQGTQVTVSS

SEQ ID NO: 390 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSSPIVGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGNSDRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 391 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCATTGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 392 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSSPIVGWFRQAPGKEREFVAALISTGGNTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 393 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCASTGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 394 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRLAEYDYWGQGTQVTVSS

SEQ ID NO: 395 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSFRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 396 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGDYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 397 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEDDYWGQGTQVTVSS

SEQ ID NO: 398 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAAPGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 399 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGDYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 400 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCTATGNSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 401 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYDSWGQGTQVTVSS

SEQ ID NO: 402 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAAPGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 403 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 404 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYGYWGQGTQVTVSS

SEQ ID NO: 405 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSYRGAYDRPTEFDYWGQGTQVTVSS

SEQ ID NO: 406 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYDHWGQGTQVTVSS

SEQ ID NO: 407 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLYL
QMNSLRPEDTAVYYCAAPGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 408 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPADYDYWGQGTQVTVSS

SEQ ID NO: 409 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYNYWGQGTQVTVSS

SEQ ID NO: 410 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGAYDRPAEYAYWGQGTQVTVSS

SEQ ID NO: 411 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAAPGDSYRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 412 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSSPIVGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGNSFRGAYDRPAEYDFWGQGTQVTVSS

SEQ ID NO: 413 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGDSYRGAYDRSAEYDYWGQGTQVTVSS

SEQ ID NO: 414 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDSYRGSYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 415 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLYL
QMNSLRPEDTAVYYCAATGDSYGGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 416 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCVATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 417 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPIVGWFRQAPGKEREFVAALISSGGSTRYADSVKGRFTISRDSAKNTLYL
QMNSLRPEDTAVYYCTATGDSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 418 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSEPIVGWFRQAPGKERDFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGDTYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 419 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFSTPITGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDDAKNTLYL
QMNSLRPEDTAVYYCAATGNSDRGAYDRPTEYDYWGQGTQVTVSS

SEQ ID NO: 420 ODY-45F5_ODY-N1083_ODY-N1084, Group D, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTVSNPIIGWFRQAPGKEREFVAALISTGGSTRYADSVKGRFTISRDNAKNTLY
LQMNSLRPEDTAVYYCAATGNSYRGAYDRPAEYDYWGQGTQVTVSS

SEQ ID NO: 421 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFDMYALGWFRQAPGKEREFVAAINRSGANTAYADSVKGRFTISRDNAKNT
LYLQMNSLRPEDTAVYYCAAQFSLPVDATPLRRYAHWGQGTQVTVSS

SEQ ID NO: 422 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFYMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 423 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFNMYALGWFRQAPGKDREFVAAISRSGTNTPYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 424 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDDAKNTL
YLQMNSLRPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTQVTVSS

SEQ ID NO: 425 ODY-N1091_ODY-N1092, Group F, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASTRTFNMYALGWFRQAPGKEREFVAAISRSGTNTPYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCAAQFSLPVDASPLRRYYYWGQGTRVTVSS

SEQ ID NO: 426 ODY-N1095, Group G, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFDSLVMGWFRQAPGKEREFVAAISWNGRSTYYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 427 ODY-N1095, Group G, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFDSLVMGWFRQAPGKEREFVAAISWNGRSTYYADSVKGRFTISRDNAKNT
MYLQMNSLRPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 428 ODY-N1095, Group G, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTFDSLVMGWFRQAPGKGREFVAAISWNGRSTYYADSVKGRFTISRDNAKN
TVYLQMNSLRPEDTAVYYCAATRKTRRSTVAGTEVDYWGQGTQVTVSS

SEQ ID NO: 429 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRQAPGKQRELVGMMYISGNTNYADSAKGRFTISRDDAKKT
VYLQMNSLRPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 430 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRQAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKT
VYLQMNSLRPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 431 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKS
TVYLQMNSLRSEDTAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 432 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRQAPGKQRELVGMMYISGNTNYADSVKGRFTISRDDAKKT
VYLQMNSLRPEDTAVYYCNAGGMRRGYWGQGTQVTVSS

SEQ ID NO: 433 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 434 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGGLTNYADSVKGRFTISRDNDKNTVY
LQMNSLRPEDTAVYYCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 435 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 436 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 437 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKG
TVYLQMNSLRSEDTAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 438 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFRPYAVGWYRQAPGKQRELVVTHTIRNKTDYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGPTLGYWGQGTQVTVSS

SEQ ID NO: 439 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRQAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKT
VYLQMNSLRPEDTAVYYCNAGGMSLGYWGQGTQVTVSS

SEQ ID NO: 440 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGLRGYWGQGTQVTVSS

SEQ ID NO: 441 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYWTNYADSAKGRFTISRDNGKNTV
YLQMNSLRPEDTAVYYCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 442 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKS
TVYLQMNSLRSEDTAVYYCTAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 443 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKS
TVYLQMNSLRSEDTAVYYCHAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 444 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGRRGYWGQGTQVTVSS

SEQ ID NO: 445 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGGLRGYWGQGTQVTVSS

SEQ ID NO: 446 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSAYAMGWYRQAPGKQREFIAQITNGGITSYADSVKGRFTISRDNDKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 447 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCHAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 448 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 449 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFEPYSIGWHRQAPGKQRELVANMTSGGSTNYADSVKGRFTISRDNAKNTIY
LQMNSLRPEDTAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 450 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIILRPYAVGWYRQAPGKQRELVVTHTIRNKTDYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGPTLGYWGQGTQVTVSS

SEQ ID NO: 451 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVATITNGGSTDYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNGGGRLRGYWGQGTQVTVSS

SEQ ID NO: 452 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGLWGYWGQGTQVTVSS

SEQ ID NO: 453 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGPRRGYWGQGTQVTVSS

SEQ ID NO: 454 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 455 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMAWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNDKNTVY
LQMNSLRPEDTAVYYCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 456 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCTAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 457 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCNAGGRRFGYWGQGTQVTVSS

SEQ ID NO: 458 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRIGYWGQGTQVTVSS

SEQ ID NO: 459 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 460 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGHWGQGTQVTVSS

SEQ ID NO: 461 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRFGYWGQGTQVTVSS

SEQ ID NO: 462 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKS
TVYLQMNSLRSEDTAVYYCNAGGPRIGYWGQGTQVTVSS

SEQ ID NO: 463 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVRNYADSTKGRFTISRDNAKST
VYLQMNSLRSEDTAVYYCNAGGPRLGYWGQGTQVTVSS

SEQ ID NO: 464 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGMNFEAYAMMWFRQAPGKQRELVASITKGGVQNYADSTKGRFTISRDNAKS
TVYLQMNSLRSEDTAVYYCNAGGPRLAYWGQGTQVTVSS

SEQ ID NO: 465 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGGLTNYADSVKGRFTISRDNDKNTVY
LQMNSLRPEDTDVYYCNAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 466 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSFYALGWYRQAPGKQRELVANMTSGGSTSYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGARLGYWGQGTQVTVSS

SEQ ID NO: 467 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSRYAAGWYRQAPGKKRELVATDTIRGVTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 468 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSAYAMGWYRQAPGKQRELVATIFNSGGTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGGLNGYWGQGTQVTVSS

SEQ ID NO: 469 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 470 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSQYAMGWYRQAPGKQRELVANIFKDGTTNYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCNAGGAALGYWGQGTQVTVSS

SEQ ID NO: 471 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSNYAVGWFRQAPGKQRELVGMMYINGNTSYADSVKGRFTISRDDAKKT
VYLQMNSLRPEDTAVYYCNAGGLRRGYWGQGTQVTVSS

SEQ ID NO: 472 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDDAKNTVY
LQMNSLRPEDTAVYYCNAGGGLRGYWGQGTQVTVSS

SEQ ID NO: 473 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLAQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGLRGYWGQGTQVTVSS

SEQ ID NO: 474 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMLWYRQAPGKERELVAIITNGGSTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGPRGYWGQGTQVTVSS

SEQ ID NO: 475 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFVATITNGGSTDYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGRRRGYWGQGTQVTVSS

SEQ ID NO: 476 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFGSYAMGWYRQAPGKQRELVAIITNGGSTNYADSVKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCNAGGRRRGYWGQGTQVTVSS

SEQ ID NO: 477 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRDMVAIITNGGSTNYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCNAGGHRRGYWGQGTQVTVSS

SEQ ID NO: 478 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVAIITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGHRRGYWGQGTQVTVSS

SEQ ID NO: 479 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWHRQAPGKQRELVAIITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGHRRGYWGQGTQVTVSS

SEQ ID NO: 480 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIMFSHYAAGWYRQAPGKERELVVEIFLGGSTNYADSLKGRATISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGGAKGYWGQGTQVTVSS

SEQ ID NO: 481 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREEVAIITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGPRRGYWGQGTQVTVSS

SEQ ID NO: 482 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITNGGTTNYADSVKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 483 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 484 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCYAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 485 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGDWGQGTQVTVSS

SEQ ID NO: 486 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCKAGGRRLGYWGQGTQVTVSS

SEQ ID NO: 487 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRSTISRDNGKNTVY
LQMNSLRPEDTAVYYCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 488 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDTGKNTVY
LQMNSLRPEDTAVYYCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 489 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRSTISRDNGKNTVY
LQMNSLRPEDTAVYYCKAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 490 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRSTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 491 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKHREFIAQITSGYWTNYADSAKGRFTISRDNDKNTV
YLQMNSLRPEDTAVYYCNAGGRRLGFWGQGTQVTVSS

SEQ ID NO: 492 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMEWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 493 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGSRLGYWGQGTQVTVSS

SEQ ID NO: 494 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGDRLGYWGQGTQVTVSS

SEQ ID NO: 495 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRSTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGSRLGYWGQGTQVTVSS

SEQ ID NO: 496 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDNGKNTVY
LQMNSLRPEDTAVYYCNAGGGRLAYWGQGTQVTVSS

SEQ ID NO: 497 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYRTNYADSVKGRFTISRDTGKNTVY
LQMNSLRPEDTAVYYCTAGGGRLGYWGQGTQVTVSS

SEQ ID NO: 498 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQREFIAQITSGYWTNYADSAKGRFTISRDNGKNTV
YLQMNSLRPEDTAVYYCNAGGHRLGYWGQGTQVTVSS

SEQ ID NO: 499 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIVFSRYSAGWFRQAPGKQRELVAEIFLGGSTNYADSLKGRFTISRDNVKNTVYL
QMNSLRPEDTAVYYCNAGGRNLGYWGQGTQVTVSS

SEQ ID NO: 500 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGGALGYWGQGTQVTVSS

SEQ ID NO: 501 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSRYAMGWGRQAPGKQRELVASIFIDDTTNYADSVKGRFTISRDNAKNTV
YLQLNSLRPEDTAVYYCNAGGGALGYWGQGTQVTVSS

SEQ ID NO: 502 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSRYAMGWYRQAPGKQRELVVSITSGGNTDYADSAKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNAGGNVLGYWGQGTQVTVSS

SEQ ID NO: 503 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSSYAAGWYRQAPGKKREVVAGITKPGDTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTGVYYCNAGGAPLGYWGQGTQVTVSS

SEQ ID NO: 504 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRISAYAMGWYRQAPGKQRELVAQNFLTGTTNYADSVKGRFTISRDNGKNTV
YLQMNSLRPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 505 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRISAYAMGWYRQAPGKMRELVAHNLLTGTTNYADSVKGRFTISRDNGKNT
VYLQMNSLRPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 506 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIIFSRYAAGWYRQAPGKKRELVATNNIRDVTNYADSVKGRFTISRDNAKNTVY
LQMNSLRPEDTAVYYCNAGGALLGYWGQGTQVTVSS

SEQ ID NO: 507 ODY-43E7_ODY-44A4, Group I, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIFISRYAMGWYRQAPGKQRELVALNGLIDGTNYADSVKGRFTMSRDNGKNT
VYLQMNSLRPEDTAVYYCNAGGERLGYWGQGTQVTVSS

SEQ ID NO: 508 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLRSEDTAVYYCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 509 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVANMTIGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLRSEDTAVYYCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 510 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRDLVANMTTGGMTTYADSVKGRFTISRDNDKK
TVYLQMNSLRSEDTAVYYCNVGGQLKGYWGQGTQVTVSS

