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(54) Title: NOVEL ANTI-CLAUDIN ANTIBODIES AND METHODS OF USE

(57) Abstract: Provided herein are novel anti-CLDN antibodies and antibody drug conjugates (ADC), including derivatives thereof, and methods of using the same to treat proliferative disorders.

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NOVEL ANTI-CLAUDIN ANTIBODIES AND METHODS OF USE

CROSS REFERENCED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/900,916 filed on November 6, 2013, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

This application contains a sequence listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 5, 2014, is named sc2701pct_S69697_1040WO_SEQL_110514.txt and is 229,316 bytes in size.

FIELD OF THE INVENTION

This application generally relates to novel anti-CLDN antibodies or immunoreactive fragments thereof and compositions, including antibody drug conjugates, comprising the same for the treatment, diagnosis or prophylaxis of cancer and any recurrence or metastasis thereof. Selected embodiments of the invention provide for the use of such anti-CLDN antibodies or antibody drug conjugates for the treatment of cancer comprising a reduction in tumorigenic cell frequency.

BACKGROUND OF THE INVENTION

Differentiation and proliferation of stem cells and progenitor cells are normal ongoing processes that act in concert to support tissue growth during organogenesis, cell repair and cell replacement. The system is tightly regulated to ensure that only appropriate signals are generated based on the needs of the organism. Cell proliferation and differentiation normally occur only as necessary for the replacement of damaged or dying cells or for growth. However, disruption of these processes can be triggered by many factors including the under- or overabundance of various signaling chemicals, the presence of altered microenvironments, genetic mutations or a combination thereof. Disruption of normal cellular proliferation and/or differentiation can lead to various disorders including proliferative diseases such as cancer.

Conventional therapeutic treatments for cancer include chemotherapy, radiotherapy and

immunotherapy. Often these treatments are ineffective and surgical resection may not provide a viable clinical alternative. Limitations in the current standard of care are particularly evident in those cases where patients undergo first line treatments and subsequently relapse. In such cases refractory tumors, often aggressive and incurable, frequently arise. The overall survival rates for many solid tumors have remained largely unchanged over the years due, at least in part, to the failure of existing therapies to prevent relapse, tumor recurrence and metastasis. There remains therefore a great need to develop more targeted and potent therapies for proliferative disorders. The current invention addresses this need.

SUMMARY OF THE INVENTION

The invention is broadly directed to antibodies and antibody drug conjugates (ADC) that bind to at least one member of the claudin (CLDN) family of proteins.

In selected embodiments the invention comprises an antibody that binds to cancer stem cells expressing at least one protein of the CLDN family. In another embodiment the antibodies of the invention bind specifically to CLND6 or specifically to CLDN6 and CLDN9. In another embodiment, the antibodies of the invention bind to CLDN6 and CLDN9 with substantially the same apparent binding affinity. Any of the anti-CLDN antibodies of the invention may be internalizing antibodies.

In one embodiment the antibody of the invention binds to at least one member of the CLDN family and competes for binding with an antibody comprising: a light chain variable region (VL) of SEQ ID NO: 21 and a heavy chain variable region (VH) of SEQ ID NO: 23; or a VL of SEQ ID NO: 25 and a VH of SEQ ID NO: 27; or a VL of SEQ ID NO: 29 and a VH of SEQ ID NO: 31; or a VL of SEQ ID NO: 33 and a VH of SEQ ID NO: 35; or a VL of SEQ ID NO: 37 and a VH of SEQ ID NO: 39; or a VL of SEQ ID NO: 41 and a VH of SEQ ID NO: 43; or a VL of SEQ ID NO: 45 and a VH of SEQ ID NO: 47; or a VL of SEQ ID NO: 49 and a VH of SEQ ID NO: 51; or a VL of SEQ ID NO: 53 and a VH of SEQ ID NO: 55; or a VL of SEQ ID NO: 57 and a VH of SEQ ID NO: 59.

In another embodiment the antibody of the invention binds specifically to CLND6; or binds specifically to CLDN6 and CLDN9 and competes for binding with an antibody comprising: a light chain variable region (VL) of SEQ ID NO: 21 and a heavy chain variable region (VH) of SEQ ID NO: 23; or a VL of SEQ ID NO: 25 and a VH of SEQ ID NO: 27; or a VL of SEQ ID NO: 29 and a VH of SEQ ID NO: 31; or a VL of SEQ ID NO: 33 and a VH of SEQ ID NO: 35; or a VL of SEQ ID NO: 37 and a VH of SEQ ID NO: 39; or a VL of SEQ ID NO: 41 and a VH of SEQ ID NO: 43; or a VL of SEQ ID NO: 45 and a VH of SEQ ID NO: 47; or a VL of SEQ ID NO: 49 and a VH of SEQ

ID NO: 51; or a VL of SEQ ID NO: 53 and a VH of SEQ ID NO: 55; or a VL of SEQ ID NO: 57 and a VH of SEQ ID NO: 59.

Any of the anti-CLDN antibodies disclosed herein may be a chimeric, CDR grafted, humanized or recombinant antibody, or a fragment thereof.

In a particular embodiment the invention comprises a humanized antibody that binds to at least one protein of the CLDN family and competes for binding with an antibody comprising three variable light chain CDRs (CDRL) as set forth in SEQ ID NO: 61; and three variable heavy chain CDRs (CDRH) as set forth in SEQ ID NO: 63; or three CDRL as set forth in SEQ ID NO: 65 and three CDRH as set forth in SEQ ID NO: 67; or three CDRL as set forth in SEQ ID NO: 69 and three CDRH as set forth in SEQ ID NO: 71; three CDRL as set forth in SEQ ID NO: 73 and three CDRH as set forth in SEQ ID NO: 75.

In a further embodiment the invention comprises a humanized antibody that binds to at least one protein of the CLDN family and competes for binding with an antibody comprising a VH and VL, wherein the VL has three CDRL comprising a CDRL1 of SEQ ID NO: 151, a CDRL2 of SEQ ID NO: 152 and a CDRL3 of SEQ ID NO: 153; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 157, a CDRL2 of SEQ ID NO: 158 and a CDRL3 of SEQ ID NO: 159; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 163, a CDRL2 of SEQ ID NO: 164 and a CDRL3 of SEQ ID NO: 165; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 169, a CDRL2 of SEQ ID NO: 170 and a CDRL3 of SEQ ID NO: 171.

In a further embodiment the invention comprises a humanized antibody that binds to at least one protein of the CLDN family and competes for binding with an antibody comprising a VL and a VH, wherein the VH has three CDRs (CDRH) comprising a CDRH1 of SEQ ID NO: 154, a CDRH2 of SEQ ID NO: 155 and a CDRH3 of SEQ ID NO: 156; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 160, a CDRH2 of SEQ ID NO: 161 and a CDRH3 of SEQ ID NO: 162; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 166, a CDRH2 of SEQ ID NO: 167 and a CDRH3 of SEQ ID NO: 168; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 172, a CDRH2 of SEQ ID NO: 173 and a CDRH3 of SEQ ID NO: 174.

In a further embodiment the invention comprises a humanized antibody that binds to at least one protein of the CLDN family and competes for binding with an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 151, a CDRL2 of SEQ ID NO: 152 and a CDRL3 of SEQ ID NO: 153 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 154, a CDRH2 of SEQ ID NO: 155 and a CDRH3 of SEQ ID NO: 156; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ

ID NO: 157, a CDRL2 of SEQ ID NO: 158 and a CDRL3 of SEQ ID NO: 159 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 160, a CDRH2 of SEQ ID NO: 161 and a CDRH3 of SEQ ID NO: 162; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 163, a CDRL2 of SEQ ID NO: 164 and a CDRL3 of SEQ ID NO: 165 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 166, a CDRH2 of SEQ ID NO: 167 and a CDRH3 of SEQ ID NO: 168; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 169, a CDRL2 of SEQ ID NO: 170 and a CDRL3 of SEQ ID NO: 171 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 172, a CDRH2 of SEQ ID NO: 173 and a CDRH3 of SEQ ID NO: 174.

In one embodiment the invention comprises a humanized antibody that binds to at least one protein of the CLDN family comprising a full length light chain set forth as SEQ ID NO: 114 and a full length heavy chain set forth as SEQ ID NO: 115; or a full length light chain set forth as SEQ ID NO: 116 and a full length heavy chain set forth as SEQ ID NO: 117; or a full length light chain set forth as SEQ ID NO: 118 and a full length heavy chain set forth as SEQ ID NO: 119; or a full length light chain set forth as SEQ ID NO: 120 and a full length heavy chain set forth as SEQ ID NO: 121.

In one embodiment the invention comprises an antibody drug conjugate (ADC) comprising any anti-CLDN antibody disclosed herein, wherein the antibody is conjugated to a payload. In another embodiment the invention comprises a pharmaceutical composition comprising an ADC, wherein the ADC comprises an anti-CLDN antibody of the invention conjugated to a payload.

In another embodiment the invention comprises a nucleic acid encoding the antibody of any of the anti-CLDN antibodies disclosed herein. In a related embodiment, the invention comprises a vector comprising one or more of the nucleic acids encoding an anti-CLDN antibody disclosed herein or a host cell comprising said vector.

In a preferred embodiment, the invention comprises an antibody drug conjugate (ADC) comprising a chimeric, CDR grafted, humanized or recombinant human antibody, or a fragment thereof, which binds to cancer stem cells expressing at least one protein of the CLDN family, wherein the antibody is conjugated to a cytotoxic agent.

In another embodiment the invention comprises an ADC of the formula Ab-[L-D]n, wherein Ab is any one of the anti-CLDN antibodies disclosed herein; L is an optional linker; D is a drug; and n is an integer from about 1 to about 20.

In one embodiment the invention comprises a method of treating cancer comprising administering to a subject in need thereof a pharmaceutical composition comprising an ADC, wherein the ADC comprises an anti-CLDN antibody of the invention conjugated to a payload.

In some embodiments the invention comprises a method of treating cancer comprising administering to a subject in need thereof a pharmaceutical composition comprising an anti-CLDN ADC, wherein the cancer is selected from ovarian cancer, lung cancer, e.g. lung adenocarcinoma, breast cancer and pancreatic cancer.

In one embodiment the invention comprises a method of treating cancer comprising administering to a subject in need thereof a pharmaceutical composition comprising an anti-CLDN ADC and at least one additional therapeutic moiety.

In one embodiment the invention comprises a method of reducing cancer stem cells in a tumor cell population, wherein the method comprises contacting a tumor cell population comprising cancer stem cells and tumor cells other than cancer stem cells with an anti-CLDN ADC; whereby the frequency of cancer stem cells is reduced, for example, such contacting can be performed *in vivo* or *in vitro*.

In one embodiment the invention comprises a method of delivering a cytotoxin to a cell comprising contacting the cell with an ADC comprising any anti-CLDN antibody disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the relative mRNA expression levels of CDLN4, CLDN6, and CLDN9 determined by whole transcriptome (SOLiD) sequencing in selected patient-derived xenograft (PDX) tumors. Tumor types are denoted according the abbreviations listed in Table 4;

FIG. 2A shows the relative mRNA expression of CLDN4, CLDN6 and CLDN9 in cancer stem cells (CSCs; grey bar), compared to non-tumorigenic (NTG; white bar) cells and in matched normal tissue (black bar), as determined by qRT-PCR;

FIGS. 2B - 2D show relative mRNA expression levels of CLDN4, CLDN6 and CLDN9, respectively, in PDX tumors determined by qRT-PCR;

FIGS. 2E - 2G show the relative levels of mRNA expression of CLDN4 (FIG. 2E), CLDN6 (FIG. 2F) or CLDN9 (FIG. 2G) as measured by qRT-PCR in whole tumor specimens (black dot) or matched normal adjacent tissue (white dot) from patients with one of eighteen different tumor types;

FIGS. 3A and 3B show relative mRNA expression of CLDN6 (FIG. 3A) and CLDN9 (FIG. 3B) across a large number of tumor and normal tissues derived from a public database;

FIG. 3C shows the relative mRNA expression of CLDN6 (x-axis) versus that of CLDN9 (y-axis) for individual tumor samples for five tumor types derived from a public database;

FIG. 3D shows a plot of the centroids (center of mass) of the scatter graphs for the five different tumor types shown in FIG. 3C, as well as a best fit regression line for the plotted centroids;

FIG. 4A is a dendrogram showing the relative degree of similarity between the 30 CLDN proteins encoded by the 23 human CLDN genes;

FIG. 4B shows a tabular representation of the percent identity of amino acid residues in extracellular domain (ECD) 1 or ECD2 in CLDN4, CLDN6 and CLDN9;

FIG. 4C shows a tabular representation of the percent identity of amino acid residues in the ECD1 and ECD2 loops amongst the 16 proteins comprising the set of human, rat, mouse and cynomolgus monkey orthologs of CLDN4, CLDN6 and CLDN9;

FIGS. 5A-5H provide amino acid and nucleic acid sequences of mouse and humanized anti-CLDN antibodies. FIGS. 5A and 5B show light chain (FIG. 5A) and heavy chain (FIG. 5B) variable region amino acid sequences of exemplary mouse and humanized anti-CLDN antibodies (SEQ ID NOS: 21-75, odd numbers) and variants of hSC27.22, hSC27.108 and hSC27.204. FIG. 5C shows the nucleic acid sequences of the same light and heavy chain variable regions of such exemplary mouse and humanized anti-CLDN antibodies (SEQ ID NOS: 20-74, even numbers) and variants of hSC27.22, hSC27.108 and hSC27.204. FIG. 5D shows the amino acid sequences of the full length light and heavy chains of humanized antibodies hSC27.1 and hSC27.22, thirteen variants of hSC27.22, one variant of hSC27.108 and fifteen variants of hSC27.204. FIGS. 5E-5H show annotated amino acid sequences (numbered as per Kabat et al.) of the light and heavy chain variable regions of the humanized anti-CLDN antibodies, hSC27.1 (FIG. 5E), hSC27.22 (FIG. 5F), hSC27.108 (FIG. 5G), and hSC27.204 (FIG. 5H), wherein the CDRs are derived using Kabat, Chothia, ABM and Contact methodology;

FIG. 6A shows the ability of anti-CLDN antibodies SC27.1 and SC27.22 to bind HEK-293T cells overexpressing human CLDN4, CLDN6 and CLDN9 as detected by flow cytometry, where results are shown as change in mean fluorescence intensity (ΔMFI) and a histogram, with the solid black line indicating the binding of the indicated antibody to cells overexpressing the indicated CLDN protein compared to fluorescence minus one (FMO) isotype-control (gray-fill);

FIG. 6B shows the ability of anti-CLDN antibodies to bind HEK-293T cells overexpressing CLDN4, CLDN6 and CLDN9 as detected by flow cytometry, where the results are shown as mean fluorescence intensity (MFI) for each antibody binding to each cell line;

FIG. 6C shows the apparent binding affinity of an exemplary anti-CLDN antibody for CLDN6 and CLDN9 as determined by a titration of the amount of antibody versus a fixed number of cells expressing the antigen of interest;

FIG. 7 shows expression of CLDN4, CLDN6, and CLDN9 proteins in cell populations derived from liver, lung, ovarian and pancreatic PDX tumors (solid black line) compared to fluorescence minus one (FMO) isotype-control (gray-fill);

FIG. 8A shows expression of CLDN4, CLDN6, and CLDN9 proteins in human CSC (solid black line) compared to non-tumorigenic (dashed line) ovarian, pancreatic and lung tumor cell populations and FMO isotype controls (gray-fill);

FIG. 8B shows the growth of tumors in mice transplanted with $CLDN^+$ (closed circles) or $CLDN^-$ (open circles) ovarian tumor cells where $CLDN^+$ tumor cells exhibit enhanced tumorigenicity compared to $CLDN^-$ ovarian tumor cells;

FIGS. 9A and 9B show that anti-CLDN antibodies SC27.1 and SC27.22 are able to internalize into cells overexpressing human CLDN4, CLDN6 and CLDN9 and mediate the delivery of saporin cytotoxin;

FIG. 10A shows expression of CLND6 in various PDX lung, breast and ovarian tumor cells using immunohistochemistry; and

FIG. 10B shows expression of CLND6 in various primary ovarian tumors using immunohistochemistry.

DETAILED DESCRIPTION OF THE INVENTION

The invention may be embodied in many different forms. Disclosed herein are non-limiting, illustrative embodiments of the invention that exemplify the principles thereof. Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. For the purposes of the instant disclosure all identifying sequence accession numbers may be found in the NCBI Reference Sequence (RefSeq) database and/or the NCBI GenBank® archival sequence database unless otherwise noted.

CLDN has surprisingly been found to be a biological marker of a number of tumor types and this association may be exploited for the treatment of such tumors. It has also unexpectedly been found that CLDN is associated with tumorigenic cells and may be effectively exploited to inhibit or eliminate them. Tumorigenic cells, which will be described in more detail below, are known to exhibit resistance to many conventional treatments. In contrast to the teachings of the prior art, the disclosed compounds and methods effectively overcome this inherent resistance.

The invention provides anti-CLDN antibodies (including antibody drug conjugates) and their use in the prognosis, diagnosis, theragnosis, treatment and/or prevention of a variety of CLDN-associated cancers regardless of any particular mechanism of action or specifically targeted cellular or molecular component.

I Claudin (CLDN) Physiology

Claudins are integral membrane proteins comprising a major structural protein of tight junctions, the most apical cell-cell adhesion junction in polarized cell types such as those found in epithelial or endothelial cell sheets. Tight junctions are composed of strands of networked proteins that form continuous seals around cells to provide a physical but modulatable barrier to the transport of solutes and water in the paracellular space. The claudin family of proteins in humans is comprised of at least 23 members, ranging in size from 22-34 kDa. All claudins possess a tetraspanin topology in which both protein termini are located on the intracellular face of the membrane, resulting in the formation of two extracellular (EC) loops, EC1 and EC2. The EC loops mediate head-to-head homophilic, and for certain combinations of claudins, heterophilic interactions that lead to formation of tight junctions. The specific claudin-claudin interactions and claudin EC sequences are a key determinant of ion selectivity and tight junction strength (for example, see Nakano *et al.*, 2009, PMID: 19696885). Typically, EC1 is about 50-60 amino acids in size, contains a conserved disulfide bond within a larger W-X(17-22)-W-X(2)-C-X(8-10)-C motif, and numerous charged residues that participate in ion channel formation (Turksen and Troy, 2004, PMID: 15159449). EC2 is smaller than EC1, being approximately 25 amino acids. Due to its helix-turn-helix conformation, it has been suggested that EC2 contributes to dimer or multimer formation of claudins on opposing cell membranes, although mutations in both loops may perturb complex formation. Claudin-claudin complexes *in vitro* may range in size from dimers to hexamers, depending upon the specific claudins involved (Krause *et al.*, 2008, PMID: 18036336). Individual claudins show a range of tissue specific expression patterns, as well as developmentally regulated expression as determined by PCR analyses (Krause *et al.*, 2008, PMID:18036336; Turksen, 2011, PMID:21526417).

Sequence analysis can be used to construct phylogenetic trees for the claudin family members, indicating the relationship and degrees of relatedness of the protein sequences (FIG. 4A). For instance, it can be seen that the CLDN6 and CLDN9 proteins are closely related which, given the adjacent head-to-head location of their genes at the chromosomal location 16p3.3, is suggestive of an ancestral gene duplication. These similarities likely translate to an ability of these

family members to interact heterotypically. Similarly, the CLDN3 and CLDN4 proteins are closely related by sequence analysis, and their genes can be found in tandem at the chromosomal location 7r11.23. High homology in the EC1 or EC2 loops between certain family members (e.g. FIG. 4B) provides opportunity to develop antibodies that are multi-reactive with various claudin family members.

CLDN6, also known as skullin, is a developmentally regulated claudin. Representative CLDN6 protein orthologs include, but are not limited to, human (NP_067018), chimpanzee (XP_523276), rhesus monkey (NP_001180762), mouse (NP_061247), and rat (NP_001095834). In humans, the *CLDN6* gene consists of 2 exons spanning approximately 3.5 kBp at the chromosomal location 16p13.3. Transcription of the *CLDN6* locus yields a mature 1.4 kB mRNA transcript (NM_021195), encoding a 219 amino acid protein (NP_061247). CLDN6 is expressed in ES cell derivatives committed to an epithelial fate (Turksen and Troy, 2001, PMID: 11668606), in the periderm (Morita et al., 2002, PMID: 12060405), and in the suprabasal level of the epidermis (Turkson and Troy, 2002, PMID: 11923212). It is also expressed in developing mouse kidney (Abuazza *et al.,* 2006, PMID: 16774906), although expression is not detected in adult kidney (Reyes *et al.*, 2002, PMID: 12110008). CLDN6 is also a coreceptor for hepatitis C virus, along with CLDN1 and CLDN9 (Zheng *et al.*, 2007, PMID: 17804490).

CLDN9 is the most closely related family member to CLDN6. Representative CLDN9 protein orthologs include, but are not limited to, human (NP_066192), chimpanzee (XP_003314989), rhesus monkey (NP_001180758), mouse (NP_064689), and rat (NP_001011889). In humans, the *CLDN9* gene consists of a single exon spanning approximately 2.1 kBp at the chromosomal locus 16p13.3. Transcription of the intronless *CLDN9* locus yields a 2.1 kB mRNA transcript (NM_020982), encoding a 217 amino acid protein (NP_0066192). CLDN9 is expressed in various structures of the inner ear (Kitarjiri et al., 2004, PMID:14698084; Nankano *et al.*, 2009, PMID: 19696885), the cornea (Ban et al., 2003, PMID:12742348), the liver (Zheng *et al.*, 2007, PMID:17804490) and developing kidney (Abuazza *et al.,* 2006, PMID:16774906). Consistent with its expression in the cochlea, animals expressing a CLDN9 protein with a missense mutation show defects in hearing likely due to altered paracellular K^+ permeability with consequent perturbation of ion currents critical for depolarization of hair cells involved in sound detection. Expression of CLDN9 in cells of the inner ear is specifically localized to a subdomain underneath more apical tight-junction strands formed by other claudins, indicating that not all claudins in normal tissues are found in the most apical and accessible tight junctions (Nankano *et al.*, 2009, PMID: 19696885). In

contrast to the results in the cochlea, mice expressing missense CLDN9 showed no signs of hepatic or renal defects (Nankano *et al.*, 2009, PMID: 19696885).

CLDN4 is also known as the *Clostridium perfringens* enterotoxin receptor, due to its high affinity binding of this toxin responsible for food poisoning and other gastrointestinal illnesses. Representative CLDN4 protein orthologs include, but are not limited to, human (NP_001296), chimpanzee (XP_519142), rhesus monkey (NP_001181493), mouse (NP_034033), and rat (NP_001012022). In humans, the intronless *CLDN4* gene spans approximately 1.82 kBp at the chromosomal location 17q11.23. Transcription of the *CLDN4* locus yields a 1.82 kB mRNA transcript (NM_001305), encoding a 209 amino acid protein (NP_001296). Consistent with the ability of CLDN4 to bind a toxin produced by a gastrointestinal pathogen, CDLN4 expression can be detected throughout the GI tract as well as in prostate, bladder, breast, and lung (Rahner *et al.,* 2001, PMID:11159882; Tamagawa *et al.*, 2003, PMID:12861044; Wang *et al.*, 2003, PMID:12600828; Nichols *et al.*, 2004, PMID:14983936).

Although claudins are important in the function and homeostasis of normal tissues, tumor cells frequently exhibit abnormal tight junction function. This may be linked to disregulated expression and/or localization of claudins as a consequence of the dedifferentiation of tumor cells, or the requirement of rapidly growing cancerous tissues to efficiently absorb nutrients within a tumor mass with abnormal vascularization (Morin, 2005, PMID: 16266975). Individual claudin family members may be up-regulated in certain cancer types, yet down-regulated in others. For example, CLDN3 and CLDN4 expression is elevated in certain pancreatic, breast and ovarian cancers, yet may be lower in other breast (e.g., “claudin-low”) carcinomas. Claudin proteins may be particularly good targets for antibody drug conjugates (ADCs) since it is known that claudins undergo endocytosis, turnover time of some claudins is short relative to other membrane proteins (Van Itallie *et al.*, 2004, PMID: 15366421), claudin expression is disregulated in cancer cells and tight junctions structures among tumor cells are disrupted in cancer cells. These properties may afford more opportunities for antibodies to bind claudin proteins in neoplastic but not in normal tissues. Although antibodies specific to individual claudins may be useful, it is also possible that polyreactive claudin antibodies would be more likely to facilitate the delivery of payloads to a broader patient population. Specifically, polyreactive claudin antibodies may permit more efficient targeting of cells expressing multiple claudin proteins due to higher aggregate antigen density, reduce the likelihood of escape of tumor cells with low levels of antigen expression of any individual claudin, and as can be seen in the expression examples below, expand the number of therapeutic indications for a single ADC.

II Cancer Stem Cells

According to the current models, a tumor comprises non-tumorigenic cells and tumorigenic cells. Non-tumorigenic cells do not have the capacity to self-renew and are incapable of reproducibly forming tumors, even when transplanted into immunocompromised mice in excess cell numbers. Tumorigenic cells, also referred to herein as "tumor initiating cells" (TICs), which make up 0.1-40% of a tumor's cell population, have the ability to form tumors. Tumorigenic cells encompass both tumor perpetuating cells (TPCs), referred to interchangeably as cancer stem cells (CSCs) and tumor progenitor cells (TProgs).

CSCs, like normal stem cells that support cellular hierarchies in normal tissue, are able to self-replicate indefinitely while maintaining the capacity for multilineage differentiation. CSCs are able to generate both tumorigenic progeny and non-tumorigenic progeny and are able to completely recapitulate the heterogeneous cellular composition of the parental tumor as demonstrated by serial isolation and transplantation of low numbers of isolated CSCs into immunocompromised mice.

TProgs, like CSCs have the ability to fuel tumor growth in a primary transplant. However, unlike CSCs, they are not able to recapitulate the cellular heterogeneity of the parental tumor and are less efficient at reinitiating tumorigenesis in subsequent transplants because TProgs are typically only capable of a finite number of cell divisions as demonstrated by serial transplantation of low numbers of highly purified TProg into immunocompromised mice. TProgs may further be divided into early TProgs and late TProgs, which may be distinguished by phenotype (e.g., cell surface markers) and their different capacities to recapitulate tumor cell architecture. While neither can recapitulate a tumor to the same extent as CSCs, early TProgs have a greater capacity to recapitulate the parental tumor's characteristics than late TProgs. Notwithstanding the foregoing distinctions, it has been shown that some TProg populations can, on rare occasion, gain self-renewal capabilities normally attributed to CSCs and can themselves become CSCs.

CSCs exhibit higher tumorigenicity and are relatively more quiescent than: (i) TProgs (both early and late TProgs); and (ii) non-tumorigenic cells such as tumor-infiltrating cells, for example, fibroblasts/stroma, endothelial and hematopoietic cells that may be derived from CSCs and typically comprise the bulk of a tumor. Given that conventional therapies and regimens have, in large part, been designed to debulk tumors and attack rapidly proliferating cells, CSCs are more resistant to conventional therapies and regimens than the faster proliferating TProgs and other bulk tumor cell populations such as non-tumorigenic cells. Other characteristics that may make CSCs

relatively chemoresistant to conventional therapies are increased expression of multi-drug resistance transporters, enhanced DNA repair mechanisms and anti-apoptotic gene expression. These properties in CSCs constitute a key reason for the failure of standard oncology treatment regimens to ensure long-term benefit for most patients with advanced stage neoplasia because standard chemotherapy does not target the CSCs that actually fuel continued tumor growth and recurrence.

It has surprisingly been discovered that CLDN expression is associated with various tumorigenic cell subpopulations. The invention provides anti-CLDN antibodies that may be particularly useful for targeting tumorigenic cells and may be used to silence, sensitize, neutralize, reduce the frequency, block, abrogate, interfere with, decrease, hinder, restrain, control, deplete, moderate, mediate, diminish, reprogram, eliminate, or otherwise inhibit (collectively, "inhibit") tumorigenic cells, thereby facilitating the treatment, management and/or prevention of proliferative disorders (e.g. cancer). Advantageously, the novel anti-CLDN antibodies of the invention may be selected so they preferably reduce the frequency or tumorigenicity of tumorigenic cells upon administration to a subject regardless of the form of the CLDN determinant (e.g., phenotypic or genotypic). The reduction in tumorigenic cell frequency may occur as a result of (i) inhibition or eradication of tumorigenic cells; (ii) controlling the growth, expansion or recurrence of tumorigenic cells; (iii) interrupting the initiation, propagation, maintenance, or proliferation of tumorigenic cells; or (iv) by otherwise hindering the survival, regeneration and/or metastasis of the tumorigenic cells. In some embodiments, the inhibition of tumorigenic cells may occur as a result of a change in one or more physiological pathways. The change in the pathway, whether by inhibition of the tumorigenic cells, modification of their potential (for example, by induced differentiation or niche disruption) or otherwise interfering with the ability of tumorigenic cells to influence the tumor environment or other cells, allows for the more effective treatment of CLDN associated disorders by inhibiting tumorigenesis, tumor maintenance and/or metastasis and recurrence.

Methods that can be used to assess the reduction in the frequency of tumorigenic cells, include but are not limited to, cytometric or immunohistochemical analysis, preferably by *in vitro* or *in vivo* limiting dilution analysis (Dylla *et al.* 2008, PMID: PMC2413402 and Hoey *et al.* 2009, PMID: 19664991).

In vitro limiting dilution analysis may be performed by culturing fractionated or unfractionated tumor cells (e.g. from treated and untreated tumors, respectively) on solid medium that fosters colony formation and counting and characterizing the colonies that grow. Alternatively, the tumor cells can be serially diluted onto plates with wells containing liquid medium and each well can be

scored as either positive or negative for colony formation at any time after inoculation but preferably more than 10 days after inoculation.

In vivo limiting dilution is performed by transplanting tumor cells, from either untreated controls or from tumors exposed to selected therapeutic agents, into immunocompromised mice in serial dilutions and subsequently scoring each mouse as either positive or negative for tumor formation. The scoring may occur at any time after the implanted tumors are detectable but is preferably done 60 or more days after the transplant. The analysis of the results of limiting dilution experiments to determine the frequency of tumorigenic cells is preferably done using Poisson distribution statistics or assessing the frequency of predefined definitive events such as the ability to generate tumors *in vivo* or not (Fazekas et al., 1982, PMID: 7040548).

Flow cytometry and immunohistochemistry may also be used to determine tumorigenic cell frequency. Both techniques employ one or more antibodies or reagents that bind art recognized cell surface proteins or markers known to enrich for tumorigenic cells (see WO 2012/031280). As known in the art, flow cytometry (e.g. florescence activated cell sorting (FACS)) can also be used to characterize, isolate, purify, enrich or sort for various cell populations including tumorigenic cells. Flow cytometry measures tumorigenic cell levels by passing a stream of fluid, in which a mixed population of cells is suspended, through an electronic detection apparatus which is able to measure the physical and/or chemical characteristics of up to thousands of particles per second. Immunohistochemistry provides additional information in that it enables visualization of tumorigenic cells *in situ* (e.g., in a tissue section) by staining the tissue sample with labeled antibodies or reagents which bind to tumorigenic cell markers.

The antibodies of the invention may be useful for identifying, characterizing, monitoring, isolating, sectioning or enriching populations or subpopulations of tumorigenic cells through methods such as, for example, flow cytometry, magnetic activated cell sorting (MACS), laser mediated sectioning or FACS. FACS is a reliable method used to isolate cell subpopulations at more than 99.5% purity based on specific cell surface markers. Other compatible techniques for the characterization and manipulation of tumorigenic cells including CSCs can be seen, for example, in U.S.P.N.s 12/686,359, 12/669,136 and 12/757,649.

Listed below are markers that have been associated with CSC populations and have been used to isolate or characterize CSCs: ABCA1, ABCA3, ABCG2, ADAM9, ADCY9, ADORA2A, AFP, AXIN1, B7H3, BCL9, Bmi-1, BMP-4, C20orf52, C4.4A, carboxypeptidase M, CAV1, CAV2, CD105, CD133, CD14, CD16, CD166, CD16a, CD16b, CD2, CD20, CD24, CD29, CD3, CD31, CD324, CD325, CD34, CD38, CD44, CD45, CD46, CD49b, CD49f, CD56, CD64, CD74, CD9, CD90,

CEACAM6, CELSR1, CPD, CRIM1, CX3CL1, CXCR4, DAF, decorin, easyh1, easyh2, EDG3, eed, EGFR, ENPP1, EPCAM, EPHA1, EPHA2, FLJ10052, FLVCR, FZD1, FZD10, FZD2, FZD3, FZD4, FZD6, FZD7, FZD8, FZD9, GD2, GJA1, GLI1, GLI2, GPNMB, GPR54, GPRC5B, IL1R1, IL1RAP, JAM3, Lgr5, Lgr6, LRP3, LY6E, MCP, mf2, mllt3, MPZL1, MUC1, MUC16, MYC, N33, Nanog, NB84, nestin, NID2, NMA, NPC1, oncostatin M, OCT4, OPN3, PCDH7, PCDHA10, PCDHB2, PPAP2C, PTPN3, PTS, RARRES1, SEMA4B, SLC19A2, SLC1A1, SLC39A1, SLC4A11, SLC6A14, SLC7A8, smarcA3, smarcD3, smarcE1, smarcA5, Sox1, STAT3, STEAP, TCF4, TEM8, TGFBR3, TMEPAI, TMPRSS4, transferrin receptor, TrkA, WNT10B, WNT16, WNT2, WNT2B, WNT3, WNT5A, YY1 and β-catenin. See, for example, Schulenburg *et al.*, 2010, PMID: 20185329, U.S.P.N. 7,632,678 and U.S.P.N.s. 2007/0292414, 2008/0175870, 2010/0275280, 2010/0162416 and 2011/0020221.

Similarly, non-limiting examples of cell surface phenotypes associated with CSCs of certain tumor types include $CD44^{hi}CD24^{low}$, $ALDH^{+}$, $CD133^{+}$, $CD123^{+}$, $CD34^{+}CD38^{-}$, $CD44^{+}CD24^{-}$, $CD46^{hi}CD324^{+}CD66c^{-}$, $CD133^{+}CD34^{+}CD10^{-}CD19^{-}$, $CD138^{-}CD34^{-}CD19^{+}$, $CD133^{+}RC2^{+}$, $CD44^{+}\alpha_2\beta_1{}^{hi}CD133^{+}$, $CD44^{+}CD24^{+}ESA^{+}$, $CD271^{+}$, $ABCB5^{+}$ as well as other CSC surface phenotypes that are known in the art. See, for example, Schulenburg *et al.*, 2010, supra, Visvader *et al.*, 2008, PMID: 18784658 and U.S.P.N. 2008/0138313. Of particular interest with respect to the instant invention are CSC preparations comprising $CD46^{hi}CD324^{+}$ phenotypes. "Positive," "low" and "negative" expression levels as they apply to markers or marker phenotypes are defined as follows. Cells with negative expression (i.e."-") are herein defined as those cells expressing less than, or equal to, the 95th percentile of expression observed with an isotype control antibody in the channel of fluorescence in the presence of the complete antibody staining cocktail labeling for other proteins of interest in additional channels of fluorescence emission. Those skilled in the art will appreciate that this procedure for defining negative events is referred to as "fluorescence minus one", or "FMO", staining. Cells with expression greater than the 95th percentile of expression observed with an isotype control antibody using the FMO staining procedure described above are herein defined as "positive" (i.e."+"). As defined herein there are various populations of cells broadly defined as "positive." A cell is defined as positive if the mean observed expression of the antigen is above the 95th percentile determined using FMO staining with an isotype control antibody as described above. The positive cells may be termed cells with low expression (i.e. "lo") if the mean observed expression is above the 95^{th} percentile determined by FMO staining and is within one standard deviation of the 95^{th} percentile. Alternatively, the positive cells may be termed cells with high expression (i.e. "hi") if the mean observed expression is above the 95^{th} percentile

determined by FMO staining and greater than one standard deviation above the 95th percentile.In other embodiments the 99th percentile may preferably be used as a demarcation point between negative and positive FMO staining and in particularly preferred embodiments the percentile may be greater than 99%.

The CD46^{hi}CD324^{+} marker phenotype and those exemplified immediately above may be used in conjunction with standard flow cytometric analysis and cell sorting techniques to characterize, isolate, purify or enrich TIC and/or TPC cells or cell populations for further analysis.

The ability of the antibodies of the current invention to reduce the frequency of tumorigenic cells can therefore be determined using the techniques and markers described above. In some instances, the anti-CLDN antibodies may reduce the frequency of tumorigenic cells by 10%, 15%, 20%, 25%, 30% or even by 35%. In other embodiments, the reduction in frequency of tumorigenic cells may be in the order of 40%, 45%, 50%, 55%, 60% or 65%. In certain embodiments, the disclosed compounds my reduce the frequency of tumorigenic cells by 70%, 75%, 80%, 85%, 90% or even 95%. It will be appreciated that any reduction of the frequency of tumorigenic cells is likely to result in a corresponding reduction in the tumorigenicity, persistence, recurrence and aggressiveness of the neoplasia.

III Antibodies

A. Antibody structure

Antibodies and variants and derivatives thereof, including accepted nomenclature and numbering systems, have been extensively described, for example, in Abbas *et al.* (2010), *Cellular and Molecular Immunology* (6th Ed.), W.B. Saunders Company; or Murphey *et al.* (2011), *Janeway's Immunobiology* (8th Ed.), Garland Science.

As used herein an "antibody" or "intact antibody" typically refers to a Y-shaped tetrameric protein comprising two heavy (H) and two light (L) polypeptide chains held together by covalent disulfide bonds and non-covalent interactions. Human light chains are classified as kappa or lambda light chains. Each light chain is composed of one variable domain (VL) and one constant domain (CL). Each heavy chain comprises one variable domain (VH) and a constant region, which in the case of IgG, IgA, and IgD, comprises three domains termed CH1, CH2, and CH3 (IgM and IgE have a fourth domain, CH4). In IgG, IgA, and IgD classes the CH1 and CH2 domains are separated by a flexible hinge region, which is a proline and cysteine rich segment of variable length (generally from about 10 to about 60 amino acids in IgG). The variable domains in both the light

and heavy chains are joined to the constant domains by a “J” region of about 12 or more amino acids and the heavy chain also has a “D” region of about 10 additional amino acids. Each class of antibody further comprises inter-chain and intra-chain disulfide bonds formed by paired cysteine residues.

As used herein the term "antibody" includes polyclonal antibodies, multiclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized and primatized antibodies, CDR grafted antibodies, human antibodies, recombinantly produced antibodies, intrabodies, multispecific antibodies, bispecific antibodies, monovalent antibodies, multivalent antibodies, anti-idiotypic antibodies, synthetic antibodies, including muteins and variants thereof, immunospecific antibody fragments such as Fd, Fab, $F(ab')_2$, F(ab') fragments, single-chain fragments (e.g. ScFv and ScFvFc); and derivatives thereof including Fc fusions and other modifications, and any other immunoreactive molecule so long as it exhibits preferential association or binding with a determinant. Moreover, unless dictated otherwise by contextual constraints the term further comprises all classes of antibodies (i.e. IgA, IgD, IgE, IgG, and IgM) and all subclasses (i.e., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2). Heavy-chain constant domains that correspond to the different classes of antibodies are typically denoted by the corresponding lower case Greek letter α, δ, ε, γ, and μ, respectively. Light chains of the antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

The variable domains of antibodies show considerable variation in amino acid composition from one antibody to another and are primarily responsible for antigen recognition and binding. Variable regions of each light/heavy chain pair form the antibody binding site such that an intact IgG antibody has two binding sites (i.e. it is bivalent). V_H and V_L domains comprise three regions of extreme variability, which are termed hypervariable regions, or more commonly, complementarity-determining regions (CDRs), framed and separated by four less variable regions known as framework regions (FRs). The non-covalent association between the V_H and the V_L region forms the Fv fragment (for "fragment variable") which contains one of the two antigen-binding sites of the antibody. ScFv fragments (for single chain fragment variable), which can be obtained by genetic engineering, associates in a single polypeptide chain, the V_H and the V_L region of an antibody, separated by a peptide linker.