SEQ ID NO: 511 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLRSEDTAVYYCNVGGRLKGYWGQGTQVTVSS

SEQ ID NO: 512 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSRYAMGWYRQAPGKQRDLVASMTNGGMTTYADSVKGRFTISRDNDKK
TVYLQMNSLRSEDTAVYYCNVGGQEMGYWGQGTQVTVSS

SEQ ID NO: 513 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVANMTTGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLRSEDTAVYYCNVGGQLKGYWGQGTQVTVSS

SEQ ID NO: 514 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSAYAMGWYRQAPGKQRELVASMTAGGMTTYADSVKGRFTISRDNDKKT
VYLQMNSLRSEDTAVYYCNVGGQLLGYWGQGTQVTVSS

SEQ ID NO: 515 ODY-N1242, Group J, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKQRELVATITNGGITNYADSVKGRFTISRDNAKNTM
YLQMNSLRPEDTAVYYCNVGGQLRGYWGQGTQVTVSS

SEQ ID NO: 516 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMIAFITSGGSTNYADSVKGRFTISRDNAKSTA
YLQMNSLRPEDTAVYYCNQGGPKGYWGQGTQVTVSS

SEQ ID NO: 517 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYADSVKGRFTISRDNAKNTSY
LQMNSLRPEDTAVYYCNEGGLKGYWGQGTQVTVSS

SEQ ID NO: 518 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYADSVKGRFTISRDNAKNTSY
LQMNSLRPEDTAVYYCNGGGLKGYWGQGTQVTVSS

SEQ ID NO: 519 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYADSLKGRFTISRDNAKN
TVYLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 520 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVALITNSGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQRGYWGQGTQVTVSS

SEQ ID NO: 521 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMIAFITSGGSTNYADSVKGRFTISRDNAKSTA
YLQMNSLRPEDTAVYYCNPGGPKGYWGQGTQVTVSS

SEQ ID NO: 522 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFRAYAMGWYRQAPGKQREMVAFITSGGSTNYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTDVYYCNSGGLKGYWGQGTQVTVSS

SEQ ID NO: 523 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNT
TYLQMNSLRPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 524 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYADSVKGRFTISRDNAKDT
VYLQMNSLRPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 525 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYADSLKGRSTISRDNAKST
VYLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 526 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAVGWYRQAPGKQRELVAQLTINGDTTYADSVKGRFTISRDNAKATV
YLQMNSLRPEDTAVYYCNLGGSKGYWGQGTQVTVSS

SEQ ID NO: 527 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYADSVKGRFTISRDNAKKTA
YLQMNSLRPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 528 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYADSVKGRFTISRDNAKSTA
YLQMNSLRPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 529 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYADSVKGRFTISRDNAKST
AYLQMNSLRPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 530 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMGWYRQAPGKQRDMVAFITSGGSTNYADSVKGRFTISRDNAKKTA
YLQMNSLRPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 531 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGIRFSSYAMGWYRQAPGKERELVAVIFSGGGTNYADSVKGRFTISRDNAKNTSY
LQMNSLRPEDTAVYYCNPGGLKGYWGQGTQVTVSS

SEQ ID NO: 532 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNTA
YLQMNSLRPEDTAVYYCNQGGGKGYWGQGTQVTVSS

SEQ ID NO: 533 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNT
TYLQMNSLRPEDTAVYYCNQGGRKGYWGQGTQVTVSS

SEQ ID NO: 534 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNTA
YLQMNSLRPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 535 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNTA
YLQMNSLRPEDTAVYYCNQGGSKGYWGQGTQVTVSS

SEQ ID NO: 536 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNTA
YLQMNSLRPEDTAVYYCNPGGSKGYWGQGTQVTVSS

SEQ ID NO: 537 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMFWYRQAPGKQRDMVAFITSGGGTNYADSVKGRFTISRDNAKNT
TYLQMNSLRPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 538 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSSYAMVWYRQAPGKQRDMVAWITSGGRTNYADSVKGRFTISRDNAKNT
AYLQMNSLRPEDTAVYYCNQGGTKGYWGQGTQVTVSS

SEQ ID NO: 539 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSSYAMVWYRQAPGKQRDMVALITSGGRTNYADSVKGRFTISRDNAKDT
VYLQMNSLRPEDTAVYYCNHGGSKGYWGQGTQVTVSS

SEQ ID NO: 540 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYADSLKGRSTISRDNAKNT
VYLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 541 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVAMITNGGTTNYADSVKGRFTISRDNAKDT
VYLQMNSLRSEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 542 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGLTNYADSLKGRSTISRDNAKST
VYLQMNSLRPEDTAVYYCNQGGQQGYWGQGTQVTVSS

SEQ ID NO: 543 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVAWITNGGITNYADSLKGRFTISRDNAKNTL
YLQMNSLRPEDTAVYYCNQGGRKGYWGQGTQVTVSS

SEQ ID NO: 544 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAVGWYRQAPGKQRESVATITNGGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 545 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYADSLKGRFTISRDNAKN
TVYLQMNSLRPEDTAVYYCNQGGQQGYWGQGTQVTVSS

SEQ ID NO: 546 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYADSLKGRFTISRDNAKN
TVYLQMNSLRPEDTAVYYCNQGGQRGYWGQGTQVTVSS

SEQ ID NO: 547 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRWAMGWYRQAPGKQRELVAWITNGGATNYADSLKGRFTISRDNAKN
TVYLQMNSLRPEDTAVYYCNQGGQKAYWGQGTQVTVSS

SEQ ID NO: 548 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAVGWYRQAPGKQRELVAQLTINGDTTYADSVKGRFTISRDNAKATV
YLQMNSLRPEDTAVYYCNLGGSKGYRGQGTQVTVSS

SEQ ID NO: 549 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCATSGIRFEAYAMGWYRQAPGKQREMVALITSGGNTNYADSAKGRFTISRDNAKNT
VYLQMNSLRPEDTDVYYCNSGGLKGYWGQGTQVTVSS

SEQ ID NO: 550 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRDLVALITNSGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQRGYWGQGTQVTVSS

SEQ ID NO: 551 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVALITNSGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 552 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRWAMGWYRQAPGKQRELVALITNSGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQQGYWGQGTQVTVSS

SEQ ID NO: 553 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSIFSRYAMVWYRQAPGKQRELVAWISNGGITNYADSLKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 554 ODY-44A1, Group K, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCASSGSRFSRYAMGWYRQAPGKQRELVAWISNGGITNYADSLKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNQGGQKGYWGQGTQVTVSS

SEQ ID NO: 637 ODY-N1091_ODY-N1092, Group F, CDR1, amino acid sequence
TRTFDMYA

SEQ ID NO: 875 ODY-N1091_ODY-N1092, Group F, CDR2, amino acid sequence
INRSGANT

SEQ ID NO: 1113 ODY-N1091_ODY-N1092, Group F, CDR3, amino acid sequence
AAQFSLPVDATPLRRYAH

SEQ ID NO: 1351 ODY-N1091_ODY-N1092, Group F, VHH DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCTCCTGTGCAGCCTC
TACTCGCACCTTCGATATGTATGCCTTGGGCTGGTTCCGCCAGGCTCCAGGGAAGGAGCGTGAGTTTGTAGCAGCT
ATTAATCGGAGTGGTGCCAACACAGCCTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC
AACAACTTACTGTATCTGCGCATGAACAGCCTGGAACCTGAGGACACGGCCGTGTATTACTGTGCGGCACAATTCT
CGCTGCCAGTAGACGCTACCCCCCTTAGACGGTATGCCCACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 1607 ODY-N1117, Group M, CDR1, amino acid sequence
GGTASEYG

SEQ ID NO: 1608 ODY-N1117, Group M, CDR2, amino acid sequence
ISTSGGVT

SEQ ID NO: 1609 ODY-N1117, Group M, CDR3, amino acid sequence
AADGLPYGDWFGDQFDV

SEQ ID NO: 1610 ODY-N1129, Group N, CDR1, amino acid sequence
EQTMTGFW

SEQ ID NO: 1611 ODY-N1129, Group N, CDR2, amino acid sequence
ISASGSRV

SEQ ID NO: 1612 ODY-N1129, Group N, CDR3, amino acid sequence
AFNKWGRLSADLDDYFR

SEQ ID NO: 1613 ODY-N1186, Group O, CDR1, amino acid sequence
GLRFSNYA

SEQ ID NO: 1614 ODY-N1186, Group O, CDR2, amino acid sequence
ITKGGIT

SEQ ID NO: 1615 ODY-N1186, Group O, CDR3, amino acid sequence
NMHRSYDISFYDN

SEQ ID NO: 1616 ODY-N1264, Group P, CDR1, amino acid sequence
GGTVSGYA

SEQ ID NO: 1617 ODY-N1264, Group P, CDR2, amino acid sequence
INSGGPT

SEQ ID NO: 1618 ODY-N1264, Group P, CDR3, amino acid sequence
RRYDDYGS

SEQ ID NO: 1619 ODY-N1117, Group M, non-humanized, amino acid sequence
EVQLVESGGGLVQAGSSLRLSCVASGGTASEYGMGWFRRAPGKEREFVSRISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNDLKPEDTAVYYCAADGLPYGDWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1620 ODY-N1129, Group N, non-humanized, amino acid sequence
EVQLVESGGGLVQPGDSLRLSCKRSEQTMTGFWMGWFRQALGKEREFVGAISASGSRVVYADSVKGRFAISKDNSDN
TLFLLMNSLKPEDTAVYYCAFNKWGRLSADLDDYFRWGQGTQVTVSS

SEQ ID NO: 1621 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQYGGSLRLSCAASGLRFSNYAMGWYRQAPGKQREFVAFITKGGITNYTDSVKGRFTISRDNAKNTV
YLEMSSLEPEDTGVYYCNMHRSYDISFYDNWGQGTQVTVSS

SEQ ID NO: 1622 ODY-N1264, Group P, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGGTVSGYAMGWYRRTPGKEREFVAAINSGGPTWYADSVQGRATISRDNAKN
TVYLQLNSLKPEDTAVYYCRRYDDYGSWGQGTQVTVSS

SEQ ID NO: 1623 ODY-N1117, Group M, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGGTASEYGMGWFRQAPGKEREFVSRISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCAADGLPYGDWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1624 ODY-N1129, Group N, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCARSEQTMTGFWMGWFRQAPGKEREFVGAISASGSRVVYADSVKGRFTISKDNSKN
TLYLQMNSLRPEDTAVYYCAFNKWGRLSADLDDYFRWGQGTQVTVSS

SEQ ID NO: 1625 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSNYAMGWYRQAPGKQREFVAFITKGGITNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTGVYYCNMHRSYDISFYDNWGQGTQVTVSS

SEQ ID NO: 1626 ODY-N1264, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGGTVSGYAMGWYRQAPGKEREFVAAINSGGPTWYADSVKGRATISRDNAKNT
VYLQLNSLRPEDTAVYYCRRYDDYGSWGQGTQVTVSS

SEQ ID NO: 1627 ODY-N1117, Group M, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTTCAGGCTGGGAGTTCTCTAAGGCTCTCCTGCGTAGCCTCT
GGAGGCACCGCCAGTGAGTATGGCATGGGCTGGTTCCGCCGGGCTCCAGGGAAGGAGCGTGAATTTGTATCGCG
TATTAGTACGAGTGGTGGAGTGACAAGATATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGC
CAAGAACACGGTGTATCTACAAATGAACGATCTAAAACCTGAGGACACGGCCGTTTATTACTGTGCAGCAGATGG
CCTCCCCTATGGAGATTGGTTCGGCGATCAGTTTGACGTCTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 1628 ODY-N1129, Group N, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGATTGGTGCAACCTGGGGACTCTCTGAGACTCTCCTGTAAACGCTCT
GAGCAGACCATGACTGGCTTTTGGATGGGCTGGTTCCGCCAGGCTCTAGGGAAGGAGCGTGAGTTTGTAGGCGC
AATTTCCGCCAGTGGTAGTAGGGTAGTCTATGCAGACTCCGTGAAGGGCCGATTCGCCATCTCCAAAGACAACTCC
GACAACACGCTGTTTCTACTGATGAACAGCCTGAAACCTGAGGACACGGCCGTTTATTACTGTGCATTCAACAAAT
GGGGACGCCTTAGTGCCGACTTAGATGACTATTTCAGGTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 1629 ODY-N1186, Group O, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGTATGGGGGGTCTCTGAGACTCTCCTGTGCAGCCTC
TGGATTGAGATTCAGTAATTATGCCATGGGCTGGTACCGCCAGGCTCCAGGGAAACAGCGCGAGTTCGTCGCGTT
TATTACTAAAGGTGGTATCACAAACTATACGGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACACGGTGTATCTAGAAATGAGCAGCCTGGAACCTGAGGACACGGGCGTCTATTACTGTAATATGCATCGGTCG
TACGATATTAGTTTCTATGACAACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 1630 ODY-N1264, Group P, non-humanized DNA, nucleotide sequence
GAGGTGCAGCTGGTGGAGTCTGGGGGGGGATTGGTGCAGGCTGGGGGCTCTCTGAGACTCGCCTGTGCAGCCTC
TGGAGGCACCGTCAGTGGCTACGCCATGGGCTGGTACCGCCGGACTCCAGGGAAGGAGCGCGAATTCGTCGCAG
CAATTAATAGCGGTGGTCCGACATGGTATGCAGACTCTGTGCAGGGCCGAGCCACCATCTCCAGAGACAACGCCA
AGAACACGGTGTATCTGCAATTGAACAGCCTGAAACCTGAGGACACGGCCGTTTATTACTGTCGGCGTTACGATG
ACTATGGCTCATGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 1643 ODY-N1117, Group M, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLSCVASGRTASEYGMGWFRQAPGKEREFVARISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNSLKHEDTAVYYCAADGPPYSSWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1644 ODY-N1117, Group M, non-humanized, amino acid sequence
EVQLVESGGGLVQAGSSLRLSCVVSGRTASEYGMGWFRQAPGKEREFVARISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNSLKPEDTAVYYCAADGLPYGDWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1645 ODY-N1117, Group M, non-humanized, amino acid sequence
EVQLVESGGGLVQAGSSLRLSCVASGGTASEYGMGWFRQAPGKEREFVSRISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNDLKPEDTAVYYCAADGLPYGDWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1646 ODY-N1129, Group N, non-humanized, amino acid sequence
EVQLVESGGGLVQPGDSLRLSCRRSEQTMTGFWMGWFRQALGKEREFVGAISASGSRVVYADSVKGRFAISKDNSDN
TMFLLMNSLKPEDTAVYYCAFNKWGRLSADLNDYFRWGQGTQVTVSS

SEQ ID NO: 1647 ODY-N1129, Group N, non-humanized, amino acid sequence
EVQLVESGGGLVQPGDSLRLSCARSEQTMTGFTMGWFRQALGKEREFVGAISASGSRVVYADSVKGRFAISKDNSDN
TMFLLMNSLKPEDTAVYYCAFNKWGRLSADLDDYFRWGQGTQVTVSS

SEQ ID NO: 1648 ODY-N1186, Group O, non-humanized, amino acid sequence
EMQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKNT
VYLQMSSLKPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1649 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKSTV
YLQMSSLKPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1650 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYAIDFYDNWGQGTQVTVSS

SEQ ID NO: 1651 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1652 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVHPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1653 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQSGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYAIDFYDNWGQGTQVTVSS

SEQ ID NO: 1654 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGSTNYADSVEGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYAIDFYDNWGQGTQVTVSS

SEQ ID NO: 1655 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLTLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMSSLKPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1656 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1657 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFASYAMGWYRQTPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMSSLKPEDTAVYYCNTHRSYAISFYDNWGQGTQVTVSS

SEQ ID NO: 1658 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLTLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMSSLNPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1659 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVHPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYDIGFYDNWGQGTQVTVSS

SEQ ID NO: 1660 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVHPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRGNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1661 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLTLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGTTNYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1662 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYVFRFYDNWGQGTQVTVSS

SEQ ID NO: 1663 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVHPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNMHRSYVFRFYDNWGQGTQVTVSS

SEQ ID NO: 1664 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLALSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMSSLKPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1665 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFASYAMGWYRQTPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMRSLKPEDTAVYYCNTHRSYAISFYDNWGQGTQVTVSS

SEQ ID NO: 1666 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFASYAMGWYRQTPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMSSLKPEDTAVYYCNTHRSYAISFYDNWGQGTQVTVSS

SEQ ID NO: 1667 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGSTNYADSVKGRFTISRDNAKNTV
YLHMSSLKPEDTAVYYCNMHRSYAIDFYDNWGQGTQVTVSS

SEQ ID NO: 1668 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVHPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTA
YLQMSSLKPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1669 ODY-N1186, Group O, non-humanized, amino acid sequence
EVQLVESGGGLVQYGGSLRLSCAASGLRFSNYAMGWYRQAPGKQREFVAFITKGGITNYTDSVKGRFTISRDNAKNTV
YLEMSSLEPEDTGVYYCNMHRSYDISFYDYWGQGTQVTVSS

SEQ ID NO: 1670 ODY-N1264, Group P, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACAASGGTVSGYAMGWYRRTPGKEREFVAAINSGGPTWYADSVQGRATISRDNAKN
TVYLQLNSLKPEDTAVYYCRRYDDYDSWGQGTQVTVSS

SEQ ID NO: 1671 ODY-N1264, Group P, non-humanized, amino acid sequence
EVQLVESGGGLVQAGGSLRLACTASRGTFSGYAMGWYRRTPGKEREFVAAINSGGPTWYADSVQGRAIISRDNAKNT
VSLQLNSLKPEDTAVYYCRRYDDYDSWGQGTQVTVSS

SEQ ID NO: 1672 ODY-N1117, Group M, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGRTASEYGMGWFRQAPGKEREFVARISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNSLRHEDTAVYYCAADGPPYSSWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1673 ODY-N1117, Group M, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAVSGRTASEYGMGWFRQAPGKEREFVARISTSGGVTRYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCAADGLPYGDWFGDQFDVWGQGTQVTVSS

SEQ ID NO: 1674 ODY-N1129, Group N, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCARSEQTMTGFWMGWFRQAPGKEREFVGAISASGSRVVYADSVKGRFTISKDNSKN
TMYLQMNSLRPEDTAVYYCAFNKWGRLSADLNDYFRWGQGTQVTVSS

SEQ ID NO: 1675 ODY-N1129, Group N, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCARSEQTMTGFTMGWFRQAPGKEREFVGAISASGSRVVYADSVKGRFTISKDNSKNT
MYLQMNSLRPEDTAVYYCAFNKWGRLSADLDDYFRWGQGTQVTVSS

SEQ ID NO: 1676 ODY-N1186, Group O, humanized, amino acid sequence
EMQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1677 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKSTV
YLQMNSLRPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1678 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGSTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNMHRSYAIDFYDNWGQGTQVTVSS

SEQ ID NO: 1679 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSRYAMGWYRQAPGKQREFVAFITNGGITNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNTHRAYAIDLYDNWGQGTQVTVSS

SEQ ID NO: 1680 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1681 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1682 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFASYAMGWYRQAPGKQREFVAFITNGGNTNYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCNTHRSYAISFYDNWGQGTQVTVSS

SEQ ID NO: 1683 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNMHRSYDIGFYDNWGQGTQVTVSS

SEQ ID NO: 1684 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRGNAKNTV
YLQMNSLRPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1685 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGTTNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNTHRSYAINFYDNWGQGTQVTVSS

SEQ ID NO: 1686 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTAVYYCNMHRSYVFRFYDNWGQGTQVTVSS

SEQ ID NO: 1687 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFASYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNT
VYLQMNSLRPEDTAVYYCNTHRSYAISFYDNWGQGTQVTVSS

SEQ ID NO: 1688 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSSYAMGWYRQAPGKQREFVAFITNGGNTSYADSVKGRFTISRDNAKNTA
YLQMNSLRPEDTAVYYCNMHRSYDIRFYDNWGQGTQVTVSS

SEQ ID NO: 1689 ODY-N1186, Group O, humanized, amino acid sequence
EVQLVESGGGLVQPGGSLRLSCAASGLRFSNYAMGWYRQAPGKQREFVAFITKGGITNYADSVKGRFTISRDNAKNTV
YLQMNSLRPEDTGVYYCNMHRSYDISFYDYWGQGTQVTVSS

SEQ ID NO: 1690 ODY-N1264, Group P, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASGGTVSGYAMGWYRQAPGKEREFVAAINSGGPTWYADSVKGRATISRDNAKNT
VYLQLNSLRPEDTAVYYCRRYDDYDSWGQGTQVTVSS

SEQ ID NO: 1691 ODY-N1264, Group P, humanized, amino acid sequence
EVQLLESGGGLVQPGGSLRLSCAASRGTFSGYAMGWYRQAPGKEREFVAAINSGGPTWYADSVKGRATISRDNAKNT
VYLQLNSLRPEDTAVYYCRRYDDYDSWGQGTQVTVSS

Claims

1. An antigen-binding protein that specifically binds cadherin 17 (CDH17), comprising a complementarity determining region 3 (CDR3) comprising an amino acid sequence selected from

   a). A(A/L)CLLRFE(S/T)CLEYNRAQY(N/P)Y (SEQ ID NO: 83);

   b). AAVR(A/S)GSDWWTTM(R/T)QR(D/H)YD(F/Y) (SEQ ID NO: 85);

   c). AARDSR(K/R)GGLFADLN(E/G)YDY (SEQ ID NO: 88);

   d). AATG(D/N)(L/S)YRGAYDRP(A/T)EYDY (SEQ ID NO: 90);

   e). VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

   f). AAQFSLPVDA(S/T)PLRRY(A/Y)(H/Y) (SEQ ID NO: 93);

   g). AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

   h). AARNGGYDLNDYAY (SEQ ID NO: 44);

   i). NAGG(G/P/A)(A/R)(L/R)GY (SEQ ID NO: 98);

   j). NVGGQL(K/L/R)GY (SEQ ID NO: 101);

   k). NQGG(Q/S)KGY (SEQ ID NO: 104);

   l). AADG(L/P)PY(G/S)(D/S)WFGDQFDV (SEQ ID NO: 1633);

   m). AFNKWGRLSADL(D/N)DYFR (SEQ ID NO: 1636);

   n). N(M/T)HRSY(A/D)I(D/N/R/S)FYDN (SEQ ID NO: 1639); and

   o). RRYDDY(D/G)S (SEQ ID NO: 1642).

2. The antigen-binding protein of claim 1, wherein the CDR3 comprises an amino acid sequence selected from ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3); AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8); AARDSRRGGLFADLNEYDY (SEQ ID NO: 13); AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18); AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22); AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25); VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29); AAQFSLPVDASPLRRYYY (SEQ ID NO: 34); AATRKTRRSTVAGTEVDY (SEQ ID NO: 39); AARNGGYDLNDYAY (SEQ ID NO: 44); NAGGGRLGY (SEQ ID NO: 49); NAGGAALGY (SEQ ID NO: 54); NVGGQLLGY (SEQ ID NO: 59); NQGGSKGY (SEQ ID NO: 64); AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113); AADGLPYGDWFGDQFDV (SEQ ID NO: 1609); AFNKWGRLSADLDDYFR (SEQ ID NO: 1612); NMHRSYDISFYDN (SEQ ID NO: 1615); and RRYDDYGS (SEQ ID NO: 1618).

3. The antigen-binding protein of claim 1 or 2, further comprising a CDR1 comprising an amino acid sequence selected from

a). GFTLSN(T/Y)N (SEQ ID NO: 81);

b). GSPLDYYA (SEQ ID NO: 6);

c). RL(A/N/T)(F/S)(N/S)(R/S)(S/T)T;

d). GRTFS(E/T)PI (SEQ ID NO: 89);

e). GRTFSSPI (SEQ ID NO: 28);

f). TRTF(D/N)MYA (SEQ ID NO: 91);

g). GRTF(D/S)S(L/Y)(L/V) (SEQ ID NO: 94);

h). GRTDSILN (SEQ ID NO: 42);

i). G(I/M)RFS(S/Q)YA (SEQ ID NO: 96);

j). GIRFS(A/S)YA (SEQ ID NO: 99);

k). GS(I/R)FS(R/S)(W/Y)A (SEQ ID NO: 102);

l). G(G/R)TASEYG (SEQ ID NO: 1631);

m). EQTMTGF(T/W) (SEQ ID NO: 1634);

n). GLRFS(S/N)YA (SEQ ID NO: 1637); and

o). (G/R)GT(F/V)SGYA (SEQ ID NO: 1640).