As used herein, the assignment of amino acids to each domain, framework region and CDR may be in accordance with one of the numbering schemes provided by Kabat *et al.* (1991) *Sequences of Proteins of Immunological Interest* (5^{th} Ed.), US Dept. of Health and Human

Services, PHS, NIH, NIH Publication no. 91-3242; Chothia *et al.*, 1987, PMID: 3681981; Chothia *et al.*, 1989, PMID: 2687698; MacCallum *et al.*,1996, PMID: 8876650; or Dubel, Ed. (2007) *Handbook of Therapeutic Antibodies,* 3rd Ed., Wily-VCH Verlag GmbH and Co. unless otherwise noted. The amino acid residues which comprise CDRs as defined by Kabat, Chothia and MacCallum (or "Contact") as obtained from the Abysis website database (infra.) are set out below.

TABLE 1

	Kabat	Chothia	MacCallum
VH CDR1	31-35	26-32	30-35
VH CDR2	50-65	52-56	47-58
VH CDR3	95-102	95-102	93-101
VL CDR1	24-34	24-34	30-36
VL CDR2	50-56	50-56	46-55
VL CDR3	89-97	89-97	89-96

Variable regions and CDRs in an antibody sequence can be identified according to general rules that have been developed in the art (as set out above, such as, for example, the Kabat *et al.* numbering system) or by aligning the sequences against a database of known variable regions. Methods for identifying these regions are described in Kontermann and Dubel, eds., Antibody Engineering, Springer, New York, NY, 2001 and Dinarello *et al.*, Current Protocols in Immunology, John Wiley and Sons Inc., Hoboken, NJ, 2000. Exemplary databases of antibody sequences are described in, and can be accessed through, the "Abysis" website at www.bioinf.org.uk/abs (maintained by A.C. Martin in the Department of Biochemistry & Molecular Biology University College London, London, England) and the VBASE2 website at www.vbase2.org, as described in Retter *et al.*, Nucl. Acids Res., 33 (Database issue): D671 -D674 (2005). Preferably the sequences are analyzed using the Abysis database, which integrates sequence data from Kabat *et al.*, IMGT and the Protein Data Bank (PDB) with structural data from the PDB. See Dr. Andrew C. R. Martin's book chapter *Protein Sequence and Structure Analysis of Antibody Variable Domains*. In: *Antibody Engineering Lab Manual* (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg, ISBN-13: 978-3540413547, also available on the website bioinforg.uk/abs). The Abysis database website further includes general rules that have been developed for identifying CDRs which can be used in accordance with the teachings herein. Unless otherwise indicated, all CDRs set forth herein are derived according to the Abysis database website as per Kabat *et al.*

For heavy chain constant region amino acid positions discussed in the invention, numbering is according to the Eu index first described in Edelman *et al.*, 1969, Proc. Natl. Acad. Sci. USA 63(1): 78-85 describing the amino acid sequence of myeloma protein Eu, which reportedly was the first human IgG1 sequenced. The EU index of Edelman is also set forth in Kabat *et al.*, 1991 (*supra.*). Thus, the terms "EU index as set forth in Kabat" or "EU index of Kabat" or "EU numbering" in the context of the heavy chain refers to the residue numbering system based on the human IgG1 Eu antibody of Edelman *et al.* as set forth in Kabat *et al.*, 1991 (*supra.*) The numbering system used for the light chain constant region amino acid sequence is similarly set forth in Kabat *et al.*, (*supra.*) An exemplary kappa light chain constant region amino acid sequence compatible with the present invention is set forth immediately below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 1).

Similarly, an exemplary IgG1 heavy chain constant region amino acid sequence compatible with the present invention is set forth immediately below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPG (SEQ ID NO: 2).

The disclosed constant region sequences, or variations or derivatives thereof, may be operably associated with the disclosed heavy and light chain variable regions using standard molecular biology techniques to provide full-length antibodies that may be used as such or incorporated in the anti-CLDN ADCs of the invention.

More generally the antibodies or immunoglobulins of the invention may be generated from any antibody that specifically recognizes or associates with the relevant determinant. As used herein "determinant" or "target" means any detectable trait, property, marker or factor that is identifiably associated with, or specifically found in or on a particular cell, cell population or tissue. Determinants or targets may be morphological, functional or biochemical in nature and are

preferably phenotypic. In certain preferred embodiments a determinant is a protein that is differentially expressed (over- or under-expressed) by specific cell types or by cells under certain conditions (e.g., during specific points of the cell cycle or cells in a particular niche). For the purposes of the instant invention a determinant preferably is differentially expressed on aberrant cancer cells and may comprise a CLDN protein, or any of its splice variants, isoforms or family members, or specific domains, regions or epitopes thereof. An "antigen", "immunogenic determinant", "antigenic determinant" or "immunogen" means any protein or any fragment, region or domain thereof that can stimulate an immune response when introduced into an immunocompetent animal and is recognized by the antibodies produced from the immune response. The presence or absence of the determinants contemplated herein may be used to identify a cell, cell subpopulation or tissue (e.g., tumors, tumorigenic cells or CSCs).

There are two types of disulfide bridges or bonds in immunoglobulin molecules: interchain and intrachain disulfide bonds. As is well known in the art the location and number of interchain disulfide bonds vary according to the immunoglobulin class and species. While the invention is not limited to any particular class or subclass of antibody, the IgG1 immunoglobulin shall be used throughout the instant disclosure for illustrative purposes. In wild-type IgG1 molecules there are twelve intrachain disulfide bonds (four on each heavy chain and two on each light chain) and four interchain disulfide bonds. Intrachain disulfide bonds are generally somewhat protected and relatively less susceptible to reduction than interchain bonds. Conversely, interchain disulfide bonds are located on the surface of the immunoglobulin, are accessible to solvent and are usually relatively easy to reduce. Two interchain disulfide bonds exist between the heavy chains and one from each heavy chain to its respective light chain. It has been demonstrated that interchain disulfide bonds are not essential for chain association. The IgG1 hinge region contain the cysteines in the heavy chain that form the interchain disulfide bonds, which provide structural support along with the flexibility that facilitates Fab movement. The heavy/heavy IgG1 interchain disulfide bonds are located at residues C226 and C229 (Eu numbering) while the IgG1 interchain disulfide bond between the light and heavy chain of IgG1 (heavy/light) are formed between C214 of the kappa or lambda light chain and C220 in the upper hinge region of the heavy chain.

B. Antibody generation and production

Antibodies of the invention can be produced using a variety of methods known in the art.

1. Generation of polyclonal antibodies in host animals

The production of polyclonal antibodies in various host animals is well known in the art (see for example, Harlow and Lane (Eds.) (1988) Antibodies: A Laboratory Manual, CSH Press; and Harlow *et al.* (1989) Antibodies, NY, Cold Spring Harbor Press). In order to generate polyclonal antibodies, an immunocompetent animal is immunized with an antigenic protein or cells or preparations comprising an antigenic protein. After a period of time, polyclonal antibody-containing serum is obtained by bleeding or sacrificing the animal. The serum may be used in the form obtained from the animal or the antibodies may be partially or fully purified to provide immunoglobulin fractions or isolated antibody preparations.

Any form of antigen, or cells or preparations containing the antigen, can be used to generate an antibody that is specific for a determinant. The term “antigen” is used in a broad sense and may comprise any immunogenic fragment or determinant of the selected target including a single epitope, multiple epitopes, single or multiple domains or the entire extracellular domain (ECD). The antigen may be an isolated full-length protein, a cell surface protein (e.g., immunizing with cells expressing at least a portion of the antigen on their surface), or a soluble protein (e.g., immunizing with only the ECD portion of the protein). The antigen may be produced in a genetically modified cell. Any of the aforementioned antigens may be used alone or in combination with one or more immunogenicity enhancing adjuvants known in the art. The DNA encoding the antigen may be genomic or non-genomic (e.g., cDNA) and may encode at least a portion of the ECD, sufficient to elicit an immunogenic response. Any vectors may be employed to transform the cells in which the antigen is expressed, including but not limited to adenoviral vectors, lentiviral vectors, plasmids, and non-viral vectors, such as cationic lipids.

2. Monoclonal antibodies

In selected embodiments, the invention contemplates use of monoclonal antibodies. The term "monoclonal antibody" or “mAb” refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible mutations (e.g., naturally occurring mutations), that may be present in minor amounts.

Monoclonal antibodies can be prepared using a wide variety of techniques including hybridoma techniques, recombinant techniques, phage display technologies, transgenic animals (e.g., a XenoMouse®) or some combination thereof. For example, in preferred embodiments monoclonal antibodies can be produced using hybridoma and biochemical and genetic engineering techniques such as described in more detail in An, Zhigiang (ed.) *Therapeutic Monoclonal Antibodies: From Bench to Clinic*, John Wiley and Sons, 1st ed. 2009; Shire et. al. (eds.) *Current Trends in Monoclonal Antibody Development and Manufacturing*, Springer Science + Business Media LLC, 1st ed. 2010; Harlow *et al.*, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 2nd ed. 1988; Hammerling, *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981). Following generation of a number of monoclonal antibodies that bind specifically to a determinant, particularly suitable antibodies may be selected through various screening processes, based on, for example, affinity for the determinant or rate of internalization. In particularly preferred embodiments monoclonal antibodies produced as described herein may be used as source antibodies and further modified to, for example, to improve affinity for the target, improve its production in cell culture, reduce immunogenicity *in vivo*, create multispecific constructs, etc. A more detailed description of monoclonal antibody production and screening is set out below and in the appended Examples.

3. Human antibodies

The antibodies may comprise fully human antibodies. The term “human antibody” refers to an antibody (preferably a monoclonal antibody) which possesses an amino acid sequence that corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies described below.

In one embodiment, recombinant human antibodies may be isolated by screening a recombinant combinatorial antibody library prepared using phage display. In one embodiment, the library is a scFv phage or yeast display library, generated using human VL and VH cDNAs prepared from mRNA isolated from B-cells.

Human antibodies can also be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated and human immunoglobulin genes have been introduced. Upon challenge antibody generation is observed which closely resembles that seen in humans in all respects, including gene rearrangement, assembly and fully human antibody repertoire. This approach is described, for example, in U.S.P.Ns. 5,545,807; 5,545,806; 5,569,825; 5,625,126;

5,633,425; 5,661,016, and U.S.P.Ns. 6,075,181 and 6,150,584 regarding XenoMouse® technology; and Lonberg and Huszar, 1995, PMID: 7494109). Alternatively, a human antibody may be prepared via immortalization of human B lymphocytes producing an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual suffering from a neoplastic disorder or may have been immunized *in vitro*). See, e.g., Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner *et al.*, 1991, PMID: 2051030; and U.S.P.N. 5,750,373.

4. Derived Antibodies:

Once the source antibodies have been generated, selected and isolated as described above they may be further altered to provide anti-CLDN antibodies having improved pharmaceutical characteristics. Preferably the source antibodies are modified or altered using known molecular engineering techniques to provide derived antibodies having the desired therapeutic properties.

4.1 Chimeric and humanized antibodies

Selected embodiments of the invention comprise murine antibodies that immunospecifically bind to CLDN and, for the purposes of the instant disclosure, may be considered “source” antibodies. In selected embodiments, antibodies compatible with the invention can be derived from such “source” antibodies through optional modification of the constant region and/or the antigen binding amino acid sequences of the source antibody. In certain embodiments an antibody is “derived” from a source antibody if selected amino acids in the source antibody are altered through deletion, mutation, substitution, integration or combination. In another embodiment, a “derived” antibody is one in which fragments of the source antibody (e.g., one or more CDRs or the entire heavy and light chain variable regions) are combined with or incorporated into an acceptor antibody sequence to provide the derivative antibody (e.g. chimeric or humanized antibodies). These “derived” antibodies can be generated using standard molecular biological techniques as described below, such as, for example, to improve affinity for the determinant; to improve antibody stability; to improve production and yield in cell culture; to reduce immunogenicity *in vivo*; to reduce toxicity; to facilitate conjugation of an active moiety; or to create a multispecific antibody. Such antibodies may also be derived from source antibodies through modification of the mature molecule (e.g., glycosylation patterns or pegylation) by chemical means or post-translational modification.

In one embodiment, the chimeric antibodies of the invention comprise chimeric antibodies that are derived from protein segments from at least two different species or class of antibodies that have been covalently joined. The term "chimeric" antibody is directed to constructs in which a portion of the heavy and/or light chain is identical or homologous to corresponding sequences in antibodies from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical or homologous to corresponding sequences in antibodies from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies (U.S. P.N. 4,816,567; Morrison *et al.*, 1984, PMID: 6436822). In some preferred embodiments chimeric antibodies of the instant invention may comprise all or most of the selected murine heavy and light chain variable regions operably linked to human light and heavy chain constant regions. In other particularly preferred embodiments, anti-CLDN antibodies may be “derived” from the mouse antibodies disclosed herein.

In other embodiments, the chimeric antibodies of the invention are "CDR grafted" antibodies, where the CDRs (as defined using Kabat, Chothia, McCallum, etc.) are derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody is derived from an antibody from another species or belonging to another antibody class or subclass. For use in humans, one or more selected rodent CDRs (e.g., mouse CDRs) may be grafted into a human acceptor antibody, replacing one or more of the naturally occurring CDRs of the human antibody. These constructs generally have the advantages of providing full strength human antibody functions, e.g., complement dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) while reducing unwanted immune responses to the antibody by the subject. In particularly preferred embodiments the CDR grafted antibodies will comprise one or more CDRs obtained from a mouse incorporated in a human framework sequence.

Similar to the CDR-grafted antibody is a “humanized” antibody. As used herein, a “humanized” antibody is a human antibody (acceptor antibody) comprising one or more amino acid sequences (e.g. CDR sequences) derived from one or more non-human antibodies (donor or source antibody). In certain embodiments, “back mutations” can be introduced into the humanized antibody, in which residues in one or more FRs of the variable region of the recipient human antibody are replaced by corresponding residues from the non-human species donor antibody. Such back mutations may to help maintain the appropriate three-dimensional configuration of the grafted CDR(s) and thereby improve affinity and antibody stability. Antibodies from various donor species may be used including, without limitation, mouse, rat, rabbit, or non-human primate.

Furthermore, humanized antibodies may comprise new residues that are not found in the recipient antibody or in the donor antibody to, for example, further refine antibody performance. CDR grafted and humanized antibodies compatible with the instant invention are provided as set forth in Example 7 below.

Various art recognized techniques can be used to determine which human sequences to use as acceptor antibodies to provide humanized constructs in accordance with the instant invention. Compilations of compatible human germline sequences and methods of determining their suitability as acceptor sequences are disclosed, for example, in Tomlinson, I. A. *et al.* (1992) *J. Mol. Biol*. 227:776-798; Cook, G. P. *et al.* (1995) *Immunol. Today* 16: 237-242; Chothia, D. *et al.* (1992) *J. Mol. Biol.* 227:799-817; and Tomlinson *et al.* (1995) *EMBO J* 14:4628-4638 each of which is incorporated herein in its entirety. The V-BASE directory (VBASE2 – Retter *et al.*, Nucleic Acid Res. 33; 671-674, 2005) which provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, I. A. *et al.* MRC Centre for Protein Engineering, Cambridge, UK) may also be used to identify compatible acceptor sequences. Additionally, consensus human framework sequences described, for example, in U.S.P.N. 6,300,064 may also prove to be compatible acceptor sequences are can be used in accordance with the instant teachings. In general, human framework acceptor sequences are selected based on homology with the murine source framework sequences along with an analysis of the CDR canonical structures of the source and acceptor antibodies. The derived sequences of the heavy and light chain variable regions of the derived antibody may then be synthesized using art recognized techniques.

By way of example CDR grafted and humanized antibodies, and associated methods, are described in U.S.P.Ns. 6,180,370 and 5,693,762. For further details, see, e.g., Jones *et al.*, 1986, PMID: 3713831); and U.S.P.Ns. 6,982,321 and 7,087,409.

The sequence identity or homology of the CDR grafted or humanized antibody variable region to the human acceptor variable region may be determined as discussed herein and, when measured as such, will preferably share at least 60% or 65% sequence identity, more preferably at least 70%, 75%, 80%, 85%, or 90% sequence identity, even more preferably at least 93%, 95%, 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.

It will be appreciated that the annotated CDRs and framework sequences as provided in the appended Figures are defined as per Kabat *et al*. using a proprietary Abysis database. However, as discussed herein one skilled in the art could readily identify the CDRs in accordance with the numbering schemes provided by Chothia et al. or MacCallum et al.

4.2 Site-specific antibodies

The antibodies of the instant invention may be engineered to facilitate conjugation to a cytotoxin or other anti-cancer agent (as discussed in more detail below). It is advantageous for the antibody drug conjugate (ADC) preparation to comprise a homogenous population of ADC molecules in terms of the position of the cytotoxin on the antibody and the drug to antibody ratio (DAR). Based on the instant disclosure one skilled in the art could readily fabricate site-specific engineered constructs as described herein. As used herein a "site-specific antibody" or "site-specific construct" means an antibody, or immunoreactive fragment thereof, wherein at least one amino acid in either the heavy or light chain is deleted, altered or substituted (preferably with another amino acid) to provide at least one free cysteine. Similarly, a "site-specific conjugate" shall be held to mean an ADC comprising a site-specific antibody and at least one cytotoxin or other compound conjugated to the unpaired cysteine(s). In certain embodiments the unpaired cysteine residue will comprise an unpaired intrachain residue. In other preferred embodiments the free cysteine residue will comprise an unpaired interchain cysteine residue. The engineered antibody can be of various isotypes, for example, IgG, IgE, IgA or IgD; and within those classes the antibody can be of various subclasses, for example, IgG1, IgG2, IgG3 or IgG4. For IgG constructs the light chain of the antibody can comprise either a kappa or lambda isotype each incorporating a C214 that, in preferred embodiments, may be unpaired due to a lack of a C220 residue in the IgG1 heavy chain.

In one embodiment the engineered antibody comprises at least one amino acid deletion or substitution of an intrachain or interchain cysteine residue. As used herein "interchain cysteine residue" means a cysteine residue that is involved in a native disulfide bond either between the light and heavy chain of an antibody or between the two heavy chains of an antibody while an "intrachain cysteine residue" is one naturally paired with another cysteine in the same heavy or light chain. In one embodiment the deleted or substituted interchain cysteine residue is involved in

the formation of a disulfide bond between the light and heavy chain. In another embodiment the deleted or substituted cysteine residue is involved in a disulfide bond between the two heavy chains. In a typical embodiment, due to the complementary structure of an antibody, in which the light chain is paired with the VH and C_H1 domains of the heavy chain and wherein the CH2 and C_H3 domains of one heavy chain are paired with the CH2 and CH3 domains of the complementary heavy chain, a mutation or deletion of a single cysteine in either the light chain or in the heavy chain would result in two unpaired cysteine residues in the engineered antibody.

In some embodiments an interchain cysteine residue is deleted. In other embodiments an interchain cysteine is substituted for another amino acid (e.g., a naturally occurring amino acid). For example, the amino acid substitution can result in the replacement of an interchain cysteine with a neutral (e.g. serine, threonine or glycine) or hydrophilic (e.g. methionine, alanine, valine, leucine or isoleucine) residue. In one particularly preferred embodiment an interchain cysteine is replaced with a serine.

In some embodiments contemplated by the invention the deleted or substituted cysteine residue is on the light chain (either kappa or lambda) thereby leaving a free cysteine on the heavy chain. In other embodiments the deleted or substituted cysteine residue is on the heavy chain leaving the free cysteine on the light chain constant region. Upon assembly it will be appreciated that deletion or substitution of a single cysteine in either the light or heavy chain of an intact antibody results in a site-specific antibody having two unpaired cysteine residues.

In one particularly preferred embodiment the cysteine at position 214 (C214) of the IgG light chain (kappa or lambda) is deleted or substituted. In another preferred embodiment the cysteine at position 220 (C220) on the IgG heavy chain is deleted or substituted. In further embodiments the cysteine at position 226 or position 229 on the heavy chain is deleted or substituted. In one embodiment C220 on the heavy chain is substituted with serine (C220S) to provide the desired free cysteine in the light chain. In another embodiment C214 in the light chain is substituted with serine (C214S) to provide the desired free cysteine in the heavy chain. Such site-specific constructs provided in Example 8. A summary of these preferred constructs is shown in Table 2 immediately below where all numbering is according to the EU index as set forth in Kabat and WT stands for “wild-type” or native constant region sequences without alterations and delta (Δ) designates the deletion of an amino acid residue (e.g., C214Δ indicates that the cysteine at position 214 has been deleted).

TABLE 2

Designation	Antibody Component	Alteration
ss1	Heavy Chain Light Chain	C220S WT
ss2	Heavy Chain Light Chain	C220Δ WT
ss3	Heavy Chain Light Chain	WT C214Δ
ss4	Heavy Chain Light Chain	WT C214S

In an analogous manner preferred embodiments may comprise site-specific IgG4 antibodies where the C127 residue of the heavy chain is altered or eliminated to provide a free cysteine at the 220 position of the light chain. As set forth in the Examples below, such embodiments may exhibit improved stability and reduced toxicity.

The strategy for generating antibody-drug conjugates with defined sites and stoichiometries of drug loading, as disclosed herein, is broadly applicable to all anti-CLDN antibodies as it primarily involves engineering of the conserved constant domains of the antibody. As the amino acid sequences and native disulfide bridges of each class and subclass of antibody are well documented, one skilled in the art could readily fabricate engineered constructs of various antibodies without undue experimentation and, accordingly, such constructs are expressly contemplated as being within the scope of the instant invention.

4.3 Constant region modifications and altered glycosylation

Selected embodiments of the present invention may also comprise substitutions or modifications of the constant region (i.e. the Fc region), including without limitation, amino acid residue substitutions, mutations and/or modifications, which result in a compound with preferred characteristics including, but not limited to: altered pharmacokinetics, increased serum half-life, increase binding affinity, reduced immunogenicity, increased production, altered Fc ligand binding to an Fc receptor (FcR), enhanced or reduced ADCC or CDC, altered glycosylation and/or disulfide bonds and modified binding specificity.

Compounds with improved Fc effector functions can be generated, for example, through changes in amino acid residues involved in the interaction between the Fc domain and an Fc

receptor (e.g., FcγRI, FcγRIIA and B, FcγRIII and FcRn), which may lead to increased cytotoxicity and/or altered pharmacokinetics, such as increased serum half-life (see, for example, Ravetch and Kinet, Annu. Rev. Immunol 9:457-92 (1991); Capel *et al.*, Immunomethods 4:25-34 (1994); and de Haas *et al.*, J. Lab. Clin. Med. 126:330-41 (1995).

In selected embodiments, antibodies with increased *in vivo* half-lives can be generated by modifying (e.g., substituting, deleting or adding) amino acid residues identified as involved in the interaction between the Fc domain and the FcRn receptor (see, e.g., International Publication Nos. WO 97/34631; WO 04/029207; U.S.P.N. 6,737,056 and U.S.P.N. 2003/0190311). With regard to such embodiments, Fc variants may provide half-lives in a mammal, preferably a human, of greater than 5 days, greater than 10 days, greater than 15 days, preferably greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. The increased half-life results in a higher serum titer which thus reduces the frequency of the administration of the antibodies and/or reduces the concentration of the antibodies to be administered. Binding to human FcRn in vivo and serum half-life of human FcRn high affinity binding polypeptides can be assayed, e.g., in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides with a variant Fc region are administered. WO 2000/42072 describes antibody variants with improved or diminished binding to FcRns. See also, e.g., Shields et al. J. Biol. Chem. 9(2):6591-6604 (2001).

In other embodiments, Fc alterations may lead to enhanced or reduced ADCC or CDC activity. As in known in the art, CDC refers to the lysing of a target cell in the presence of complement, and ADCC refers to a form of cytotoxicity in which secreted Ig bound onto FcRs present on certain cytotoxic cells (e.g., Natural Killer cells, neutrophils, and macrophages) enables these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. In the context of the instant invention antibody variants are provided with "altered" FcR binding affinity, which is either enhanced or diminished binding as compared to a parent or unmodified antibody or to an antibody comprising a native sequence FcR. Such variants which display decreased binding may possess little or no appreciable binding, e.g., 0-20% binding to the FcR compared to a native sequence, e.g. as determined by techniques well known in the art. In other embodiments the variant will exhibit enhanced binding as compared to the native immunoglobulin Fc domain. It will be appreciated that these types of Fc variants may advantageously be used to enhance the effective anti-neoplastic properties of the disclosed antibodies. In yet other embodiments, such alterations lead to increased binding affinity, reduced

immunogenicity, increased production, altered glycosylation and/or disulfide bonds (e.g., for conjugation sites), modified binding specificity, increased phagocytosis; and/or down regulation of cell surface receptors (e.g. B cell receptor; BCR), etc.

Still other embodiments comprise one or more engineered glycoforms, e.g., a site-specific antibody comprising an altered glycosylation pattern or altered carbohydrate composition that is covalently attached to the protein (e.g., in the Fc domain). See, for example, Shields, R. L. *et al.* (2002) *J. Biol. Chem.* 277:26733-26740. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function, increasing the affinity of the antibody for a target or facilitating production of the antibody. In certain embodiments where reduced effector function is desired, the molecule may be engineered to express an aglycosylated form. Substitutions that may result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site are well known (see e.g. U.S.P.Ns. 5,714,350 and 6,350,861). Conversely, enhanced effector functions or improved binding may be imparted to the Fc containing molecule by engineering in one or more additional glycosylation sites.

Other embodiments include an Fc variant that has an altered glycosylation composition, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes (for example N-acetylglucosaminyltransferase III (GnTIII)), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed (see, for example, WO 2012/117002).

4.4 Fragments

Regardless of which form of antibody (e.g. chimeric, humanized, etc.) is selected to practice the invention it will be appreciated that immunoreactive fragments, either by themselves or as part of an antibody drug conjugate, of the same may be used in accordance with the teachings herein. An “antibody fragment" comprises at least a portion of an intact antibody. As used herein, the term "fragment" of an antibody molecule includes antigen-binding fragments of antibodies, and the term “antigen-binding fragment” refers to a polypeptide fragment of an immunoglobulin or antibody that immunospecifically binds or reacts with a selected antigen or immunogenic determinant thereof or

competes with the intact antibody from which the fragments were derived for specific antigen binding.

Exemplary site-specific fragments include: variable light chain fragments (VL), an variable heavy chain fragments (VH), scFv, F(ab')2 fragment, Fab fragment, Fd fragment, Fv fragment, single domain antibody fragments, diabodies, linear antibodies, single-chain antibody molecules and multispecific antibodies formed from antibody fragments. In addition, an active site-specific fragment comprises a portion of the antibody that retains its ability to interact with the antigen/substrates or receptors and modify them in a manner similar to that of an intact antibody (though maybe with somewhat less efficiency). Such antibody fragments may further be engineered to comprise one or more free cysteines.

In other embodiments, an antibody fragment is one that comprises the Fc region and that retains at least one of the biological functions normally associated with the Fc region when present in an intact antibody, such as FcRn binding, antibody half-life modulation, ADCC function and complement binding. In one embodiment, an antibody fragment is a monovalent antibody that has an *in vivo* half-life substantially similar to an intact antibody. For example, such an antibody fragment may comprise an antigen binding arm linked to an Fc sequence comprising at least one free cysteine capable of conferring *in vivo* stability to the fragment.

As would be well recognized by those skilled in the art, fragments can be obtained by molecular engineering or via chemical or enzymatic treatment (such as papain or pepsin) of an intact or complete antibody or antibody chain or by recombinant means. See, e.g., Fundamental Immunology, W. E. Paul, ed., Raven Press, N.Y. (1999), for a more detailed description of antibody fragments.

4.5 Multivalent constructs

In other embodiments, the antibodies and conjugates of the invention may be monovalent or multivalent (e.g., bivalent, trivalent, etc.). As used herein, the term "valency" refers to the number of potential target binding sites associated with an antibody. Each target binding site specifically binds one target molecule or specific position or locus on a target molecule. When an antibody is monovalent, each binding site of the molecule will specifically bind to a single antigen position or epitope. When an antibody comprises more than one target binding site (multivalent), each target binding site may specifically bind the same or different molecules (e.g., may bind to different ligands or different antigens, or different epitopes or positions on the same antigen). See, for example, U.S.P.N. 2009/0130105.

In one embodiment, the antibodies are bispecific antibodies in which the two chains have different specificities, as described in Millstein *et al.*, 1983, *Nature*, 305:537-539. Other embodiments include antibodies with additional specificities such as trispecific antibodies. Other more sophisticated compatible multispecific constructs and methods of their fabrication are set forth in U.S.P.N. 2009/0155255, as well as WO 94/04690; Suresh *et al.*, 1986, *Methods in Enzymology*, 121:210; and WO96/27011.

Multivalent antibodies may immunospecifically bind to different epitopes of the desired target molecule or may immunospecifically bind to both the target molecule as well as a heterologous epitope, such as a heterologous polypeptide or solid support material. While preferred embodiments only bind two antigens (i.e. bispecific antibodies), antibodies with additional specificities such as trispecific antibodies are also encompassed by the instant invention. Bispecific antibodies also include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S.P.N. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. P.N. 4,676,980, along with a number of cross-linking techniques.

In certain preferred embodiments the antibodies of the invention may be utilized in adoptive immunity gene therapy to treat tumors. In one embodiment the antibodies of the invention (e.g. ScFv fragments) may be used to generate a chimeric antigen receptor (CAR). A “CAR” is a fused protein made up of an ECD comprising the anti-CLDN antibodies of the invention or immunoreactive fragments thereof (e.g. ScFv fragments), a transmembrane domain, and at least one intracellular domain. In one embodiment, T-cells, natural killer cells or dendritic cells that have been genetically engineered to express CARs can be introduced into a subject suffering from cancer in order to stimulate the immune system of the subject to specifically target tumor cells expressing CLDN. In preferred embodiments the CARs of the invention will comprise an intracellular domain that initiates a primary cytoplasmic signaling sequence, that is, a sequence for initiating antigen-dependent primary activation via a T-cell receptor complex, for example, intracellular domains derived from CD3ζ, FcRγ, FcRβ, CD3γ, CD3 δ, CD3ε, CD5, CD22, CD79a, CD79b, and CD66d. In other preferred embodiments, the CARs of the invention will comprise an intracellular domain that initiates a secondary or co-stimulating signal, for example, intracellular

domains derived from CD2, CD4, CD5, CD8α, CD8β, CD28, CD134, CD137, ICOS, CD154, 4-1BB and glucocorticoid-induced tumor necrosis factor receptor (see U.S.P.N. US/2014/0242701).

In yet other embodiments, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences, such as an immunoglobulin heavy chain constant domain comprising at least part of the hinge, CH2, and/or CH3 regions, using methods well known to those of ordinary skill in the art.

5. Recombinant production of antibodies

Antibodies and fragments thereof may be produced or modified using genetic material obtained from antibody producing cells and recombinant technology (see, for example, Berger and Kimmel, Guide to Molecular Cloning Techniques, *Methods in Enzymology* vol. 152 Academic Press, Inc., San Diego, CA; Sambrook and Russell (Eds.) (2000) *Molecular Cloning: A Laboratory Manual* (3rd Ed.), NY, Cold Spring Harbor Laboratory Press; Ausubel *et al.* (2002) *Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology*, Wiley, John & Sons, Inc.; and U.S.P.N. 7,709,611).

Another aspect of the invention pertains to nucleic acid molecules that encode the antibodies of the invention. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or rendered substantially pure when separated from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. A nucleic acid of the invention can be, for example, DNA (e.g. genomic DNA, cDNA), RNA and artificial variants thereof (e.g., peptide nucleic acids), whether single-stranded or double-stranded or RNA, RNA and may or may not contain introns. In a preferred embodiment, the nucleic acid is a cDNA molecule.

Nucleic acids of the invention can be obtained using standard molecular biology techniques. For antibodies expressed by hybridomas (e.g., hybridomas prepared as set forth in the Examples below), cDNAs encoding the light and heavy chains of the antibody can be obtained by standard PCR amplification or cDNA cloning techniques. For antibodies obtained from an immunoglobulin gene library (e.g., using phage display techniques), nucleic acid encoding the antibody can be recovered from the library.

DNA fragments encoding VH and VL segments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length

antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. The term "operatively linked", as used in this context, means that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat, et al. (1991) (*supra*)) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region. An exemplary IgG1 constant region is set forth in SEQ ID NO: 2. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL. The sequences of human light chain constant region genes are known in the art (see e.g., Kabat, et al. (1991) (*supra*)) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region. In this respect an exemplary compatible kappa light chain constant region is set forth in SEQ ID NO: 1.

Contemplated herein are certain polypeptides (e.g. antigens or antibodies) that exhibit "sequence identity", sequence similarity" or "sequence homology" to the polypeptides of the invention. A "homologous" polypeptide may exhibit 65%, 70%, 75%, 80%, 85%, or 90% sequence identity. In other embodiments a "homologous" polypeptides may exhibit 93%, 95% or 98% sequence identity. As used herein, the percent homology between two amino acid sequences is equivalent to the percent identity between the two sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions×100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two

sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.,*4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the XBLAST program (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the antibody molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

Residue positions which are not identical may differ by conservative amino acid substitutions or by non-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 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. In cases where there is a substitution with a non-conservative amino acid, in preferred embodiments the polypeptide exhibiting sequence identity will retain the desired function or activity of the polypeptide of the invention (e.g., antibody.)

Also contemplated herein are nucleic acids that that exhibit "sequence identity", sequence similarity" or "sequence homology" to the nucleic acids of the invention. A "homologous sequence" means a sequence of nucleic acid molecules exhibiting at least about 65%, 70%, 75%, 80%, 85%, or 90% sequence identity. In other embodiments, a "homologous sequence" of nucleic acids may

exhibit 93%, 95% or 98% sequence identity to the reference nucleic acid.

The instant invention also provides vectors comprising such nucleic acids described above, which may be operably linked to a promoter (see, e.g., WO 86/05807; WO 89/01036; and U.S.P.N. 5,122,464); and other transcriptional regulatory and processing control elements of the eukaryotic secretory pathway. The invention also provides host cells harboring those vectors and host-expression systems.

As used herein, the term "host-expression system" includes any kind of cellular system that can be engineered to generate either the nucleic acids or the polypeptides and antibodies of the invention. Such host-expression systems include, but are not limited to microorganisms (e.g., *E. coli* or *B. subtilis*) transformed or transfected with recombinant bacteriophage DNA or plasmid DNA; yeast (e.g., *Saccharomyces*) transfected with recombinant yeast expression vectors; or mammalian cells (e.g., COS, CHO-S, HEK-293T, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells or viruses (e.g., the adenovirus late promoter). The host cell may be co-transfected with two expression vectors, for example, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide.

Methods of transforming mammalian cells are well known in the art. See, for example, U.S.P.N.s. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. The host cell may also be engineered to allow the production of an antigen binding molecule with various characteristics (e.g. modified glycoforms or proteins having GnTIII activity).

For long-term, high-yield production of recombinant proteins stable expression is preferred. Accordingly, cell lines that stably express the selected antibody may be engineered using standard art recognized techniques and form part of the invention. Rather than using expression vectors that contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter or enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Any of the selection systems well known in the art may be used, including the glutamine synthetase gene expression system (the GS system) which provides an efficient approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with EP 0 216 846, EP 0 256 055, EP 0 323 997 and EP 0 338 841 and U.S.P.N.s 5,591,639 and 5,879,936. Another preferred expression system for the development of stable cell lines is the Freedom™ CHO-S Kit (Life Technologies).

Once an antibody of the invention has been produced by recombinant expression or any other of the disclosed techniques, it may be purified or isolated by methods known in the art,

meaning that it is identified and separated and/or recovered from its natural environment and separated from contaminants that would interfere with diagnostic or therapeutic uses for the antibody. Isolated antibodies include antibodies *in situ* within recombinant cells.

These isolated preparations may be purified using various art recognized techniques, such as, for example, ion exchange and size exclusion chromatography, dialysis, diafiltration, and affinity chromatography, particularly Protein A or Protein G affinity chromatography.

6. Post-production Selection

No matter how obtained, antibody-producing cells (e.g., hybridomas, yeast colonies, etc.) may be selected, cloned and further screened for desirable characteristics including, for example, robust growth, high antibody production and desirable antibody characteristics such as high affinity for the antigen of interest. Hybridomas can be expanded *in vitro* in cell culture or *in vivo* in syngeneic immunocompromised animals. Methods of selecting, cloning and expanding hybridomas and/or colonies are well known to those of ordinary skill in the art. Once the desired antibodies are identified the relevant genetic material may be isolated, manipulated and expressed using common, art-recognized molecular biology and biochemical techniques.

The antibodies produced by naïve libraries (either natural or synthetic) may be of moderate affinity (K_a of about 10^6 to 10^7 M^{-1}). To enhance affinity, affinity maturation may be mimicked *in vitro* by constructing antibody libraries (e.g., by introducing random mutations *in vitro* by using error-prone polymerase) and reselecting antibodies with high affinity for the antigen from those secondary libraries (e.g. by using phage or yeast display). WO 9607754 describes a method for inducing mutagenesis in a CDR of an immunoglobulin light chain to create a library of light chain genes.

Various techniques can be used to select antibodies, including but not limited to, phage or yeast display in which a library of human combinatorial antibodies or scFv fragments is synthesized on phages or yeast, the library is screened with the antigen of interest or an antibody-binding portion thereof, and the phage or yeast that binds the antigen is isolated, from which one may obtain the antibodies or immunoreactive fragments (Vaughan *et al.*, 1996, PMID: 9630891; Sheets *et al.*, 1998, PMID: 9600934; Boder *et al.*, 1997, PMID: 9181578; Pepper *et al.*, 2008, PMID: 18336206). Kits for generating phage or yeast display libraries are commercially available. There also are other methods and reagents that can be used in generating and screening antibody display libraries (see U.S.P.N. 5,223,409; WO 92/18619, WO 91/17271, WO 92/20791, WO 92/15679, WO 93/01288, WO 92/01047, WO 92/09690; and Barbas *et al.*, 1991, PMID: 1896445).

Such techniques advantageously allow for the screening of large numbers of candidate antibodies and provide for relatively easy manipulation of sequences (e.g., by recombinant shuffling).

IV Characteristics of antibodies

In selected embodiments, antibody-producing cells (e.g., hybridomas or yeast colonies) may be selected, cloned and further screened for favorable properties including, for example, robust growth, high antibody production and, as discussed in more detail below, desirable site-specific antibody characteristics. In other cases characteristics of the antibody may be imparted by selecting a particular antigen (e.g., a specific CLDN isoform) or immunoreactive fragment of the target antigen for inoculation of the animal. In still other embodiments the selected antibodies may be engineered as described above to enhance or refine immunochemical characteristics such as affinity or pharmacokinetics.

A. Neutralizing antibodies

In selected embodiments the antibodies of the invention may be “antagonists” or “neutralizing” antibodies, meaning that the antibody may associate with a determinant and block or inhibit the activities of said determinant either directly or by preventing association of the determinant with a binding partner such as a ligand or a receptor, thereby interrupting the biological response that otherwise would result from the interaction of the molecules. A neutralizing or antagonist antibody will substantially inhibit binding of the determinant to its ligand or substrate when an excess of antibody reduces the quantity of binding partner bound to the determinant by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% or more as measured, for example, by target molecule activity or in an *in vitro* competitive binding assay. It will be appreciated that the modified activity may be measured directly using art recognized techniques or may be measured by the impact the altered activity has downstream (e.g., oncogenesis or cell survival).

B. Internalizing antibodies

There is evidence that a substantial portion of expressed CLDN protein remains associated with the tumorigenic cell surface, thereby allowing for localization and internalization of the disclosed antibodies or ADCs. In preferred embodiments such antibodies will be associated with, or conjugated to, one or more drugs that kill the cell upon internalization. In particularly preferred embodiments the ADCs of the instant invention will comprise an internalizing site-specific ADC.