4. The antigen-binding protein of claim 3, wherein the CDR1 comprises an amino acid sequence selected from GFTLSNYN (SEQ ID NO: 1); GSPLDYYA (SEQ ID NO: 6); RLNFSRTT (SEQ ID NO: 11); GRTFSEPI (SEQ ID NO: 16); GRTFSTPI (SEQ ID NO: 21); GRTFSEPI (SEQ ID NO: 16); GRTFSSPI (SEQ ID NO: 28); TRTFNMYA (SEQ ID NO: 32); GRTFSSYL (SEQ ID NO: 37); GRTDSILN (SEQ ID NO: 42); GIRFSSYA (SEQ ID NO: 47); GMRFSQYA (SEQ ID NO: 52); GIRFSAYA (SEQ ID NO: 57); GSRFSSYA (SEQ ID NO: 62); TRTFDMYA (SEQ ID NO: 637); GGTASEYG (SEQ ID NO: 1607); EQTMTGFW (SEQ ID NO: 1610); GLRFSNYA (SEQ ID NO: 1613); and GGTVSGYA (SEQ ID NO: 1616).

5. The antigen-binding protein of any one of claims 1-4, further comprising a CDR2 comprising an amino acid sequence selected from

a). (F/I)SRGGRT (SEQ ID NO: 82);

b). ISTSGR(C/S)T (SEQ ID NO: 84);

c). SGW(A/S)R(G/T)RT (SEQ ID NO: 87);

d). LISTGGST (SEQ ID NO: 17);

e). I(N/S)RSG(A/T)NT (SEQ ID NO: 92);

f). ISWN(D/G)RST (SEQ ID NO: 95);

g). ISWFRGET (SEQ ID NO: 43);

h). I(F/T)(I/K/N/S)(D/G)(G/Y)(R/S/T)T;

i). MT(A/N/T)GGMT (SEQ ID NO: 100);

j). IT(N/S)GG(G/R/S)T (SEQ ID NO: 103);

k). ISTSGGVT (SEQ ID NO: 1632);

l). ISASGSRV (SEQ ID NO: 1635);

m). IT(N/K)GG(I/N/S)T (SEQ ID NO: 1638); and

n). INSGGPT (SEQ ID NO: 1641).

6. The antigen-binding protein of claim 5, wherein the CDR2 comprises an amino acid sequence selected from ISRGGRT (SEQ ID NO: 2); ISTSGRCT (SEQ ID NO: 7); SGWARGRT (SEQ ID NO: 12); LISTGGST (SEQ ID NO: 17); ISRSGTNT (SEQ ID NO: 33); ISWNDRST (SEQ ID NO: 38); ISWFRGET (SEQ ID NO: 43); ITSGYRT (SEQ ID NO: 48); IFKDGTT (SEQ ID NO: 53); MTAGGMT (SEQ ID NO: 58); ITSGGRT (SEQ ID NO: 63); INRSGANT (SEQ ID NO: 875); ISTSGGVT (SEQ ID NO: 1608); ISASGSRV (SEQ ID NO: 1611); ITKGGIT (SEQ ID NO: 1614); and INSGGPT (SEQ ID NO: 1617).

7. An antigen-binding protein that specifically binds cadherin 17 (CDH17), comprising a CDR1 comprising an amino acid sequence selected from SEQ ID Nos: 1, 6, 11, 16, 21, 28, 32, 37, 42, 47, 52, 57, 62, 555-792, 1607, 1610, 1613, 1616, 1692-1720; a CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 2, 7, 12, 17, 33, 38, 43, 48, 53, 58, 63, 793-1030, 1608, 1611, 1614, 1617, 1721-1748; and/or a CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 3, 8, 13, 18, 22, 25, 29, 34, 39, 44, 49, 54, 59, 64, 1031-1268, 1609, 1612, 1615, 1618, 1749-1777.

8. The antigen-binding protein of any one of claims 1-7, wherein the antigen-binding protein comprises

i). a CDR1 comprising an amino acid sequence of GFTLSNYN (SEQ ID NO: 1), a CDR2 comprising an amino acid sequence of ISRGGRT (SEQ ID NO: 2), and a CDR3 comprising an amino acid sequence of ALCLLRFETCLEYNRAQYPY (SEQ ID NO: 3);

ii). a CDR1 comprising an amino acid sequence of GSPLDYYA (SEQ ID NO: 6), a CDR2 comprising an amino acid sequence of ISTSGRCT (SEQ ID NO: 7), and a CDR3 comprising an amino acid sequence of AAVRSGSDWWTTMTQRHYDF (SEQ ID NO: 8);

iii). a CDR1 comprising an amino acid sequence of RLNFSRTT (SEQ ID NO: 11), a CDR2 comprising an amino acid sequence of SGWARGRT (SEQ ID NO: 12), and a CDR3 comprising an amino acid sequence of AARDSRRGGLFADLNEYDY (SEQ ID NO: 13);

iv). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDSYRGAYDRPAEYDY (SEQ ID NO: 18);

v). a CDR1 comprising an amino acid sequence of GRTFSTPI (SEQ ID NO: 21), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGNSYRGAYDRPTEYDY (SEQ ID NO: 22);

vi). a CDR1 comprising an amino acid sequence of GRTFSEPI (SEQ ID NO: 16), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO: 17), and a CDR3 comprising an amino acid sequence of AATGDLYRGAYDRPAEYDY (SEQ ID NO: 25);

vii). a CDR1 comprising an amino acid sequence of GRTFSSPI (SEQ ID NO: 28), a CDR2 comprising an amino acid sequence of LISTGGST (SEQ ID NO:17), and a CDR3 comprising an amino acid sequence of VATGNTYRGAYDRPAEYDF (SEQ ID NO: 29);

viii). a CDR1 comprising an amino acid sequence of TRTFNMYA (SEQ ID NO: 32), a CDR2 comprising an amino acid sequence of ISRSGTNT (SEQ ID NO: 33), and a CDR3 comprising an amino acid sequence of AAQFSLPVDASPLRRYYY (SEQ ID NO: 34);

ix). a CDR1 comprising an amino acid sequence of GRTFSSYL (SEQ ID NO: 37), a CDR2 comprising an amino acid sequence of ISWNDRST (SEQ ID NO: 38), and a CDR3 comprising an amino acid sequence of AATRKTRRSTVAGTEVDY (SEQ ID NO: 39);

x). a CDR1 comprising an amino acid sequence of GRTDSILN (SEQ ID NO: 42), a CDR2 comprising an amino acid sequence of ISWFRGET (SEQ ID NO: 43), and a CDR3 comprising an amino acid sequence of AARNGGYDLNDYAY (SEQ ID NO: 44);

xi). a CDR1 comprising an amino acid sequence of GIRFSSYA (SEQ ID NO: 47), a CDR2 comprising an amino acid sequence of ITSGYRT (SEQ ID NO: 48), and a CDR3 comprising an amino acid sequence of NAGGGRLGY (SEQ ID NO: 49);

xii). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54);

xiii). a CDR1 comprising an amino acid sequence of GIRFSAYA (SEQ ID NO: 57), a CDR2 comprising an amino acid sequence of MTAGGMT (SEQ ID NO: 58), and a CDR3 comprising an amino acid sequence of NVGGQLLGY (SEQ ID NO: 59);

xiv). a CDR1 comprising an amino acid sequence of GSRFSSYA (SEQ ID NO: 62), a CDR2 comprising an amino acid sequence of ITSGGRT (SEQ ID NO: 63), and a CDR3 comprising an amino acid sequence of NQGGSKGY (SEQ ID NO: 64);

xv). a CDR1 comprising an amino acid sequence of TRTFDMYA (SEQ ID NO: 637), a CDR2 comprising an amino acid sequence of INRSGANT (SEQ ID NO: 875), and a CDR3 comprising an amino acid sequence of AAQFSLPVDATPLRRYAH (SEQ ID NO: 1113);

xvi). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO:1609);

xvii) a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

xviii) a CDR1 comprising an amino acid sequence of GLRFSNYA (SEQ ID NO: 1613), a CDR2 comprising an amino acid sequence of ITKGGIT (SEQ ID NO: 1614), and a CDR3 comprising an amino acid sequence of NMHRSYDISFYDN (SEQ ID NO: 1615); or

xix). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

9. The antigen-binding protein of any one of claims 1-8, wherein the antigen-binding protein comprises

a). a CDR1 comprising an amino acid sequence of GGTASEYG (SEQ ID NO: 1607), a CDR2 comprising an amino acid sequence of ISTSGGVT (SEQ ID NO: 1608), and a CDR3 comprising an amino acid sequence of AADGLPYGDWFGDQFDV (SEQ ID NO: 1609);

b). a CDR1 comprising an amino acid sequence of EQTMTGFW (SEQ ID NO: 1610), a CDR2 comprising an amino acid sequence of ISASGSRV (SEQ ID NO: 1611), and a CDR3 comprising an amino acid sequence of AFNKWGRLSADLDDYFR (SEQ ID NO: 1612);

c). a CDR1 comprising an amino acid sequence of GMRFSQYA (SEQ ID NO: 52), a CDR2 comprising an amino acid sequence of IFKDGTT (SEQ ID NO: 53), and a CDR3 comprising an amino acid sequence of NAGGAALGY (SEQ ID NO: 54); or

d). a CDR1 comprising an amino acid sequence of GGTVSGYA (SEQ ID NO: 1616), a CDR2 comprising an amino acid sequence of INSGGPT (SEQ ID NO: 1617), and a CDR3 comprising an amino acid sequence of RRYDDYGS (SEQ ID NO: 1618).

10. The antigen-binding protein of any one of claims 1-9, wherein the antigen-binding protein is a single-domain antibody.

11. The antigen-binding protein of claim 10, wherein the single-domain antibody is a VHH, a VNAR, or a VH domain.

12. The antigen-binding protein of claim 11, wherein the VHH is a camelid VHH.

13. The antigen-binding protein of claim 12, wherein the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 105-342, 1619-1622, 1643-1671, and 1778-1806, or an amino acid sequence having at least 75% identity thereto.

14. The antigen-binding protein of claim 12 or 13, wherein the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 4, 9, 14, 19, 23, 26, 30, 35, 40, 45, 50, 55, 60, 65, 187, and 1619-1622, or an amino acid sequence having at least 75% identity thereto.

15. The antigen-binding protein of any one of claims 12-14, wherein the VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 55, 1619, 1620, and 1622, or an amino acid sequence having at least 75% identity thereto.

16. The antigen-binding protein of claim 11, wherein the VHH is a humanized VHH.

17. The antigen-binding protein of claim 16, wherein the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66 343-554, 1623-1626, and 1672-1691, or an amino acid sequence having at least 75% identity thereto.

18. The antigen-binding protein of claim 17, wherein the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 10, 15, 20, 24, 27, 31, 36, 41, 46, 51, 56, 61, 66, 421, and 1623-1626, or an amino acid sequence having at least 75% identity thereto.

19. The antigen-binding protein of claim 17 or 18, wherein the humanized VHH comprises an amino acid sequence selected from any one of SEQ ID NOs: 56, 1623, 1624, and 1626, or an amino acid sequence having at least 75% identity thereto.

20. The antigen-binding protein of any one of claims 1-19, wherein the antigen-binding protein binds to human CDH17.

21. The antigen-binding protein of claim 20, wherein the antigen-binding protein binds to human CDH17 with a K_D of about 2.2×10^{-7} M or less.

22. The antigen-binding protein of claim 21, wherein the antigen-binding protein binds to human CDH17 with a K_D of about 1.5×10^{-7} M or less.

23. The antigen-binding protein of any one of claims 1-22, wherein the antigen-binding protein binds to cyno CDH17.

24. The antigen-binding protein of claim 23, wherein the antigen-binding protein binds to cyno CDH17 with a K_D of about 2×10^{-8} M or less.

25. The antigen-binding protein of any one of claims 1-23, wherein the antigen-binding protein binds to mouse CDH17.

26. The antigen-binding protein of any one of claims 1-25, wherein the antigen-binding protein binds to the extracellular cadherin domain 6 (EC6) and/or extracellular cadherin domain 7 (EC7) of human CDH17.

27. The antigen-binding protein of any one of claims 1-26, wherein the antigen-binding protein binds to an extracellular region C-terminal to the tripeptide motif, RGD, in EC6 of human CDH17.

28. The antigen-binding protein of any one of claims 1-25, wherein the antigen-binding protein binds to the extracellular cadherin domain 1 (EC1) of human CDH17.