As used herein, an antibody that "internalizes" is one that is taken up (along with any cytotoxin) by the cell upon binding to an associated antigen or receptor. For therapeutic applications, internalization will preferably occur *in vivo* in a subject in need thereof. The number of ADCs internalized may be sufficient to kill an antigen-expressing cell, especially an antigen-expressing cancer stem cell. Depending on the potency of the cytotoxin or ADC as a whole, in some instances, the uptake of a single antibody molecule into the cell is sufficient to kill the target cell to which the antibody binds. For example, certain drugs are so highly potent that the internalization of a few molecules of the toxin conjugated to the antibody is sufficient to kill the tumor cell. Whether an antibody internalizes upon binding to a mammalian cell can be determined by various art-recognized assays including those described in the Examples below. Methods of detecting whether an antibody internalizes into a cell are also described in U.S.P.N. 7,619,068.

C. Depleting antibodies

In other embodiments the antibodies of the invention are depleting antibodies. The term "depleting" antibody refers to an antibody that preferably binds to an antigen on or near the cell surface and induces, promotes or causes the death of the cell (e.g., by CDC, ADCC or introduction of a cytotoxic agent). In preferred embodiments, the selected depleting antibodies will be conjugated to a cytotoxin. Preferably a depleting antibody will be able to kill at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, or 99% of CLDN-expressing cells in a defined cell population. The term "apparent IC50", as used herein, refers to the concentration at which a primary antibody linked to a toxin kills 50 percent of the cells expressing the antigen(s) recognized by the primary antibody. The toxin can be directly conjugated to the primary antibody, or can be associated with the primary antibody via a secondary antibody or antibody fragment that recognizes the primary antibody, and which secondary antibody or antibody fragment is directly conjugated to a toxin. Preferably a depleting antibody will have an IC50 of less than 5 μM. less than 1 μM, less than 100 nM, less than 50 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 2 nM or less than 1 nM. In some embodiments the cell population may comprise enriched, sectioned, purified or isolated tumorigenic cells, including cancer stem cells. In other embodiments the cell population may comprise whole tumor samples or heterogeneous tumor extracts that comprise cancer stem cells. Standard biochemical techniques may be used to monitor and quantify the depletion of tumorigenic cells in accordance with the teachings herein.

D. Binding affinity

Disclosed herein are antibodies that have a high binding affinity for a specific determinant e.g. CLDN. The term "K_D" refers to the dissociation constant of a particular antibody-antigen interaction. An antibody of the invention can immunospecifically bind its target antigen when the dissociation constant K_D (k_{off}/k_{on}) is ≤ 10^{-7} M. The antibody specifically binds antigen with high affinity when the K_D is ≤ $5x10^{-9}$ M, and with very high affinity when the K_D is ≤ $5x10^{-10}$ M. In one embodiment of the invention, the antibody has a K_D of ≤ 10^{-9} M and an off-rate of about $1x10^{-4}$ /sec. In one embodiment of the invention, the off-rate is < $1x10^{-5}$ /sec. In other embodiments of the invention, the antibodies will bind to a determinant with a K_D of between about 10^{-7} M and 10^{-10} M, and in yet another embodiment it will bind with a K_D ≤ $2x10^{-10}$ M. Still other selected embodiments of the invention comprise antibodies that have a K_D (k_{off}/k_{on}) of less than 10^{-6} M, less than $5x10^{-6}$ M, less than 10^{-7} M, less than $5x10^{-7}$ M, less than 10^{-8} M, less than $5x10^{-8}$ M, less than 10^{-9} M, less than $5x10^{-9}$ M, less than 10^{-10} M, less than $5x10^{-10}$ M, less than 10^{-11} M, less than $5x10^{-11}$ M, less than 10^{-12} M, less than $5x10^{-12}$ M, less than 10^{-13} M, less than $5x10^{-13}$ M, less than 10^{-14} M, less than $5x10^{-14}$ M, less than 10^{-15} M or less than $5x10^{-15}$ M.

In certain embodiments, an antibody of the invention that immunospecifically binds to a determinant e.g. CLDN may have an association rate constant or k_{on} (or $k_{a)}$ rate (antibody + antigen (Ag)$^{k}_{on}$←antibody-Ag) of at least 10^5 $M^{-1}s^{-1}$, at least $2x10^5$ $M^{-1}s^{-1}$, at least $5x10^5$ $M^{-1}s^{-1}$, at least 10^6 $M^{-1}s^{-1}$, at least $5x10^6$ $M^{-1}s^{-1}$, at least 10^7 $M^{-1}s^{-1}$, at least $5x10^7$ $M^{-1}s^{-1}$, or at least 10^8 $M^{-1}s^{-1}$.

In another embodiment, an antibody of the invention that immunospecifically binds to a determinant e.g. CLDN may have a disassociation rate constant or k_{off} (or $k_{d)}$ rate (antibody + antigen (Ag)$^{k}_{off}$←antibody-Ag) of less than 10^{-1} s^{-1}, less than $5x10^{-1}$ s^{-1}, less than 10^{-2} s^{-1}, less than $5x10^{-2}$ s^{-1}, less than 10^{-3} s^{-1}, less than $5x10^{-3}$ s^{-1}, less than 10^{-4} s^{-1}, less than $5x10^{4}$ s^{-1}, less than 10^{-5} s^{-1}, less than $5x10^{-5}$ s^{-1}, less than 10^{-6} s^{-1}, less than $5x10^{-6}$ s^{-1} less than 10^{-7} s^{-1}, less than $5x10^{-7}$ s^{-1}, less than 10^{-8} s^{-1}, less than $5x10^{-8}$ s^{-1}, less than 10^{-9} s^{-1}, less than $5x10^{-9}$ s^{-1} or less than 10^{-10} s^{-1}.

Binding affinity may be determined using various techniques known in the art, for example, surface plasmon resonance, bio-layer interferometry, dual polarization interferometry, static light scattering, dynamic light scattering, isothermal titration calorimetry, ELISA, analytical ultracentrifugation, and flow cytometry.

The term "apparent binding affinity" as used herein, refers to the apparent binding of an antibody to its target antigen when the antigen is overexpressed on the surface of a cell. The apparent binding affinity of an antibody for an antigen is described herein as an "apparent EC50",

which is the concentration of antibody at which 50% maximal binding to cells overexpressing the antigen occurs. In one embodiment, two antibodies can be said to have "substantially the same" apparent binding affinity for an antigen, with >99% confidence, if they have apparent EC50 values that do not differ from one another by more than 45%, by more than 40%, by more than 35%, by more than 30%, by more than 25%, by more than 20%, by more than 10% or by more than 5%. In another embodiment an antibody that binds multiple target antigens, e.g. is multireactive towards one or more CLDN proteins, can be said to have "substantially the same" apparent binding affinity for the multiple antigens, with >99% confidence, if the apparent EC50 values of the antibody for each of the antigens do not differ from one another by more than 45%, by more than 40%, by more than 35%, by more than 30%, by more than 25%, by more than 20%, by more than 10% or by more than 5%. Since the assays used to determine the apparent binding affinity of an antibody for an antigen typically utilize cells overexpressing the antigen and which are exposed to antibodies under presumed equilibrium or near equilibrium conditions, the apparent EC50 value is reflective of the avidity, or combined or accumulated strength of multiple apparent binding affinities. Thus, in a related embodiment two antibodies will share substantially the same avidity for a target cell line expressing the antigen, with >99% confidence, if their apparent binding affinities for the cell line, expressed as apparent EC50 values, do not differ from one another by more than 45%, by more than 40%, by more than 35%, by more than 30%, by more than 25%, by more than 20%, by more than 10% or by more than 5%. Similarly an antibody that binds multiple target antigens, e.g. is multireactive towards one or more CLDN proteins, can be said to have substantially the same avidity for multiple antigens, with >99% confidence, if the apparent EC50 values for each of the antigens do not differ from one another by more than 45%, by more than 40%, by more than 35%, by more than 30%, by more than 25%, by more than 20%, by more than 10% or by more than 5%.

E. Binning and epitope mapping

As used herein, the term "binning" refers to methods used to group antibodies into "bins" based on their antigen binding characteristics and whether they compete with each other. The initial determination of bins may be further refined and confirmed by epitope mapping and other techniques as described herein. However it will be appreciated that empirical assignment of antibodies to individual bins provides information that may be indicative of the therapeutic potential of the disclosed antibodies.

More specifically, one can determine whether a selected reference antibody (or fragment thereof) competes for binding with a second test antibody (i.e., is in the same bin) by using

methods known in the art and set forth in the Examples herein. In one embodiment, a reference antibody is associated with CLDN antigen under saturating conditions and then the ability of a secondary or test antibody to bind to CLDN is determined using standard immunochemical techniques. If the test antibody is able to substantially bind to CLDN at the same time as the reference anti-CLDN antibody, then the secondary or test antibody binds to a different epitope than the primary or reference antibody. However, if the test antibody is not able to substantially bind to CLDN at the same time, then the test antibody binds to the same epitope, an overlapping epitope, or an epitope that is in close proximity (at least sterically) to the epitope bound by the primary antibody. That is, the test antibody competes for antigen binding and is in the same bin as the reference antibody.

The term "compete" or "competing antibody" when used in the context of the disclosed antibodies means competition between antibodies as determined by an assay in which a test antibody or immunologically functional fragment being tested inhibits specific binding of a reference antibody to a common antigen. Typically, such an assay involves the use of purified antigen (e.g., CLDN or a domain or fragment thereof) bound to a solid surface or cells, an unlabeled test antibody and a labeled reference antibody. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antibody. Usually the test antibody is present in excess and/or allowed to bind first. Additional details regarding methods for determining competitive binding are provided in the Examples herein. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

Conversely, when the reference antibody is bound it will preferably inhibit binding of a subsequently added test antibody (i.e., an anti-CLDN antibody) by at least 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding of the test antibody is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

Generally binning or competitive binding may be determined using various art-recognized techniques, such as, for example, immunoassays such as western blots, radioimmunoassays, enzyme linked immunosorbent assay (ELISA), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays and protein A immunoassays. Such immunoassays are routine and well known in the art (see, Ausubel et al, eds, (1994) *Current Protocols in Molecular Biology*, Vol. 1, John Wiley &

Sons, Inc., New York). Additionally, cross-blocking assays may be used (see, for example, WO 2003/48731; and Harlow *et al.* (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane).

Other technologies used to determine competitive inhibition (and hence "bins"), include: surface plasmon resonance using, for example, the BIAcore™ 2000 system (GE Healthcare); bio-layer interferometry using, for example, a ForteBio® Octet RED (ForteBio); or flow cytometry bead arrays using, for example, a FACSCanto II (BD Biosciences) or a multiplex LUMINEX™ detection assay (Luminex).

Luminex is a bead-based immunoassay platform that enables large scale multiplexed antibody pairing. The assay compares the simultaneous binding patterns of antibody pairs to the target antigen. One antibody of the pair (capture mAb) is bound to Luminex beads, wherein each capture mAb is bound to a bead of a different color. The other antibody (detector mAb) is bound to a fluorescent signal (e.g. phycoerythrin (PE)). The assay analyzes the simultaneous binding (pairing) of antibodies to an antigen and groups together antibodies with similar pairing profiles. Similar profiles of a detector mAb and a capture mAb indicates that the two antibodies bind to the same or closely related epitopes. In one embodiment, pairing profiles can be determined using Pearson correlation coefficients to identify the antibodies which most closely correlate to any particular antibody on the panel of antibodies that are tested. In preferred embodiments a test/detector mAb will be determined to be in the same bin as a reference/capture mAb if the Pearson's correlation coefficient of the antibody pair is at least 0.9. In other embodiments the Pearson's correlation coefficient is at least 0.8, 0.85, 0.87 or 0.89. In further embodiments, the Pearson's correlation coefficient is at least 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99 or 1. Other methods of analyzing the data obtained from the Luminex assay are described in U.S.P.N. 8,568,992. The ability of Luminex to analyze 100 different types of beads (or more) simultaneously provides almost unlimited antigen and/or antibody surfaces, resulting in improved throughput and resolution in antibody epitope profiling over a biosensor assay (Miller, et al., 2011, PMID: 21223970).

"Surface plasmon resonance," refers to an optical phenomenon that allows for the analysis of real-time specific interactions by detection of alterations in protein concentrations within a biosensor matrix.

In other embodiments, a technique that can be used to determine whether a test antibody "competes" for binding with a reference antibody is "bio-layer interferometry", an optical analytical technique that analyzes the interference pattern of white light reflected from two surfaces: a layer

of immobilized protein on a biosensor tip, and an internal reference layer. Any change in the number of molecules bound to the biosensor tip causes a shift in the interference pattern that can be measured in real-time. Such biolayer interferometry assays may be conducted using a ForteBio® Octet RED machine as follows. A reference antibody (Ab1) is captured onto an anti-mouse capture chip, a high concentration of non-binding antibody is then used to block the chip and a baseline is collected. Monomeric, recombinant target protein is then captured by the specific antibody (Ab1) and the tip is dipped into a well with either the same antibody (Ab1) as a control or into a well with a different test antibody (Ab2). If no further binding occurs, as determined by comparing binding levels with the control Ab1, then Ab1 and Ab2 are determined to be "competing" antibodies. If additional binding is observed with Ab2, then Ab1 and Ab2 are determined not to compete with each other. This process can be expanded to screen large libraries of unique antibodies using a full row of antibodies in a 96-well plate representing unique bins. In preferred embodiments a test antibody will compete with a reference antibody if the reference antibody inhibits specific binding of the test antibody to a common antigen by at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In other embodiments, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

Once a bin, encompassing a group of competing antibodies, has been defined further characterization can be carried out to determine the specific domain or epitope on the antigen to which the antibodies in a bin bind. Domain-level epitope mapping may be performed using a modification of the protocol described by Cochran *et al.*, 2004, PMID: 15099763. Fine epitope mapping is the process of determining the specific amino acids on the antigen that comprise the epitope of a determinant to which the antibody binds. The term "epitope" is used in its common biochemical sense and refers to that portion of the target antigen capable of being recognized and specifically bound by a particular antibody. In certain embodiments, epitopes or immunogenic determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. In certain embodiments, an antibody is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules.

When the antigen is a polypeptide such as CLDN, epitopes may generally be formed from both contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein ("conformational epitopes"). In such conformational epitopes the points of interaction occur across amino acid residues on the protein that are linearly separated from one another. Epitopes

formed from contiguous amino acids (sometimes referred to as “linear” or “continuous” epitopes) are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. An antibody epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of epitope determination or “epitope mapping” are well known in the art and may be used in conjunction with the instant disclosure to identify epitopes on CLDN bound by the disclosed antibodies.

Compatible epitope mapping techniques include alanine scanning mutants, peptide blots (Reineke (2004) Methods Mol Biol 248:443-63), or peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). In other embodiments Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) provides a method that categorizes large numbers of monoclonal antibodies directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (U.S.P.N. 2004/0101920). This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. It will be appreciated that MAP may be used to sort the anti-CLDN antibodies of the invention into groups of antibodies binding different epitopes

Once a desired epitope on an antigen is determined, it is possible to generate antibodies to that epitope, e.g., by immunizing with a peptide comprising the epitope using techniques described in the present invention. Alternatively, during the discovery process, the generation and characterization of antibodies may elucidate information about desirable epitopes located in specific domains or motifs. From this information, it is then possible to competitively screen antibodies for binding to the same epitope. An approach to achieve this is to conduct competition studies to find antibodies that compete for binding to the antigen. A high throughput process for binning antibodies based upon their cross-competition is described in WO 03/48731. Other methods of binning or domain level or epitope mapping comprising antibody competition or antigen fragment expression on yeast are well known in the art.

V Antibody conjugates

In certain preferred embodiments the antibodies of the invention may be conjugated with pharmaceutically active moiety or diagnostic moieties to form an “antibody drug conjugate” (ADC) or “antibody conjugate”. The term “conjugate” is used broadly and means the covalent or non-covalent association of any pharmaceutically active moiety or diagnostic moiety with an antibody of

the instant invention regardless of the method of association. In certain embodiments the association is effected through a lysine or cysteine residue of the antibody. In particularly preferred embodiments the pharmaceutically active or diagnostic moieties may be conjugated to the antibody via one or more site-specific free cysteine(s). The disclosed ADCs may be used for therapeutic and diagnostic purposes.

The ADCs of the instant invention may be used to deliver cytotoxins or other payloads to the target location (e.g., tumorigenic cells and/or cells expressing CLDN). As used herein the terms "drug" or "warhead" may be used interchangeably and will mean a biologically active or detectable molecule or compound, including anti-cancer agents as described below. A "payload" may comprise a drug or warhead in combination with an optional linker compound. The warhead on the conjugate may comprise peptides, proteins, prodrugs which are metabolized to an active agent in vivo, polymers, nucleic acid molecules, small molecules, binding agents, mimetic agents, synthetic drugs, inorganic molecules, organic molecules and radioisotopes. In an advantageous embodiment, the disclosed ADCs will direct the bound payload to the target site in a relatively unreactive, non-toxic state before releasing and activating the payload. This targeted release of the payload is preferably achieved through stable conjugation of the payloads via one or more cysteines or lysines and the relatively homogeneous composition of the ADC preparations which minimize over-conjugated toxic species. Coupled with drug linkers that are designed to largely release the drug once it has been delivered to the tumor site, the conjugates of the instant invention can substantially reduce undesirable non-specific toxicity. This advantageously provides for relatively high levels of the active cytotoxin at the tumor site while minimizing exposure of non-targeted cells and tissue thereby providing an enhanced therapeutic index.

It will be appreciated that, while preferred embodiments of the invention comprise payloads of therapeutic moieties (e.g., cytotoxins), other payloads such as diagnostic agents and biocompatible modifiers may benefit from the targeted release provided by the disclosed conjugates. Accordingly, any disclosure directed to exemplary therapeutic payloads is also applicable to payloads comprising diagnostic agents or biocompatible modifiers as discussed herein unless otherwise dictated by context. The selected payload may be covalently or non-covalently linked to, the antibody and exhibit various stoichiometric molar ratios depending, at least in part, on the method used to effect the conjugation. The conjugates of the instant invention may be represented by the formula:

Ab-[L-D]n or a pharmaceutically acceptable salt thereof wherein

a) Ab comprises an anti-CLDN antibody;

b) L comprises an optional linker;

c) D comprises a drug; and

d) n is an integer from about 1 to about 20.

Those of skill in the art will appreciate that conjugates according to the aforementioned formula may be fabricated using a number of different linkers and drugs and that conjugation methodology will vary depending on the selection of components. As such, any drug or drug linker compound that associates with a reactive residue (e.g., cysteine or lysine) of the disclosed antibodies are compatible with the teachings herein. Similarly, any reaction conditions that allow for conjugation (e.g., site-specific conjugation) of the selected drug to an antibody are within the scope of the present invention. Notwithstanding the foregoing, particularly preferred embodiments of the instant invention comprise selective conjugation of the drug or drug linker to free cysteines using stabilization agents in combination with mild reducing agents as described herein. Such reaction conditions tend to provide more homogeneous preparations with less non-specific conjugation and contaminants and correspondingly less toxicity.

Exemplary payloads compatible with the teachings herein are set forth below:

A. Therapeutic agents

The antibodies of the invention may be conjugated, linked or fused to or otherwise associated with a pharmaceutically active moiety which is a therapeutic moiety or a drug such as an anti-cancer agent including, but not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapeutic agents, targeted anti-cancer agents, biological response modifiers, cancer vaccines, cytokines, hormone therapies, anti-metastatic agents and immunotherapeutic agents.

Preferred exemplary anti-cancer agents (including homologs and derivatives thereof) comprise 1-dehydrotestosterone, anthramycins, actinomycin D, bleomycin, calicheamicin, colchicin, cyclophosphamide, cytochalasin B, dactinomycin (formerly actinomycin), dihydroxy anthracin, dione, emetine, epirubicin, ethidium bromide, etoposide, glucocorticoids, gramicidin D, lidocaine, maytansinoids such as DM-1 and DM-4 (Immunogen), mithramycin, mitomycin, mitoxantrone, paclitaxel, procaine, propranolol, puromycin, tenoposide, tetracaine and pharmaceutically acceptable salts or solvates, acids or derivatives of any of the above.

Additional compatible cytotoxins comprise dolastatins and auristatins, including monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) (Seattle Genetics), amanitins such as alpha-amanitin, beta-amanitin, gamma-amanitin or epsilon-amanitin (Heidelberg Pharma), DNA minor groove binding agents such as duocarmycin derivatives (Syntarga), alkylating agents such as modified or dimeric pyrrolobenzodiazepines (PBD), mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BCNU), lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C and cisdichlorodiamine platinum (II) (DDP) cisplatin, splicing inhibitors such as meayamycin analogs or derivatives (e.g., FR901464 as set forth in U.S.P.N. 7,825,267), tubular binding agents such as epothilone analogs and paclitaxel and DNA damaging agents such as calicheamicins and esperamicins, antimetabolites such as methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, and 5-fluorouracil decarbazine, anti-mitotic agents such as vinblastine and vincristine and anthracyclines such as daunorubicin (formerly daunomycin) and doxorubicin and pharmaceutically acceptable salts or solvates, acids or derivatives of any of the above.

In one embodiment the antibodies of the instant invention may be associated with anti-CD3 binding molecules to recruit cytotoxic T-cells and have them target tumorigenic cells (BiTE technology; see e.g., Fuhrmann *et. al.* (2010) Annual Meeting of AACR Abstract No. 5625).

In further embodiments ADCs of the invention may comprise therapeutic radioisotopes conjugated using appropriate linkers. Exemplary radioisotopes that may be compatible with such embodiments include, but are not limited to, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I,), carbon (^{14}C), copper (^{62}Cu, ^{64}Cu, ^{67}Cu), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In,), bismuth (^{212}Bi, ^{213}Bi), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142} Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{117}Sn, ^{225}Ac, ^{76}Br, and ^{211}At. Other radionuclides are also available as diagnostic and therapeutic agents, especially those in the energy range of 60 to 4,000 keV.

In certain preferred embodiments, the ADCs of the invention may comprise pyrrolobenzodiazepines (PBDs) as a cytotoxic agent and pharmaceutically acceptable salts or solvates, acids or derivatives thereof. PBDs are alkylating agents that exert antitumor activity by covalently binding to DNA in the minor groove and inhibiting nucleic acid synthesis. PBDs have been shown to have potent antitumor properties while exhibiting minimal bone marrow depression. PBDs compatible with the invention may be linked to an antibody using several types of linkers (e.g., a peptidyl linker comprising a maleimido moiety with a free sulfhydryl), and in certain embodiments are dimeric in form (i.e., PBD dimers). Compatible PBDs (and optional linkers) that

may be conjugated to the disclosed antibodies are described, for example, in U.S.P.N.s 6,362,331, 7,049,311, 7,189,710, 7,429,658, 7,407,951, 7,741,319, 7,557,099, 8,034,808, 8,163,736, 2011/0256157, WO2011/130613, WO2011/128650, WO2011/130616 and WO2014/057074.

Antibodies of the present invention may also be conjugated to biological response modifiers. For example, in particularly preferred embodiments the drug moiety can be a polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, Onconase (or another cytotoxic RNase), pseudomonas exotoxin, cholera toxin, diphtheria toxin; an apoptotic agent such as tumor necrosis factor e.g. TNF- α or TNF-β, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, AIM I (WO 97/33899), AIM II (WO 97/34911), Fas Ligand (Takahashi *et al.*, 1994, PMID: 7826947), and VEGI (WO 99/23105), a thrombotic agent, an anti-angiogenic agent, e.g., angiostatin or endostatin, a lymphokine, for example, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), and granulocyte colony stimulating factor (G-CSF), or a growth factor e.g., growth hormone (GH).

B. Diagnostic or detection agents

In other preferred embodiments, the antibodies of the invention, or fragments or derivatives thereof, are conjugated to a diagnostic or detectable agent, marker or reporter which may be, for example, a biological molecule (e.g., a peptide or nucleotide), a small molecule, fluorophore, or radioisotope. Labeled antibodies can be useful for monitoring the development or progression of a hyperproliferative disorder or as part of a clinical testing procedure to determine the efficacy of a particular therapy including the disclosed antibodies (i.e. theragnostics) or to determine a future course of treatment. Such markers or reporters may also be useful in purifying the selected antibody, for use in antibody analytics (e.g., epitope binding or antibody binning), separating or isolating tumorigenic cells or in preclinical procedures or toxicology studies.

Such diagnosis, analysis and/or detection can be accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes comprising for example horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as but not limited to streptavidinlbiotin and avidin/biotin; fluorescent materials, such as but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as but not limited to iodine (^{131}I, ^{125}I,

^{123}I, ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In,), and technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin; positron emitting metals using various positron emission tomographies, non-radioactive paramagnetic metal ions, and molecules that are radiolabeled or conjugated to specific radioisotopes. In such embodiments appropriate detection methodology is well known in the art and readily available from numerous commercial sources.

In other embodiments the antibodies or fragments thereof can be fused or conjugated to marker sequences or compounds, such as a peptide or fluorophore to facilitate purification or diagnostic or analytic procedures such as immunohistochemistry, bio-layer interferometry, surface plasmon resonance, flow cytometry, competitive ELISA, FACs, etc. In preferred embodiments, the marker comprises a histidine tag such as that provided by the pQE vector (Qiagen), among others, many of which are commercially available. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "flag" tag (U.S.P.N. 4,703,004).

C. Biocompatible modifiers

In selected embodiments the antibodies of the invention may be conjugated with biocompatible modifiers that may be used to adjust, alter, improve or moderate antibody characteristics as desired. For example, antibodies or fusion constructs with increased *in vivo* half-lives can be generated by attaching relatively high molecular weight polymer molecules such as commercially available polyethylene glycol (PEG) or similar biocompatible polymers. Those skilled in the art will appreciate that PEG may be obtained in many different molecular weights and molecular configurations that can be selected to impart specific properties to the antibody (e.g. the half-life may be tailored). PEG can be attached to antibodies or antibody fragments or derivatives with or without a multifunctional linker either through conjugation of the PEG to the N- or C-terminus of said antibodies or antibody fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity may be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure optimal conjugation of PEG molecules to antibody molecules. Unreacted PEG can be separated from antibody-PEG conjugates by, e.g., size exclusion or ion-exchange

chromatography. In a similar manner, the disclosed antibodies can be conjugated to albumin in order to make the antibody or antibody fragment more stable *in vivo* or have a longer half-life *in vivo*. The techniques are well known in the art, see e.g., WO 93/15199, WO 93/15200, and WO 01/77137; and EP 0 413, 622. Other biocompatible conjugates are evident to those of ordinary skill and may readily be identified in accordance with the teachings herein.

D. Linker compounds

Numerous linker compounds can be used to conjugate the antibodies of the invention to the relevant drug. Preferably linkers will covalently bind with the reactive residue (preferably a cysteine or lysine) and the selected drug compound. Accordingly, any linker that reacts with the selected antibody residue and may be used to provide the relatively stable conjugates (site-specific or otherwise) of the instant invention is compatible with the teachings herein.

Numerous compatible linkers can advantageously bind to reduced cysteines and lysines, which are nucleophilic. Conjugation reactions involving reduced cysteines and lysines include, but are not limited to, thiol-maleimide, thiol-halogeno (acyl halide), thiol-ene, thiol-yne, thiol-vinylsulfone, thiol-bisulfone, thiol-thiosulfonate, thiol-pyridyl disulfide and thiol-parafluoro reactions. As further discussed herein, thiol-maleimide bioconjugation is one of the most widely used approaches due to its fast reaction rates and mild conjugation conditions. One issue with this approach is the possibility of the retro-Michael reaction and loss or transfer of the maleimido-linked payload from the antibody to other proteins in the plasma, such as, for example, human serum albumin. However, in preferred embodiments the use of selective reduction and site-specific antibodies as set forth herein in Example 15 may be used to stabilize the conjugate and reduce this undesired transfer. Thiol-acyl halide reactions provide bioconjugates that cannot undergo retro-Michael reaction and therefore are more stable. However, the thiol-halide reactions in general have slower reaction rates compared to maleimide-based conjugations and are thus not as efficient. Thiol-pyridyl disulfide reaction is another popular bioconjugation route. The pyridyl disulfide undergoes fast exchange with free thiol resulting in the mixed disulfide and release of pyridine-2-thione. Mixed disulfides can be cleaved in the reductive cell environment releasing the payload. Other approaches gaining more attention in bioconjugation are thiol-vinylsulfone and thiol-bisulfone reactions, each of which are compatible with the teachings herein and expressly included within the scope of the invention.

In preferred embodiments compatible linkers will confer stability on the ADCs in the extracellular environment, prevent aggregation of the ADC molecules and keep the ADC freely

soluble in aqueous media and in a monomeric state. Before transport or delivery into a cell, the ADC is preferably stable and remains intact, i.e. the antibody remains linked to the drug moiety. While the linkers are stable outside the target cell they are designed to be cleaved or degraded at some efficacious rate inside the cell. Accordingly an effective linker will: (i) maintain the specific binding properties of the antibody; (ii) allow intracellular delivery of the conjugate or drug moiety; (iii) remain stable and intact, i.e. not cleaved or degraded, until the conjugate has been delivered or transported to its targeted site; and (iv) maintain a cytotoxic, cell-killing effect or a cytostatic effect of the drug moiety. The stability of the ADC may be measured by standard analytical techniques such as mass spectroscopy, hydrophobic interaction chromatography (HIC), HPLC, and the separation/analysis technique LC/MS. As set forth above covalent attachment of the antibody and the drug moiety requires the linker to have 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 MMAE and site-specific antibodies are known, and methods have been described to provide their resulting conjugates.

Linkers compatible with the present invention may broadly be classified as cleavable and non-cleavable linkers. Cleavable linkers, which may include acid-labile linkers, protease cleavable linkers and disulfide linkers, are internalized into the target cell and are cleaved in the endosomal–lysosomal pathway inside the cell. Release and activation of the cytotoxin relies on endosome/lysosome acidic compartments that facilitate cleavage of acid-labile chemical linkages such as hydrazone or oxime. If a lysosomal-specific protease cleavage site is engineered into the linker the cytotoxins will be released in proximity to their intracellular targets. Alternatively, linkers containing mixed disulfides provide an approach by which cytotoxic payloads are released intracellularly as they are selectively cleaved in the reducing environment of the cell, but not in the oxygen-rich environment in the bloodstream. By way of contrast, compatible non-cleavable linkers containing amide linked polyethyleneglycol or alkyl spacers liberate toxic payloads during lysosomal degradation of the ADC within the target cell. In some respects the selection of linker will depend on the particular drug used in the conjugate.

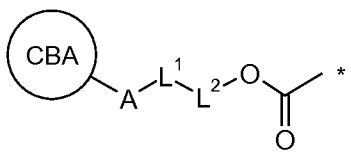
Accordingly, certain embodiments of the invention comprise a linker that is cleavable by a cleaving agent that is present in the intracellular environment (e.g., within a lysosome or endosome or caveolae). The linker can be, for example, a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin, each of which is known

to hydrolyze dipeptide drug derivatives resulting in the release of active drug inside target cells. Exemplary peptidyl linkers that are cleavable by the thiol-dependent protease Cathepsin-B are peptides comprising Phe-Leu since cathepsin-B has been found to be highly expressed in cancerous tissue. Other examples of such linkers are described, for example, in U.S.P.N. 6,214,345. In a specific preferred embodiment, the peptidyl linker cleavable by an intracellular protease is a Val-Cit linker, a Val-Ala linker or a Phe-Lys linker such as is described in U.S.P.N. 6,214,345. One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high.

In other embodiments, the cleavable linker is pH-sensitive. Typically, the pH-sensitive linker will be hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (e.g., a hydrazone, oxime, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like) can be used (See, e.g., U.S.P.N. 5,122,368; 5,824,805; 5,622,929). Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome.

In yet other embodiments, the linker is cleavable under reducing conditions (e.g., a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-S-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio) butyrate) and SMPT (N-succinimidyl-oxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene). In yet other specific embodiments, the linker is a malonate linker (Johnson et al., 1995, *Anticancer Res.* 15:1387-93), a maleimidobenzoyl linker (Lau et al., 1995, *Bioorg-Med-Chem.* 3(10):1299-1304), or a 3′-N-amide analog (Lau et al., 1995, *Bioorg-Med-Chem.* 3(10):1305-12).

In particularly preferred embodiments (set forth in U.S.P.N. 2011/0256157) compatible peptidyl linkers will comprise:



where the asterisk indicates the point of attachment to the drug, CBA is the anti-CLDN antibody, L^1 is a linker, A is a connecting group connecting L^1 to a reactive residue on the antibody,

L^2 is a covalent bond or together with -OC(=O)- forms a self-immolative linker, and L^1 or L^2 is a cleavable linker.

L^1 is preferably the cleavable linker, and may be referred to as a trigger for activation of the linker for cleavage.

The nature of L^1 and L^2, where present, can vary widely. These groups are chosen on the basis of their cleavage characteristics, which may be dictated by the conditions at the site to which the conjugate is delivered. Those linkers that are cleaved by the action of enzymes are preferred, although linkers that are cleavable by changes in pH (e.g. acid or base labile), temperature or upon irradiation (e.g. photolabile) may also be used. Linkers that are cleavable under reducing or oxidising conditions may also find use in the present invention.

L^1 may comprise a contiguous sequence of amino acids. The amino acid sequence may be the target substrate for enzymatic cleavage, thereby allowing release of the drug.

In one embodiment, L^1 is cleavable by the action of an enzyme. In one embodiment, the enzyme is an esterase or a peptidase.

In one embodiment, L^1 comprises a dipeptide. The dipeptide may be represented as -NH-X_1-X_2-CO-, where -NH- and -CO- represent the N- and C-terminals of the amino acid groups X_1 and X_2 respectively. The amino acids in the dipeptide may be any combination of natural amino acids. Where the linker is a cathepsin labile linker, the dipeptide may be the site of action for cathepsin-mediated cleavage.

Additionally, for those amino acids groups having carboxyl or amino side chain functionality, for example Glu and Lys respectively, CO and NH may represent that side chain functionality.

In one embodiment, the group -X_1-X_2- in dipeptide, -NH-X_1-X_2-CO-, is selected from: -Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, -Val-Cit-, -Phe-Cit-, -Leu-Cit-, -Ile-Cit-, -Phe-Arg- and -Trp-Cit- where Cit is citrulline.

Preferably, the group -X_1-X_2- in dipeptide, -NH-X_1-X_2-CO-, is selected from:-Phe-Lys-, -Val-Ala-, -Val-Lys-, -Ala-Lys-, and -Val-Cit-.

Most preferably, the group -X_1-X_2- in dipeptide, -NH-X_1-X_2-CO-, is -Phe-Lys- or -Val-Ala-.

In one embodiment, L^2 is present and together with -C(=O)O- forms a self-immolative linker. In one embodiment, L^2 is a substrate for enzymatic activity, thereby allowing release of the drug.

In one embodiment, where L^1 is cleavable by the action of an enzyme and L^2 is present, the enzyme cleaves the bond between L^1 and L^2.

L^1 and L^2, where present, may be connected by a bond selected from: -C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(=O)O-, -OC(=O)NH-, and -NHC(=O)NH-.

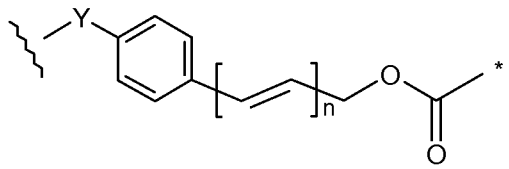
An amino group of L^1 that connects to L^2 may be the N-terminus of an amino acid or may be derived from an amino group of an amino acid side chain, for example a lysine amino acid side chain.

A carboxyl group of L^1 that connects to L^2 may be the C-terminus of an amino acid or may be derived from a carboxyl group of an amino acid side chain, for example a glutamic acid amino acid side chain.

A hydroxyl group of L^1 that connects to L^2 may be derived from a hydroxyl group of an amino acid side chain, for example a serine amino acid side chain.

The term "amino acid side chain" includes those groups found in: (i) naturally occurring amino acids such as alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine; (ii) minor amino acids such as ornithine and citrulline; (iii) unnatural amino acids, beta-amino acids, synthetic analogs and derivatives of naturally occurring amino acids; and (iv) all enantiomers, diastereomers, isomerically enriched, isotopically labelled (e.g. ^2H, ^3H, ^{14}C, ^{15}N), protected forms, and racemic mixtures thereof.

In one embodiment, -C(=O)O- and L^2 together form the group:



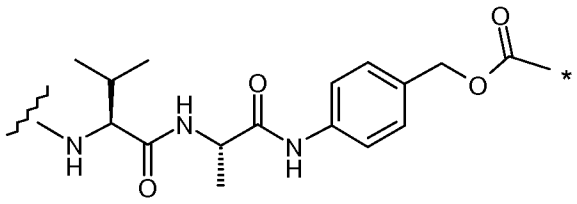
where the asterisk indicates the point of attachment to the drug or cytotoxic agent position, the wavy line indicates the point of attachment to the linker L^1, Y is -N(H)-, -O-, -C(=O)N(H)- or -C(=O)O-, and n is 0 to 3. The phenylene ring is optionally substituted with one, two or three substituents as described herein. In one embodiment, the phenylene group is optionally substituted with halo, NO_2, R or OR.

In one embodiment, Y is NH.

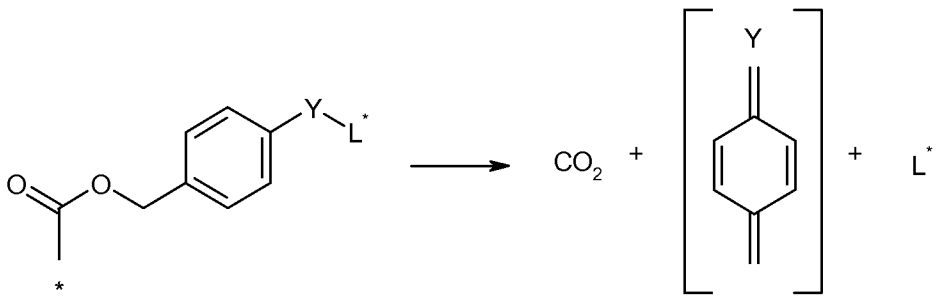
In one embodiment, n is 0 or 1. Preferably, n is 0.

Where Y is NH and n is 0, the self-immolative linker may be referred to as a p-aminobenzylcarbonyl linker (PABC).

In another particularly preferred embodiments the linker may include a self-immolative linker and the dipeptide together form the group -NH-Val-Ala-CO-NH-PABC-, which is illustrated below:



where the asterisk indicates the point of attachment to the selected cytotoxic moiety, and the wavy line indicates the point of attachment to the remaining portion of the linker (e.g., the spacer-antibody binding segments) which may be conjugated to the antibody. Upon enzymatic cleavage of the dipeptide the self-immolative linker will allow for clean release of the protected compound (i.e., the cytotoxin) when a remote site is activated, proceeding along the lines shown below:



where L^* is the activated form of the remaining portion of the linker comprising the now cleaved peptidyl unit. The clean release of the drug ensures they will maintain the desired toxic activity.

In one embodiment, A is a covalent bond. Thus, L^1 and the antibody are directly connected. For example, where L^1 comprises a contiguous amino acid sequence, the N-terminus of the sequence may connect directly to the antibody residue.

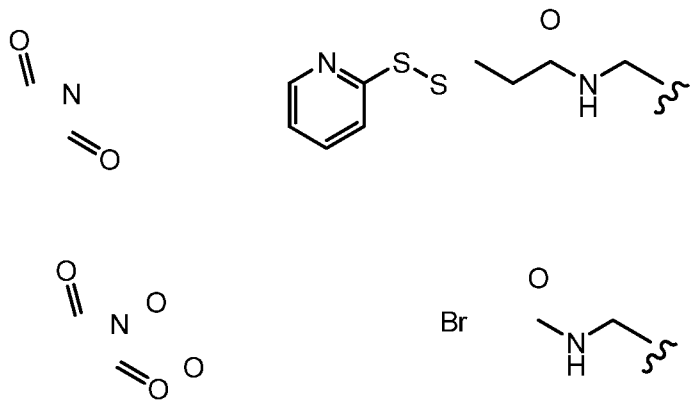
In another embodiment, A is a spacer group. Thus, L^1 and the antibody are indirectly connected.

L^1 and A may be connected by a bond selected from: -C(=O)NH-, -C(=O)O-, -NHC(=O)-, -OC(=O)-, -OC(=O)O-, -NHC(=O)O-, -OC(=O)NH-, and -NHC(=O)NH-.

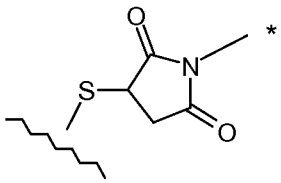
As will be discussed in more detail below the drug linkers of the instant invention will preferably be linked to reactive thiol nucleophiles on cysteines, including free cysteines. To this

end the cysteines of the antibodies may be made reactive for conjugation with linker reagents by treatment with various reducing agent such as DTT or TCEP or mild reducing agents as set forth herein. In other embodiments the drug linkers of the instant invention will preferably be linked to a lysine.

Preferably, the linker contains an electrophilic functional group for reaction with a nucleophilic functional group on the antibody. Nucleophilic groups on antibodies 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) maleimide groups (ii) activated disulfides, (iii) active esters such as NHS (N-hydroxysuccinimide) esters, HOBt (N-hydroxybenzotriazole) esters, haloformates, and acid halides; (iv) alkyl and benzyl halides such as haloacetamides; and (v) aldehydes, ketones, carboxyl, and, some of which are exemplified as follows:



In particularly preferred embodiments the connection between a site-specific antibody and the drug-linker moiety is through a thiol residue of a free cysteine of the site specific antibody and a terminal maleimide group of present on the linker. In such embodiments, the connection between the antibody and the drug-linker is:



where the asterisk indicates the point of attachment to the remaining portion of drug-linker and the wavy line indicates the point of attachment to the remaining portion of the antibody. In this embodiment, the S atom is preferably derived from a site-specific free cysteine. With regard to other compatible linkers the binding moiety comprises a terminal iodoacetamide that may be reacted with activated residues to provide the desired conjugate. In any event one skilled in the art could readily conjugate each of the disclosed drug-linker compounds with a compatible anti-CLDN site-specific antibody in view of the instant disclosure.

E. Conjugation

It will be appreciated that a number of well known different reactions may be used to attach the drug moiety and/or linker to the selected antibody. For example, various reactions exploiting sulfhydryl groups of cysteines may be employed to conjugate the desired moiety. Particularly preferred embodiments will comprise conjugation of antibodies comprising one or more free cysteines as discussed in detail below. In other embodiments ADCs of the instant invention may be generated through conjugation of drugs to solvent-exposed amino groups of lysine residues present in the selected antibody. Still other embodiments comprise activation of the N-terminal threonine and serine residues which may then be used to attach the disclosed payloads to the antibody. The selected conjugation methodology will preferably be tailored to optimize the number of drugs attached to the antibody and provide a relatively high therapeutic index.

Various methods are known in the art for conjugating a therapeutic compound to a cysteine residue and will be apparent to the skilled artisan. Under basic conditions the cysteine residues will be deprotonated to generate a thiolate nucleophile which may be reacted with soft electrophiles, such as maleimides and iodoacetamides. Generally reagents for such conjugations may react directly with a cysteine thiol of a cysteine to form the conjugated protein or with a linker-drug to form a linker-drug intermediate. In the case of a linker, several routes, employing organic chemistry reactions, conditions, and reagents are known to those skilled in the art, including: (1) reaction of a cysteine group of the protein of the invention with a linker reagent, to form a protein-linker intermediate, via

a covalent bond, followed by reaction with an activated compound; and (2) reaction of a nucleophilic group of a compound with a linker reagent, to form a drug-linker intermediate, via a covalent bond, followed by reaction with a cysteine group of a protein of the invention. As will be apparent to the skilled artisan from the foregoing, bifunctional linkers are useful in the present invention. For example, the bifunctional linker may comprise a thiol modification group for covalent linkage to the cysteine residue(s) and at least one attachment moiety (e.g., a second thiol modification moiety) for covalent or non-covalent linkage to the compound.

Prior to conjugation, antibodies may be made reactive for conjugation with linker reagents by treatment with a reducing agent such as dithiothreitol (DTT) or (*tris*(2-carboxyethyl)phosphine (TCEP). In other embodiments additional nucleophilic groups can be introduced into antibodies through the reaction of lysines with reagents, including but not limited to, 2-iminothiolane (Traut's reagent), SATA, SATP or SAT(PEG)4, resulting in conversion of an amine into a thiol.

With regard to such conjugations cysteine thiol or lysine amino groups are nucleophilic and capable of reacting to form covalent bonds with electrophilic groups on linker reagents or compound-linker intermediates or drugs 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; and (iv) disulfides, including pyridyl disulfides, via sulfide exchange. Nucleophilic groups on a compound or linker 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.

Preferred labelling reagents include maleimide, haloacetyl, iodoacetamide succinimidyl ester, isothiocyanate, sulfonyl chloride, 2,6-dichlorotriazinyl, pentafluorophenyl ester, and phosphoramidite, although other functional groups can also be used. In certain embodiments methods include, for example, the use of maleimides, iodoacetimides or haloacetyl/alkyl halides, aziridne, acryloyl derivatives to react with the thiol of a cysteine to produce a thioether that is reactive with a compound. Disulphide exchange of a free thiol with an activated piridyldisulphide is also useful for producing a conjugate (e.g., use of 5-thio-2-nitrobenzoic (TNB) acid). Preferably, a maleimide is used.

As indicated above, lysine may also be used as a reactive residue to effect conjugation as set forth herein. The nucleophilic lysine residue is commonly targeted through amine-reactive succinimidylesters. To obtain an optimal number of deprotonated lysine residues, the pH of the aqueous solution must be below the pKa of the lysine ammonium group, which is around 10.5, so

the typical pH of the reaction is about 8 and 9. The common reagent for the coupling reaction is NHS-ester which reacts with nucleophilic lysine through a lysine acylation mechanism. Other compatible reagents that undergo similar reactions comprise isocyanates and isothiocyanates which also may be used in conjunction with the teachings herein to provide ADCs. Once the lysines have been activated, many of the aforementioned linking groups may be used to covalently bind the warhead to the antibody.

Methods are also known in the art for conjugating a compound to a threonine or serine residue (preferably a N-terminal residue). For example methods have been described in which carbonyl precursors are derived from the 1,2-aminoalcohols of serine or threonine, which can be selectively and rapidly converted to aldehyde form by periodate oxidation. Reaction of the aldehyde with a 1,2-aminothiol of cysteine in a compound to be attached to a protein of the invention forms a stable thiazolidine product. This method is particularly useful for labelling proteins at N-terminal serine or threonine residues.

In particularly preferred embodiments reactive thiol groups may be introduced into the selected antibody (or fragment thereof) by introducing one, two, three, four, or more free cysteine residues (e.g., preparing antibodies comprising one or more free non-native cysteine amino acid residues). Such site-specific antibodies or engineered antibodies, allow for conjugate preparations that exhibit enhanced stability and substantial homogeneity due, at least in part, to the provision of engineered free cysteine site(s) and/or the novel conjugation procedures set forth herein. Unlike conventional conjugation methodology that fully or partially reduces each of the intrachain or interchain antibody disulfide bonds to provide conjugation sites (and is fully compatible with the instant invention), the present invention additionally provides for the selective reduction of certain prepared free cysteine sites and direction of the drug-linker to the same. The conjugation specificity promoted by the engineered sites and the selective reduction allows for a high percentage of site directed conjugation at the desired positions. Significantly some of these conjugation sites, such as those present in the terminal region of the light chain constant region, are typically difficult to conjugate effectively as they cross-react with other free cysteines. However, through molecular engineering and selective reduction of the resulting free cysteines efficient conjugation rates may be obtained which considerably reduces unwanted high-DAR contaminants and non-specific toxicity. More generally the engineered constructs and disclosed novel conjugation methods comprising selective reduction provide ADC preparations having improved pharmacokinetics and/or pharmacodynamics and, potentially, an improved therapeutic index.

The site-specific constructs present free cysteine(s), which when reduced comprise thiol groups that are nucleophilic and capable of reacting to form covalent bonds with electrophilic groups on linker moieties such as those disclosed above. Preferred antibodies of the instant invention will have reducible unpaired interchain or intrachain cysteines, i.e. cysteines providing such nucleophilic groups. Thus, in certain embodiments the reaction of free sulfhydryl groups of the reduced unpaired cysteines and the terminal maleimido or haloacetamide groups of the disclosed drug-linkers will provide the desired conjugation. In such cases the free cysteines of the antibodies may be made reactive for conjugation with linker reagents by treatment with a reducing agent such as dithiothreitol (DTT) or (*tris* (2-carboxyethyl)phosphine (TCEP). Each free cysteine will thus present, theoretically, a reactive thiol nucleophile. While such reagents are compatible it will be appreciated that conjugation of the site-specific antibodies may be effected using various reactions, conditions and reagents known to those skilled in the art.

In addition it has been found that the free cysteines of engineered antibodies may be selectively reduced to provide enhanced site-directed conjugation and a reduction in unwanted, potentially toxic contaminants. More specifically “stabilizing agents” such as arginine have been found to modulate intra- and inter-molecular interactions in proteins and may be used, in conjunction with selected reducing agents (preferably relatively mild), to selectively reduce the free cysteines and to facilitate site-specific conjugation as set forth herein. As used herein the terms “selective reduction” or “selectively reducing” may be used interchangeably and shall mean the reduction of free cysteine(s) without substantially disrupting native disulfide bonds present in the engineered antibody. In selected embodiments this may be affected by certain reducing agents. In other preferred embodiments selective reduction of an engineered construct will comprise the use of stabilization agents in combination with reducing agents (including mild reducing agents). It will be appreciated that the term “selective conjugation” shall mean the conjugation of an engineered antibody that has been selectively reduced with a cytotoxin as described herein. In this respect the use of such stabilizing agents in combination with reducing agents can markedly improve the efficiency of site-specific conjugation as determined by extent of conjugation on the heavy and light antibody chains and DAR distribution of the preparation.

While not wishing to be bound by any particular theory, such stabilizing agents may act to modulate the electrostatic microenvironment and/or modulate conformational changes at the desired conjugation site, thereby allowing relatively mild reducing agents (which do not materially reduce intact native disulfide bonds) to facilitate conjugation at the desired free cysteine site. Such agents (e.g., certain amino acids) are known to form salt bridges (via hydrogen bonding

and electrostatic interactions) and may modulate protein-protein interactions in such a way as to impart a stabilizing effect that may cause favorable conformation changes and/or may reduce unfavorable protein-protein interactions. Moreover, such agents may act to inhibit the formation of undesired intramolecular (and intermolecular) cysteine-cysteine bonds after reduction thus facilitating the desired conjugation reaction wherein the engineered site-specific cysteine is bound to the drug (preferably via a linker). Since the reaction conditions do not provide for the significant reduction of intact native disulfide bonds the conjugation reaction is naturally driven to the relatively few reactive thiols on the free cysteines (e.g., preferably 2 free thiols). As previously alluded to this considerably reduces the levels of non-specific conjugation and corresponding impurities in conjugate preparations fabricated as set forth herein.

In selected embodiments stabilizing agents compatible with the present invention will generally comprise compounds with at least one amine moiety having a basic pKa. In certain embodiments the amine moiety will comprise a primary amine while in other preferred embodiments the amine moiety will comprise a secondary amine. In still other preferred embodiments the amine moiety will comprise a tertiary amine. In other selected embodiments the amine moiety will comprise an amino acid while in other compatible embodiments the amine moiety will comprise an amino acid side chain. In yet other embodiments the amine moiety will comprise a proteinogenic amino acid. In still other embodiments the amine moiety comprises a non-proteinogenic amino acid. In particularly preferred embodiments, compatible stabilizing agents may comprise arginine, lysine, proline and cysteine. In addition compatible stabilizing agents may include guanidine and nitrogen containing heterocycles with basic pKa.

In certain embodiments compatible stabilizing agents comprise compounds with at least one amine moiety having a pKa of greater than about 7.5, in other embodiments the subject amine moiety will have a pKa of greater than about 8.0, in yet other embodiments the amine moiety will have a pKa greater than about 8.5 and in still other embodiments the stabilizing agent will comprise an amine moiety having a pKa of greater than about 9.0. Other preferred embodiments will comprise stabilizing agents where the amine moiety will have a pKa of greater than about 9.5 while certain other embodiments will comprise stabilizing agents exhibiting at least one amine moiety having a pKa of greater than about 10.0. In still other preferred embodiments the stabilizing agent will comprise a compound having the amine moiety with a pKa of greater than about 10.5, in other embodiments the stabilizing agent will comprise a compound having a amine moiety with a pKa greater than about 11.0, while in still other embodiments the stabilizing agent will comprise a amine moiety with a pKa greater than about 11.5. In yet other embodiments the stabilizing agent

will comprise a compound having an amine moiety with a pKa greater than about 12.0, while in still other embodiments the stabilizing agent will comprise an amine moiety with a pKa greater than about 12.5. Those of skill in the art will understand that relevant pKa's may readily be calculated or determined using standard techniques and used to determine the applicability of using a selected compound as a stabilizing agent.

The disclosed stabilizing agents are shown to be particularly effective at targeting conjugation to free site-specific cysteines when combined with certain reducing agents. For the purposes of the instant invention, compatible reducing agents may include any compound that produces a reduced free site-specific cysteine for conjugation without significantly disrupting the engineered antibody native disulfide bonds. Under such conditions, provided by the combination of selected stabilizing and reducing agents, the activated drug linker is largely limited to binding to the desired free site-specific cysteine site. Relatively mild reducing agents or reducing agents used at relatively low concentrations to provide mild conditions are particularly preferred. As used herein the terms "mild reducing agent" or "mild reducing conditions" shall be held to mean any agent or state brought about by a reducing agent (optionally in the presence of stabilizing agents) that provides thiols at the free cysteine site(s) without substantially disrupting native disulfide bonds present in the engineered antibody. That is, mild reducing agents or conditions are able to effectively reduce free cysteine(s) (provide a thiol) without significantly disrupting the protein's native disulfide bonds. The desired reducing conditions may be provided by a number of sulfhydryl-based compounds that establish the appropriate environment for selective conjugation. In preferred embodiments mild reducing agents may comprise compounds having one or more free thiols while in particularly preferred embodiments mild reducing agents will comprise compounds having a single free thiol. Non-limiting examples of reducing agents compatible with the instant invention comprise glutathione, n-acetyl cysteine, cysteine, 2-aminoethane-1-thiol and 2-hydroxyethane-1-thiol.

It will be appreciated that selective reduction process set forth above is particularly effective at targeted conjugation to the free cysteine. In this respect the extent of conjugation to the desired target site (defined here as "conjugation efficiency") in site-specific antibodies may be determined by various art-accepted techniques. The efficiency of the site-specific conjugation of a drug to an antibody may be determined by assessing the percentage of conjugation on the target conjugation site (in this invention the free cysteine on the c-terminus of the light chain) relative to all other conjugated sites. In certain embodiments, the method herein provides for efficiently conjugating a drug to an antibody comprising free cysteines. In some embodiments, the conjugation efficiency is

at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or more as measured by the percentage of target conjugation relative to all other conjugation sites.

It will further be appreciated that engineered antibodies capable of conjugation may contain free cysteine residues that comprise sulfhydryl groups that are blocked or capped as the antibody is produced or stored. Such caps include proteins, peptides, ions and other materials that interact with the sulfhydryl group and prevent or inhibit conjugate formation. In some cases the unconjugated engineered antibody may comprise free cysteines that bind other free cysteines on the same or different antibodies. As discussed herein such cross-reactivity may lead to various contaminants during the fabrication procedure. In some embodiments, the engineered antibodies may require uncapping prior to a conjugation reaction. In specific embodiments, antibodies herein are uncapped and display a free sulfhydryl group capable of conjugation. In specific embodiments, antibodies herein are subjected to an uncapping reaction that does not disturb or rearrange the naturally occurring disulfide bonds. It will be appreciated that in most cases the uncapping reactions will occur during the normal reduction reactions (reduction or selective reduction).

F. DAR distribution and purification

One of the advantages of conjugation with site specific antibodies of the present invention is the ability to generate relatively homogeneous ADC preparations comprising a narrow DAR distribution. In this regard the disclosed constructs and/or selective conjugation provides for homogeneity of the ADC species within a sample in terms of the stoichiometric ratio between the drug and the engineered antibody. As briefly discussed above the term “drug to antibody ratio” or “DAR” refers to the molar ratio of drug to antibody. In some embodiments a conjugate preparation may be substantially homogeneous with respect to its DAR distribution, meaning that within the preparation is a predominant species of site-specific ADC with a particular DAR (e.g., a DAR of 2 or 4) that is also uniform with respect to the site of loading (i.e., on the free cysteines). In certain embodiments of the invention it is possible to achieve the desired homogeneity through the use of site-specific antibodies or selective combination. In other preferred embodiments the desired homogeneity may be achieved through the use of site-specific constructs in combination with selective reduction. In yet other particularly preferred embodiments the preparations may be further purified using analytical or preparative chromatography techniques. In each of these embodiments the homogeneity of the ADC sample can be analyzed using various techniques known in the art

including but not limited to SDS-PAGE, HPLC (e.g. size exclusion HPLC, RP-HPLC, HIC-HPLC etc.) or capillary electrophoresis.

With regard to the purification of ADC preparations it will be appreciated that standard pharmaceutical preparative methods may be employed to obtain the desired purity. As discussed herein liquid chromatography methods such as reverse phase (RP) and hydrophobic interaction chromatography (HIC) may separate compounds in the mixture by drug loading value. In some cases, mixed-mode chromatography (MMC) may also be used to isolate species with a specific drug load. More generally, once insoluble contaminants are removed the antibody preparation may be further purified using standard techniques such as, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography of particular interest. In this regard protein A can be used to purify antibodies that are based on human IgG1, IgG2 or IgG4 heavy chains while protein G is recommended for all mouse isotypes and for human IgG3. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, chromatography on silica, chromatography on heparin, sepharose chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE and ammonium sulfate precipitation are also available depending on the antibody or conjugate to be recovered.

The disclosed ADCs and preparations thereof may comprise drug and antibody moieties in various stoichiometric molar ratios depending on the configuration of the antibody (e.g., an engineered construct) and, at least in part, on the method used to effect conjugation. In certain embodiments the drug loading per ADC may comprise from 1-20 warheads (i.e., n is 1-20). Other selected embodiments may comprise ADCs with a drug loading of from 1 to 15 warheads. In still other embodiments the ADCs may comprise from 1-12 warheads or, more preferably, from 1-10 warheads. In certain preferred embodiments the ADCs will comprise from 1 to 8 warheads.

With regard to site-specific conjugates. depending on how many and which interchain and intrachain disulfide bonds are disrupted theoretical drug loading may be relatively high though practical limitations such as free cysteine cross reactivity would limit the generation of homogeneous preparations comprising such DAR due to aggregates and other contaminants. That is, higher drug loading, e.g. >6, may cause aggregation, insolubility, toxicity, or loss of cellular permeability of certain antibody-drug conjugates. In view of such concerns practical drug loading provided by the instant invention preferably ranges from 1 to 8 drugs per conjugate, i.e. where 1, 2, 3, 4, 5, 6, 7, or 8 drugs are covalently attached to each antibody (e.g., for IgG1, other antibodies may have different loading capacity depending the number of disulfide bonds). Preferably the DAR

of compositions of the instant invention will be approximately 2, 4 or 6 and in particularly preferred embodiments the DAR will comprise approximately 2.

Despite the relatively high level of homogeneity provided by the instant invention the disclosed compositions actually comprise a mixture of conjugates with a range of drug loads (e.g., from 1 to 8 drugs per IgG1 antibody) at various concentrations (along with certain reaction contaminants primarily caused by free cysteine cross reactivity); and which comprise drug moieties that are attached to the antibody by various thiol groups. Using selective reduction and post-fabrication purification the conjugate compositions may be driven to the point where they largely contain a single predominant desired ADC species (e.g., with a drug loading of 2) with relatively low levels of other ADC species (e.g., with a drug loading of 1, 4, 6, etc.). The average DAR value represents the weighted average of drug loading for the composition as a whole (i.e., all the ADC species taken together). Due to inherent uncertainty in the quantification methodology employed and the difficulty in completely removing the non-predominant ADC species in a commercial setting, acceptable DAR values or specifications are often presented as an average, a range or distribution (i.e., an average DAR of 2 +/- 0.5). Preferably compositions comprising a measured average DAR within the range (i.e., 1.5 to 2.5) would be used in a pharmaceutical setting.

Thus, in certain preferred embodiments the present invention will comprise compositions having an average DAR of 1, 2, 3, 4, 5, 6, 7 or 8 each +/- 0.5. In other preferred embodiments the present invention will comprise an average DAR of 2, 4, 6 or 8 +/- 0.5. Finally, in selected preferred embodiments the present invention will comprise an average DAR of 2 +/- 0.5. It will be appreciated that the range or deviation may be less than 0.4 in certain preferred embodiments. Thus, in other embodiments the compositions will comprise an average DAR of 1, 2, 3, 4, 5, 6, 7 or 8 each +/- 0.3, an average DAR of 2, 4, 6 or 8 +/- 0.3, even more preferably an average DAR of 2 or 4 +/- 0.3 or even an average DAR of 2 +/- 0.3. In other embodiments IgG1 conjugate compositions will preferably comprise a composition with an average DAR of 1, 2, 3, 4, 5, 6, 7 or 8 each +/- 0.4 and relatively low levels (i.e., less than 30%) of non-predominant ADC species. In other preferred embodiments the ADC composition will comprise an average DAR of 2, 4, 6 or 8 each +/- 0.4 with relatively low levels (< 30%) of non-predominant ADC species. In particularly preferred embodiments the ADC composition will comprise an average DAR of 2 +/- 0.4 with relatively low levels (< 30%) of non-predominant ADC species. In yet other embodiments the predominant ADC species (e.g., DAR of 2) will be present at a concentration of greater than 70%, a concentration of greater than 75%, a concentration of greater that 80%, a concentration of greater than 85%, a concentration of greater than 90%, a concentration of greater than 93%, a

concentration of greater than 95% or even a concentration of greater than 97% when measured against other DAR species.

As detailed in the Examples below the distribution of drugs per antibody in preparations of ADC from conjugation reactions may be characterized by conventional means such as UV-Vis spectrophotometry, reverse phase HPLC, HIC, mass spectroscopy, ELISA, and electrophoresis. The quantitative distribution of ADC in terms of drugs per antibody may also be determined. By ELISA, the averaged value of the drugs per antibody in a particular preparation of ADC may be determined. However, the distribution of drug per antibody values is not discernible by the antibody-antigen binding and detection limitation of ELISA. Also, ELISA assay for detection of antibody-drug conjugates does not determine where the drug moieties are attached to the antibody, such as the heavy chain or light chain fragments, or the particular amino acid residues.

VI Diagnostics and Screening

A. Diagnostics

The invention provides *in vitro* and *in vivo* methods for detecting, diagnosing or monitoring proliferative disorders and methods of screening cells from a patient to identify tumor cells including tumorigenic cells. Such methods include identifying an individual having cancer for treatment or monitoring progression of a cancer, comprising contacting the patient or a sample obtained from a patient (either *in vivo* or *in vitro*) with an antibody as described herein and detecting presence or absence, or level of association, of the antibody to bound or free target molecules in the sample. In some embodiments the antibody will comprise a detectable label or reporter molecule as described herein.

In some embodiments, the association of the antibody with particular cells in the sample can denote that the sample may contain tumorigenic cells, thereby indicating that the individual having cancer may be effectively treated with an antibody as described herein.

Samples can be analyzed by numerous assays, for example, radioimmunoassays, enzyme immunoassays (e.g. ELISA), competitive-binding assays, fluorescent immunoassays, immunoblot assays, Western Blot analysis and flow cytometry assays. Compatible *in vivo* theragnostic or diagnostic assays can comprise art recognized imaging or monitoring techniques, for example, magnetic resonance imaging, computerized tomography (e.g. CAT scan), positron tomography (e.g., PET scan), radiography, ultrasound, etc.

In a particularly preferred embodiment the antibodies of the instant invention may be used to

detect and quantify levels of a particular determinant (e.g., CLDN) in a patient sample (e.g., plasma or blood) which may, in turn, be used to detect, diagnose or monitor proliferative disorders that are associated with the relevant determinant. In related embodiments the antibodies of the instant invention may be used to detect, monitor and/or quantify circulating tumor cells either *in vivo* or *in vitro* (WO 2012/0128801). In still other embodiments the circulating tumor cells may comprise tumorigenic cells.

In certain embodiments of the invention, the tumorigenic cells in a subject or a sample from a subject may be assessed or characterized using the disclosed antibodies prior to therapy or regimen to establish a baseline. In other examples, the tumorigenic cells can be assessed from a sample that is derived from a subject that was treated.

B. Screening

In certain embodiments, the antibodies can be used to screen samples in order to identify compounds or agents (e.g., antibodies or ADCs) that alter a function or activity of tumor cells by interacting with a determinant. In one embodiment, tumor cells are put in contact with an antibody or ADC and the antibody or ADC can be used to screen the tumor for cells expressing a certain target (e.g. CLDN) in order to identify such cells for purposes, including but not limited to, diagnostic purposes, to monitor such cells to determine treatment efficacy or to enrich a cell population for such target-expressing cells.

In yet another embodiment, a method includes contacting, directly or indirectly, tumor cells with a test agent or compound and determining if the test agent or compound modulates an activity or function of the determinant-associated tumor cells for example, changes in cell morphology or viability, expression of a marker, differentiation or de-differentiation, cell respiration, mitochondrial activity, membrane integrity, maturation, proliferation, viability, apoptosis or cell death. One example of a direct interaction is physical interaction, while an indirect interaction includes, for example, the action of a composition upon an intermediary molecule that, in turn, acts upon the referenced entity (e.g., cell or cell culture).

Screening methods include high throughput screening, which can include arrays of cells (e.g., microarrays) positioned or placed, optionally at pre-determined locations, for example, on a culture dish, tube, flask, roller bottle or plate. High-throughput robotic or manual handling methods can probe chemical interactions and determine levels of expression of many genes in a short period of time. Techniques have been developed that utilize molecular signals, for example via fluorophores or microarrays (Mocellin and Rossi, 2007, PMID: 17265713) and automated analyses

that process information at a very rapid rate (see, e.g., Pinhasov *et al.*, 2004, PMID: 15032660). Libraries that can be screened include, for example, small molecule libraries, phage display libraries, fully human antibody yeast display libraries (Adimab), siRNA libraries, and adenoviral transfection vectors.

VII Pharmaceutical Preparations and Therapeutic Uses

A. Formulations and routes of administration

The antibodies or ADCs of the invention can be formulated in various ways using art recognized techniques. In some embodiments, the therapeutic compositions of the invention can be administered neat or with a minimum of additional components while others may optionally be formulated to contain suitable pharmaceutically acceptable carriers. As used herein, "pharmaceutically acceptable carriers" comprise excipients, vehicles, adjuvants and diluents that are well known in the art and can be available from commercial sources for use in pharmaceutical preparation (see, e.g., Gennaro (2003) *Remington: The Science and Practice of Pharmacy with Facts and Comparisons: Drugfacts Plus*, 20th ed., Mack Publishing; Ansel *et al.* (2004) *Pharmaceutical Dosage Forms and Drug Delivery Systems,* 7th ed., Lippencott Williams and Wilkins; Kibbe *et al.*(2000) *Handbook of Pharmaceutical Excipients,* 3rd ed., Pharmaceutical Press.)

Suitable pharmaceutically acceptable carriers comprise substances that are relatively inert and can facilitate administration of the antibody or can aid processing of the active compounds into preparations that are pharmaceutically optimized for delivery to the site of action.

Such pharmaceutically acceptable carriers include agents that can alter the form, consistency, viscosity, pH, tonicity, stability, osmolarity, pharmacokinetics, protein aggregation or solubility of the formulation and include buffering agents, wetting agents, emulsifying agents, diluents, encapsulating agents and skin penetration enhancers. Certain non-limiting examples of carriers include saline, buffered saline, dextrose, arginine, sucrose, water, glycerol, ethanol, sorbitol, dextran, sodium carboxymethyl cellulose and combinations thereof. Antibodies for systemic administration may be formulated for enteral, parenteral or topical administration. Indeed, all three types of formulation may be used simultaneously to achieve systemic administration of the active ingredient. Excipients as well as formulations for parenteral and nonparenteral drug delivery are set forth in *Remington: The Science and Practice of Pharmacy* (2000) 20th Ed. Mack Publishing.

Suitable formulations for enteral administration include hard or soft gelatin capsules, pills,

tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the active ingredient is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable carriers, such as anti-oxidants, buffers, preservatives, stabilizers, bacteriostats, suspending agents, thickening agents, and solutes that render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic pharmaceutically acceptable carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection.

Compatible formulations for parenteral administration (e.g., intravenous injection) may comprise ADC or antibody concentrations of from about 10 µg/mL to about 100 mg/ mL. In certain selected embodiments antibody or ADC concentrations will comprise 20 µg/ mL, 40 µg/ mL, 60 µg/ mL, 80 µg/mL, 100 µg/mL, 200 µg/mL, 300, µg/mL, 400 µg/mL, 500 µg/mL, 600 µg/mL, 700 µg/mL, 800 µg/mL, 900 µg/mL or 1 mg/mL. In other preferred embodiments ADC concentrations will comprise 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 8 mg/mL, 10 mg/mL, 12 mg/mL, 14 mg/mL, 16 mg/mL, 18 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL or 100 mg/mL.

The compounds and compositions of the invention may be administered *in vivo,* to a subject in need thereof, by various routes, including, but not limited to, oral, intravenous, intra-arterial, subcutaneous, parenteral, intranasal, intramuscular, intracardiac, intraventricular, intratracheal, buccal, rectal, intraperitoneal, intradermal, topical, transdermal, and intrathecal, or otherwise by implantation or inhalation. The subject compositions may be formulated into preparations in solid, semi-solid, liquid, or gaseous forms; including, but not limited to, tablets, capsules, powders, granules, ointments, solutions, suppositories, enemas, injections, inhalants, and aerosols. The appropriate formulation and route of administration may be selected according to the intended application and therapeutic regimen.

B. Dosages

The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular individual, as well as empirical considerations such as pharmacokinetics (e.g., half-life, clearance

rate, etc.). Determination of the frequency of administration may be made by persons skilled in the art, such as an attending physician based on considerations of the condition and severity of the condition being treated, age and general state of health of the subject being treated and the like. Frequency of administration may be adjusted over the course of therapy based on assessment of the efficacy of the selected composition and the dosing regimen. Such assessment can be made on the basis of markers of the specific disease, disorder or condition. In embodiments where the individual has cancer, these include direct measurements of tumor size via palpation or visual observation; indirect measurement of tumor size by x-ray or other imaging techniques; an improvement as assessed by direct tumor biopsy and microscopic examination of a tumor sample; the measurement of an indirect tumor marker (e.g., PSA for prostate cancer) or an antigen identified according to the methods described herein; reduction in the number of proliferative or tumorigenic cells, maintenance of the reduction of such neoplastic cells; reduction of the proliferation of neoplastic cells; or delay in the development of metastasis.

The CLDN antibodies or ADCs of the invention may be administered in various ranges. These include about 5 μg/kg body weight to about 100 mg/kg body weight per dose; about 50 μg/kg body weight to about 5 mg/kg body weight per dose; about 100 μg/kg body weight to about 10 mg/kg body weight per dose. Other ranges include about 100 μg/kg body weight to about 20 mg/kg body weight per dose and about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose. In certain embodiments, the dosage is at least about 100 μg/kg body weight, at least about 250 μg/kg body weight, at least about 750 μg/kg body weight, at least about 3 mg/kg body weight, at least about 5 mg/kg body weight, at least about 10 mg/kg body weight.

In selected embodiments the CLDN antibodies or ADCs will be administered (preferably intravenously) at approximately 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 μg/kg body weight per dose. Other embodiments may comprise the administration of ADCs at about 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900 or 2000 μg/kg body weight per dose. In other preferred embodiments the disclosed conjugates will be administered at 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.58, 9 or 10 mg/kg. In still other embodiments the conjugates may be administered at 12, 14, 16, 18 or 20 mg/kg body weight per dose. In yet other embodiments the conjugates may be administered at 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90 or 100 mg/kg body weight per dose. With the teachings herein one of skill in the art could readily determine appropriate dosages for various CLDN antibodies or ADCs based on preclinical animal studies, clinical observations and standard medical and biochemical techniques and measurements.

Other dosing regimens may be predicated on Body Surface Area (BSA) calculations as disclosed in U.S.P.N. 7,744,877. As is well known, the BSA is calculated using the patient's height and weight and provides a measure of a subject's size as represented by the surface area of his or her body. In certain embodiments, the conjugates may be administered in dosages from 1 mg/m^2 to 800 mg/m^2, from 50 mg/m^2 to 500 mg/m^2 and at dosages of 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2 or 450 mg/m^2. It will also be appreciated that art recognized and empirical techniques may be used to determine appropriate dosage.

Anti-CLDN antibodies or ADCs may be administered on a specific schedule. Generally, an effective dose of the CLDN conjugate is administered to a subject one or more times. More particularly, an effective dose of the ADC is administered to the subject once a month, more than once a month, or less than once a month. In certain embodiments, the effective dose of the CLDN antibody or ADC may be administered multiple times, including for periods of at least a month, at least six months, at least a year, at least two years or a period of several years. In yet other embodiments, several days (2, 3, 4, 5, 6 or 7), several weeks (1, 2, 3, 4, 5, 6, 7 or 8) or several months (1, 2, 3, 4, 5, 6, 7 or 8) or even a year or several years may lapse between administration of the disclosed antibodies or ADCs.

In certain preferred embodiments the course of treatment involving conjugated antibodies will comprise multiple doses of the selected drug product over a period of weeks or months. More specifically, antibodies or ADCs of the instant invention may administered once every day, every two days, every four days, every week, every ten days, every two weeks, every three weeks, every month, every six weeks, every two months, every ten weeks or every three months. In this regard it will be appreciated that the dosages may be altered or the interval may be adjusted based on patient response and clinical practices.

Dosages and regimens may also be determined empirically for the disclosed therapeutic compositions in individuals who have been given one or more administration(s). For example, individuals may be given incremental dosages of a therapeutic composition produced as described herein. In selected embodiments the dosage may be gradually increased or reduced or attenuated based respectively on empirically determined or observed side effects or toxicity. To assess efficacy of the selected composition, a marker of the specific disease, disorder or condition can be followed as described previously. For cancer, these include direct measurements of tumor size via palpation or visual observation, indirect measurement of tumor size by x-ray or other imaging techniques; an improvement as assessed by direct tumor biopsy and microscopic examination of the tumor sample; the measurement of an indirect tumor marker (e.g., PSA for prostate cancer) or

a tumorigenic antigen identified according to the methods described herein, a decrease in pain or paralysis; improved speech, vision, breathing or other disability associated with the tumor; increased appetite; or an increase in quality of life as measured by accepted tests or prolongation of survival. It will be apparent to one of skill in the art that the dosage will vary depending on the individual, the type of neoplastic condition, the stage of neoplastic condition, whether the neoplastic condition has begun to metastasize to other location in the individual, and the past and concurrent treatments being used.

C. Combination Therapies

The CLDN proteins are expressed in the tight junctions of epithelial cells where they are thought to establish the paracellular barrier that controls the flow of molecules in the intercellular space between epithelial cells. The use of an anti-CLDN antibodies may result in the disruption of the tight junctions of epithelial cells and thus improve access of therapeutics that otherwise would not be able to penetrate cancer cells. Thus, the use of various therapies in combination with the anti-CLDN antibodies and ADCs of the invention may be useful in preventing or treating cancer and in preventing metastasis or recurrence of cancer. “Combination therapy”, as used herein, means the administration of a combination comprising at least one anti-CLDN antibody or ADC and at least one therapeutic moiety (e.g., anti-cancer agent) wherein the combination preferably has therapeutic synergy or improves the measurable therapeutic effects in the treatment of cancer over (i) the anti-CLDN antibody or ADC used alone, or (ii) the therapeutic moiety used alone, or (iii) the use of the therapeutic moiety in combination with another therapeutic moiety without the addition of an anti-CLDN antibody or ADC. The term “therapeutic synergy”, as used herein, means the combination of an anti-CLDN antibody or ADC and one or more therapeutic moiety(ies) having a therapeutic effect greater than the additive effect of the combination of the anti-CLDN antibody or ADC and the one or more therapeutic moiety(ies).

Desired outcomes of the disclosed combinations are quantified by comparison to a control or baseline measurement. As used herein, relative terms such as "improve," "increase," or "reduce" indicate values relative to a control, such as a measurement in the same individual prior to initiation of treatment described herein, or a measurement in a control individual (or multiple control individuals) in the absence of the anti-CLDN antibodies or ADCs described herein but in the presence of other therapeutic moiety(ies) such as standard of care treatment. A representative control individual is an individual afflicted with the same form of cancer as the individual being

treated, who is about the same age as the individual being treated (to ensure that the stages of the disease in the treated individual and the control individual are comparable.)

Changes or improvements in response to therapy are generally statistically significant. As used herein, the term "significance" or "significant" relates to a statistical analysis of the probability that there is a non-random association between two or more entities. To determine whether or not a relationship is "significant" or has "significance," a "p-value" can be calculated. P-values that fall below a user-defined cut-off point are regarded as significant. A p-value less than or equal to 0.1, less than 0.05, less than 0.01, less than 0.005, or less than 0.001 may be regarded as significant.

A synergistic therapeutic effect may be an effect of at least about two-fold greater than the therapeutic effect elicited by a single therapeutic moiety or anti-CLDN antibody or ADC, or the sum of the therapeutic effects elicited by the anti-CLDN antibody or ADC or the single therapeutic moiety(ies) of a given combination, or at least about five-fold greater, or at least about ten-fold greater, or at least about twenty-fold greater, or at least about fifty-fold greater, or at least about one hundred-fold greater. A synergistic therapeutic effect may also be observed as an increase in therapeutic effect of at least 10% compared to the therapeutic effect elicited by a single therapeutic moiety or anti-CLDN antibody or ADC, or the sum of the therapeutic effects elicited by the anti-CLDN antibody or ADC or the single therapeutic moiety(ies) of a given combination, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 60%, or at least 70%, or at least 80%, or at least 90%, or at least 100%, or more. A synergistic effect is also an effect that permits reduced dosing of therapeutic agents when they are used in combination.

In practicing combination therapy, the anti-CLDN antibody or ADC and therapeutic moiety(ies) may be administered to the subject simultaneously, either in a single composition, or as two or more distinct compositions using the same or different administration routes. Alternatively, treatment with the anti-CLDN antibody or ADC may precede or follow the therapeutic moiety treatment by, e.g., intervals ranging from minutes to weeks. In one embodiment, both the therapeutic moiety and the antibody or ADC are administered within about 5 minutes to about two weeks of each other. In yet other embodiments, several days (2, 3, 4, 5, 6 or 7), several weeks (1, 2, 3, 4, 5, 6, 7 or 8) or several months (1, 2, 3, 4, 5, 6, 7 or 8) may lapse between administration of the antibody and the therapeutic moiety.

The combination therapy can be administered until the condition is treated, palliated or cured on various schedules such as once, twice or three times daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months, once every six months, or may be administered continuously. The

antibody and therapeutic moiety(ies) may be administered on alternate days or weeks; or a sequence of anti-CLDN antibody or ADC treatments may be given, followed by one or more treatments with the additional therapeutic moiety. In one embodiment an anti-CLDN antibody or ADC is administered in combination with one or more therapeutic moiety(ies) for short treatment cycles. In other embodiments the combination treatment is administered for long treatment cycles. The combination therapy can be administered via any route.