29. The antigen-binding protein of any one of claims 1-28, wherein the antigen-binding protein comprises one or more modifications that reduce binding of said antigen-binding protein by pre-existing antibodies found in human blood or serum.

30. A fusion protein that specifically binds CDH17, comprising one or more of said antigen-binding proteins of any one of claims 1-29.

31. The fusion protein of claim 30, which comprises three or more said antigen-binding proteins.

32. The fusion protein of claim 30 or 31, wherein the one or more antigen-binding proteins bind to the same epitope on CDH17.

33. The fusion protein of claims 30 or 31, wherein the one or more antigen-binding proteins bind to different epitopes on CDH17.

34. The fusion protein of any one of claims 30-33, wherein the one or more antigen-binding proteins are one or more single-domain antibodies.

35. The fusion protein of claim 34, wherein one or more single-domain antibodies are one or more VHHs.

36. The fusion protein of any one of claims 30-35, which further comprises an immunoglobulin Fc region.

37. The fusion protein of claim 36, wherein the immunoglobulin Fc region is an Fc region of a human immunoglobulin.

38. The fusion protein of claim 37, wherein the immunoglobulin Fc region is an Fc region of human IgG1, IgG2, IgG3 or IgG4, or a variant thereof.

39. The fusion protein of claim 38, wherein the immunoglobulin Fc region is an Fc region of human IgG1, or a variant thereof.

40. The fusion protein of claim 39, wherein the Fc region of human IgG1 comprises one or more mutations selected from Leu234Ala (L234A), Leu234Gly (L234G), Leu234Ser (L234S), Leu234Thr (L234T), Leu234Ala (L234A), Leu235Ala (L235A), Leu235Glu (L235E), Leu235Ser (L235S), Leu235Thr (L235T), Leu235Val (L235V), Leu235Gln (L235Q), Gly236Arg (G236R), Met252Tyr (M252Y), Ser254Thr (S254T), Thr256Glu (T256E), Asp265Asn (D265N), Asp265Ala (D265A), Asp270Asn (D270N), Ser298Asn (S298N), Asn297Ala (N297A), Pro329Ala (P329A), Pro239Gly (P329G), Asn325Glu (N325E) and/or Ala327Ser (A327S) according to EU numbering.

41. The fusion protein of claim 40, wherein the Fc region of human IgG1 comprises a set of mutations selected from

    1). L234A and L235A;
    2). L234A, L235A, and P329A;
    3). D265A, N297A and P329A;
    4). L234A, L235A, and G237A;
    5). L234G, L235S, and G236R;
    6). L234S, L235T, and G236R;
    7). L234S, L235V, and G236R;
    8). L234T, L235Q, and G236R;
    9). L234T, L235T, and G236R;
    10). L234A, L235A, and P329G; and
    11). M252Y, S254T, and T256E.

42. The fusion protein of claim 38, wherein the immunoglobulin Fc region is an Fc region of human IgG4, or a variant thereof.

43. The fusion protein of claim 42, wherein the Fc region of human IgG4 comprises one or more mutations selected from Ser228Pro (S228P), Leu235Glu (L235E), Leu235Ala (L235A), Phe234Ala (F234A), and/or Pro329Gly (P329G) according to EU numbering.

44. The fusion protein of claim 43, wherein the Fc region of human IgG4 comprises a set of mutations selected from
    1). S228P and L235E;
    2). S228P and L235A;
    3). S228P, F234A, and L235E;
    4). S228P, F234A, and L235A; and
    5). P329G, S228P, and L235E.

45. The fusion protein of any one of claims 30-44, which further comprises a moiety that binds to serum albumin.

46. A conjugate comprising the antigen-binding protein of any one of claims 1-29 or the fusion protein of any one of claims 30-45, wherein the antigen-binding protein or fusion protein is conjugated to a second moiety.

47. The conjugate of claim 46, wherein the second moiety is selected from a detectable label, a drug, a toxin, a radionuclide, an enzyme, an immunomodulatory agent, a cytokine, a cytotoxic agent, a chemotherapeutic agent, a diagnostic agent, or a combination thereof.

48. A polynucleotide molecule encoding the antigen-binding protein of any one of claims 1-29 or the fusion protein of any one of claims 30-45.

49. The polynucleotide molecule of claim 48, which comprises the nucleotide sequence of any one of SEQ ID NOs: 67-80, 1269-1506, 1627-1630, and 1807-1835, or a nucleotide sequence having at least 70% identity thereto.

50. The polynucleotide molecule of claim 49, which comprises the nucleotide sequence of any one of SEQ ID NOs: 67-80, 1351, and 1627-1630, or a nucleotide sequence having at least 70% identity thereto.

51. A recombinant vector comprising the polynucleotide molecule of any one of claims 48-50.

52. A host cell comprising the polynucleotide molecule of any one of claims 48-50, or the recombinant vector of claim 51.

53. A kit comprising the antigen-binding protein of any one of claims 1-29, the fusion protein of any one of claims 30-45, the conjugate of claim 46 or 47, the polynucleotide molecule of any one of claims 48-50, or the recombinant vector of claim 51, and optionally, instructions and/or packaging for the same.

54. A pharmaceutical composition comprising the antigen-binding protein of any one of claims 1-29, the fusion protein of any one of claims 30-45, the conjugate of claim 46 or 47, the polynucleotide molecule of any one of claims 48-50, or the recombinant vector of claim 51, and a pharmaceutically acceptable carrier and/or excipient.

55. A method for preparing an antigen-binding protein or a fusion protein that specifically binds CDH17, comprising the steps of:
(a) culturing the host cell of claim 52 in a culture medium under conditions suitable for expression of the antigen-binding protein or fusion protein, and
(b) isolating the antigen-binding protein or fusion protein from the host cell and/or culture medium.

56. A method for killing a cell expressing CDH17 comprising contacting the cell with the antigen-binding protein of claim 1-29, the fusion protein of any one of claims 30-45, or the conjugate of claim 46 or 47.

57. The method of claim 56, wherein said contacting occurs *in vitro*.

58. The method of claim 56, wherein said contacting occurs *in vivo*.

59. The method of claim 58, wherein the method further comprises administering the antigen-binding protein, the fusion protein, or the conjugate into a subject in need thereof.

60. The method of any one of claims 56-59, wherein the cell expressing CDH17 is a cell of a cancer.

61. The method of claim 60, wherein the cancer is a solid tumor.

62. The method of claim 60, wherein the cancer is selected from colorectal cancer, familial GIST, familial pancreatic cancer, gastrointestinal stromal tumor (GIST), hereditary diffuse gastric cancer, hereditary pancreatitis, neuroendocrine tumor of the gastrointestinal tract, neuroendocrine tumor of the pancreas, peritoneal cancer, pancreatic cancer, small bowel cancer, and stomach cancer.

63. The method of claim 60, wherein the cancer is gastrointestinal cancer.

64. The method of claim 63, wherein the gastrointestinal cancer is colorectal cancer, gastric cancer, esophageal cancer, or pancreatic cancer.

65. The method of any one of claims 56-64, wherein the method further comprises contacting the cell with one or more additional therapeutic agents.

66. A method of treating or preventing a cancer in a subject in need thereof, said method comprising administering to the subject the antigen-binding protein of claim 1-29, the fusion protein of any one of claims 30-45, or the conjugate of claim 46 or 47.

67. The method of claim 66, wherein the cancer is a solid tumor.

68. The method of claim 66, wherein the cancer is selected from colorectal cancer, familial GIST, familial pancreatic cancer, gastrointestinal stromal tumor (GIST), hereditary diffuse gastric cancer, hereditary pancreatitis, neuroendocrine tumor of the gastrointestinal tract, neuroendocrine tumor of the pancreas, peritoneal cancer, pancreatic cancer, small bowel cancer, and stomach cancer.

69. The method of claim 66, wherein the cancer is gastrointestinal cancer.

70. The method of claim 69, wherein the gastrointestinal cancer is colorectal cancer, gastric cancer, esophageal cancer, or pancreatic cancer.

71. The method of any one of claims 66-70, wherein the method further comprises administering one or more additional therapeutic agents.

72. The method of claim 65 or 71, wherein the one or more additional therapeutic agents are selected from a chemotherapeutic agent, a vascular endothelial growth factor (VEGF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an apoptosis-inducing agent, an immunotherapeutic agent, and a combination thereof.

73. The method of claim 72, wherein the chemotherapeutic agent is selected from bleomycin, carboplatin, chlorambucil, cisplatin, colchicine, cyclophosphamide, daunorubicin, doxorubicin or liposomal doxorubicin, mitomycin C, actinomycin, diethylstilbestrol, etoposide, 5-fluorouracil, floxuridine, melphalan, methotrexate, mitomycin, 6-mercaptopurine, teniposide, 6-thioguanine, vincristine and vinblastine, leflunomide, tamoxifen, interferon α-2b, glutamic acid, plicamycin, mercaptopurine, 6-thioguanine, carmustine, BCNU, limousine, CCNU, cytosine arabinose, estramustine, hydroxyurea, procarbazine, busulfan, medroxyprogesterone, estramustine phosphate sodium, ethenyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, testolactone, melphalan, chlorambucil, mechlorethamine, thiourea, bethamethasone sodium phosphate, dicarbazine, asparagine, mitotane, vincristine sulfate, vinblastine sulfate, FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) or FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan), and a combination thereof.

74. The method of claim 72, wherein the VEGF inhibitor is bevacizumab, ramucirumab, regorafenib, or ziv-aflibercept, or a combination thereof.

75. The method of claim 72, wherein the EGFR inhibitor is cetuximab and/or panitumumab.

76. The method of claim 72, wherein the apoptosis-inducing agent is a B-cell lymphoma 2 (BCL2) inhibitor, a BCL-extra large (BCL-XL) inhibitor, or an inhibitor of apoptosis proteins (IAP) inhibitor, or a combination thereof.

77. The method of claim 72, wherein the immunotherapeutic agent is an anti-CTLA4 agent, anti-PD1 agent, anti-PD-L1 agent, anti-LAG3 agent, or anti-TIM3 agent, or a combination thereof.