In some embodiments the anti-CLDN antibodies or ADCs may be used in combination with various first line cancer treatments. In one embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and a platinum analog (e.g. ifosfamide, mytomycin C, vindesine, vinblastine, etoposide, ironitecan, gemcitabine, taxanes, vinorelbine, methotrexate, and pemetrexed) and optionally one or more other therapeutic moiety(ies).

In another embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and a platinum-based drug (e.g. carboplatin or cisplatin) and optionally one or more other therapeutic moiety(ies) (e.g. vinorelbine; gemcitabine; a taxane such as, for example, docetaxel or paclitaxel; irinotican; or pemetrexed).

In another embodiment combination therapy for the treatment of EGFR-positive NSCLC comprises the use of an anti-CLDN antibody or ADC and afatinib and optionally one or more other therapeutic moiety(ies) (e.g. erlotinib and/or bevacizumab).

In another embodiment combination therapy for the treatment of EGFR-positive NSCLC comprises the use of an anti-CLDN antibody or ADC and erlotinib and optionally one or more other therapeutic moiety(ies) (e.g. bevacizumab).

In another embodiment combination therapy for the treatment of ALK-positive NSCLC comprises the use of an anti-CLDN antibody or ADC and ceritinib and optionally one or more other therapeutic moiety(ies).

In another embodiment combination therapy for the treatment of ALK-positive NSCLC comprises the use of an anti-CLDN antibody or ADC and crizotinib and optionally one or more other therapeutic moiety(ies).

In another embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and bevacizumab and optionally one or more other therapeutic moiety(ies) (e.g. a taxane such as, for example, docetaxel or paclitaxel; and/or a platinum analog).

In another embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and bevacizumab and optionally one or more other therapeutic moiety(ies) (e.g. gemcitabine and/or a platinum analog).

In one embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and platinum-based drug (e.g. carboplatin or cisplatin) analog and optionally one or more other therapeutic moiety(ies) (e.g. a taxane such as, for example, docetaxel and paclitaxel).

In one embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and platinum-based drug (e.g. carboplatin or cisplatin) analog and optionally one or more other therapeutic moiety(ies) (e.g. a taxane such, for example, docetaxel and paclitaxel and/or gemcitabine and/or doxorubicin).

In a particular embodiment the combination therapy for the treatment of platinum-resistant tumors comprises the use of an anti-CLDN antibody or ADC and doxorubicin and/or etoposide and/or gemcitabine and/or vinorelbine and/or ifosfamide and/or leucovorin-modulated 5-fluoroucil and/or bevacizumab and/or tamoxifen; and optionally one or more other therapeutic moiety(ies).

In another embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and a PARP inhibitor and optionally one or more other therapeutic moiety(ies).

In another embodiment the combination therapy comprises the use of an anti-CLDN antibody or ADC and bevacizumab and optionally cyclophosphamide.

The invention also provides for the combination of anti-CLDN antibodies or ADCs with radiotherapy. The term “radiotherapy”, as used herein, means, any mechanism for inducing DNA damage locally within tumor cells such as gamma-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions and the like. Combination therapy using the directed delivery of radioisotopes to tumor cells is also contemplated, and may be used in combination or as a conjugate of the anti-CLDN antibodies disclosed herein. Typically, radiation therapy is administered in pulses over a period of time from about 1 to about 2 weeks. Optionally, the radiation therapy may be administered as a single dose or as multiple, sequential doses.

In other embodiments an anti-CLDN antibody or ADC may be used in combination with one or more of the anti-cancer agents described below.

D. Anti-Cancer Agents

The term “anti-cancer agent” or “chemotherapeutic agent” as used herein is one subset of “therapeutic moieties”, which in turn is a subset of the agents described as “pharmaceutically active moieties”. More particularly “anti-cancer agent” means any agent that can be used to treat a cell proliferative disorder such as cancer, and includes, but is not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, biological response

modifiers, therapeutic antibodies, cancer vaccines, cytokines, hormone therapy, anti-metastatic agents and immunotherapeutic agents. It will be appreciated that in selected embodiments as discussed above, such anti-cancer agents may comprise conjugates and may be associated with antibodies prior to administration. In certain embodiments the disclosed anti-cancer agent will be linked to an antibody to provide an ADC as disclosed herein.

The term “cytotoxic agent”, which can also be an anti-cancer agent means a substance that is toxic to the cells and decreases or inhibits the function of cells and/or causes destruction of cells. Typically, the substance is a naturally occurring molecule derived from a living organism (or a synthetically prepared natural product). Examples of cytotoxic agents include, but are not limited to, small molecule toxins or enzymatically active toxins of bacteria (e.g., Diptheria toxin, Pseudomonas endotoxin and exotoxin, Staphylococcal enterotoxin A), fungal (e.g., α-sarcin, restrictocin), plants (e.g., abrin, ricin, modeccin, viscumin, pokeweed anti-viral protein, saporin, gelonin, momoridin, trichosanthin, barley toxin, Aleurites fordii proteins, dianthin proteins, Phytolacca mericana proteins (PAPI, PAPII, and PAP-S), Momordica charantia inhibitor, curcin, crotin, saponaria officinalis inhibitor, mitegellin, restrictocin, phenomycin, neomycin, and the tricothecenes) or animals, (e.g., cytotoxic RNases, such as extracellular pancreatic RNases; DNase I, including fragments and/or variants thereof).

An anti-cancer agent can include any chemical agent that inhibits, or is designed to inhibit, a cancerous cell or a cell likely to become cancerous or generate tumorigenic progeny (e.g., tumorigenic cells). Such chemical agents are often directed to intracellular processes necessary for cell growth or division, and are thus particularly effective against cancerous cells, which generally grow and divide rapidly. For example, vincristine depolymerizes microtubules, and thus inhibits cells from entering mitosis. Such agents are often administered, and are often most effective, in combination, e.g., in the formulation CHOP. Again, in selected embodiments such anti-cancer agents may be conjugated to the disclosed antibodies.

Examples of anti-cancer agents that may be used in combination with (or conjugated to) the antibodies of the invention include, but are not limited to, alkylating agents, alkyl sulfonates, anastrozole, amanitins, aziridines, ethylenimines and methylamelamines, acetogenins, a camptothecin, BEZ-235, bortezomib, bryostatin, callystatin, CC-1065, ceritinib, crizotinib, cryptophycins, dolastatin, duocarmycin, eleutherobin, erlotinib, pancratistatin, a sarcodictyin, spongistatin, nitrogen mustards, antibiotics, enediyne dynemicin, bisphosphonates, esperamicin, chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, canfosfamide, carabicin, carminomycin, carzinophilin,

chromomycinis, cyclosphosphamide, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, exemestane, fluorouracil, fulvestrant, gefitinib, idarubicin, lapatinib, letrozole, lonafarnib, marcellomycin, megestrol acetate, mitomycins, mycophenolic acid, nogalamycin, olivomycins, pazopanib, peplomycin, potfiromycin, puromycin, quelamycin, rapamycin, rodorubicin, sorafenib, streptonigrin, streptozocin, tamoxifen, tamoxifen citrate, temozolomide, tepodina, tipifarnib, tubercidin, ubenimex, vandetanib, vorozole, XL-147, zinostatin, zorubicin; anti-metabolites, folic acid analogues, purine analogs, androgens, anti-adrenals, folic acid replenisher such as frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansinoids, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2- ethylhydrazide, procarbazine, polysaccharide complex, razoxane; rhizoxin; SF-1126, sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside; cyclophosphamide; thiotepa; taxoids, chloranbucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs, vinblastine; platinum; etoposide; ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan, topoisomerase inhibitor RFS 2000; difluorometlhylornithine; retinoids; capecitabine; combretastatin; leucovorin; oxaliplatin; XL518, inhibitors of PKC-alpha, Raf, H-Ras, EGFR and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts or solvates, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor antibodies, aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, and anti-androgens; as well as troxacitabine (a 1,3- dioxolane nucleoside cytosine analog); antisense oligonucleotides, ribozymes such as a VEGF expression inhibitor and a HER2 expression inhibitor; vaccines, PROLEUKIN® rIL-2; LURTOTECAN® topoisomerase 1 inhibitor; ABARELIX® rmRH; Vinorelbine and Esperamicins and pharmaceutically acceptable salts or solvates, acids or derivatives of any of the above.

Particularly preferred anti-cancer agents comprise commercially or clinically available compounds such as erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®,

Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®). Additional commercially or clinically available anti-cancer agents comprise oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); vinorelbine (NAVELBINE®); capecitabine (XELODA®, Roche), tamoxifen (including NOLVADEX®; tamoxifen citrate, FARESTON® (toremifine citrate) MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca).

The term “pharmaceutically acceptable salt” or “salt” means organic or inorganic salts of a molecule or macromolecule. Acid addition salts can be formed with amino groups. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1′ methylene bis-(2-hydroxy 3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another

molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Where multiple charged atoms are part of the pharmaceutically acceptable salt, the salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterion.

"Pharmaceutically acceptable solvate" or "solvate" refers to an association of one or more solvent molecules and a molecule or macromolecule. Examples of solvents that form pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine.

In other embodiments the antibodies or ADCs of the instant invention may be used in combination with any one of a number of antibodies (or immunotherapeutic agents) presently in clinical trials or commercially available. The disclosed antibodies may be used in combination with an antibody selected from the group consisting of abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lambrolizumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab, naptumomab, necitumumab, nimotuzumab, nivolumab, nofetumomabn, obinutuzumab, ocaratuzumab, ofatumumab, olaratumab, olaparib, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pemtumomab, pertuzumab, pidilizumab, pintumomab, pritumumab, racotumomab, radretumab, ramucirumab, rilotumumab, rituximab, robatumumab, satumomab, selumetinib, sibrotuzumab, siltuximab, simtuzumab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49, 3F8, MDX-1105 and MEDI4736 and combinations thereof.

Other particularly preferred embodiments comprise the use of antibodies approved for cancer therapy including, but not limited to, rituximab, gemtuzumab ozogamcin, alemtuzumab,

ibritumomab tiuxetan, tositumomab, bevacizumab, cetuximab, patitumumab, ofatumumab, ipilimumab and brentuximab vedotin. Those skilled in the art will be able to readily identify additional anti-cancer agents that are compatible with the teachings herein.

E. Radiotherapy

The present invention also provides for the combination of antibodies or ADCs with radiotherapy (i.e., any mechanism for inducing DNA damage locally within tumor cells such as gamma-irradiation, X-rays, UV-irradiation, microwaves, electronic emissions and the like). Combination therapy using the directed delivery of radioisotopes to tumor cells is also contemplated, and the disclosed antibodies or ADCs may be used in connection with a targeted anti-cancer agent or other targeting means. Typically, radiation therapy is administered in pulses over a period of time from about 1 to about 2 weeks. The radiation therapy may be administered to subjects having head and neck cancer for about 6 to 7 weeks. Optionally, the radiation therapy may be administered as a single dose or as multiple, sequential doses.

VIII Indications

The invention provides for the use of antibodies and ADCs of the invention for the diagnosis, theragnosis, treatment and/or prophylaxis of various disorders including neoplastic, inflammatory, angiogenic and immunologic disorders and disorders caused by pathogens. Particularly, key targets for treatment are neoplastic conditions comprising solid tumors, although hematologic malignancies are within the scope of the invention. In certain embodiments the antibodies of the invention will be used to treat tumors or tumorigenic cells expressing a particular determinant (e.g. CLDN). Preferably the “subject” or “patient” to be treated will be human although, as used herein, the terms are expressly held to comprise any mammalian species.

Neoplastic conditions subject to treatment in accordance with the instant invention may be benign or malignant; solid tumors or other blood neoplasia; and may be selected from the group including, but not limited to: adrenal gland tumors, AIDS-associated cancers, alveolar soft part sarcoma, astrocytic tumors, autonomic ganglia tumors, bladder cancer (squamous cell carcinoma and transitional cell carcinoma), blastocoelic disorders, bone cancer (adamantinoma, aneurismal bone cysts, osteochondroma, osteosarcoma), brain and spinal cord cancers, metastatic brain tumors, breast cancer, carotid body tumors, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer,

cutaneous benign fibrous histiocytomas, desmoplastic small round cell tumors, ependymomas, epithelial disorders, Ewing's tumors, extraskeletal myxoid chondrosarcoma, fibrogenesis imperfecta ossium, fibrous dysplasia of the bone, gallbladder and bile duct cancers, gastric cancer, gastrointestinal, gestational trophoblastic disease, germ cell tumors, glandular disorders, head and neck cancers, hypothalamic, intestinal cancer, islet cell tumors, Kaposi's Sarcoma, kidney cancer (nephroblastoma, papillary renal cell carcinoma), leukemias, lipoma/benign lipomatous tumors, liposarcoma/malignant lipomatous tumors, liver cancer (hepatoblastoma, hepatocellular carcinoma), lymphomas, lung cancers (small cell carcinoma, adenocarcinoma, squamous cell carcinoma, large cell carcinoma etc.), macrophagal disorders, medulloblastoma, melanoma, meningiomas, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancers, papillary thyroid carcinomas, parathyroid tumors, pediatric cancers, peripheral nerve sheath tumors, phaeochromocytoma, pituitary tumors, prostate cancer, posterious unveal melanoma, rare hematologic disorders, renal metastatic cancer, rhabdoid tumor, rhabdomysarcoma, sarcomas, skin cancer, soft-tissue sarcomas, squamous cell cancer, stomach cancer, stromal disorders, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid metastatic cancer, and uterine cancers (carcinoma of the cervix, endometrial carcinoma, and leiomyoma).

In other preferred embodiments, the disclosed antibodies and ADCs are especially effective at treating lung cancer, including the following subtypes: small cell lung cancer and non-small cell lung cancer (e.g. squamous cell non-small cell lung cancer or squamous cell small cell lung cancer). In selected embodiments the antibodies and ADCs can be administered to patients exhibiting limited stage disease or extensive stage disease. In other preferred embodiments the disclosed conjugated antibodies will be administered to refractory patients (i.e., those whose disease recurs during or shortly after completing a course of initial therapy); sensitive patients (i.e., those whose relapse is longer than 2-3 months after primary therapy); or patients exhibiting resistance to a platinum based agent (e.g. carboplatin, cisplatin, oxaliplatin) and/or a taxane (e.g. docetaxel, paclitaxel, larotaxel or cabazitaxel).

The invention also provides for a preventative or prophylactic treatment of subjects who present with benign or precancerous tumors. No particular type of tumor or proliferative disorder is excluded from treatment using the antibodies of the invention.

IX Articles of Manufacture

The invention includes pharmaceutical packs and kits comprising one or more containers,

wherein a container can comprise one or more doses of an antibody or ADC of the invention. In certain embodiments, the pack or kit contains a unit dosage, meaning a predetermined amount of a composition comprising, for example, an antibody or ADC of the invention, with or without one or more additional agents and optionally, one or more anti-cancer agents.

The kit of the invention will generally contain in a suitable container a pharmaceutically acceptable formulation of the antibody or ADC of the invention and, optionally, one or more anti-cancer agents in the same or different containers. The kits may also contain other pharmaceutically acceptable formulations or devices, either for diagnosis or combination therapy. Examples of diagnostic devices or instruments include those that can be used to detect, monitor, quantify or profile cells or markers associated with proliferative disorders (for a full list of such markers, see above). In particularly preferred embodiments the devices may be used to detect, monitor and/or quantify circulating tumor cells either *in vivo* or *in vitro* (see, for example, WO 2012/0128801). In still other preferred embodiments the circulating tumor cells may comprise tumorigenic cells. The kits contemplated by the invention can also contain appropriate reagents to combine the antibody or ADC of the invention with an anti-cancer agent or diagnostic agent (e.g., see U.S.P.N. 7,422,739).

When the components of the kit are provided in one or more liquid solutions, the liquid solution can be non-aqueous, however, an aqueous solution is preferred, with a sterile aqueous solution being particularly preferred. The formulation in the kit can also be provided as dried powder(s) or in lyophilized form that can be reconstituted upon addition of an appropriate liquid. The liquid used for reconstitution can be contained in a separate container. Such liquids can comprise sterile, pharmaceutically acceptable buffer(s) or other diluent(s) such as bacteriostatic water for injection, phosphate-buffered saline, Ringer's solution or dextrose solution. Where the kit comprises the antibody or ADC of the invention in combination with additional therapeutics or agents, the solution may be pre-mixed, either in a molar equivalent combination, or with one component in excess of the other. Alternatively, the antibody or ADC of the invention and any optional anti-cancer agent or other agent can be maintained separately within distinct containers prior to administration to a patient.

The kit can comprise one or multiple containers and a label or package insert in, on or associated with the container(s), indicating that the enclosed composition is used for diagnosing or treating the disease condition of choice. Suitable containers include, for example, bottles, vials, syringes, etc. The containers can be formed from a variety of materials such as glass or plastic. The container(s) can comprise a sterile access port, for example, the container may be an

intravenous solution bag or a vial having a stopper that can be pierced by a hypodermic injection needle.

In some embodiments the kit can contain a means by which to administer the antibody and any optional components to a patient, e.g., one or more needles or syringes (pre-filled or empty), an eye dropper, pipette, or other such like apparatus, from which the formulation may be injected or introduced into the subject or applied to a diseased area of the body. The kits of the invention will also typically include a means for containing the vials, or such like, and other components in close confinement for commercial sale, such as, e.g., blow-molded plastic containers into which the desired vials and other apparatus are placed and retained.

X Miscellaneous

Unless otherwise defined herein, scientific and technical terms used in connection with the invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. In addition, ranges provided in the specification and appended claims include both end points and all points between the end points. Therefore, a range of 2.0 to 3.0 includes 2.0, 3.0, and all points between 2.0 and 3.0.

Generally, techniques of cell and tissue culture, molecular biology, immunology, microbiology, genetics and chemistry described herein are those well known and commonly used in the art. The nomenclature used herein, in association with such techniques, is also commonly used in the art. The methods and techniques of the invention are generally performed according to conventional methods well known in the art and as described in various references that are cited throughout the present specification unless otherwise indicated.

XI References

The complete disclosure of all patents, patent applications, and publications, and electronically available material (including, for example, nucleotide sequence submissions in, e.g., GenBank and RefSeq, and amino acid sequence submissions in, e.g., SwissProt, PIR, PRF, PBD, and translations from annotated coding regions in GenBank and RefSeq) cited herein are incorporated by reference, regardless of whether the phrase “incorporated by reference” is or is not used in relation to the particular reference. The foregoing detailed description and the examples that follow have been given for clarity of understanding only. No unnecessary limitations are to be

understood therefrom. The invention is not limited to the exact details shown and described. Variations obvious to one skilled in the art are included in the invention defined by the claims. Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

XII Sequence Listing Summary

Appended to the instant application is a sequence listing comprising a number of nucleic acid and amino acid sequences. The following Table 3 provides a summary of the included sequences.

TABLE 3

SEQ ID NO	Description
1	Kappa light chain (LC) constant region protein
2	IgGl heavy chain (HC) constant region protein
3-19	Reserved
20	SC27.1 VL DNA
21	SC27.1 VL protein
22	SC27.1 VH DNA
23	SC27.1 VH protein
24-59	Additional mouse clones as in SEQ ID NOs: 20-23
60	hSC27.1 VL DNA
61	hSC27.1 VL protein
62	hSC27.1 VH DNA
63	hSC27.1 VH protein
64-75	Additional humanized clones as in SEQ ID NOs: 60-63
76-77	hSC27.108v1 VL DNA and protein
78-79	hSC27.22-VH1-8 VH DNA and protein
80-81	hSC27.22-VH1-46 VH DNA and protein
82-83	hSC27.22-VH1-69 VH DNA and protein
84-85	hSC27.204v1 DNA and protein
86-87	hSC27.204v2 DNA and protein
88-89	hSC27.204v3 DNA and protein

90-91	hSC27.204v4 DNA and protein
92-93	hSC27.204v5 DNA and protein
94-95	hSC27.204v6 DNA and protein
96-97	hSC27.204v7 DNA and protein
98-99	hSC27.204v8 DNA and protein
100-101	hSC27.204v9 DNA and protein
102-103	hSC27.204v10 DNA and protein
104-105	hSC27.204v11 DNA and protein
106-107	hSC27.204v12 DNA and protein
108-109	hSC27.204v13 DNA and protein
110-111	hSC27.204v14 DNA and protein
112-113	hSC27.204v15 DNA and protein
114-115	hSC27.1 full length LC and HC protein
116-117	hSC27.22 full length LC and HC protein
118-119	hSC27.108 full length LC and HC protein
120-121	hSC27.204 full length LC and HC protein
122	hSC27.22ss1 full length HC protein
123	hSC27.22-VH1-8 full length HC protein
124	hSC27.22-VH1-46 full length HC protein
125	hSC27.22-VH1-69 full length HC protein
126	hSC27.22 IgG2 full length HC protein
127	hSC27.22 IgG4 R409K full length HC protein
128	hSC27.22 IgG4 S228P full length HC protein
129	hSC27.22 IgG4 S228P K370E R409K full length HC protein
130	hSC27.22 IgG4 K370E full length HC protein
131	hSC27.22 IgG4 S228P K370E full length HC protein
132	hSC27.22 IgG4 C127S S228P full length HC protein
133	hSC27.22 IgG4 C127S K370E full length HC protein
134	hSC27.22 IgG4 C127S S228P K370E full length HC protein
135	hSC27.108v1 full length LC protein
136	hSC27.204v1 full length HC protein
137	hSC27.204v2 full length HC protein

138	hSC27.204v3 full length HC protein
139	hSC27.204v4 full length HC protein
140	hSC27.204v5 full length HC protein
141	hSC27.204v6 full length HC protein
142	hSC27.204v7 full length HC protein
143	hSC27.204v8 full length HC protein
144	hSC27.204v9 full length HC protein
145	hSC27.204v10 full length HC protein
146	hSC27.204v11 full length HC protein
147	hSC27.204v12 full length HC protein
148	hSC27.204v13 full length HC protein
149	hSC27.204v14 full length HC protein
150	hSC27.204v15 full length HC protein
151-156	hSC27.1 CDRL1; CDRL2; CDRL3, CDRH1; CDRH2; CDRH3
157-162	hSC27.22 CDRL1; CDRL2; CDRL3, CDRH1; CDRH2; CDRH3
163-168	hSC27.108 CDRL1; CDRL2; CDRL3, CDRH1; CDRH2; CDRH3
169-174	hSC27.204 CDRL1; CDRL2; CDRL3, CDRH1; CDRH2; CDRH3
175	CDRH2 of hSC27.204v1; hSC27.204v5 and hSC27.405v13
176	CDRH2 of hSC27.204v2; hSC27.204v6 and hSC27.405v14
177	CDRH2 of hSC27.204v3; hSC27.204v7 and hSC27.405v15
178	Codon optimized hSC27.22ss1 full length HC DNA

XIII Examples

The invention, thus generally described above, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the instant invention. The examples are not intended to represent that the experiments below are all or the only experiments performed. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

PDX tumor cell types are denoted by an abbreviation followed by a number, which indicates the particular tumor cell line. The passage number of the tested sample is indicated by p0-p# appended to the sample designation where p0 is indicative of an unpassaged sample obtained

directly from a patient tumor and p# is indicative of the number of times the tumor has been passaged through a mouse prior to testing. As used herein, the abbreviations of the tumor types and subtypes are shown in Table 4 as follows:

TABLE 4

Tumor Type	Abbreviation	Tumor subtype	Abbreviation
Bladder	BL		
Breast	BR		
		basal-like	BR-Basal Like
		estrogen receptor positive and/or progesterone receptor positive	BR-ERPR
		ERBB2/Neu positive	BR- ERBB2/Neu
		HER2 positive	BR-HER2
		triple-negative	TNBC
		luminal A	BR-lumA
		claudin subtype of triple-negative	TNBC-CL
		claudin low	BR-CLDN-Low
Cervical	CER		
Colorectal	CR		
Endometrial	EM		
Gastric	GA		
		diffuse adenocarcinoma	GA-Ad-Dif/Muc
		intestinal adenocarcinoma	GA-Ad-Int
		stromal tumors	GA-GIST
Glioblastoma	GB		
Head and neck	HN		
Kidney	KDY		
		clear renal cell carcinoma	KDY-CC
		papillary renal cell carcinoma	KDY-PAP
		transitional cell or urothelial carcinoma	KDY-URO
		unknown	KDY-UNK
Liver	LIV		
		hepatocellular carcinoma	LIV-HCC
		cholangiocarcinoma	LIV-CHOL
Lymphoma	LN		

Lung	LU		
		adenocarcinoma	LU-Ad
		carcinoid	LU-CAR
		large cell neuroendocrine	LU-LCC
		non-small cell	NSCLC
		squamous cell	LU-SCC
		small cell	SCLC
		spindle cell	LU-SPC
Ovarian	OV		
		clear cell	OV-CC
		endometroid	OV-END
		mixed subtype	OV-MIX
		malignant mixed mesodermal	OV-MMMT
		mucinous	OV-MUC
		neuroendocrine	OV-NET
		papillary serous	OV-PS
		serous	OV-S
		small cell	OV-SC
		transitional cell carcinoma	OV-TCC
Pancreatic	PA		
		acinar cell carcinoma	PA-ACC
		duodenal carcinoma	PA-DC
		mucinous adenocarcinoma	PA-MAD
		neuroendocrine	PA-NET
		adenocarcinoma	PA-PAC
		adenocarcinoma exocrine type	PA-PACe
		ductal adenocarcinoma	PA-PDAC
		ampullary adenocarcinoma	PA-AAC
Prostate	PR		
Skin	SK		
		melanoma	MEL
		squamous cell carcinomas	SK-SCC
		uveal melanoma	UVM
Testicular	TES		
Thyroid	THY		

EXAMPLE 1
IDENTIFICATION OF CLDN4, CLDN6 AND CLDN9 EXPRESSION USING WHOLE TRANSCRIPTOME SEQUENCING

To characterize the cellular heterogeneity of solid tumors as they exist in cancer patients, aid in the identification of CSCs using particular phenotypic markers and identify clinically relevant therapeutic targets, a large PDX tumor bank was developed and maintained using art recognized techniques. The PDX tumor bank, comprising a large number of discrete tumor cell lines, was propagated in immunocompromised mice through multiple passages of heterogeneous tumor cells

originally obtained from numerous cancer patients afflicted by a variety of solid tumor malignancies. The continued availability of a large number of discrete early passage PDX tumor cell lines having well defined lineages greatly facilitates the identification and isolation of CSCs as the PDX tumors allow for the reproducible and repeated characterization of CSCs. The use of minimally passaged PDX tumor cell lines simplifies *in vivo* experimentation and provides readily verifiable results. Moreover, early passage PDX tumors respond to therapeutic agents such as irinotecan (i.e. Camptosar®), which provides clinically relevant insight into underlying mechanisms driving tumor growth, resistance to current therapies and tumor recurrence.

To generate RNA from the PDX tumor cell lines, tumors were resected from mice after they reached 800 - 2,000 mm^3 and the tumors were dissociated into single cell suspensions using art-recognized enzymatic digestion techniques (see, for example, U.S.P.N. 2007/0292414). Select dissociated PDX tumor cell preparations were depleted of mouse cells and sorted based on their expression of $CD46^{hi}$ and/or CD324, markers of CSC subpopulations (see U.S.P.N 2013/0260385 for the definition of $CD46^{hi}$). Cells that expressed human EpCAM, $CD46^{hi}$ and/or CD324 (i.e. CSC) or EpCAM but not $CD46^{hi}$ and/or CD324 (i.e. NTG cells), were isolated by FACS using a BD FACSAria cell sorter and lysed in RLTplus RNA lysis buffer (Qiagen) per the manufacturer's instructions. The lysates were then stored at -80 °C and thawed for RNA extraction. Upon thawing, total RNA was extracted using an RNeasy isolation kit (Qiagen, GmbH) following the vendor's instructions and then quantified using a Nanodrop spectrophotometer (Thermo Scientific) and/or a Bioanalyzer 2100 (Agilent Technologies), again using the manufacturer's protocols and recommended instrument settings. The resulting total RNA preparations were assessed by genetic sequencing and gene expression analyses.

Whole transcriptome sequencing of qualified, high quality RNA was performed using an Applied Biosystems (ABI) Sequencing by Oligo Ligation/Detection (SOLiD) 4.5 or SOLiD 5500xl next generation sequencing system (Life Technologies). cDNA was generated from 1 ng total RNA samples using either a modified whole transcriptome protocol from ABI designed for low input total RNA or the Ovation RNA-Seq System V2™ (NuGEN Technologies). The resulting cDNA library was fragmented and barcode adapters were added to allow pooling of fragment libraries from different samples during sequencing runs. Data generated by the SOLiD platform mapped to 34,609 genes as annotated by RefSeq version 47 using NCBI version hg19.2 of the published human genome and provided verifiable measurements of RNA levels in most samples. Sequencing data from the SOLiD platform is nominally represented as a transcript expression value using the metrics RPM (reads per million) or RPKM (read per kilobase per million) mapped to exon regions of genes,

enabling basic gene expression analysis to be normalized and enumerated as RPM_Transcript or RPKM_Transcript.

The results of whole transcriptome sequencing using SOLiD showed elevated expression of CLDN4 mRNA in sorted CSC compared to NTG in the following PDX cell lines: BR13, BR22, OV100, PA20 and PA3, as well as high expression in additional CSC populations including BR36, OV106MET, OV72MET, and OV91MET (FIG. 1). CLDN6 mRNA was elevated in sorted CSC populations including BR36, OV106MET, OV72MET, and OV91MET (FIG.1). Unlike the case for CLDN4 or CLDN6, the related family member, CLDN9, was observed to have low expression in all sorted tumor populations. In contrast to the tumor samples, normal ovary and pancreas tissues showed no or very low mRNA expression of all three family members, CLDN4, CLDN6 and CLDN9.

The identification of elevated CLDN4 and CLDN6 mRNA expression in different types of human tumor indicated these antigens merited further evaluation as a potential diagnostic and/or immunotherapeutic targets.

EXAMPLE 2
EXPRESSION OF CLDN4, CLDN6 AND CLDN9 MRNA IN TUMORS USING QRT-PCR

To confirm expression of CLDN4, CLDN6 and further delineate CLDN9 expression in tumor cell subpopulations, qRT-PCR was run on RNA samples obtained from sorted CSC and NTG populations (as described in Example 1) from various PDX models. qRT-PCR was performed using the Fluidigm BioMark™ HD System according to industry standard protocols. 1 ng of RNA, prepared as described in Example 1, was converted to cDNA using the High Capacity cDNA Archive kit (Life Technologies) according to the manufacturer's instructions. cDNA material, pre-amplified using CLDN4, CLDN6 and CLDN9 specific Taqman assays, was then used for subsequent qRT-PCR experiments.

As shown in FIG. 2A, CLDN4 exhibited elevated expression in CSC subpopulations of BR31 (TNBC), LU86 (SCLC) and PA14 compared to NTG populations from the same PDX tumor lines. Compared to expression in normal lung and pancreas, sorted CSC populations showed 10-100 fold higher expression of CLDN4, suggesting a therapeutic window and potential benefit for targeting the CSC of these PDX models. CLDN6 was also found to exhibit elevated expression in CSC subpopulations of BR13 (TNBC), CR81 and PA3 when compared to NTG populations derived from the same PDX tumor lines, with CSC expression of CLDN6 approximately 10,000 fold greater

than CLDN6 expression in normal pancreas and colon (FIG. 2A). Finally, CLDN9 was also found to show elevated expression in CSC populations of BR13 (TNBC), CR81, OV27MET (OV-S) and OV44 (OV-S) as compared with NTG populations obtained from the same PDX tumor lines, with expression of CLDN9 approximately 10,000 fold higher than that found in normal colon cells. These findings validate the results obtained from whole transcriptome sequencing of similar populations with regard to CLDN4 and CLDN6 and clearly show that, in various sorted CSC populations, CDLN4, CLDN6 and/or CLDN9 are highly overexpressed.

To further determine the expression levels of CLDN4, CLDN6 and CLDN9 in additional tumor specimens, mRNA expression of the relevant CLDN family members in various bulk (non-sorted) PDX tumor cell lines was compared to mRNA expression in normal tissues that might be of concern for intolerable toxicity when using ADC therapeutics (NormTox: colon, stomach, small intestine, lung and pancreas) and normal tissues of less concern in terms of toxicity (Norm: breast, ovary). CLDN4 mRNA expression was found to be elevated in many bulk BR, CR, LU-SCC and PA PDX lines, with highest expression seen in BR-TNBC, CR, LU-SCC, PA (FIG. 2B). CLDN6 mRNA was highly overexpressed in OV-S and OV-PS (FIG. 2C), while CLDN6 mRNA levels were also elevated in BR-TNBC and in subsets of LU-Ad and CR PDX lines (FIG. 2C). Finally, CLDN9 mRNA was found to be elevated in certain PDX cell lines including BR-TNBC, CR, LU-Ad, OV and PA PDX lines (FIG. 2D) when compared with the levels found in normal tissues. These results demonstrate that CLDN4, CLDN6 and CLDN9 expression is elevated across different PDX tumor models, indicating that antibodies against CLDN4, CLDN6 and CLDN9 will allow for comprehensive targeting of multiple cancer indications. These findings further suggest that, in certain selected embodiments multireactive antibodies (i.e. those that immunospecifically bind to more than one of the CLDN4, CLDN6 and CLDN9 antigens) may be particularly effective in reducing or eliminating tumorigenic cells.

To further expand the analysis to a larger group of primary human tumor samples as well as normal tissue samples, a qRT-PCR assay was performed using CLDN4, CLDN6 or CLDN9-specific Taqman assays on a TissueScan™ qPCR (Origene Technologies) 384-well array according to the manufacturer's instructions. This array enables comparison of gene expression across 18 different tumor types, with multiple patient derived samples for each tumor type. Significantly, the Origene assay also enables the comparison of expression from normal tissue versus tumor tissue of the same tissue types. FIGS. 2E, 2F and 2G show the expression levels of CLDN4, CLDN6 and CLDN9, respectively, in various whole tumors specimens (black dots) normalized against β-actin and plotted relative to expression in the matched normal tissue (white

dots) for each tumor type analyzed. Specimens not amplified were assigned a cycle count value (Ct) of 45, which represents the last cycle of amplification in the experimental protocol. Each dot represents a single tissue specimen, with the mean geometric value of the samples for an indicated tumor or matched normal tissue type represented as a black line.

Overexpression of CLDN4 relative to matched normal tissue was seen in cervical, endometrial, and ovarian tumors, and in a subset of esophageal, liver, gastric, lung, testicular and bladder tumors (FIG. 2E). This includes 2/2 cholangiocarcinomas of the liver, 1/3 adenomas of the liver and 3/12 hepatocellular carcinomas. The gastric tumor subsets with overexpression of CLDN4 included 7/7 adenocarcinomas and 1/1 villous adenomas (data not shown). Overexpression of CLDN6 relative to matched normal tissue was seen in endometrial, ovarian and testicular tumors, as well as subsets of adrenal, breast, esophageal, liver, lung, lymphoma and gastric tumors (FIG. 2F). This includes 2/2 cholangiocarcinomas of the liver, 2/3 adenomas of the liver and 7/12 hepatocellular carcinomas (data not shown). Overexpression of CLDN9 relative to matched normal tissue was seen in adrenal, endometrial, esophageal, and ovarian tumors, and a subset of breast, lung and bladder tumors (FIG. 2G). These data suggest that abnormal CLDN4, CLDN6 and CLDN9 expression may be indicative of and/or implicated in tumorigenesis and/or tumor progression in the above-mentioned tumors, and again demonstrate that antibodies directed to these claudin proteins may be used to effectively treat various tumors.

EXAMPLE 3
CLDN EXPRESSION PROFILES IN PRIMARY TUMORS FROM THE CANCER GENOME ATLAS

Overexpression of mRNA of CLDN6 and CLDN9 family members was confirmed in various tumors using a large, publically available dataset of tumors and normal samples known as The Cancer Genome Atlas (TCGA, National Cancer Institute). Exon level 3 expression data from the IlluminaHiSeq_RNASeqV2 platform was downloaded from the TCGA Data Portal (https://tcga-data.nci.nih.gov/tcga/tcgaDownload.jsp) and parsed to aggregate the reads from the individual exons of each single gene to generate a single value read per kilobase of exon per million mapped reads (RPKM) for each gene in each sample. The rolled up data was then displayed using Tableau software. The parsed data for CLDN6 and CLDN9 are shown in FIGS. 3A and 3B, respectively, in which each sample is represented as a single dot, and the black horizontal lines represent the quartile boundaries for the setoff data points within a given normal tissue or tumor subtype. FIG. 3A shows that CLDN6 expression is elevated in OV tumors, which were subtyped as ovarian

serous cystadenocarcinomas, compared to all other normal tissues. In addition, CLDN6 is elevated in a large number of LU-Ad samples compared to normal lung samples, and a substantial number of breast invasive carcinoma tumors (BRCA). Similar overexpression patterns can be see for CLDN9 as those observed for CLDN6 (FIG. 3B). Again, these data indicate that CLDN6 and CLDN9 expression levels are indicative of tumorigenesis in various tumors and reinforce their selection as potential therapeutic targets.

In five selected tumor types found in the TCGA data: OV, LU-Ad, LU-SC (squamous cell carcinoma), BR, and SK, the relative expression of CLDN6 versus CLDN9, for samples showing non-zero RPKM expression values for both genes, was plotted (FIG. 3C). These tumor types were selected to encompass a range of relative expression levels, from high (OV) to low (SK). FIG. 3C shows a progressive shift in the co-expression of both genes, from high (upper right quadrant in scatter plots) to low (lower left quadrant) across the indications, suggesting the expression of these genes may be linked. This can be more easily visualized by plotting the centroids (center of mass) from each of the scatterplots (FIG. 3D). The centroids show a very tight correlation of high significance for the CLDN6 and CLDN9 genes (r^2 = 0.0996; p = 0.0001), which are proximal to one another (head to head on chromosome 16). In these same five indications, there was no significant correlation between: the expression of CLDN6 and a different claudin gene, CLDN1 (r^2=0.14); between CLDN6 and another tetraspanin, CD81 (r^2=0.02); or between CLDN6 and its other neighboring gene on chromosome 16, TNFRSF12A (r^2=0.47) (data not shown). A more modest yet significant correlation was seen in the co-expression of CLDN6 and CLDN4 genes (r^2=0.80; $p<0.05$) (data not shown). This rather surprisingly strong correlation between CLDN6 and CLDN9 is likely the result of the proximity of these two genes to one another, but is also suggestive of a functional link or functional co-disregulation of these genes. The tight co-expression pattern between CLDN6 and CLDN9 in several cancer indications provides a rationale for targeting multiple CLDN proteins as a therapeutic strategy.

EXAMPLE 4
CLONING AND EXPRESSION OF RECOMBINANT CLDN PROTEINS AND ENGINEERING OF CELL LINES OVEREXPRESSING CELL SURFACE CLDN PROTEINS

In order to deduce the relationship between claudin protein sequences, the AlignX program of the Vector NTI software package was used to align 30 claudin protein sequences from 23 human CLDN genes. The results of this alignment are depicted as a dendrogram in FIG. 4A. A

review of the figure shows that CLDN6 and CLDN9 are very closely related in sequence, appearing adjacent to one another on the same branch of the dendrogram. FIG. 4A also shows that CLDN4 is the next most closely related family member to CLDN6. A more detailed review of the data shows that the human CLDN6 protein is very closely related to the human CLDN9 protein sequence in the extracellular domains (ECD), with >98% identity in ECD1 and >91% identity in ECD2 (FIG. 4B). Human CLDN4 was also found to be closely related to human CLDN6 in the ECD sequences, with >84% identity in ECD1 and >78% identity in ECD2 (FIG. 4B). Based upon these protein sequence relationships, it was hypothesized that immunization with a human CLDN6 antigen would yield antibodies recognizing human CLDN6 that will also be cross-reactive with human CLDN9, and perhaps also cross-reactive with human CLDN4.