78. The method of any one of claims 66-77, wherein the subject is a mammal.

79. The method of claim 78, wherein the mammal is human.

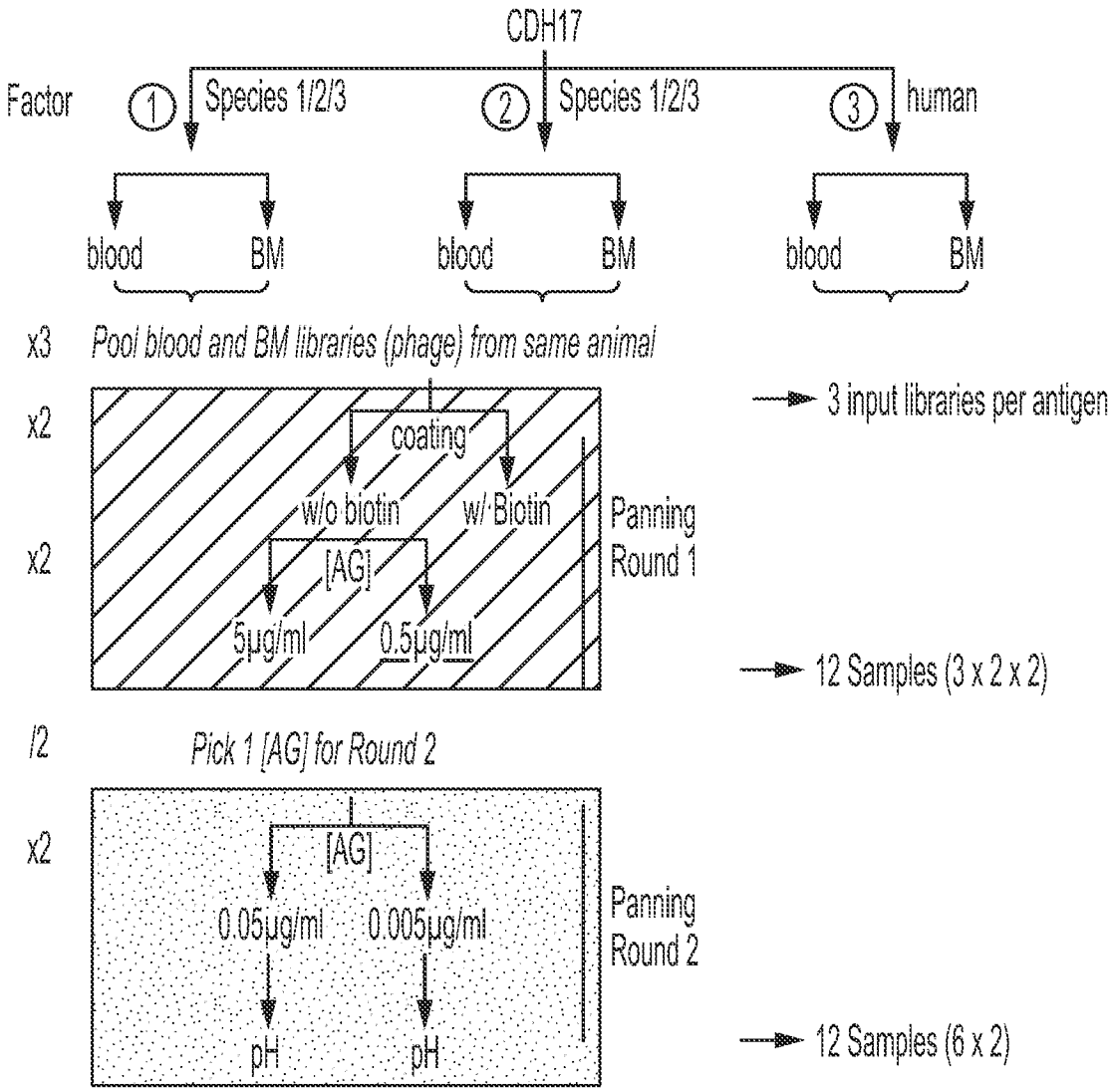

CDH17
Factor
1
Species 1/2/3
2
Species 1/2/3
3
human
blood
BM
blood
BM
blood
BM
x3
Pool blood and BM libraries (phage) from same animal
3 input libraries per antigen
x2
coating
w/o biotin
w/ Biotin
Panning Round 1
x2
[AG]
5µg/ml
0.5µg/ml
12 Samples (3 x 2 x 2)
/2
Pick 1 [AG] for Round 2
x2
[AG]
0.05µg/ml
0.005µg/ml
Panning Round 2
pH
pH
12 Samples (6 x 2)

FIG. 1

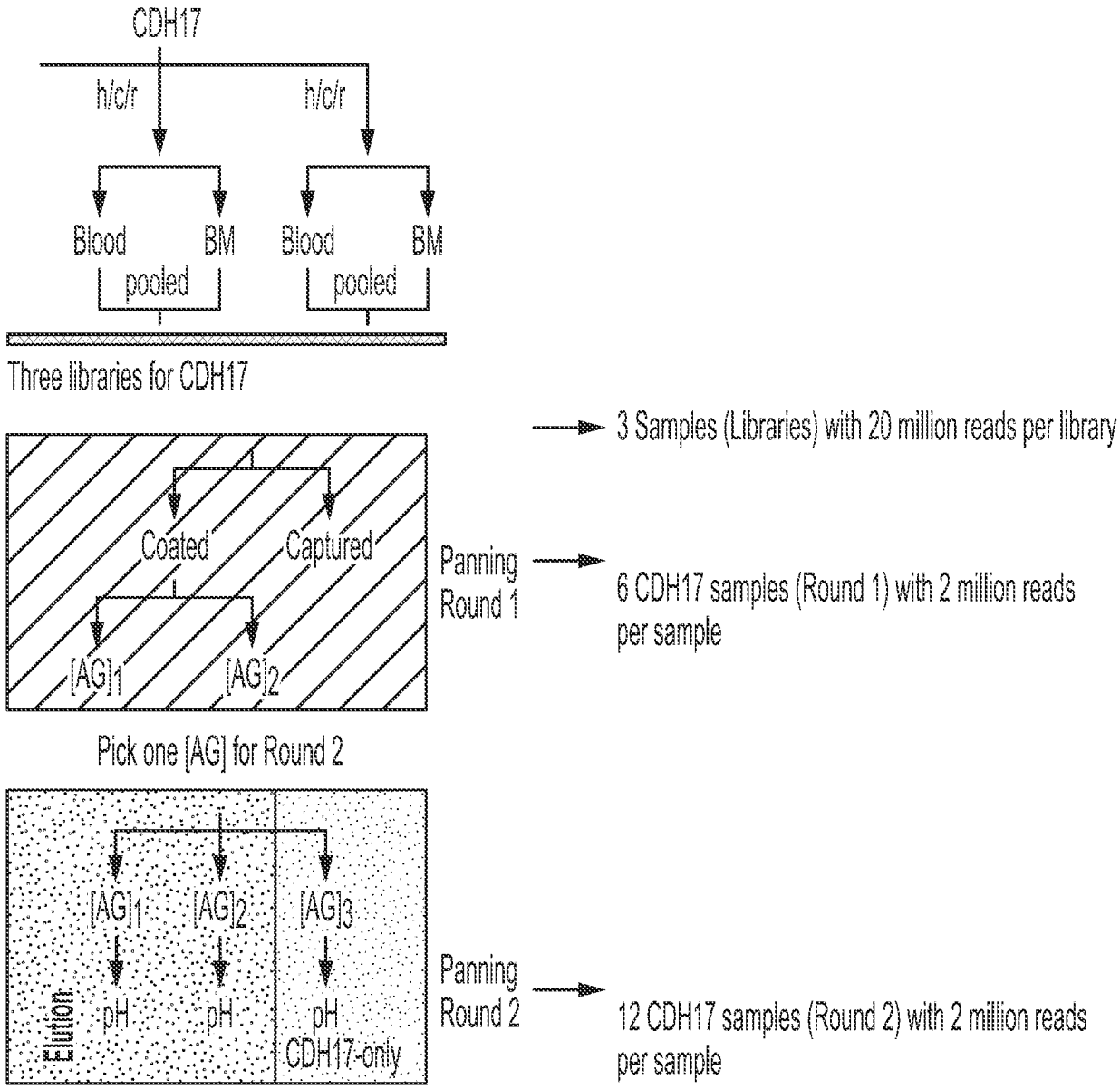
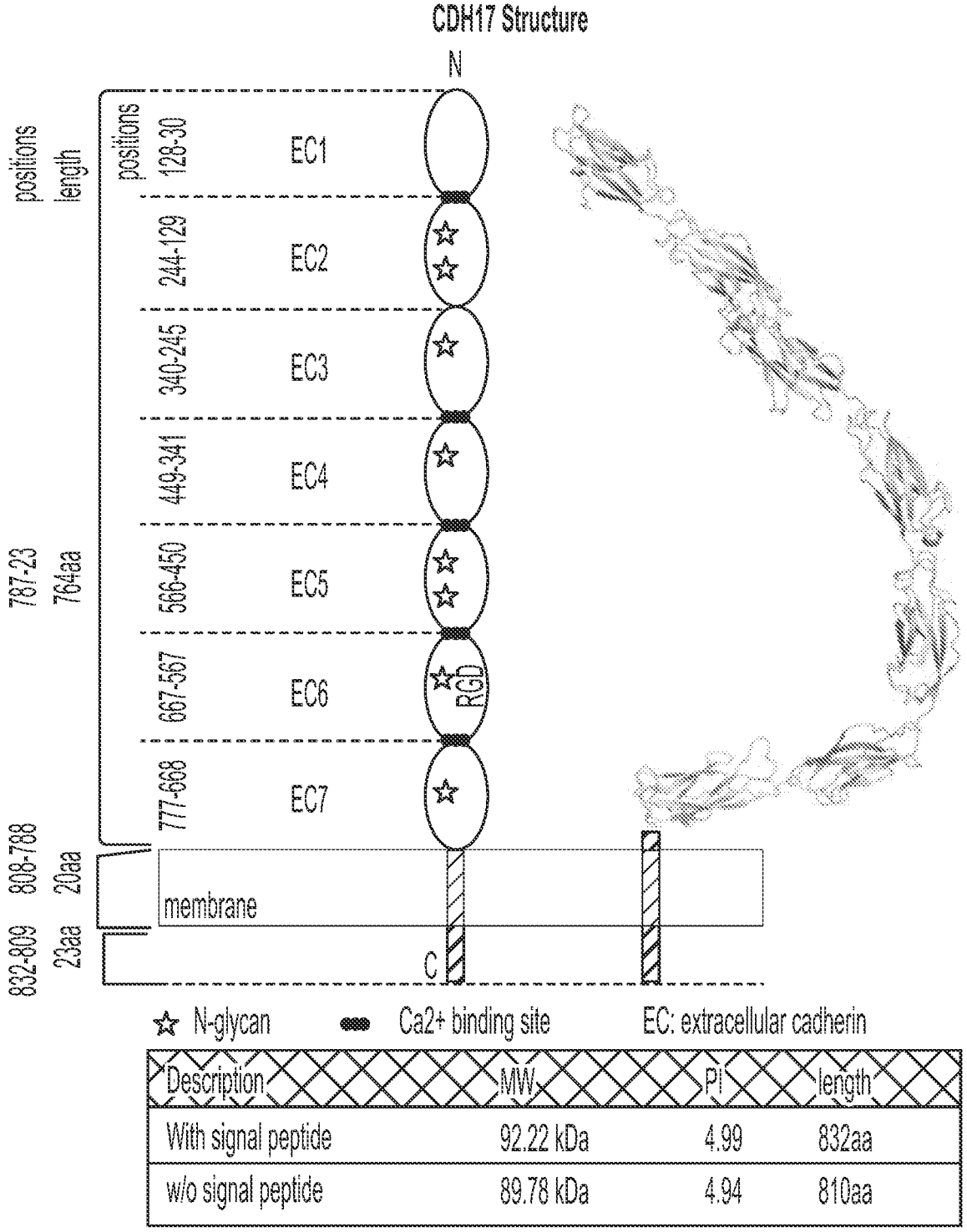

CDH17
h/c/r
h/c/r
Blood
BM
Blood
BM
pooled
pooled
Three libraries for CDH17
3 Samples (Libraries) with 20 million reads per library
Coated
Captured
[AG]1
[AG]2
Panning Round 1
6 CDH17 samples (Round 1) with 2 million reads per sample
Pick one [AG] for Round 2
[AG]1
[AG]2
[AG]3
Elution
pH
pH
pH
CDH17-only
Panning Round 2
12 CDH17 samples (Round 2) with 2 million reads per sample

FIG. 2

Amplicon generation
Barcode fusion
Illumina NGS
250 bp Fwd & Rev
VHH
Phagemid
CATGCATG
CATGCATG
CATGCATG
CATGCATG
CATGCATG
CATGCATG
5' CATGCATG 3'
3' CATGCATG 5'
Merge forward & reverse pairs
CDR3-based clustering
Annotate VHH and CDRs
CDR1 CDR2 CDR3
CATGCATG
CATGCATG
Enrichment analysis
Phylogenetic analysis
CDR3 length distribution
Cluster abundance
Cluster A
Cluster B
Cluster C
Cluster D
Cluster E
Cluster F
Cluster G
Length Count
CDR3 Length
Library
Panning Round 1
Panning Round 2
Enrichment
Enrichment
Selection of up to 500 promising V-body candidates

FIG. 3



Description	MW	PI	length
With signal peptide	92.22 kDa	4.99	832aa
w/o signal peptide	89.78 kDa	4.94	810aa

FIG. 4

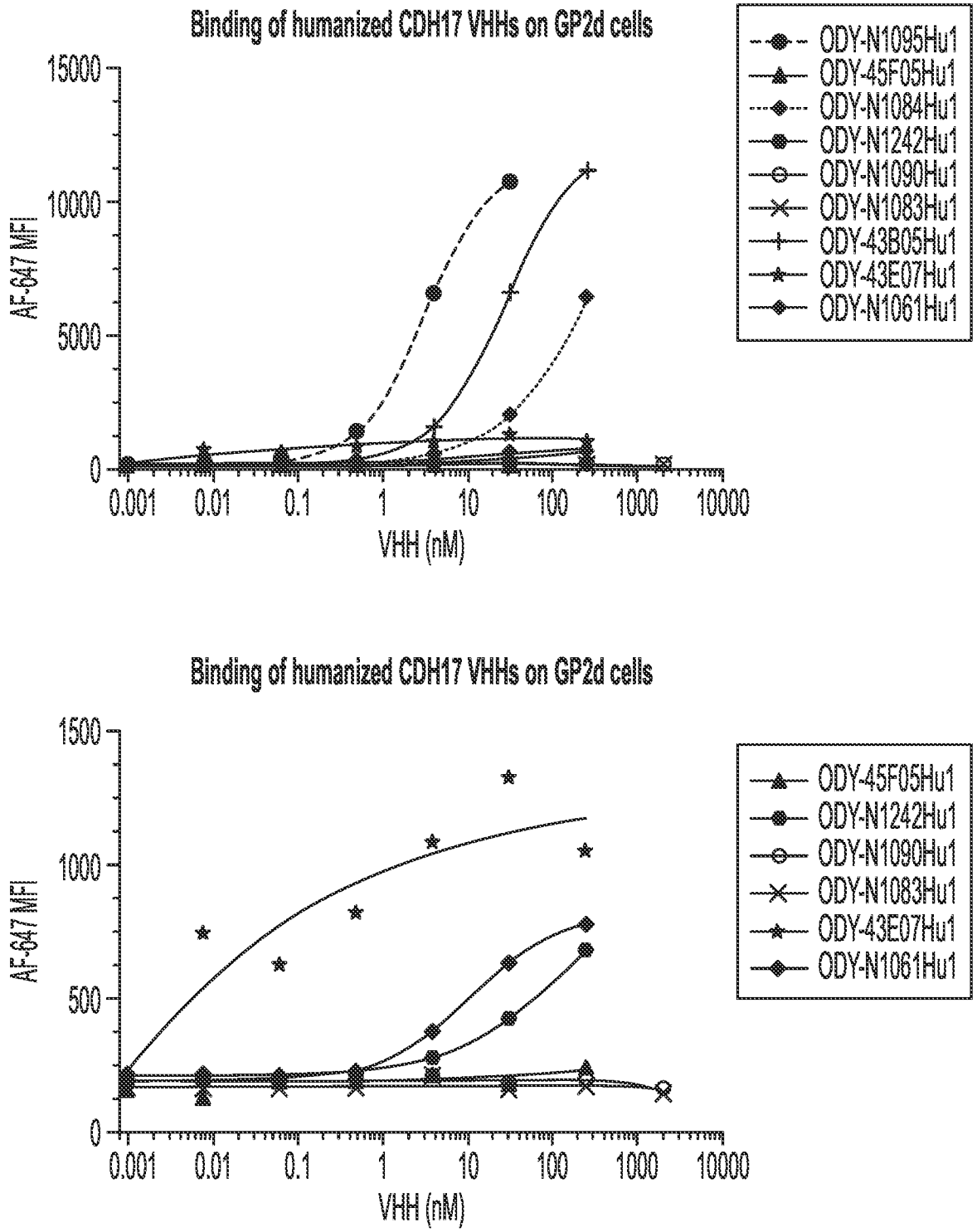

Binding of humanized CDH17 VHHs on GP2d cells
AF-647 MFI
15000
10000
5000
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-N1095Hu1
ODY-45F05Hu1
ODY-N1084Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43B05Hu1
ODY-43E07Hu1
ODY-N1061Hu1
Binding of humanized CDH17 VHHs on GP2d cells
AF-647 MFI
1500
1000
500
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-45F05Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43E07Hu1
ODY-N1061Hu1

FIG. 5A

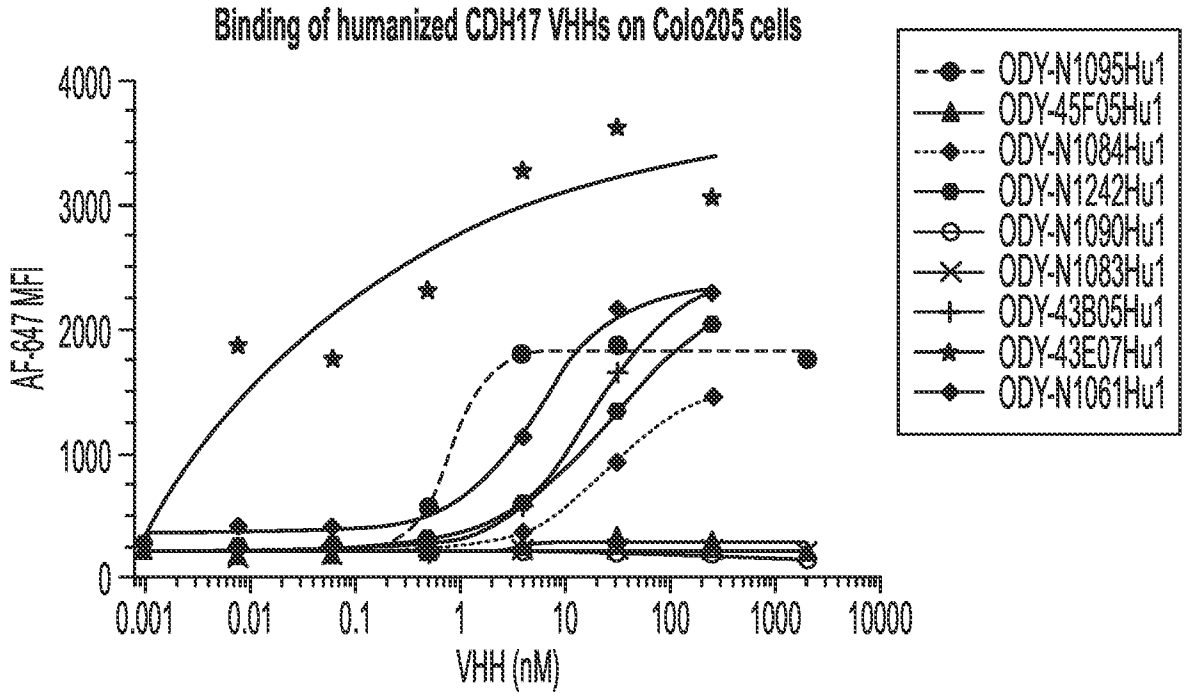

Binding of humanized CDH17 VHHs on Colo205 cells
AF-647 MFI
4000
3000
2000
1000
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-N1095Hu1
ODY-45F05Hu1
ODY-N1084Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43B05Hu1
ODY-43E07Hu1
ODY-N1061Hu1

FIG. 5B

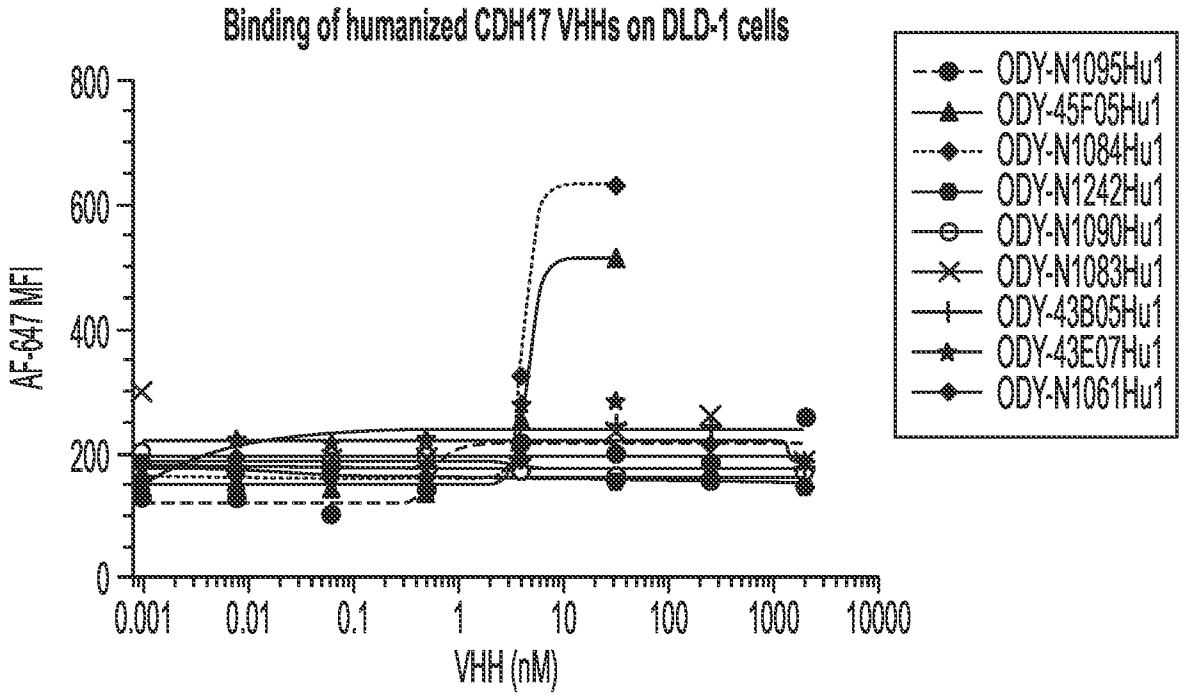

Binding of humanized CDH17 VHHs on DLD-1 cells
AF-647 MFI
800
600
400
200
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-N1095Hu1
ODY-45F05Hu1
ODY-N1084Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43B05Hu1
ODY-43E07Hu1
ODY-N1061Hu1

FIG. 5C

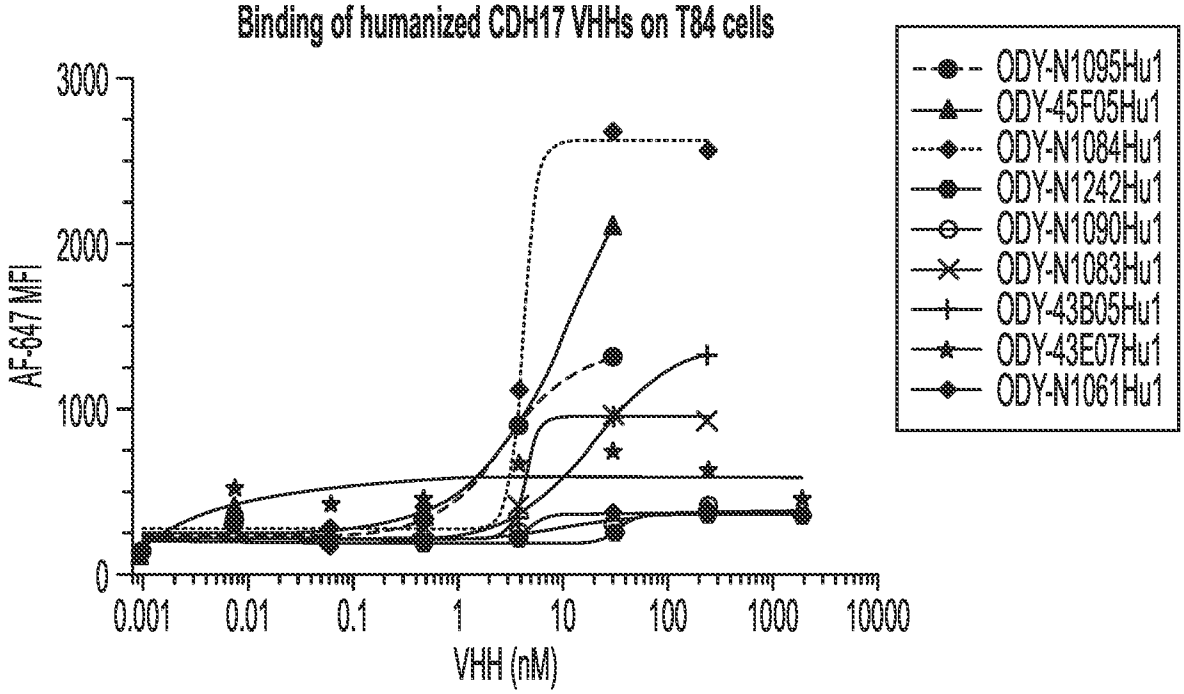

Binding of humanized CDH17 VHHs on T84 cells
AF-647 MFI
3000
2000
1000
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-N1095Hu1
ODY-45F05Hu1
ODY-N1084Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43B05Hu1
ODY-43E07Hu1
ODY-N1061Hu1