In order to determine which species orthologs of CLDN6, CLDN9 and CLDN4 would be required for screening these multireactive claudin antibodies, ECD sequences of CLDN4, CLDN6 and CLDN9 were analyzed from each of the following species: human, cynomolgus monkey, mouse and rat. The analysis was performed using AlignX and NCBI database protein sequences when available (NP accession numbers of human, mouse and rat proteins are indicated in FIG. 4C). Alternatively, protein sequences were deduced from translation of the cynomolgus monkey CLDN genes assembled by BLAST of human CLDN open reading frame sequences versus cynomolgus monkey whole genome shotgun sequencing contigs. Inspection of these alignments reveals that: (1) deduced cynomolgus monkey protein ECD sequences for CLDN4, CLDN6, and CLDN9 proteins are 100% identical to the respective human ECD sequences; (2) mouse and rat CLDN9 ECD sequences are 100% identical to the human ortholog sequence; (3) and mouse and rat CLDN4 and CLDN6 ECD sequences differ from one another and from the respective human orthologs. Therefore, generation of a set of seven constructs comprising human CLDN4, human CLDN6, human CLDN9, mouse CLDN4, mouse CLDN6, rat CLDN4 and rat CLDN6 should enable determination of cross-reactivity for any antibody with all possible 12 orthologs.

DNA fragments encoding human CLDN6, CLDN4, and CLDN9 proteins.

To generate all molecular and cellular materials required in the present invention pertaining to the human CLDN6 (hCLDN6) protein, a codon-optimized DNA fragment encoding a protein identical to NCBI protein accession NP_067018 was synthesized (IDT). This DNA clone was used for all subsequent engineering of constructs expressing the mature hCLDN6 protein or fragments thereof. Similarly, codon-optimized DNA fragments encoding proteins identical to NCBI protein accession NP_001296 for human CLDN4 (hCLDN4), or NCBI protein accession NP_066192 for

human CLDN9 (hCLDN9) were purchased and used for all subsequent engineering of constructs expressing the hCLDN4 or hCLDN9 proteins or fragments thereof.

DNA fragments encoding mouse CLDN6 and CLDN4 proteins.

To generate all molecular and cellular materials required in the present invention pertaining to the mouse CLDN6 (mCLDN6) protein, a codon-optimized DNA fragment encoding a protein identical to NCBI protein accession NP_061247 was synthesized (IDT). This DNA clone was used for all subsequent engineering of constructs expressing the mature mCLDN6 protein or fragments thereof. Similarly, a codon-optimized DNA fragment encoding a protein identical to NCBI protein accession NP_034033 for mouse CLDN4 (mCLDN4) was purchased and used for all subsequent engineering of constructs expressing the mature mCLDN4 protein or fragments thereof.

DNA fragments encoding rat CLDN6 and CLDN4 proteins.

To generate all molecular and cellular materials required in the present invention pertaining to the rat CLDN6 (rCLDN6) protein, a codon-optimized DNA fragment encoding a protein identical to NCBI protein accession NP_001095834 was synthesized (IDT). This DNA clone was used for all subsequent engineering of constructs expressing the mature rCLDN6 protein or fragments thereof. Similarly, a codon-optimized DNA fragment encoding a protein identical to NCBI protein accession NP_001012022 for rat CLDN4 (rCLDN4) was purchased and used for all subsequent engineering of constructs expressing the mature rCLDN4 protein or fragments thereof.

Cell line engineering

Engineered cell lines overexpressing the various CLDN proteins listed above were constructed using lentiviral vectors to transduce HEK-293T or 3T3 cell lines using art recognized techniques. First, PCR was used to amplify the DNA fragments encoding the protein of interest (e.g., hCLDN6, mCLDN6, rCLDN6, hCLDN9, hCLDN4, mCLDN4, or rCLDN4) using the commercially synthesized DNA fragments described above as templates. Then, the individual PCR products were subcloned into the multiple cloning site (MCS) of the lentiviral expression vector, pCDH-EF1-MCS-T2A-GFP (System Biosciences), to generate a suite of lentiviral vectors. The T2A sequence in resultant pCDH-EF1-CLDN-T2A-GFP vectors promotes ribosomal skipping of a peptide bond condensation, resulting in expression of two independent proteins: high level expression of the specific CLDN protein encoded upstream of the T2A peptide, with co-expression of the GFP marker protein encoded downstream of the T2A peptide. This suite of lentiviral vectors

was used to create separate stable HEK-293T or 3T3 cell lines overexpressing individual CLDN proteins using standard lentiviral transduction techniques well known to those skilled in the art. CLDN-positive cells were selected with FACS using high-expressing HEK-293T subclones, which were also strongly positive for GFP.

EXAMPLE 5
GENERATION OF ANTI-CLDN ANTIBODIES

Because CLDN6 is most homologous to CLDN4 and CLDN9 (see FIG. 4A and analysis as described in Example 4, above), CLDN6 was used as the immunogen with which to generate multireactive anti-CLDN antibodies. Mice were inoculated with HEK-293T cells or 3T3 cells overexpressing hCLDN6 (generated as described in Example 4) in order to produce antibody-generating hybridomas. Six mice (two each of the following strains: Balb/c, CD-1, FVB) were inoculated with 1 million hCLDN6-HEK-293T cells emulsified with an equal volume of TiterMax® adjuvant. A second, separate inoculation of six mice (two each of the following strains: Balb/c, CD-1, FVB) was performed using 3T3 cells overexpressing CLDN6. Following the initial inoculation the mice were injected twice weekly for 4 weeks with cells overexpressing CLDN6 emulsified with an equal volume of alum adjuvant.

Mice were sacrificed and draining lymph nodes (popliteal, inguinal, and medial iliac) were dissected and used as a source for antibody producing cells. A single cell suspension of B cells ($305x10^6$ cells) were fused with non-secreting P3x63Ag8.653 myeloma cells (ATCC #CRL-1580) at a ratio of 1:1 by electro cell fusion using a model BTX Hybrimmune System (BTX Harvard Apparatus). Cells were resuspended in hybridoma selection medium: DMEM medium (Cellgro) supplemented with azaserine (Sigma), 15% fetal clone I serum (Hyclone), 10% BM condimed (Roche Applied Sciences), 1 mM sodium pyruvate, 4 mM L-glutamine, 100 IU penicillin-streptomycin, 50 µM 2-mercaptoethanol, and 100 µM hypoxanthine, and cultured in three T225 flasks in 90 mL selection medium per flask. The flasks were placed in a humidified 37 °C incubator containing 5% CO_2 and 95% air for 6 days. The library was frozen down in 6 vials of CryoStor CS10 buffer (BioLife Solutions), with approximately $15x10^6$ viable cells per vial, and stored in liquid nitrogen.

One vial from the library was thawed at 37 °C and the frozen hybridoma cells were added to 90 mL hybridoma selection medium, described above, and placed in a T150 flask. The cells were cultured overnight in a humidified 37 °C incubator with 5% CO_2 and 95% air. The following day

hybridoma cells were collected from the flask and plated at one cell per well (using a FACSAria I cell sorter) in 200 µL of supplemented hybridoma selection medium into 48 Falcon 96-well U-bottom plates. The hybridomas were cultured for 10 days and the supernatants were screened for antibodies specific to hCLDN6, hCLDN4 or hCLDN9 proteins using flow cytometry. Flow cytometry was performed as follows: $1x10^5$ per well of HEK-293T cells, stably transduced with lentiviral vectors encoding hCLDN6, hCLDN4 or hCLDN9, were incubated for 30 mins. with 100 µL hybridoma supernatent. Cells were washed with PBS/2% FCS and then incubated with 50 µL per sample DyeLight 649 labeled goat-anti-mouse IgG, Fc fragment specific secondary antibody diluted 1:200 in PBS/2%FCS. After a 15 min. incubation cells were washed twice with PBS/2%FCS and re-suspended in PBS/2%FCS with DAPI (to detect dead cells) and analyzed by flow cytometry for fluorescence exceeding that of cells stained with an isotype control antibody. Selected hybridomas that tested positive for antibodies directed to one or more of the CLDN antigens were set aside for further characterization. Remaining, unused hybridoma library cells were frozen in liquid nitrogen for future library testing and screening.

EXAMPLE 6
SEQUENCING OF ANTI-CLDN ANTIBODIES

Anti-CLDN antibodies were generated as described above and then sequenced as follows. Total RNA was purified from selected hybridoma cells using the RNeasy Miniprep Kit (Qiagen) according to the manufacturer's instructions. Between 10^4 and 10^5 cells were used per sample. Isolated RNA samples were stored at –80 °C until used. The variable region of the Ig heavy chain of each hybridoma was amplified using two 5' primer mixes comprising 86 mouse specific leader sequence primers designed to target the complete mouse VH repertoire in combination with a 3' mouse Cγ primer specific for all mouse Ig isotypes. Similarly, two primer mixes containing 64 5' VK leader sequences designed to amplify each of the VK mouse families was used in combination with a single reverse primer specific to the mouse kappa constant region in order to amplify and sequence the kappa light chain. The VH and VL transcripts were amplified from 100 ng total RNA using the Qiagen One Step RT-PCR kit as follows. A total of four RT-PCR reactions were run for each hybridoma, two for the VK light chain and two for the VH heavy chain. PCR reaction mixtures included 1.5 µL of RNA, 0.4 µL of 100 µM of either heavy chain or kappa light chain primers (custom synthesized by IDT), 5 µL of 5x RT-PCR buffer, 1 µL dNTPs, and 0.6 µL of enzyme mix containing reverse transcriptase and DNA polymerase. The thermal cycler program included the following steps: RT step 50 °C for 60 min., 95 °C for 15 min. followed by 35 cycles of (94.5 °C for

30 seconds, 57 °C for 30 seconds, 72 °C for 1 min.), and a final incubation at 72 °C for 10 min. The extracted PCR products were sequenced using the same specific variable region primers as described above. PCR products were sent to an external sequencing vendor (MCLAB) for PCR purification and sequencing services.

FIG. 5A depicts the contiguous amino acid sequences of numerous novel mouse light chain variable regions from anti-CLDN antibodies (SEQ ID NOS: 21-57, odd numbers). FIG. 5B depicts the contiguous amino acid sequences of novel mouse heavy chain variable regions from the same anti-CLDN antibodies (SEQ ID NOS: 23-59, odd numbers). Mouse light and heavy chain variable region nucleic acid sequences are provided in FIG. 5C (SEQ ID NOS: 20-58, even numbers). Taken together FIGS. 5A and 5B provide the annotated sequences of 10 mouse anti-CLDN antibodies, termed SC27.1, SC27.22, SC27.103, SC27.104, SC27.105, SC27.106, SC27.108 (identical to SC27.109), SC27.201, SC27.203 and SC27.204. The amino acid sequences are annotated to identify the framework regions (i.e. FR1 – FR4) and the complementarity determining regions (i.e. CDRL1 – CDRL3 in FIG. 5A or CDRH1 – CDRH3 in FIG. 5B) defined as per Kabat. The variable region sequences were analyzed using a proprietary version of the Abysis database to provide the CDR and FR designations. Though the CDRs are numbered according to Kabat those skilled in art will appreciate that the CDR and FR designations can also be defined according to Chothia, McCallum or any other accepted nomenclature system.

The SEQ ID NOS of each particular antibody are sequential odd numbers. Thus the monoclonal anti-CLDN antibody, SC27.1, comprises amino acid SEQ ID NOS: 21 and 23 for the VL and VH, respectively; and SC27.22 comprises SEQ ID NOS: 25 and 27 etc.. The corresponding nucleic acid sequence for each antibody amino acid sequence is included in FIG. 5C and has the SEQ ID NO immediately preceding the corresponding amino acid SEQ ID NO. Thus, for example, the SEQ ID NOS of the nucleic acid sequences of the VL and VH of the SC27.1 antibody are SEQ ID NOS: 20 and 22, respectively.

EXAMPLE 7
GENERATION OF CHIMERIC AND HUMANIZED ANTI-CLDN ANTIBODIES

Chimeric anti-CLDN antibodies were generated using art-recognized techniques as follows. Total RNA was extracted from the anti-CLDN antibody-producing hybridomas using the method described in Example 6 and the RNA was PCR amplified. Data regarding V, D and J gene segments of the VH and VL chains of the mouse antibodies were obtained from the nucleic acid sequences of the anti-CLDN antibodies of the invention (see FIG. 5C for nucleic acid sequences).

Primer sets specific to the framework sequence of the VH and VL chain of the antibodies were designed using the following restriction sites: AgeI and XhoI for the VH fragments, and XmaI and DraIII for the VL fragments. PCR products were purified with a Qiaquick PCR purification kit (Qiagen), followed by digestion with restriction enzymes AgeI and XhoI for the VH fragments and XmaI and DraIII for the VL fragments. The VH and VL digested PCR products were purified and ligated into IgH or IgK expression vectors, respectively. Ligation reactions were performed in a total volume of 10 µL with 200 U T4-DNA Ligase (New England Biolabs), 7.5 µL of digested and purified gene-specific PCR product and 25 ng linearized vector DNA. Competent *E. coli* DH10B bacteria (Life Technologies) were transformed via heat shock at 42 °C with 3 µL ligation product and plated onto ampicillin plates at a concentration of 100 µg/mL. Following purification and digestion of the amplified ligation products, the VH fragment was cloned into the AgeI-XhoI restriction sites of the pEE6.4 expression vector (Lonza) comprising HuIgG1 (pEE6.4HuIgG1) and the VL fragment was cloned into the XmaI-DraIII restriction sites of the pEE12.4 expression vector (Lonza) comprising a human kappa light constant region (pEE12.4Hu-Kappa).

Chimeric antibodies were expressed by co-transfection of either HEK-293T or CHO-S cells with pEE6.4HuIgG1 and pEE12.4Hu-Kappa expression vectors. Prior to transfection the HEK-293T cells were cultured in 150 mm plates under standard conditions in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat inactivated FCS, 100 µg/mL streptomycin and 100 U/mL penicillin G. For transient transfections cells were grown to 80% confluency. 2.5 µg each of pEE6.4HuIgG1 and pEE12.4Hu-Kappa vector DNA were added to 10 µL HEK-293T transfection reagent in 1.5 mL Opti-MEM. The mix was incubated for 30 min. at room temperature and added to cells. Supernatants were harvested three to six days after transfection. For CHO-S cells, 2.5 µg each of pEE6.4HuIgG1 and pEE12.4Hu-Kappa vector DNA were added to 15 µg PEI transfection reagent in 400 µL Opti-MEM. The mix was incubated for 10 min. at room temperature and added to cells. Supernatants were harvested three to six days after transfection. Culture supernatants containing recombinant chimeric antibodies were cleared from cell debris by centrifugation at 800×g for 10 min. and stored at 4 °C. Recombinant chimeric antibodies were purified with Protein A beads

Mouse anti-CLDN antibodies were humanized using a proprietary computer-aided CDR-grafting method (Abysis Database, UCL Business) and standard molecular engineering techniques as follows. Human framework regions of the variable regions were designed based on the highest homology between the framework sequences and CDR canonical structures of human germline antibody sequences, and the framework sequences and CDRs of the relevant mouse antibodies.

For the purpose of the analysis the assignment of amino acids to each of the CDR domains was done in accordance with Kabat numbering. Once the variable regions were selected, they were generated from synthetic gene segments (Integrated DNA Technologies). Humanized antibodies were cloned and expressed using the molecular methods described above for chimeric antibodies.

The VL and VH amino acid sequences of the humanized antibodies were derived from the VL and VH sequences of the corresponding mouse antibody (e.g. hSC27.1 is derived from mouse SC27.1). There were no framework changes or back mutations made in the light or heavy chain variable regions of the four humanized antibodies generated: hSC27.1,hSC27.22, hSC17.108 and hSC27.204.

To address stability concerns, three variants of hSC27.22 were produced using different VH frameworks in the same VH1 family. The variants were termed hSC27.22-VH1-8; hSC27.22-VH1-46; hSC27.22-VH1-69. In addition, one variant of hSC27.108 was constructed, termed hSC27.108v1, which shares the same heavy chain as hSC27.108 (SEQ ID NO: 119) but differs in light chain compared to hSC27.108. In addition, several variants of hSC27.204 were generated, termed hSC27.204v1 through hSC27.204v15, all of which share the same light chain (SEQ ID NO: 120) but differ in the heavy chain. The heavy chains of hSC27.204 and hSC27.204v4 differ in a single framework region mutation, T28D. hSC27.204v1 through hSC27.204v3 and hSC27.204v5 through hSC27.204v7 incorporate conservative mutations in the CDRs to address stability concerns. Specifically, hSC27.204v1, hSC27.204v2, and hSC27.204v3 contain the modifications N58K, N58Q, and T60N, respectively, on the hSC27.204 heavy chain background. Similarly, hSC27.204v5, hSC27.204v6, and hSC27.204v7 contain the modifications N58K, N58Q, and T60N, respectively on the hSC27.204v4 background. Lastly, variants hSC27.204v8 and hSC27.204v9 do not include a back mutation at position 93 of the heavy chain in order to minimize immunogenicity. Specifically, variants hSC27.204v8, hSC27.204v9, hSC27.204v10, hSC27.204v11, hSC27.204v12, hSC27.204v13, hSC27.204v14, and hSC27.204v15 correspond to variants hSC27.204, hSC27.204v1, hSC27.204v2, hSC27.204v3, hSC27.204v4, hSC27.204v5, hSC27.204 6, and hSC27.204v7, respectively, except that variants 8-15 lack the A93T back mutation.

In addition, 9 variants of the hSC27.22 humanized antibody constant region were constructed. The first variant, hSC27.22ss1 is a site specific variant and is described in more detail in Example 8 below. The other variants were constructed by substituting the IgG isotype with either IgG2 (termed, “hSC27.22 IgG2”) or mutated forms of IgG4 (termed, “hSC27.22 IgG4 R409K”; “hSC27.22 IgG4 S228P”; “hSC27.22 IgG4 S228P K370E R409K”; “hSC27.22 IgG4 K370E”; “hSC27.22 IgG4 S228P K370E”; “hSC27.22 IgG4 C127S S228P”; “hSC27.22 IgG4 C127S

K370E"; and "hSC27.22 IgG4 C127S S228P K370E"). Table 5 below shows a summary of the humanized anti CLDN antibodies and their variants, numbered according to Kabat *et al*.

In each case, the binding affinity of the humanized antibody was checked to ensure that it was substantially equivalent to the corresponding mouse antibody. FIG. 5A depicts the contiguous amino acid sequences of the VL of exemplary humanized antibodies and their variants. FIG. 5B depicts the contiguous amino acid sequences of the VH of exemplary humanized antibodies and their variants. The nucleic acid sequences of the light and heavy chain variable regions of the anti-CLDN humanized antibodies are provided in FIG. 5C.

FIG. 5D shows the full length sequences of the light and heavy chains of exemplary humanized antibodies and their variants. hSC27.1 (SEQ ID NOS: 75 and 76) and hSC27.22 (SEQ ID NOS: 77 and 78).

FIGS. 5E to 5H comprise annotated amino acid sequences (numbered as per Kabat *et al.*) of the light and heavy chain variable regions of hSC27.1 (FIG. 5E); hSC27.22 (FIG. 5F); hSC27.108 (FIG. 5G); and hSC27.204 (FIG. 5H) humanized antibodies showing CDRs as determined using Kabat, Chothia, ABM and Contact methodology.

TABLE 5

mAb	Isotype	human VH	human JH	VH FR changes	VH CDR Changes	human VK	human JK	VK FR changes	VK CDR Changes
hSC27.1	IgG1	IGHV1-3*01	JH1	None	None	IGKV1-12*01	JK2	None	None
hSC27.22	IgG1	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22ss1	IgG1 C220S	IGHV1-8*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22-VH1-8	IgG1	IGHV1-8*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 VH1-46	IgG1	IGHV1-46*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 VH1-69	IgG1	IGHV1-69*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG2	IgG2	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 R409K	IgG4 R409K	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 S228P	IgG4 S228P	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 S228P K370E R409K	IgG4 S228P R409K K370E	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 K370E	IgG4 K370E	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 S228P K370E	IgG4 S228P K370E	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 C127S S228P	IgG4 C127S S228P	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 C127S K370E	IgG4 C127S K370E	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.22 IgG4 C127S S228P K370E	IgG4 C127S S228P K370E	IGHV1-3*01	JH6	None	None	IGKV4-1*01	JK2	None	None
hSC27.108	IgG1	IGHV1-18*01	JH1	None	None	IGKV3-11*01	JK4	None	None
hSC27.108 v1	IgG1	IGHV1-18*01	JH1	None	None	IGKV6-21*01	JK4	L47W K49Y	None
hSC27.204	IgG1	IGHV3-23*01	JH1	A93T K94G	None	IGKV1-16*01	JK4	None	None
hSC27.204 v1	IgG1	IGHV3-23*01	JH1	A93T K94G	N58K	IGKV1-16*01	JK4	None	None

hSC27.204v2	IgG1	IGHV3-23*01	JH1	A93T K94G	N58Q	IGKV1-16*01	JK4	None	None
hSC27.204v3	IgG1	IGHV3-23*01	JH1	A93T K94G	T60N	IGKV1-16*01	JK4	None	None
hSC27.204v4	IgG1	IGHV3-23*01	JH1	T28D, A93T K94G	None	IGKV1-16*01	JK4	None	None
hSC27.204v5	IgG1	IGHV3-23*01	JH1	T28D, A93T K94G	N58K	IGKV1-16*01	JK4	None	None
hSC27.204v6	IgG1	IGHV3-23*01	JH1	T28D, A93T K94G	N58Q	IGKV1-16*01	JK4	None	None
hSC27.204v7	IgG1	IGHV3-23*01	JH1	T28D, A93T K94G	T60N	IGKV1-16*01	JK4	None	None
hSC27.204v8	IgG1	IGHV3-23*01	JH1	K94G	None	IGKV1-16*01	JK4	None	None
hSC27.204v9	IgG1	IGHV3-23*01	JH1	K94G	N58K	IGKV1-16*01	JK4	None	None
hSC27.204v10	IgG1	IGHV3-23*01	JH1	K94G	N58Q	IGKV1-16*01	JK4	None	None
hSC27.204v11	IgG1	IGHV3-23*01	JH1	K94G	T60N	IGKV1-16*01	JK4	None	None
hSC27.204v12	IgG1	IGHV3-23*01	JH1	T28D, K94G	None	IGKV1-16*01	JK4	None	None
hSC27.204v13	IgG1	IGHV3-23*01	JH1	T28D, K94G	N58K	IGKV1-16*01	JK4	None	None
hSC27.204v14	IgG1	IGHV3-23*01	JH1	T28D, K94G	N58Q	IGKV1-16*01	JK4	None	None
hSC27.204v15	IgG1	IGHV3-23*01	JH1	T28D, K94G	T60N	IGKV1-16*01	JK4	None	None

EXAMPLE 8
GENERATION OF SITE-SPECIFIC ANTI-CLDN ANTIBODIES

An engineered human IgG1/kappa anti-CLDN site-specific antibody was constructed comprising a native light chain (LC) constant region and mutated heavy chain (HC) constant region, wherein cysteine 220 (C220) in the upper hinge region of the HC, which forms an interchain disulfide bond with cysteine 214 (C214) in the LC, was substituted with serine (C220S). When assembled, the HCs and LCs form an antibody comprising two free cysteines that are suitable for conjugation to a therapeutic agent. Unless otherwise noted, all numbering of constant region residues is in accordance with the EU numbering scheme as set forth in Kabat et al.

The engineered antibody was generated as follows. The nucleic acid sequence of the HC of the hSC27.22 antibody (SEQ ID NO: 67) was codon optimized by DNA2.0 (Menlo Park, CA) to generate the following nucleic acid sequence:

CAAGTGCAGCTCGTCCAGTCCGGTGCCGAAGTCAAGAAGCCGGGCGCATCAGTGAAAG
TGTCGTGCAAAGCCTCCGGGTACACCTTCACCTCATACTGGATGAACTGGGTCCGCCAAGCC
CCGGGACAGAGACTGGAGTGGATGGGCATGATTCACCCATCCGATTCCGAGATCCGGCTGAA
CCAGAAGTTCAAGGACCGCGTGACCATCACCCGGGACACCAGCGCCAGCACTGCCTACATG
GAATTGAGCTCGCTGCGGTCCGAGGATACCGCTGTGTACTATTGCGCGAGGATCGACTCCTA
CTACGGCTACCTTTTCTACTTCGACTACTGGGGACAAGGGACGACCGTGACTGTGTCGAGC
(SEQ ID NO: 178).

The optimized nucleic acid was cloned onto an expression vector containing the C220S mutation in the constant region of the HC. The vector encoding the mutant C220S HC of hSC27.22 was co-transfected in CHO-S cells with a vector encoding the native IgG1 kappa LC of hSC27.22, and expressed using a mammalian transient expression system. The engineered anti-CLDN site-specific antibody containing the C220S mutant was termed hSC27.22ss1. The amino acid sequence of the full length HC of the hSC27.22ss1 site specific antibody is shown in FIG. 5D (SEQ ID NO: 122). The amino acid sequence of the LC of hSC27.22ss1 is identical to that of hSC27.22 (SEQ ID NO: 123).

Engineered human IgG4/kappa anti-CLDN site-specific antibodies were also constructed comprising a native LC constant region and mutated HC constant region, wherein cysteine 127 (C127) in the CH1 of the IgG4 heavy chain, which forms an interchain disulfide bond with cysteine 220 (C220) in the LC, was substituted with serine (C127S). When assembled the HCs and LCs form an antibody comprising two free cysteines that are suitable for conjugation to a therapeutic

agent. This modification was made using the Quikchange Site Directed Mutagenesis Kit (Agilent) according to the manufacturer's protocols using the IgG4 expression vector as a template.

The engineered antibodies were generated as follows. The codon optimized nucleic acid sequence of hSC27.22 (SEQ ID NO: 178), was cloned onto an expression vector containing the C127S mutation in the constant region of the HC. The vector encoding the mutant C127S HC of hSC27.22 was co-transfected in CHO-S cells with a vector encoding the native IgG1 kappa LC of hSC27.22, and expressed using a mammalian transient expression system. The C127S modification was applied to the various modified IgG4 constructs generated as described in Example 7 above. The resulting IgG4 site specific constructs are shown in Table 5 above and FIG. 5D and are termed: hSC27.22 IgG4 S228P ;hSC27.22 IgG4 R409K; hSC27.22 IgG4 S228P K370E R409K; hSC27.22 IgG4 K370E; hSC27.22 IgG4 S228P K370E; hSC27.22 IgG4 C127S S228P; hSC27.22 IgG4 C127S K370E; and hSC27.22 IgG4 C127S S228P K370E.

The engineered anti-CLDN site specific antibodies were characterized by SDS-PAGE to confirm that the correct mutants had been generated. SDS-PAGE was conducted on a pre-cast 10% Tris-Glycine mini gel from Life Technologies in the presence and absence of a reducing agent such as DTT (dithiothreitol). Following electrophoresis, the gels were stained with a colloidal coomassie solution (data not shown). Under reducing conditions, two bands corresponding to the free LCs and free HCs, were observed. This pattern is typical of IgG molecules in reducing conditions. Under non-reducing conditions, the band patterns were different from native IgG molecules, indicative of the absence of a disulfide bond between the HC and LC. A band around 98 kD corresponding to the HC-HC dimer was observed. In addition, a faint band corresponding to the free LC and a predominant band around 48 kD that corresponded to a LC-LC dimer was observed. The formation of some amount of LC-LC species is expected due to the free cysteines on the c-terminus of each LC.

EXAMPLE 9
SPECIFICITY OF ANTI-CLDN ANTIBODIES

The mouse antibodies generated as described in Example 5, were characterized to determine whether they cross reacted with CLDN family members and orthologs of CLDN family members.

Flow cytometry analyses were performed as follows: HEK-293T cells were stably transduced with (i) lentiviral vectors encoding hCLDN6, mCLDN6, and rCLDN6; (ii) hCLDN9; or (iii) hCLDN4, mCLDN4 and rCLDN4, made as described in Example 4 above. $1x10^5$ HEK-293T cells stably transduced with the aforementioned expression constructs were incubated at 4 °C for 30 mins. with

either hSC27.1 or hSC27.22 antibodies, diluted to 10 µg/ml into a final volume of 50 µl PBS/2%FCS. Following incubation, cells were washed with 200 µL PBS/2%FCS, pelleted by centrifugation, supernatant was discarded, and cell pellets were resuspended in 50 µL per sample DyeLight 649 labeled goat-anti-mouse IgG, Fc fragment specific secondary antibody diluted 1:200 in PBS/2%FCS. After a 15 min. incubation at 4 °C cells were washed and pelleted twice with PBS/2%FCS as previously described and resuspended in 100 µL PBS/2%FCS with 2 µg/mL 4',6-diamidino-2-phenylindole dihydrochloride (DAPI). Samples were analyzed by flow cytometry and live cells were assessed with DyeLight 649 for fluorescence exceeding that of cells stained with an isotype control antibody.

The flow cytometry assay described above resulted in the identification of numerous anti-CLDN antibodies. Cross reactivity was determined based on the change in geometric mean fluorescence intensity (ΔMFI) for the binding of the antibody to the cell lines specifically overexpressing the indicated CLDN family member versus the signal determined using a fluorescence minus one (FMO) isotype-control (gray-fill) (FIG. 6A). Thus, the two hCLDN6-binding antibodies SC27.1 and SC27.22 can be described as claudin multireactive antibodies since they cross react in this assay with three members of the human CLDN family: hCLDN6, hCLDN4 and hCLDN9. SC27.1 and SC27.22 antibodies also bound to mouse and rat orthologs of CLDN4 and CLDN9 (data not shown).

To test the ability of various additional mouse antibodies to bind to CLDN family members, flow cytometry was performed using cell lines overexpressing human CLDN4, CLDN6 or CLND9 that had been incubated with 10 µg/mL of purified primary anti-CLDN antibody, or a mouse IgG2b control antibody, followed by incubation with an Alexa 647 anti-mouse secondary antibody. As shown in FIG. 6B, all the antibodies bound to CLDN6, whereas some were CLDN6-specific (e.g. SC27.102, SC27.105, and SC27.108), and others were multireactive and bound to both CLDN6 and CLDN9 (e.g., SC27.103 and SC27.204), or to CLDN6 and CLDN4 (e.g., SC27.104). Thus a wide range of multireactive binding profiles was obtained for the antibodies of the invention.

To compare the apparent binding affinity of the multireactive anti-CLDN antibodies for CLDN6 and CLDN9, flow cytometry was performed with a serial dilution of humanized anti-CLDN antibody hSC27.22. The antibody was serially diluted to concentrations ranging from 50 pg/ml to 100 µg/ml and was added to a 96 well plate containing HEK-293T cells overexpressing CLDN6 or CLDN9, and kept on ice for one hour. A secondary anti-human antibody (Jackson ImmunoResearch Cat. # 109-605-098) was added and incubated for one hour in the dark. The cells were washed twice in PBS after which Fixable Viability Dye (eBioscience Cat # 65-0863-14) was added for 10 mins.. Following additional washing with PBS, cells were fixed with

paraformaldehyde (PFA) and read on a BD FACS Canto II flow cytometer in accordance with the manufacturer's instructions. MFI values were normalized using fluorescent microspheres (Bangs Laboratories) according to manufacturer's instructions. Normalized maximal MFI values observed for the binding of the antibody to either CLDN6 or CLDN9 expressing cells were used to transform the data into fraction maximal binding for each overexpressing cell, using the equation: fraction maximal binding = (observed normalized MFI / maximal normalized MFI). Apparent EC50 values for the binding of hSC27.22 to each cell line were then calculated using a four parameter variable slope curve fitting for a log (inhibitor) vs. response model supplied in the GraphPad Prism software package (La Jolla, CA). FIG. 6C shows that the humanized multireactive anti-CLDN6 antibody, hSC27.22, has an apparent EC50 for CLDN6 which is substantially the same as that for CLDN9. (apparent EC50 CLDN6 – 3.45 μg/mL (r^2 for goodness of fit = 0.9987, 99% confidence bounds: 2.51 – 4.75 μg/mL); apparent EC50 CLDN9 – 4.66 μg/mL (r^2 for goodness of fit = 0.9998, 99% confidence bounds: 4.09 – 5.31 μg/mL)).

EXAMPLE 10
DETECTION OF CLDN PROTEIN EXPRESSION ON PDX TUMORS USING FLOW CYTOMETRY

Flow cytometry was used to assess the ability of the two representative hCLDN6-binding antibodies hSC27.1 and hSC27.22 to specifically detect the presence of hCLDN proteins on the surface of PDX tumor cells. Isotype-stained and fluorescence minus one (FMO) controls were employed to confirm staining specificity.

Art-recognized enzymatic tissue digestion techniques were used to obtain single cell suspensions of PDX tumor cells (see, for example, U.S.P.N. 2007/0292414). PDX tumors were harvested, dissociated, and co-stained with commercially available anti-mouse CD45 and H-2kD antibodies (to demarcate mouse cells) and anti-human EpCAM and anti-CLDN antibodies. The anti-hCLDN antibody, hSC27.1, demonstrated positive staining on a subset of human (i.e. mCD45 and H-2kD negative) EpCAM-positive tumor cells, including OV-S (e.g., OV44, OV54), OV-PS (e.g. OV63MET), PA, LU-SCC (e.g., LU22), LU-Ad (e.g., LU134, LU135), and LIV (FIG. 7). Isotype control antibodies and FMO controls were employed to confirm staining specificity as is standard practice in the art. Flow cytometry was performed using a BD FACS Canto II flow cytometer in accordance with the manufacturer's instructions.

The levels of hCLDN staining varied across different PDX tumor cell lines, where some tumor cells did not stain at all (data not shown) while other tumor cell lines exhibited nearly uniformly positive staining of the human tumor cells (e.g. OV63MET) compared to isotype controls (FIG. 7).

These data suggest that hCLDNs are expressed on the surface of a subpopulation of human tumor subtypes, which may be amenable to treatment using anti-CLDN antibodies or ADCs of the invention.

EXAMPLE 11
ENRICHMENT OF CLDN EXPRESSION IN CANCER STEM CELL POPULATIONS

Tumor cells can be divided broadly into two types of cell subpopulations: non-tumorigenic cells (NTG) and tumor initiating cells or tumorigenic cells. Tumorigenic cells have the ability to form tumors when implanted into immunocompromised mice, whereas non-tumorigenic cells do not. Cancer stem cells (CSCs) are a subset of tumorigenic cells and are able to self-replicate indefinitely while maintaining the capacity for multilineage differentiation.

To confirm the observations in Examples 1 and 2, which showed overexpression of CLDN4, CLDN6 and CLDN9 in CSC subpopulations of various tumors, and to determine whether the anti-CLDN antibodies of the invention are able to detect tumorigenic CSC populations, PDX tumors were dissociated into single cell suspensions as described in Example 10 above and selective markers, $CD46^{hi}CD324^{+}$, were used to enrich for CSC tumor cell subpopulations (see WO 2012/031280) as follows.

PDX tumor single cell suspensions were incubated with the following antibodies: anti-CLDN SC27.1; anti-human EPCAM; anti-human CD46; anti-human CD324; and anti-mouse CD45 and H-2kD antibodies. The tumor cells were then assessed for staining by flow cytometry using a BD FACS Canto II flow cytometer. The human $EPCAM^{+}CD46^{hi}CD324^{+}$ CSC tumor cell subpopulations of OV-S (e.g., OV44 and OV54MET), OV-PS (e.g. OV91MET), PA, LU-Ad (e.g., LU135), and LU-Sq (e.g., LU22) PDX tumors demonstrated positive staining with the anti-CLDN SC27.1 antibody, whereas NTG cells ($CD46^{lo/-}$ and/or $CD324^{-}$) demonstrated significantly less staining with anti-CLDN antibodies (FIG. 8A). Isotype control antibodies and FMO controls were employed to confirm staining specificity as is standard practice in the art. A table summarizing the differential staining of anti-CLDN antibodies observed on the surface of CSC and NTG cells is shown in FIG. 8A, with expression enumerated as the change in geometric mean fluorescence intensity (ΔMFI) between the indicated anti-CLDN antibody and the isotype control for the respective tumor cell subpopulations. These data confirm the expression of hCLDN proteins on CSCs and again suggest anti-CLDN antibodies may be effective for the treatment of cancer.

To determine whether CLDN expression in tumors could be correlated with enhanced tumorigenicity, the following study was conducted. Human OV PDX tumor samples (OV91MET) were grown in immunocompromised mice and were resected after the tumor reached 800 -

2,000 mm^3. The tumors were dissociated into single cell suspensions using art-recognized enzymatic digestion techniques (see, for example, U.S.P.N. 2007/0292414). Human OV PDX tumor cells were stained with mouse anti-CD45 or anti-H2kD antibodies, and with anti-ESA antibodies to differentiate between human tumor cells and mouse cells. The tumors were also stained with anti-CLDN antibody (SC27.22) and then sorted using a FACSAria™ Flow Cytometer (BD Biosciences). The human OV PDX tumor cells were separated into $CLDN^+$ and $CLDN^-$ subpopulations. Five female NOD/SCID immunocompromised mice were injected subcutaneously with 200 $CLDN^+$ OV tumor cells; and five mice were injected with 200 $CLDN^-$ OV tumor cells. Tumor volumes were measured on a weekly basis for four months.

FIG. 8B shows that $CLDN^+$ (closed circles) tumor cells were able to functionally reconstitute tumors *in vivo*, whereas $CLDN^-$ tumors (open circles) were not. Thus, tumor cells expressing CLDN were much more tumorigenic than those tumor cells that did not express CLDN, suggesting that the CLDN protein can functionally define a tumorigenic subpopulation within human tumors, and supporting the concept that selected anti-CLDN ADCs can be used to target a tumorigenic subpopulation of tumor cells, which could result in significant tumor regression and prevention of tumor recurrence.

EXAMPLE 12
ANTI-CLDN ANTIBODIES FACILITATE DELIVERY OF CYTOTOXIC AGENTS IN VITRO

To determine whether anti-CLDN antibodies are able to internalize and mediate the delivery of cytotoxic agents to live tumor cells, an *in vitro* cell killing assay was performed using selected anti-CLDN antibodies and saporin linked to a secondary anti-mouse antibody FAB fragment. Saporin is a plant toxin that deactivates ribosomes, thereby inhibiting protein synthesis and resulting in the death of the cell. Saporin is only cytotoxic inside the cell where it has access to ribosomes, but is unable to internalize on its own. Therefore, saporin-mediated cellular cytotoxicity in these assays is indicative of the ability of the anti-mouse FAB-saporin conjugate to internalize into the target cell only upon binding and internalization of anti-CLDN antibodies.

Single cell suspensions of HEK-293T cells and HEK-293T cells overexpressing hCLDN6, hCLDN4, or hCLDN9 were plated at 500 cells per well into BD Tissue Culture plates (BD Biosciences). One day later, 250 pM of purified SC27.1, SC27.22, or isotype control (mIgG1) antibodies and a fixed concentration of 2 nM anti-Mouse IgG FAB-saporin conjugate (Advanced Targeting Systems) were added to the culture. The HEK-293T cells were incubated for 72 hours post antibody treatment. After the incubation, viable cells were enumerated using CellTiter-Glo®

(Promega) as per the manufacturer's instructions. Raw luminescence counts using cultures containing cells incubated only with the secondary FAB-saporin conjugate were set as 100% reference values and all other counts calculated accordingly. Both of the anti-CLDN antibodies, SC27.1 and SC27.22, at a concentration of 250 pM effectively killed HEK-293T cells overexpressing hCLDN6 and hCLDN9 (FIG. 9A), whereas the mouse IgG1 isotype control antibody (mIgG1) at the same concentration did not. Naïve HEK-293T cells were not effectively killed by the treatment whereas HEK-293T cells overexpressing hCLDN4 were effectively killed by SC27.1 but were not killed by SC27.22 treatment at the dose tested. The dashed horizontal line represents the level at which no cytotoxicity was observed.

In order to determine the apparent IC50 of additional antibodies for CLDN4, CLDN6 or CLDN9, the experiment described in the paragraph above was repeated with titrations of antibodies, across a concentration range of 0.15 nM to 1000 nM (FIG. 9B). The percentage of cell killing observed at each antibody concentration was enumerated by CellTiter-Glo® as described above, and a curve was fitted to the resulting data in order to calculate an apparent IC50 for the killing activity of antibody on each cell line. Antibodies which had an apparent IC50 of >2000 nM were deemed not to kill a particular cell line and are denoted as "NK" in FIG. 9B. A control mouse IgG1 antibody also did not kill any of the cell lines tested. Although this cytotoxicity assay measures the ability of various antibodies to mediate delivery of a cytotoxin via internalization of bound antigen rather than providing a direct measure of antibody binding affinity, the apparent IC50 of the antibodies shown in FIG. 9B in general correlates well with the single point flow cytometry data presented in FIG. 6B. For example, in both experiments SC27.108 is shown to be CLDN6-specific (apparent IC50 = 100nM). Similarly, by flow cytometry SC27.103 shows strong binding to CLDN6 and moderate binding to CLDN9, which correlates with an apparent IC50 value of 58 nM for CLDN6 and 466 nM for CLDN9. However, it is also clear that detectable binding above background does not always result in detectable killing (e.g., SC27.104 binds to CLDN9 (see FIG. 6B) but is not able to effectively internalize and kill CLDN9-overexpressing cells (see FIG. 9B); whereas SC27.201 binds CLDN9 (see FIG. 6B) and is able to internalize into cells expressing CLDN9 and kill those cells (see FIG. 9B)).

Together, the above results demonstrate the ability of multireactive anti-CLDN antibodies to mediate internalization and their ability to deliver cytotoxic payloads, supporting the hypothesis that anti-CLDN antibodies may have therapeutic utility as the targeting moiety for an ADC.

EXAMPLE 13
DETECTION OF CLDN6 ON THE SURFACE OF TUMORS USING IMMUNOHISTOCHEMISTRY

To assess the extent of CLDN6 protein expression in tumors, immunohistochemistry (IHC) was performed on formalin fixed paraffin embedded (FFPE) PDX tumors and tissue microarrays (TMAs) of primary ovarian tumors (Oklahoma University).

Planar sections of cell pellet blocks were cut and mounted on glass microscope slides. After xylene de-paraffinization 5 µm sections were pre-treated with Antigen Retrieval Solution (Dako) for 20 min. at 99 °C, cooled to 75 °C and then treated with 0.3% hydrogen peroxide in PBS followed by treatment with Avidin/Biotin Blocking Solution (Vector Laboratories). FFPE slides were then blocked with 10% donkey serum in 3% BSA in PBS buffer and incubated with a primary anti-CLDN6 rabbit polyclonal antibody purchased from IBL America (Catalog # 18865), diluted to 10 µg/ml in 3% BSA/PBS, for 30 min. at room temperature. FFPE slides were incubated with biotin-conjugated donkey anti-rabbit antibody (Vector Laboratories), diluted to 2.5 µg/ml in 3% BSA/PBS, for 30 min. at room temperature followed by incubation with streptavidin-HRP (ABC Elite Kit; Vector Laboratories). Chromogenic detection was developed with 3,3'-diaminobenzidine (Thermo Scientific) for 5 min. at room temperature and tissues were counterstained with Meyer's hematoxylin (IHC World), washed with alcohol and immersed in xylene.

To confirm the specificity of the primary anti-CLDN6 antibody, IHC was performed on FFPE slides of HEK-293T cells overexpressing hCLDN6, hCLDN4 or hCLND9. The anti-CLDN6 polyclonal antibody specifically stained hCLDN6-overexpressing HEK-293T cell pellets but did not stain overexpressing cell lines of hCLDN4 and hCLDN9 (data not shown).

FIG. 10A shows a summary overview of hCLDN6 expression in OV, BR, and LU PDX tumors, as determined by IHC. Staining intensity was scored from no staining (-) to high staining intensity (+++). The percentage of tumor cells that expressed CLDN6 is also noted. CLDN6 expression was observed in LU, BR and OV tumors with many PDX lines showing expression in 90% of the cells on the FFPE slide.

To determine the penetrance of hCLDN6 expression in ovarian cancer patients, IHC was also performed on FFPE slides generated from TMAs made from 125 primary ovarian tumors resected from cancer patients (Oklahoma University). The H-Score was generated utilizing the Leica Biosystems Tissue IA software on digitally scanned images of the TMAs. Briefly, staining preferences specific to hCLDN6 were assigned in the Measure Stained Cells Algorithm under the Tissue IA Optimiser. TMA cores were then individually annotated so that the image analysis would only analyze tumor cells and not other tissue constituents such as stroma. The TMA was analyzed

using the hCLDN6 Membrane Stain algorithm which produced an H-score. The H-score algorithm was calculated for membrane staining of tumor cells using the following formula; H-Score = (% staining intensity at 0) * 0 + (% staining intensity at 1+) * 1 + (% staining intensity at 2+) * 2 + (% staining intensity at 3+) * 3. Thus, this score produces a continuous variable that ranges from 0 to 300. The results in the table in FIG. 10B show level of expression of CLDN6 in the 125 tumor samples of the TMA, with 70% of the tumors expressing some level of CLDN6.

Together, these IHC data demonstrate that CLDN6 is expressed on the cell surface of ovarian, breast and lung tumors as well as in primary human tumors, reconfirming that claudins are relevant targets for the development of antibody and ADC therapeutics for treatment of a significant number of cancer patients. Anti-CLDN6 may have diagnostic utility in these and possibly additional cancer indications.

EXAMPLE 14
PREPARATION OF ANTI-CLDN6 ANTIBODY-DRUG CONJUGATES

Anti-CLDN antibody drug conjugates (ADCs) are prepared having the Ab-[L-D] structure, where Ab refers to the anti-CLDN antibody, L refers to an optional linker (e.g. a linker comprising a terminal maleimido moiety with a free sulfhydryl group) and D refers to a drug or cytotoxin (e.g. auristatins, calicheamicin etc.). Each ADC comprises an anti-CLDN antibody covalently linked to a linker-drug. ADCs are synthesized and purified using techniques known in the art, for example, essentially as follows. The cystine bonds of anti-CLDN antibodies are partially reduced with a pre-determined molar addition of mol tris(2-carboxyethyl)-phosphine (TCEP) per mol antibody for 90 min. at 20 °C in phosphate buffered saline (PBS) with 5 mM EDTA. The linker-drug, dissolved in dimethyl acetamide (DMA), is added at a ratio of 3 mol/mol anti-CLDN antibody. The reaction is allowed to proceed for 30 min. Using a 10 mM stock solution of N-acetyl cysteine (NAC) prepared in water, the reaction is quenched with the addition of excess NAC to linker-drug. After a minimum quench time of 20 mins., the pH is adjusted to 6.0 with the addition of 0.5 M acetic acid and buffer exchanged by diafiltration into diafiltration buffer using a 30 kDa membrane. The dialfiltered anti-CLDN ADC is then formulated with sucrose and polysorbate-20 to the target final concentration. The resulting anti-CLDN ADCs are analyzed for protein concentration (by measuring UV), aggregation (SEC), drug to antibody ratio (DAR) by reverse-phase HPLC (RP-HPLC) and *in vitro* cytotoxicity.

EXAMPLE 15
CONJUGATION OF SITE SPECIFIC ANTI-CLDN ANTIBODIES USING A SELECTIVE REDUCTION PROCESS

Anti-CLDN antibody drug conjugates (ADCs) are prepared having the Ab-[L-D] structure as described in Example 14 above, wherein the Ab moiety is a site specific antibody, for example, hSC27.22ss1, generated as set forth in Example 8 above. The desired product is an ADC that is maximally conjugated on the unpaired cysteine (C214 in the case of IgG1 site specific antibodies or C127 on IgG4 site specific antibodies) on each LC constant region and that minimizes ADCs having a drug to antibody ratio (DAR) which is greater than 2 (DAR>2) or less than 2 (DAR<2) while maximizing ADCs having a DAR of 2 (DAR=2).

In order to further improve the specificity of the conjugation and homogeneity of the final site-specific ADC, the site specific antibody (e.g. "hSC27.22ss1" or "hSC27.22 IgG4 C127S S228P") is selectively reduced using, for example, a process comprising a stabilizing agent (e.g. L-arginine) and a mild reducing agent (e.g. glutathione) prior to conjugation with the linker-drug, followed by preparative hydrophobic interaction chromatography (HIC) that is used to separate the different DAR species. The above procedures are conducted, for example, essentially as described below.

A preparation of the site specific antibody is partially reduced in a buffer containing 1M L-arginine/5 mM glutathione, reduced (GSH)/5 mM EDTA, pH 8.0 for a minimum of one hour at room temperature. All preparations are then buffer exchanged into a 20 mM Tris/3.2 mM EDTA, pH 8.2 buffer using a 30 kDa membrane (Millipore Amicon Ultra) to remove the reducing buffer. The resulting partially reduced preparations are then conjugated to a cytotoxin (e.g. auristatin, calicheamicin etc.) via a linker (e.g. maleimide linker) for a minimum of 30 mins. at room temperature. The reaction is then quenched with the addition of excess NAC to linker-drug using a 10 mM stock solution of NAC prepared in water. After a minimum quench time of 20 mins., the pH is adjusted to 6.0 with the addition of 0.5 M acetic acid. The site specific ADC is buffer exchanged into diafiltration buffer using a 30 kDa membrane. The site specific ADC preparation is then diluted with a high salt buffer to increase the conductivity to promote binding onto the resin, and then loaded on a Butyl HP resin chromatography column (GE Life Sciences). A decreasing salt gradient is then employed to separate the different DAR species based on hydrophobicity, where DAR=0 species elute first, followed by DAR=1, DAR=2, and then higher DAR species.

The final ADC "HIC purified DAR=2" preparation is analyzed using RP-HPLC to determine the percent conjugation on the HCs and LCs and the DAR distribution. The samples are also analyzed using analytical HIC to determine the amount of DAR=2 species relative to the unwanted DAR>2 and DAR<2 species.

EXAMPLE 16
HUMANIZED ANTI-CLDN ANTIBODY DRUG CONJUGATES SUPPRESS TUMOR GROWTH *IN VIVO*

The anti-CLDN ADCs, generated, for example, as described in Examples 14 and 15 above, are tested using art-recognized techniques, essentially as described below, to demonstrate their ability to suppress ovarian tumor growth in immunodeficient mice.

PDX tumor lines expressing CLDN and control tumor lines which do not express CLDN are grown subcutaneously in the flanks of female NOD/SCID mice using art-recognized techniques. Tumor volumes and mouse weights are monitored once or twice per week. When tumor volumes reach 150-250 mm^3, mice are randomly assigned to treatment groups and injected intraperitoneally with a single dose of 1 or 2 mg/kg humanized anti-CLDN ADC, a single dose of 2 mg/kg anti-hapten control human IgG ADC or vehicle control, for example, 0.9% saline or 5% glucose. Following treatment, tumor volumes and mouse weights are monitored until tumors exceed 800 mm^3 or the mice become sick. Mice treated with humanized anti-CLDN ADC that do not exhibit any adverse health effects beyond those typically seen in immunodeficient, tumor-bearing NOD/SCID mice and that effectively reduce tumor volume compared to control IgG ADC and vehicle are selected for further analysis including toxicity studies.

EXAMPLE 17
REDUCTION OF CANCER STEM CELL FREQUENCY BY ANTI-CLDN ANTIBODY-DRUG CONJUGATES

As demonstrated in Example 11 CLDN expression is associated with cancer stem cells. Accordingly, to demonstrate that treatment with anti-CLDN ADCs reduces the frequency of cancer stem cells (CSC) that are known to be drug resistant and to fuel tumor recurrence and metastasis, *in vivo* limiting dilution assays (LDA) are performed, for example, essentially as described below.

PDX tumors (e.g. melanoma or ovarian) are grown subcutaneously in immunodeficient mice. When tumor volumes average 150 mm^3 – 250 mm^3 in size, the mice are randomly segregated into two groups. One group is injected intraperitoneally with a human IgG1 conjugated to a drug as a negative control; and the other group is injected intraperitoneally with an anti-CLDN ADC (e.g., as prepared in Examples 14 and 15). One week following dosing, two representative mice from each group are euthanized and their tumors are harvested and dispersed to single-cell suspensions. The tumor cells from each treatment group are then harvested, pooled and disaggregated as previously described in Example 1. The cells are labeled with FITC conjugated anti-mouse H2kD and anti-mouse CD45 antibodies to detect mouse cells; EpCAM to detect human

cells; and DAPI to detect dead cells. The resulting suspension is then sorted by FACS using a BD FACS Canto II flow cytometer and live human tumor cells are isolated and collected.

Four cohorts of mice are injected with either 1250, 375, 115 or 35 sorted live, human cells from tumors treated with anti-CLDN ADC. As a negative control four cohorts of mice are transplanted with either 1000, 300, 100 or 30 sorted live, human cells from tumors treated with the control IgG1 ADC. Tumors in recipient mice are measured weekly, and individual mice are euthanized before tumors reach 1500 mm^3. Recipient mice are scored as having positive or negative tumor growth. Positive tumor growth is defined as growth of a tumor exceeding 100 mm^3.

Poisson distribution statistics (L-Calc software, Stemcell Technologies) is used to calculate the frequency of CSCs in each population.

CLAIMS

1. An antibody that binds to cancer stem cells expressing at least one protein of the CLDN family.
2. The antibody of claim 1 wherein the antibody binds specifically to CLND6.
3. The antibody of claim 1 wherein the antibody binds specifically to CLDN6 and CLDN9.
4. The antibody of claim 3 wherein the antibody binds specifically to CLDN6 and CLDN9 with substantially the same apparent binding affinity.
5. The antibody of claim 1 wherein the antibody binds specifically to CLDN6 and CLDN9 with substantially the same apparent binding affinity.
6. An antibody of claims 1-5, which is an Internalizing antibody.
7. An antibody that binds to at least one member of the CLDN family and competes for binding with an antibody comprising:

   a light chain variable region (VL) of SEQ ID NO: 21 and a heavy chain variable region (VH) of SEQ ID NO: 23; or

   a VL of SEQ ID NO: 25 and a VH of SEQ ID NO: 27; or

   a VL of SEQ ID NO: 29 and a VH of SEQ ID NO: 31; or

   a VL of SEQ ID NO: 33 and a VH of SEQ ID NO: 35; or

   a VL of SEQ ID NO: 37 and a VH of SEQ ID NO: 39; or

   a VL of SEQ ID NO: 41 and a VH of SEQ ID NO: 43; or

   a VL of SEQ ID NO: 45 and a VH of SEQ ID NO: 47; or

   a VL of SEQ ID NO: 49 and a VH of SEQ ID NO: 51; or

   a VL of SEQ ID NO: 53 and a VH of SEQ ID NO: 55; or

   a VL of SEQ ID NO: 57 and a VH of SEQ ID NO: 59.
8. The antibody of claim 7 wherein the antibody binds specifically to CLND6.
9. The antibody of claim 7 wherein the antibody binds specifically to CLDN6 and CLDN9.
10. The antibody of claim 7, wherein the antibody is a chimeric, CDR grafted, humanized or recombinant antibody, or a fragment thereof.
11. The antibody of claim 7, wherein the antibody is an internalizing antibody.
12. A humanized antibody that binds to at least one protein of the CLDN family and competes for binding with an antibody comprising three variable light chain CDRs (CDRL) as set forth in SEQ ID NO: 61; and three variable heavy chain CDRs (CDRH) as set forth in SEQ ID NO: 63; or three CDRL as set forth in SEQ ID NO: 65 and three CDRH as set forth in SEQ ID NO: 67; or three CDRL as set forth in SEQ ID NO: 69 and three CDRH as set forth in

SEQ ID NO: 71; three CDRL as set forth in SEQ ID NO: 73 and three CDRH as set forth in SEQ ID NO: 75.

13. The humanized antibody of claim 12 comprising a VH and VL, wherein the VL has three CDRL comprising a CDRL1 of SEQ ID NO: 151, a CDRL2 of SEQ ID NO: 152 and a CDRL3 of SEQ ID NO: 153; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 157, a CDRL2 of SEQ ID NO: 158 and a CDRL3 of SEQ ID NO: 159; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 163, a CDRL2 of SEQ ID NO: 164 and a CDRL3 of SEQ ID NO: 165; or a VL having three CDRLs comprising a CDRL1 of SEQ ID NO: 169, a CDRL2 of SEQ ID NO: 170 and a CDRL3 of SEQ ID NO: 171.
14. The humanized antibody of claim 12 comprising a VL and a VH, wherein the VH has three CDRs (CDRH) comprising a CDRH1 of SEQ ID NO: 154, a CDRH2 of SEQ ID NO: 155 and a CDRH3 of SEQ ID NO: 156; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 160, a CDRH2 of SEQ ID NO: 161 and a CDRH3 of SEQ ID NO: 162; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 166, a CDRH2 of SEQ ID NO: 167 and a CDRH3 of SEQ ID NO: 168; or the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 172, a CDRH2 of SEQ ID NO: 173 and a CDRH3 of SEQ ID NO: 174.
15. The humanized antibody of claim 12 comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 151, a CDRL2 of SEQ ID NO: 152 and a CDRL3 of SEQ ID NO: 153 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 154, a CDRH2 of SEQ ID NO: 155 and a CDRH3 of SEQ ID NO: 156; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 157, a CDRL2 of SEQ ID NO: 158 and a CDRL3 of SEQ ID NO: 159 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 160, a CDRH2 of SEQ ID NO: 161 and a CDRH3 of SEQ ID NO: 162; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 163, a CDRL2 of SEQ ID NO: 164 and a CDRL3 of SEQ ID NO: 165 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 166, a CDRH2 of SEQ ID NO: 167 and a CDRH3 of SEQ ID NO: 168; or an antibody comprising a VL and VH wherein the VL has three CDRLs comprising a CDRL1 of SEQ ID NO: 169, a CDRL2 of SEQ ID NO: 170 and a CDRL3 of SEQ ID NO: 171 and the VH has three CDRHs comprising a CDRH1 of SEQ ID NO: 172, a CDRH2 of SEQ ID NO: 173 and a CDRH3 of SEQ ID NO: 174.
16. A humanized antibody that binds to at least one protein of the CLDN family comprising a full length light chain set forth as SEQ ID NO: 114 and a full length heavy chain set forth as SEQ ID NO: 115; or a full length light chain set forth as SEQ ID NO: 116 and a full length

heavy chain set forth as SEQ ID NO: 117; or a full length light chain set forth as SEQ ID NO: 118 and a full length heavy chain set forth as SEQ ID NO: 119; or a full length light chain set forth as SEQ ID NO: 120 and a full length heavy chain set forth as SEQ ID NO: 121.

17. The antibody of any one of claims 1-16, wherein the antibody is conjugated to a payload.
18. A nucleic acid encoding the antibody of any one of claims 1-16.
19. The nucleic acid of claim 17 which is contained in a vector.
20. The nucleic acid of claim 18 which is expressing in a host cell.
21. An antibody drug conjugate (ADC) comprising a chimeric, CDR grafted, humanized or recombinant human antibody, or a fragment thereof, which binds to cancer stem cells expressing at least one protein of the CLDN family, wherein the antibody is conjugated to a cytotoxic agent.
22. An ADC of the formula Ab-[L-D]n, wherein Ab is an antibody of claims 1-16; L is an optional linker; D is a drug; and n is an integer from about 1 to about 20.
23. A pharmaceutical composition comprising an ADC of claim 22.
24. A method of treating cancer comprising administering a pharmaceutical composition of claim 23 to a subject in need thereof.
25. The method of claim 24, wherein the cancer is selected from ovarian cancer, lung cancer, breast cancer and pancreatic cancer.
26. The method of claim 25, wherein the cancer is lung adenocarcinoma.
27. The method of claim 26, wherein the cancer is ovarian cancer.
28. The method of claim 24, further comprising administering to the subject at least one additional therapeutic moiety.
29. A method of reducing cancer stem cells in a tumor cell population, wherein the method comprises contacting a tumor cell population comprising cancer stem cells and tumor cells other than cancer stem cells, with an anti-CLDN ADC; whereby the frequency of cancer stem cells is reduced.
30. The method of claim 29, wherein the contacting is performed *in vivo*.
31. The method of claim 29, wherein the contacting is performed *in vitro*.
32. A method of delivering a cytotoxin to a cell comprising contacting the cell with an ADC of claim 22.

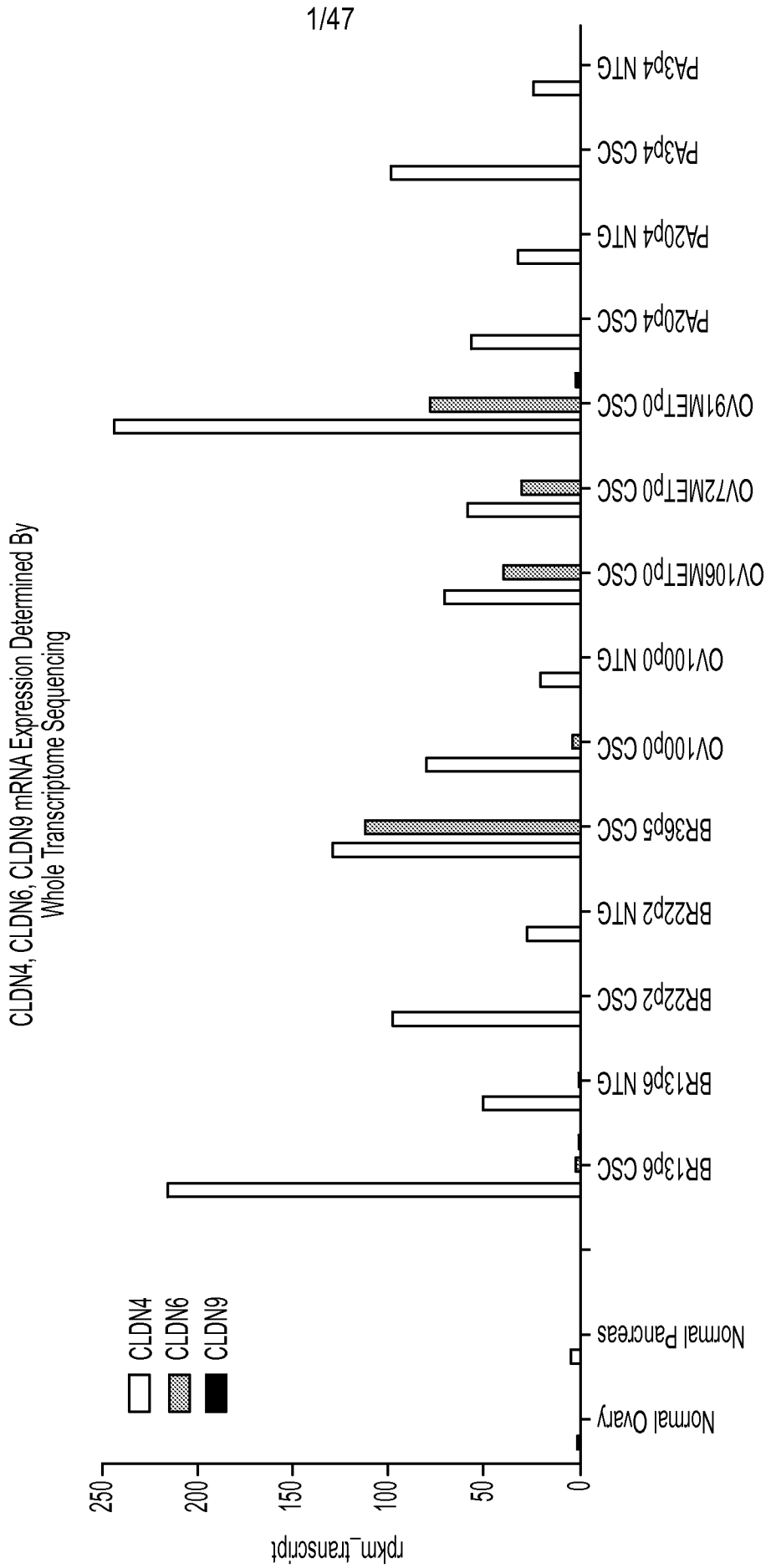

CLDN4, CLDN6, CLDN9 mRNA Expression Determined By Whole Transcriptome Sequencing
CLDN4
CLDN6
CLDN9
rpkm_transcript
250
200
150
100
50
0
Normal Ovary
Normal Pancreas
BR13p6 CSC
BR13p6 NTG
BR22p2 CSC
BR22p2 NTG
BR36p5 CSC
OV100p0 CSC
OV100p0 NTG
OV106METp0 CSC
OV72METp0 CSC
OV91METp0 CSC
PA20p4 CSC
PA20p4 NTG
PA3p4 CSC
PA3p4 NTG

FIG. 1

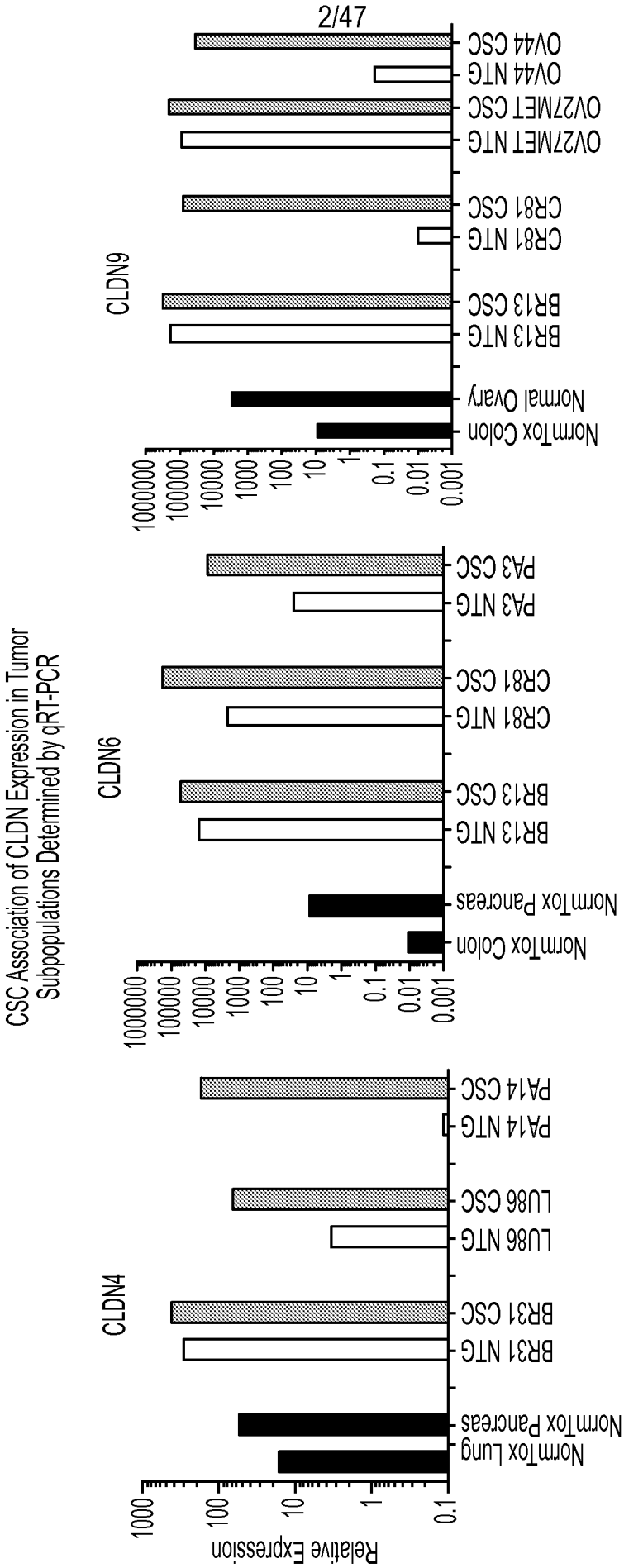

CSC Association of CLDN Expression in Tumor Subpopulations Determined by qRT-PCR
Relative Expression
1000
100
10
1
0.1
CLDN4
NormTox Lung
NormTox Pancreas
BR31 NTG
BR31 CSC
LU86 NTG
LU86 CSC
PA14 NTG
PA14 CSC
CLDN6
1000000
100000
10000
1000
100
10
1
0.1
0.01
0.001
NormTox Colon
NormTox Pancreas
BR13 NTG
BR13 CSC
CR81 NTG
CR81 CSC
PA3 NTG
PA3 CSC
CLDN9
NormTox Colon
Normal Ovary
BR13 NTG
BR13 CSC
CR81 NTG
CR81 CSC
OV27MET NTG
OV27MET CSC
OV44 NTG
OV44 CSC

FIG. 2A

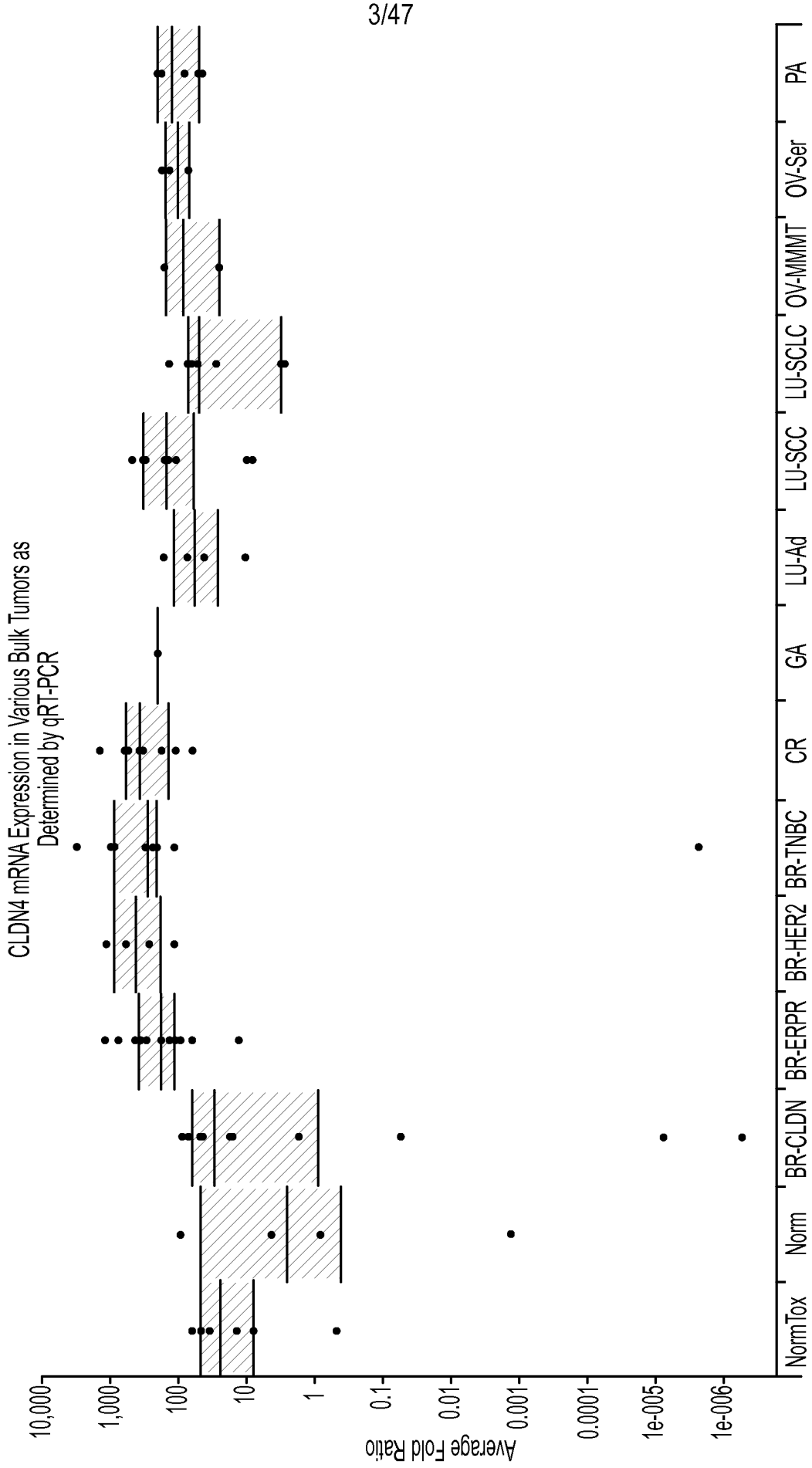

CLDN4 mRNA Expression in Various Bulk Tumors as Determined by qRT-PCR
Average Fold Ratio
10,000
1,000
100
10
1
0.1
0.01
0.001
0.0001
1e-005
1e-006
NormTox
Norm
BR-CLDN
BR-ERPR
BR-HER2
BR-TNBC
CR
GA
LU-Ad
LU-SCC
LU-SCLC
OV-MMMT
OV-Ser
PA

FIG. 2B

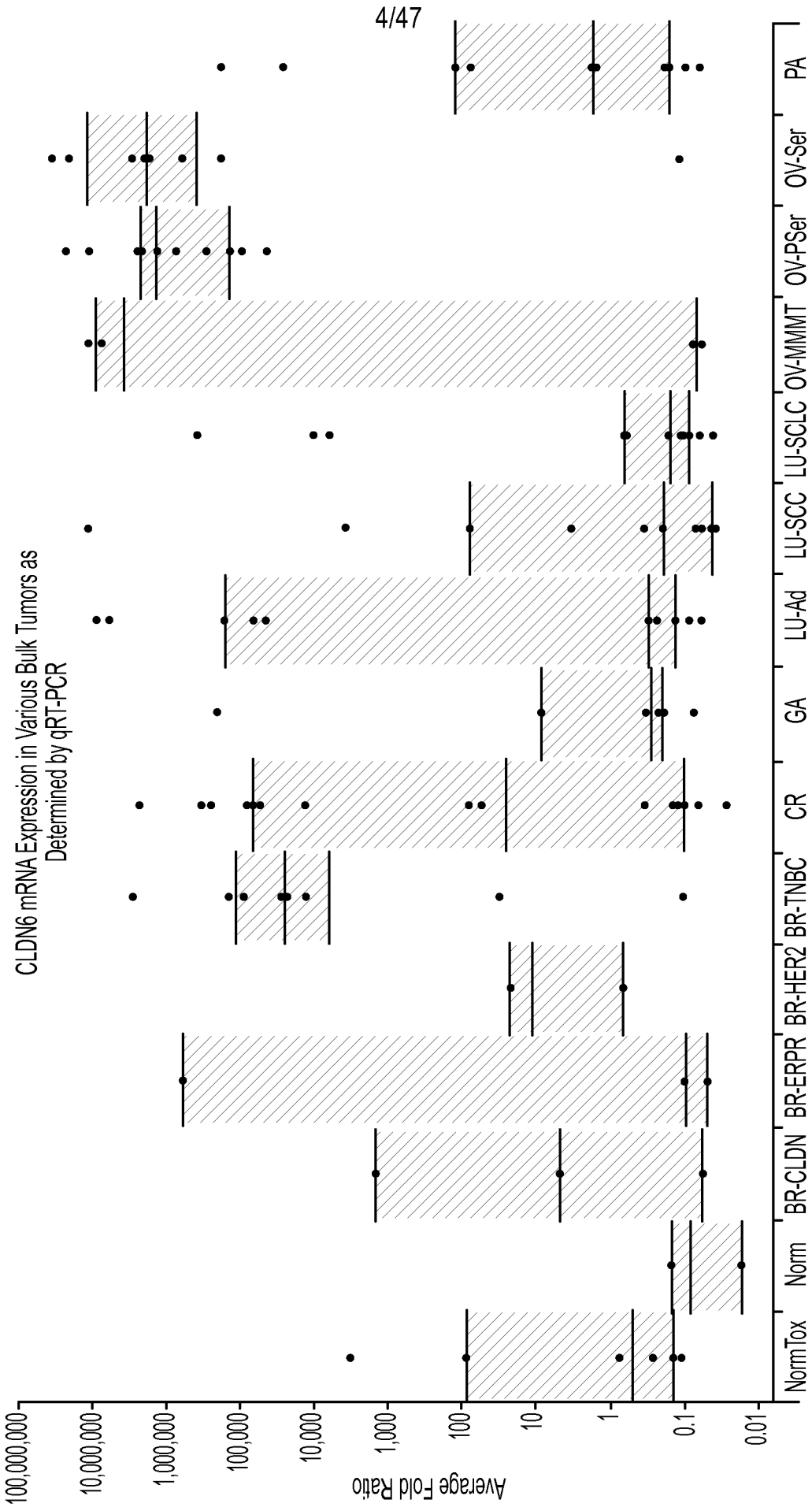

CLDN6 mRNA Expression in Various Bulk Tumors as Determined by qRT-PCR
Average Fold Ratio
100,000,000
10,000,000
1,000,000
100,000
10,000
1,000
100
10
1
0.1
0.01
NormTox
Norm
BR-CLDN
BR-ERPR
BR-HER2
BR-TNBC
CR
GA
LU-Ad
LU-SCC
LU-SCLC
OV-MMMT
OV-PSer
OV-Ser
PA

FIG. 2C

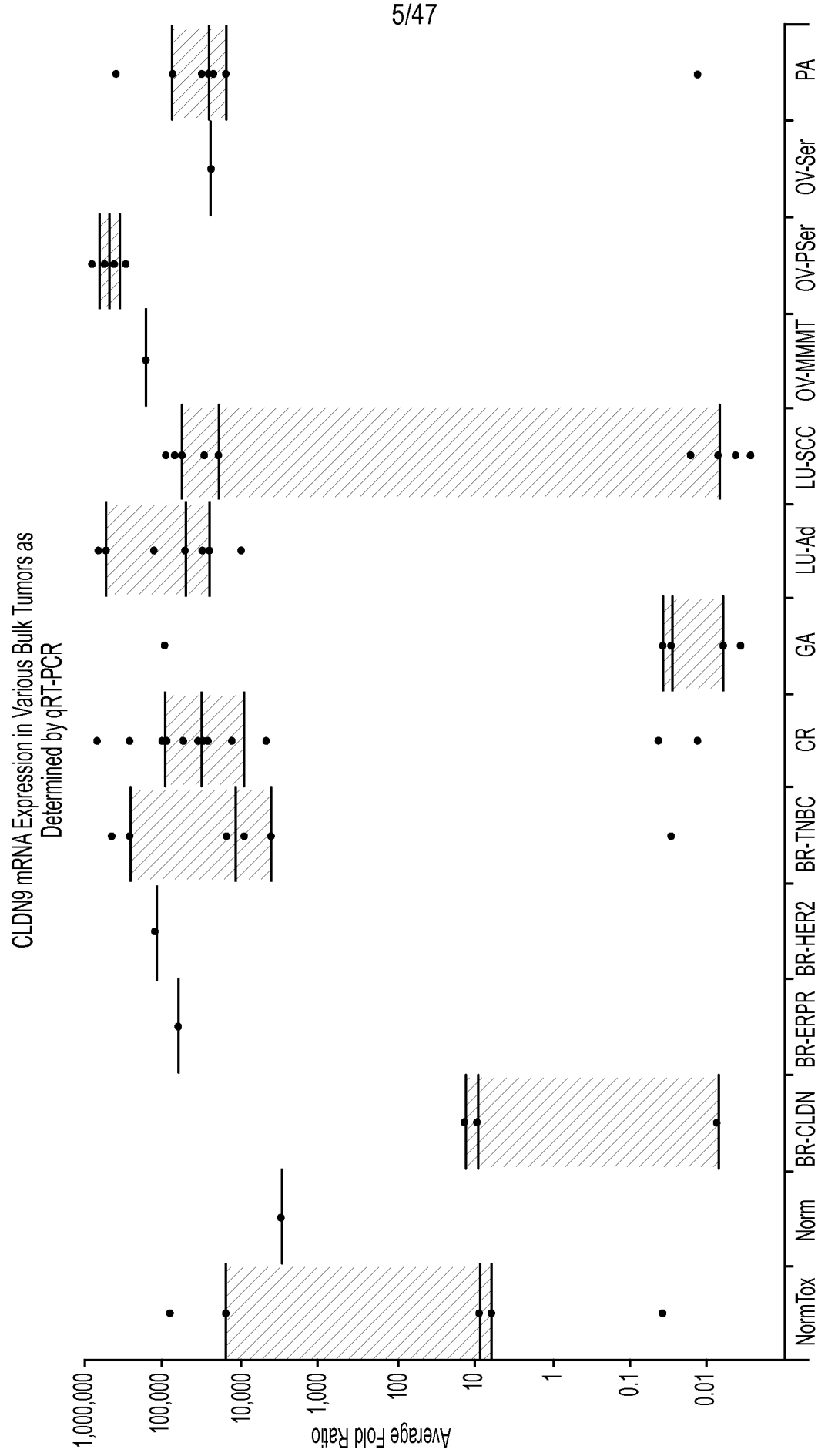

CLDN9 mRNA Expression in Various Bulk Tumors as Determined by qRT-PCR
Average Fold Ratio
1,000,000
100,000
10,000
1,000
100
10
1
0.1
0.01
NormTox
Norm
BR-CLDN
BR-ERPR
BR-HER2
BR-TNBC
CR
GA
LU-Ad
LU-SCC
OV-MMMT
OV-PSer
OV-Ser
PA