FIG. 5D

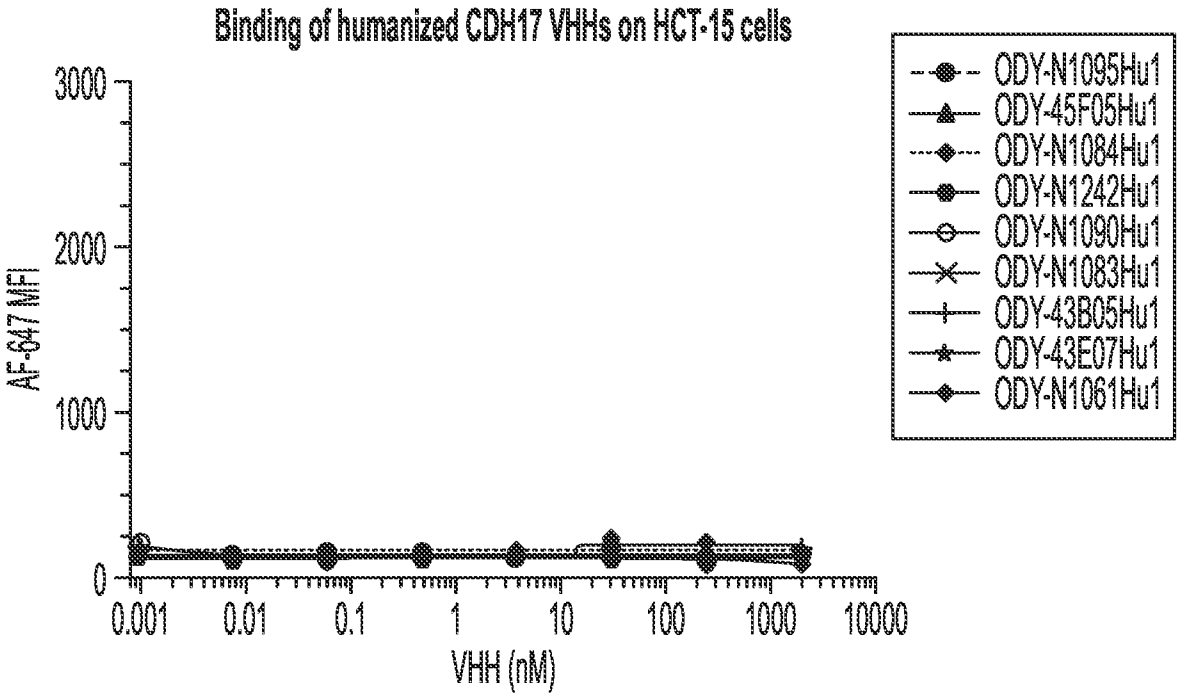

Binding of humanized CDH17 VHHs on HCT-15 cells
AF-647 MFI
3000
2000
1000
0
0.001
0.01
0.1
1
10
100
1000
10000
VHH (nM)
ODY-N1095Hu1
ODY-45F05Hu1
ODY-N1084Hu1
ODY-N1242Hu1
ODY-N1090Hu1
ODY-N1083Hu1
ODY-43B05Hu1
ODY-43E07Hu1
ODY-N1061Hu1

FIG. 5E

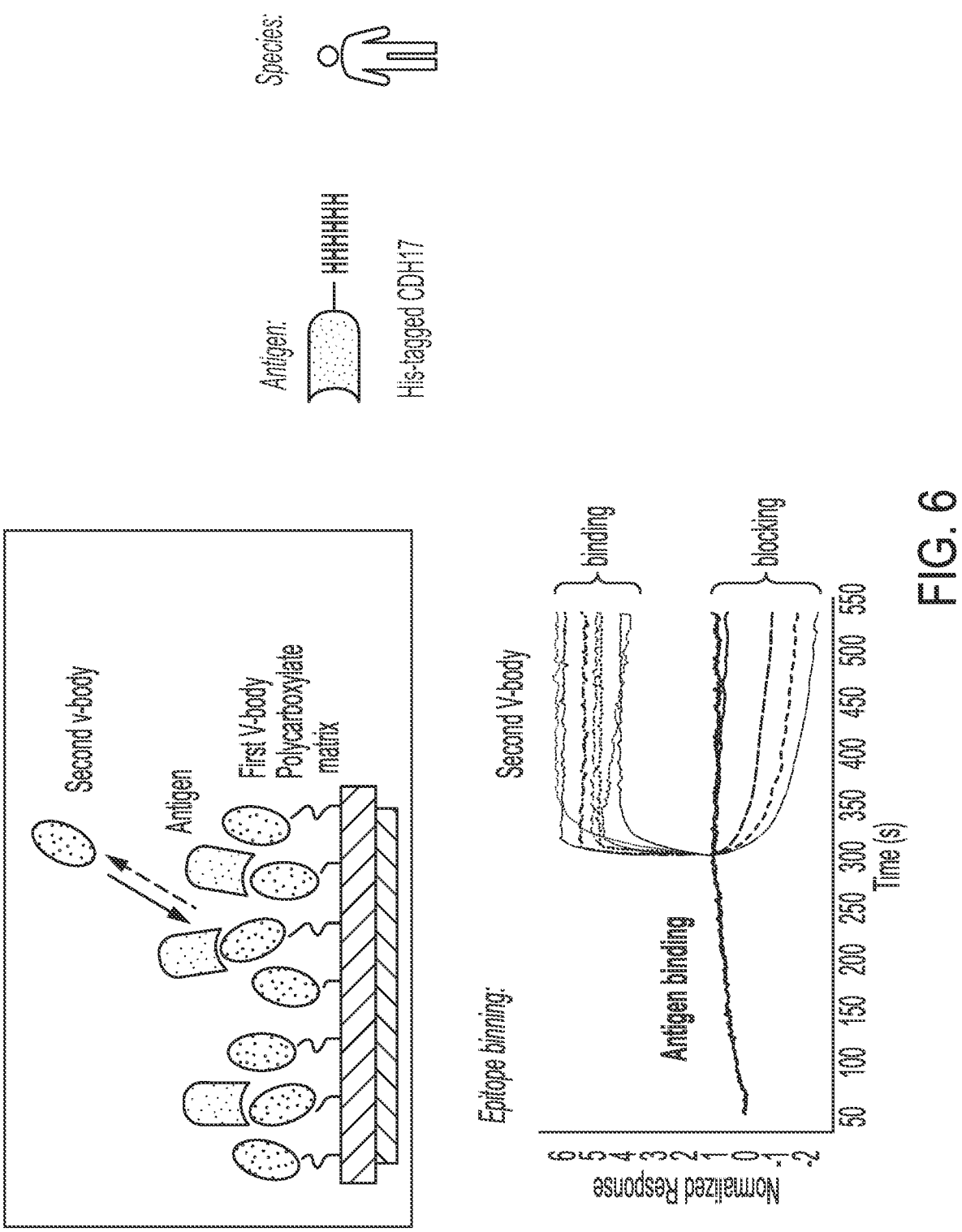

Species:
Antigen:
His-tagged CDH17
Second v-body
Antigen
First V-body
Polycarboxylate
matrix
Epitope binning:
Second V-body
binding
blocking
Antigen binding
Normalized Response
Time (s)

FIG. 6

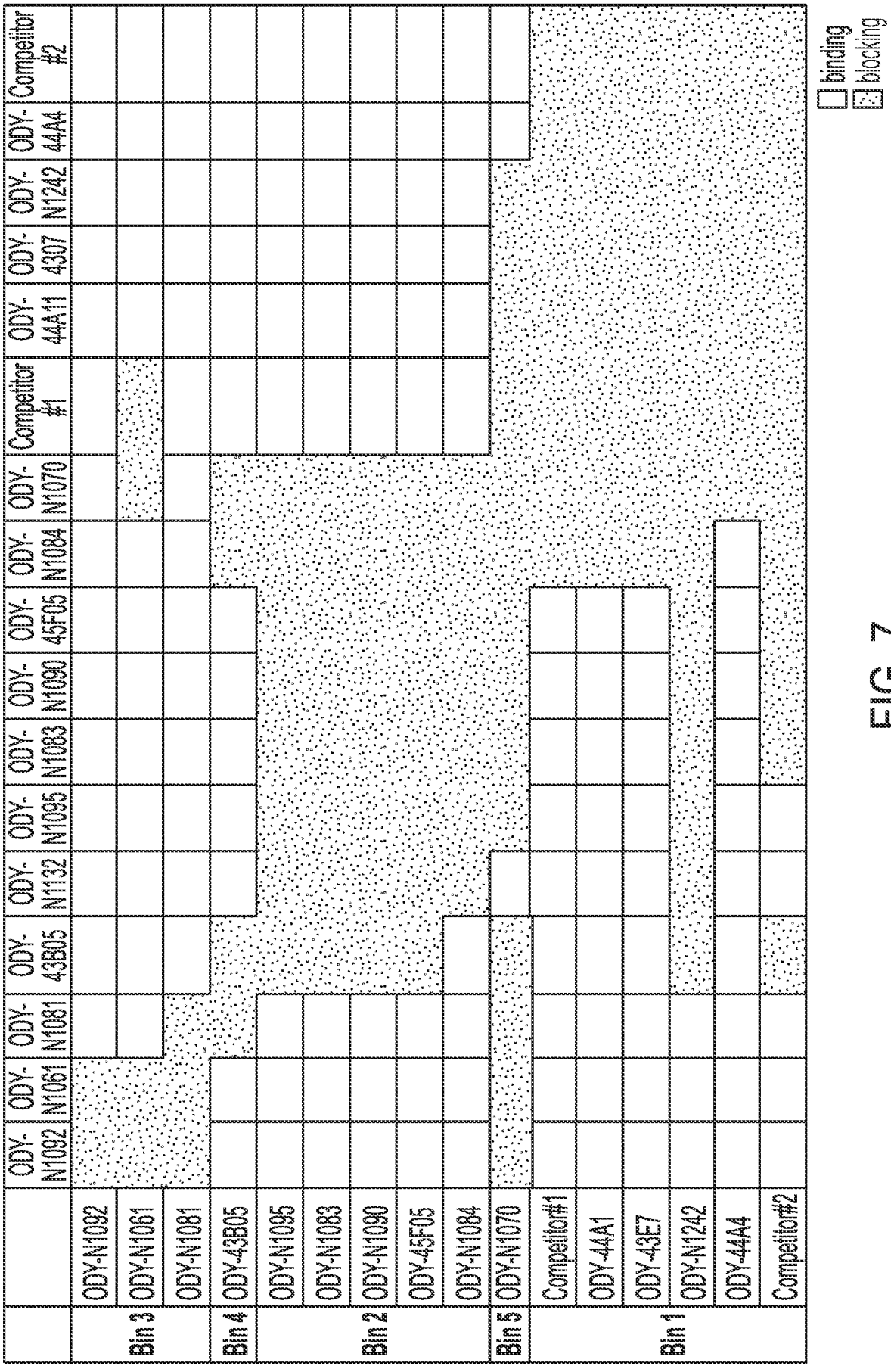

ODY-N1092
ODY-N1061
ODY-N1081
ODY-43B05
ODY-N1132
ODY-N1095
ODY-N1083
ODY-N1090
ODY-45F05
ODY-N1084
ODY-N1070
Competitor #1
ODY-44A11
ODY-4307
ODY-N1242
ODY-44A4
Competitor #2
Bin 3
ODY-N1092
ODY-N1061
ODY-N1081
Bin 4
ODY-43B05
Bin 2
ODY-N1095
ODY-N1083
ODY-N1090
ODY-45F05
ODY-N1084
Bin 5
ODY-N1070
Bin 1
Competitor#1
ODY-44A1
ODY-43E7
ODY-N1242
ODY-44A4
Competitor#2
binding
blocking

FIG. 7

	No DNA	FL CDH17	EC1	EC2	EC3	EC4	EC5	EC6	EC7
ODY-N1095Hu1	No binding	Binding							
ODY-45F05Hu1	No binding	Binding							
ODY-N1084Hu1	No binding	Binding							
ODY-N1242Hu1	No binding	Binding							
ODY-N1090Hu1	No binding	Binding							
ODY-N1083Hu1	No binding	Binding							
ODY-N1070Hu1	No binding	Binding							
ODY-N1081Hu1	No binding	Binding							
ODY-43B05Hu1	No binding	Binding							
ODY-43E07Hu1	No binding	Binding							
ODY-N1061Hu1	No binding	Binding							
ODY-N1091Hu1	No binding	Binding							
ODY-N1117Hu1	No binding	Binding							
ODY-N1129Hu1	No binding	Binding							
ODY-N1186Hu1	No binding	Binding							
ODY-N1264Hu1	No binding	Binding							
ODY-44A1	No binding	Binding							
ODY-44A4	No binding	Binding							
Competitor 1	No binding	Binding							
Competitor 2	No binding	Binding							

FIG. 8