FIG. 2D

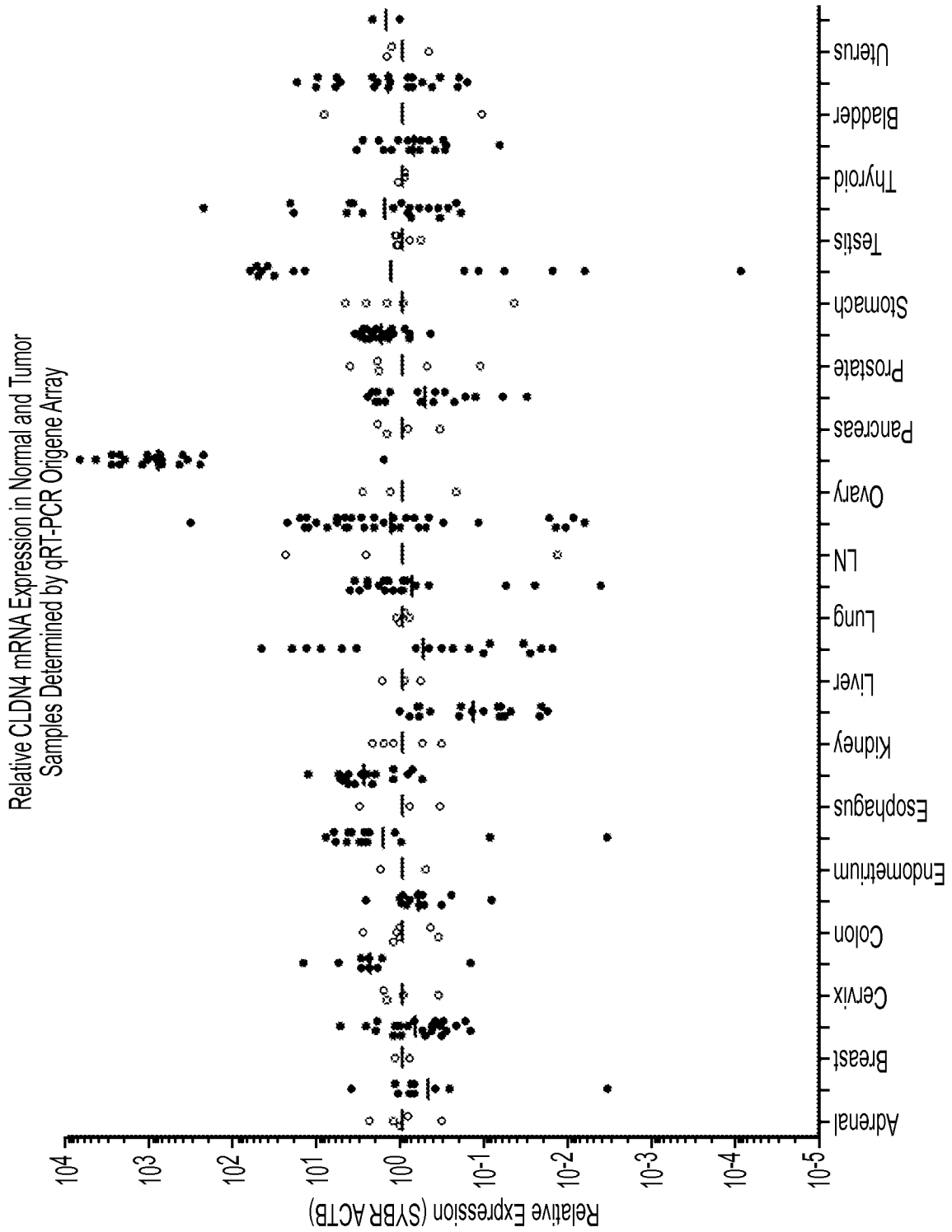

Relative CLDN4 mRNA Expression in Normal and Tumor Samples Determined by qRT-PCR Origene Array
Relative Expression (SYBR ACTB)
10^4
10^3
10^2
10^1
10^0
10^-1
10^-2
10^-3
10^-4
10^-5
Adrenal
Breast
Cervix
Colon
Endometrium
Esophagus
Kidney
Liver
Lung
LN
Ovary
Pancreas
Prostate
Stomach
Testis
Thyroid
Bladder
Uterus

FIG. 2E

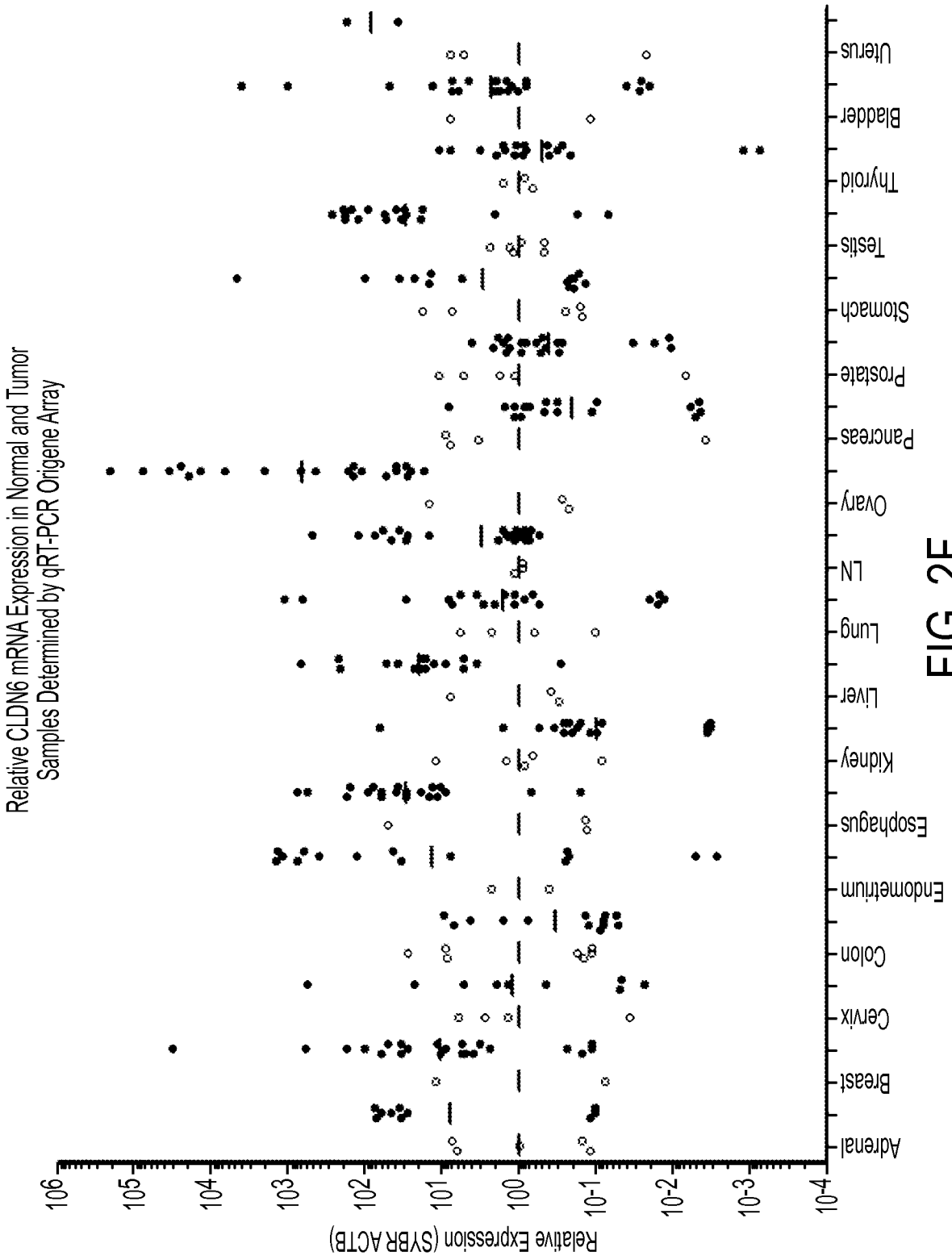

Relative CLDN6 mRNA Expression in Normal and Tumor Samples Determined by qRT-PCR Origene Array
Relative Expression (SYBR ACTB)
10^6
10^5
10^4
10^3
10^2
10^1
10^0
10^-1
10^-2
10^-3
10^-4
Adrenal
Breast
Cervix
Colon
Endometrium
Esophagus
Kidney
Liver
Lung
LN
Ovary
Pancreas
Prostate
Stomach
Testis
Thyroid
Bladder
Uterus

FIG. 2F

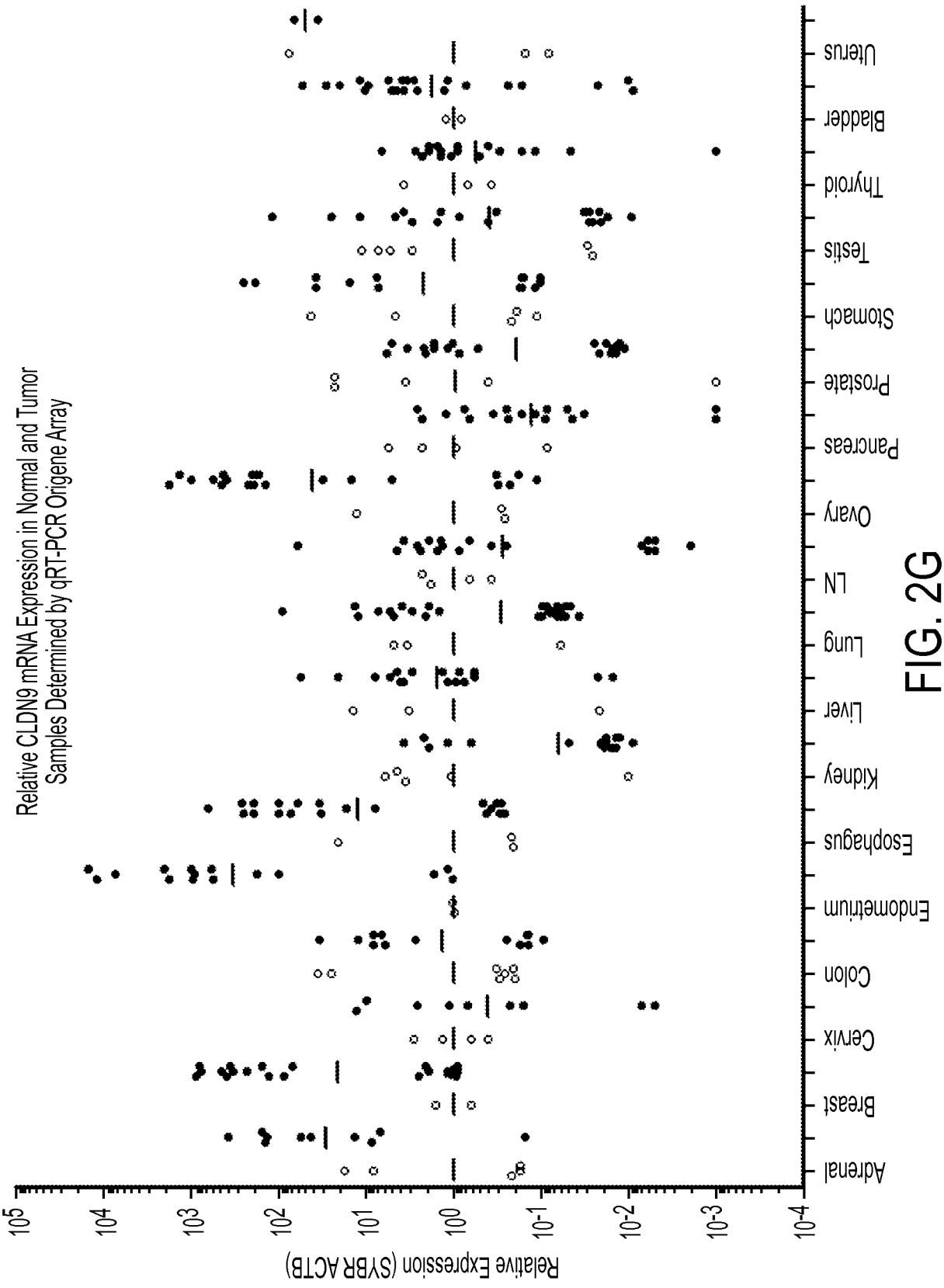

Relative CLDN9 mRNA Expression in Normal and Tumor Samples Determined by qRT-PCR Origene Array
Relative Expression (SYBR ACTB)
10^5
10^4
10^3
10^2
10^1
10^0
10^-1
10^-2
10^-3
10^-4
Adrenal
Breast
Cervix
Colon
Endometrium
Esophagus
Kidney
Liver
Lung
LN
Ovary
Pancreas
Prostate
Stomach
Testis
Thyroid
Bladder
Uterus

FIG. 2G

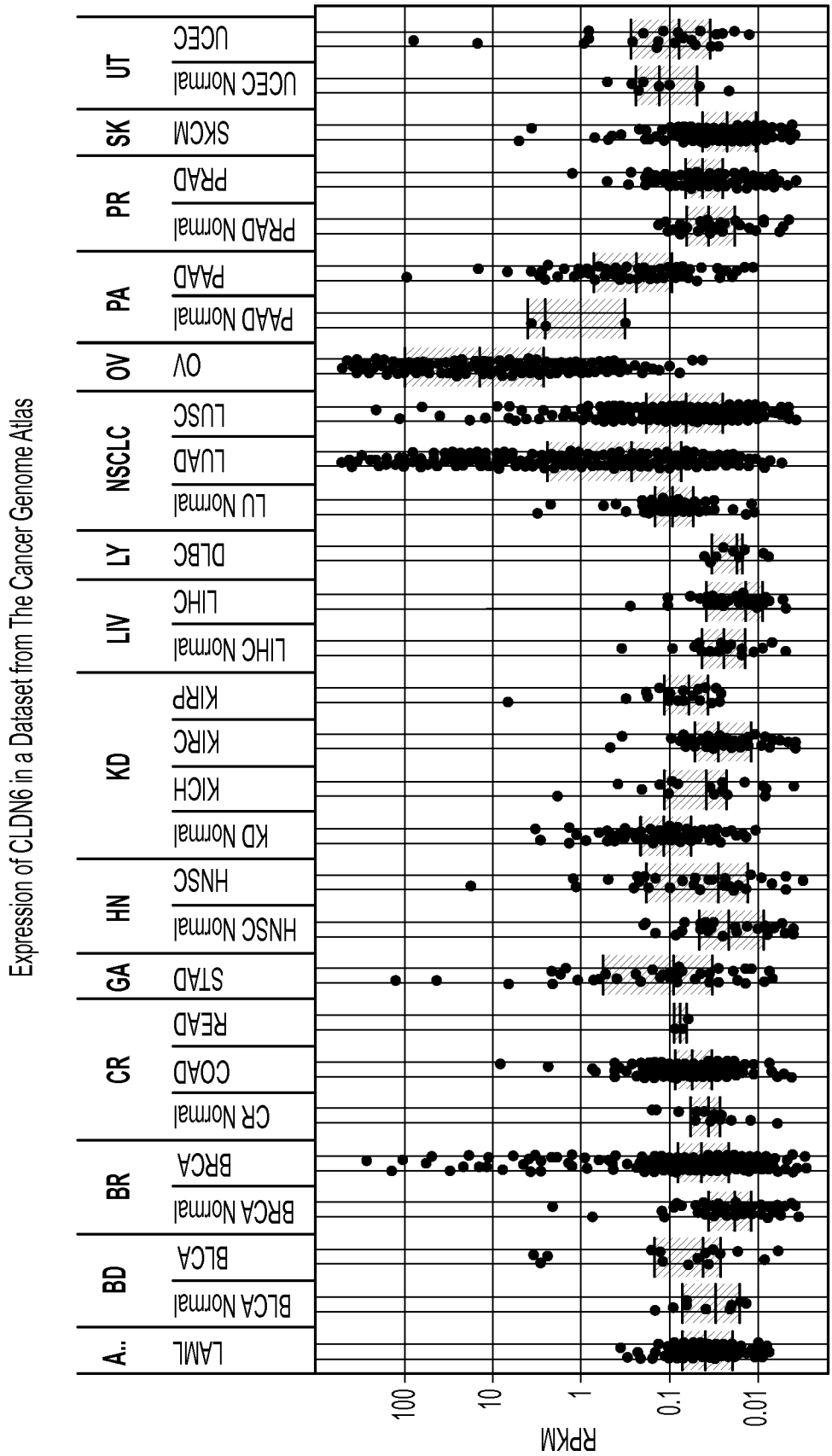

Expression of CLDN6 in a Dataset from The Cancer Genome Atlas
A..
BD
BR
CR
GA
HN
KD
LIV
LY
NSCLC
OV
PA
PR
SK
UT
LAML
BLCA Normal
BLCA
BRCA Normal
BRCA
CR Normal
COAD
READ
STAD
HNSC Normal
HNSC
KD Normal
KICH
KIRC
KIRP
LIHC Normal
LIHC
DLBC
LU Normal
LUAD
LUSC
OV
PAAD Normal
PAAD
PRAD Normal
PRAD
SKCM
UCEC Normal
UCEC
100
10
1
0.1
0.01
RPKM

FIG. 3A

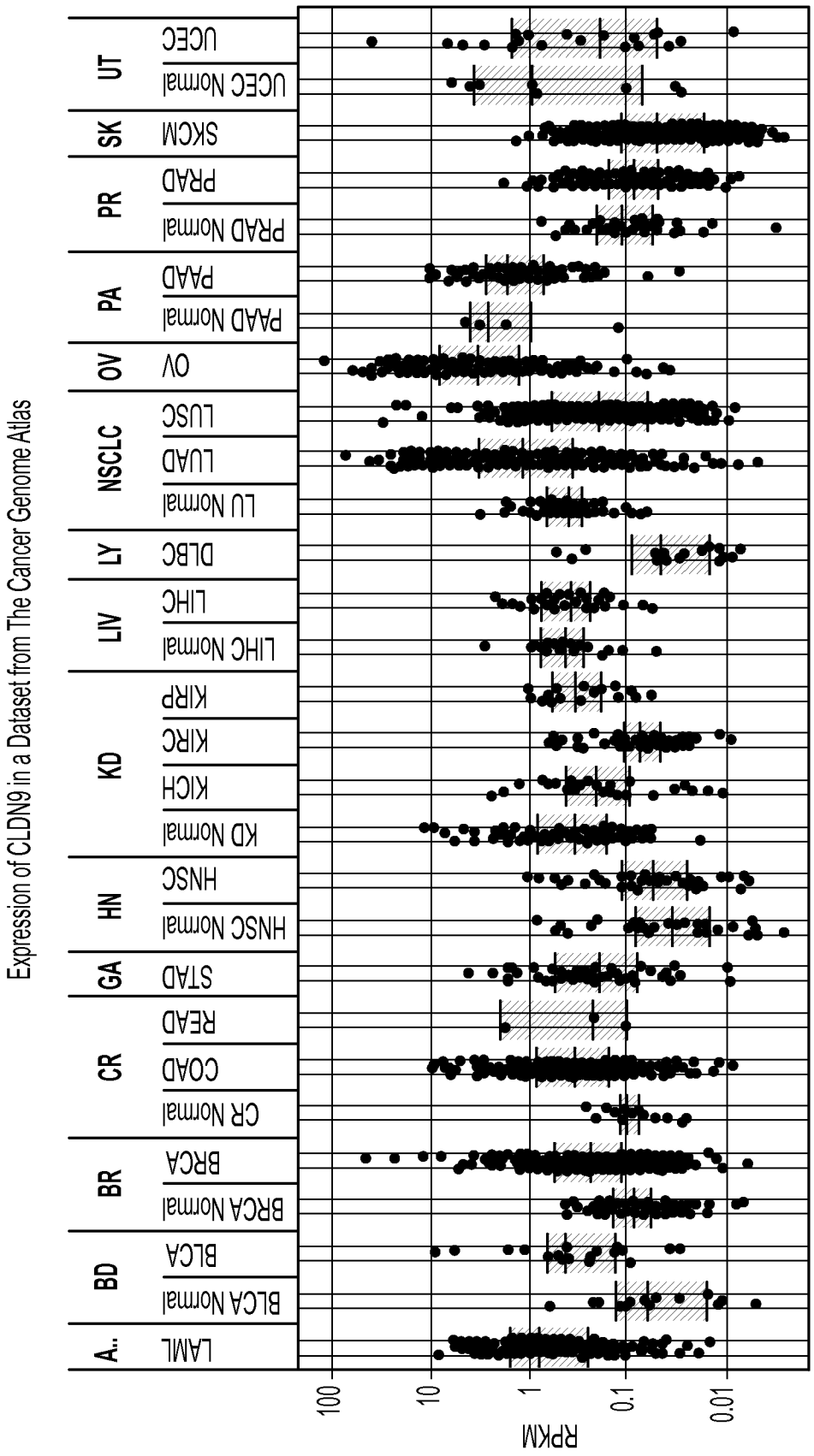

Expression of CLDN9 in a Dataset from The Cancer Genome Atlas
A..
BD
BR
CR
GA
HN
KD
LIV
LY
NSCLC
OV
PA
PR
SK
UT
LAML
BLCA Normal
BLCA
BRCA Normal
BRCA
CR Normal
COAD
READ
STAD
HNSC Normal
HNSC
KD Normal
KICH
KIRC
KIRP
LIHC Normal
LIHC
DLBC
LU Normal
LUAD
LUSC
OV
PAAD Normal
PAAD
PRAD Normal
PRAD
SKCM
UCEC Normal
UCEC
100
10
1
0.1
0.01
RPKM

FIG. 3B

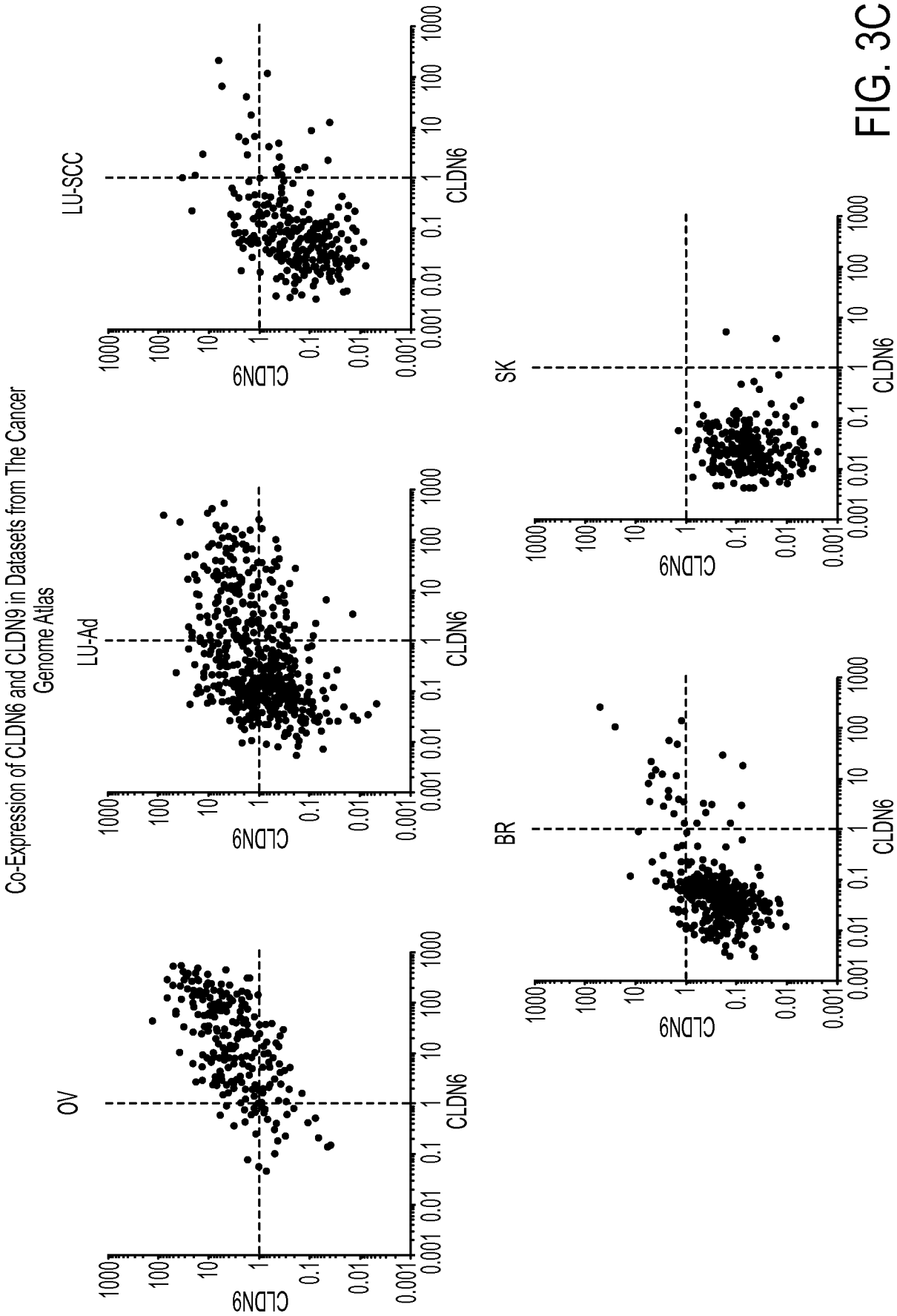

Co-Expression of CLDN6 and CLDN9 in Datasets from The Cancer Genome Atlas
LU-SCC
LU-Ad
SK
OV
BR
CLDN9
CLDN6
1000
100
10
1
0.1
0.01
0.001

FIG. 3C

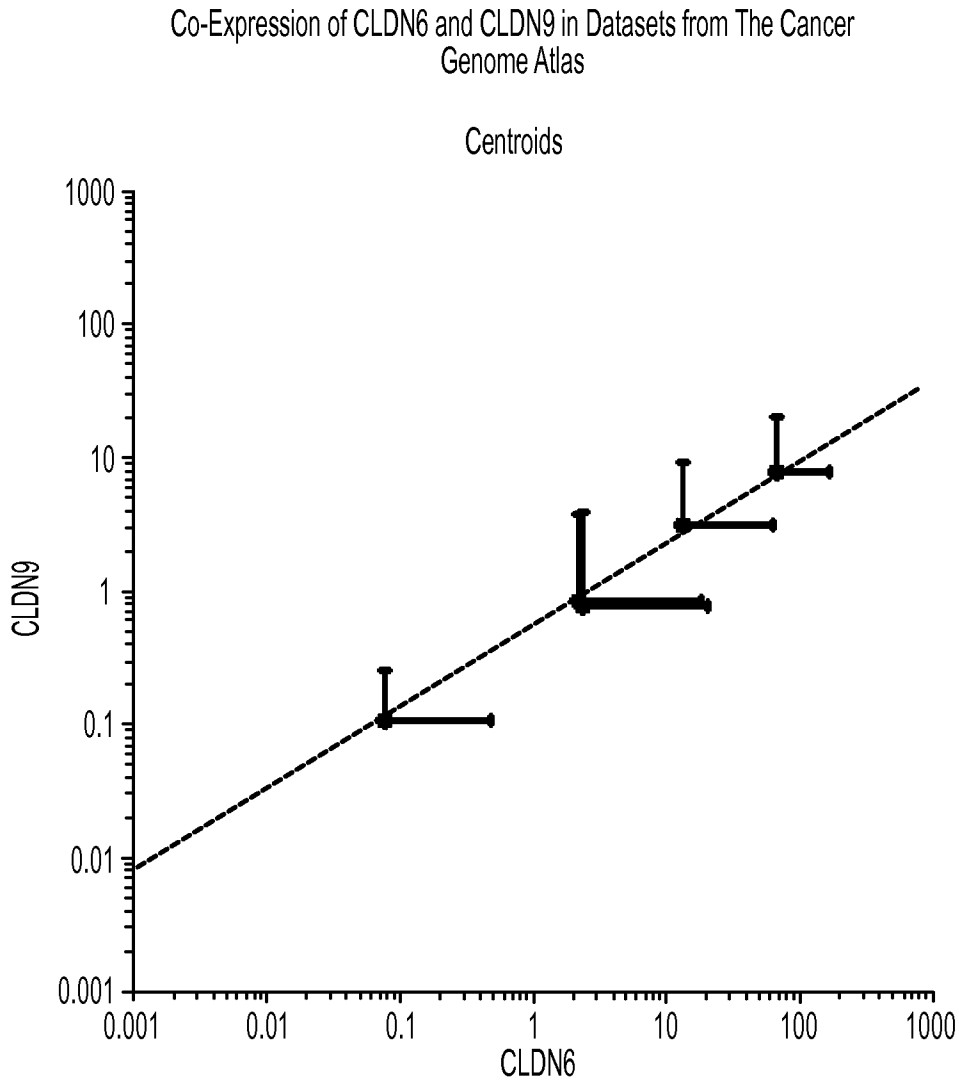

Co-Expression of CLDN6 and CLDN9 in Datasets from The Cancer Genome Atlas
Centroids
CLDN9
1000
100
10
1
0.1
0.01
0.001
0.001
0.01
0.1
1
10
100
1000
CLDN6

FIG. 3D

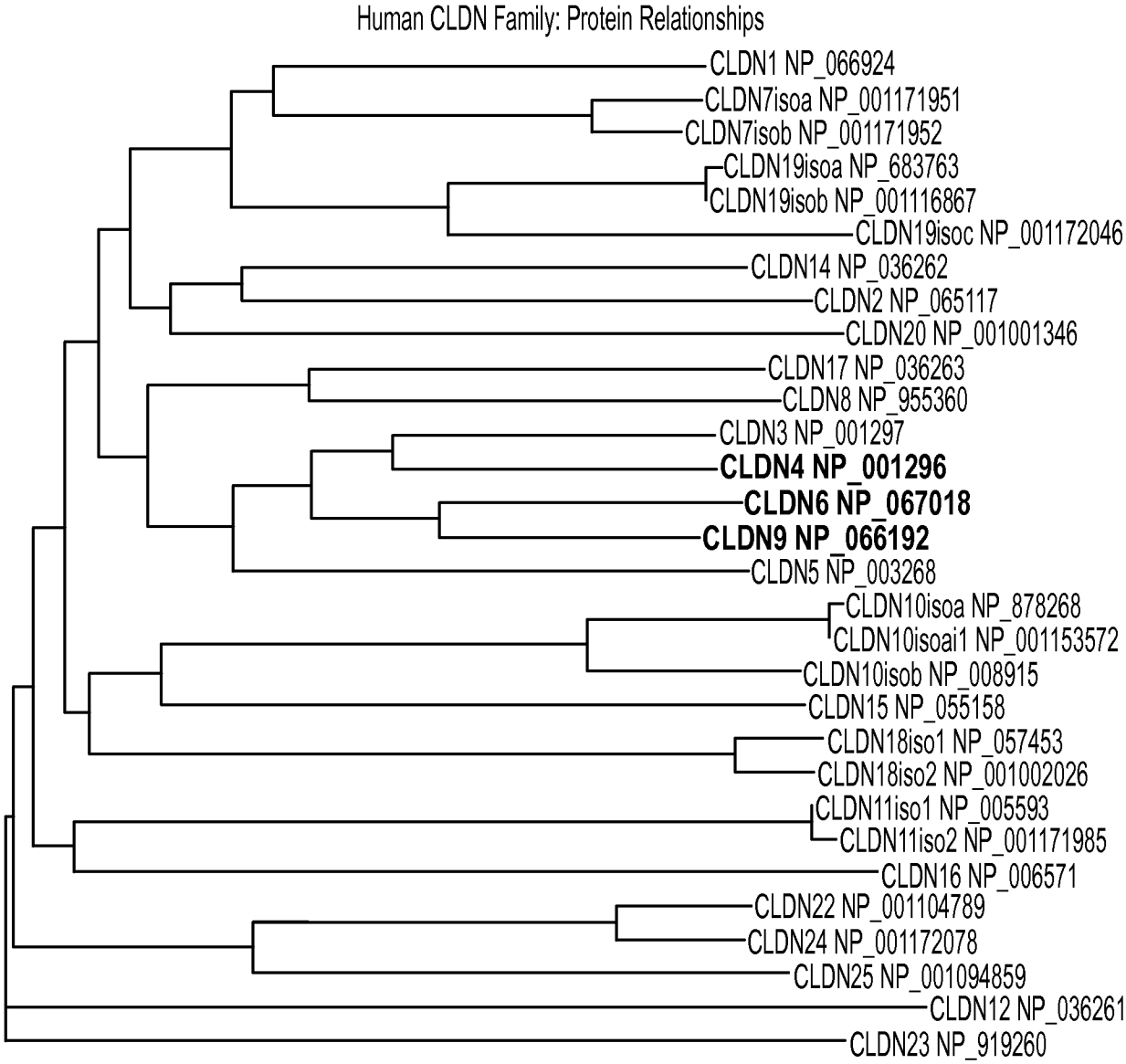

Human CLDN Family: Protein Relationships
CLDN1 NP_066924
CLDN7isoa NP_001171951
CLDN7isob NP_001171952
CLDN19isoa NP_683763
CLDN19isob NP_001116867
CLDN19isoc NP_001172046
CLDN14 NP_036262
CLDN2 NP_065117
CLDN20 NP_001001346
CLDN17 NP_036263
CLDN8 NP_955360
CLDN3 NP_001297
CLDN4 NP_001296
CLDN6 NP_067018
CLDN9 NP_066192
CLDN5 NP_003268
CLDN10isoa NP_878268
CLDN10isoai1 NP_001153572
CLDN10isob NP_008915
CLDN15 NP_055158
CLDN18iso1 NP_057453
CLDN18iso2 NP_001002026
CLDN11iso1 NP_005593
CLDN11iso2 NP_001171985
CLDN16 NP_006571
CLDN22 NP_001104789
CLDN24 NP_001172078
CLDN25 NP_001094859
CLDN12 NP_036261
CLDN23 NP_919260

FIG. 4A

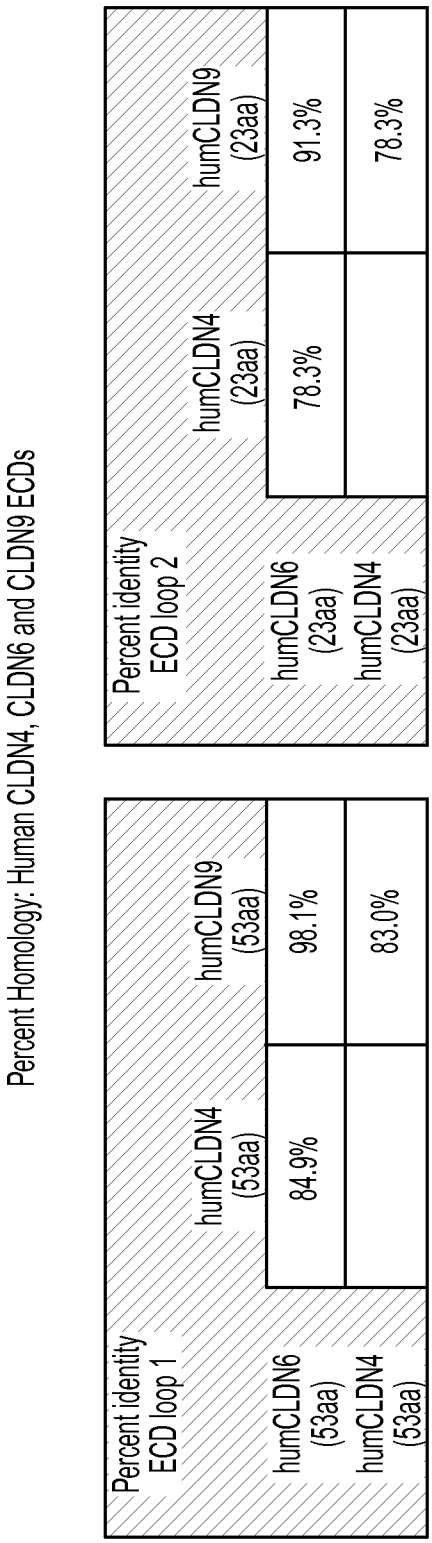

Percent Homology: Human CLDN4, CLDN6 and CLDN9 ECDs
Percent identity ECD loop 1
humCLDN4 (53aa)
humCLDN9 (53aa)
84.9%
98.1%
humCLDN6 (53aa)
83.0%
humCLDN4 (53aa)
Percent identity ECD loop 2
humCLDN4 (23aa)
humCLDN9 (23aa)
78.3%
91.3%
humCLDN6 (23aa)
78.3%
humCLDN4 (23aa)

FIG. 4B

Percent Homology of ECDs for Various CLDN Ortholog Proteins

ECD loop 1	cynoCLDN6	musCLDN6 NP_061247	ratCLDN6 NP_001095834
humCLDN6 NP_067018	100.0%	98.00%	98.00%
musCLDN6 NP_061247			99.00%

ECD loop 2	cynoCLDN6	musCLDN6 NP_061247	ratCLDN6 NP_001095834
humCLDN6 NP_067018	100.0%	86.96%	91.30%
musCLDN6 NP_061247			95.65%

ECD loop 1	cynoCLDN9	musCLDN9 NP_064689	ratCLDN9 NP_001011889
humCLDN9 NP_006192	100.0%	100.0%	100.0%
musCLDN9 NP_064689			100.0%

ECD loop 2	cynoCLDN9	musCLDN9 NP_064689	ratCLDN9 NP_001011889
humCLDN9 NP_006192	100.0%	100.0%	100.0%
musCLDN9 NP_064689			100.0%

ECD loop 1	cynoCLDN4	musCLDN4 NP_034033	ratCLDN4 NP_001012022
humCLDN4 NP_001296	100.0%	92.31%	92.31%
musCLDN4 NP_034033			100.0%

ECD loop 2	cynoCLDN4	musCLDN4 NP_034033	ratCLDN4 NP_001012022
humCLDN4 NP_001296	100.0%	86.96%	91.30%
musCLDN4 NP_034033			95.65%

FIG. 4C

SUBSTITUTE SHEET (RULE 26)

Anti-CLDN Mouse Antibody Light Chain Variable Region Amino Acid Sequences

Name	FR1	CDRL1	FR2	CDRL2	FR3	CDRL3	FR4	SEQ ID NO
SC27.1	DIQMTQSSSSFSVSLGDRVTITC	KASEDIYNRLA	WYQQKPGNAPRLLIS	GATSLET	GTPSRFSGSGSGKDYTLSITSLRTEDAATYYC	QQYWSTPLT	FGTGTKLELK	21
SC27.22	DIVLTQSPASLAVSLGQRATISC	RASQTVSTSSYSYMH	WFQQKPGQPPKLLIK	FASNVES	GVPARFSGSGSGTDFTLNIHPVEEEDISTYYC	QHSWEIPWT	FGGGTKLEIK	25
SC27.103	QIVLTQSPAIMSASLGERVTMTC	TASSSVSSSYLH	WYQQKPGSSPTLWIY	RTSDLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	HQYHRSPWT	FGGGTRLEIK	29
SC27.104	DIQMTQSSSSFSVSLGDRVTITC	KASEDIYNRLA	WYQQKPGNAPRLLIS	GATSLET	GVPSRFSGSGSGKDYTLSITSLQTEDVATYYC	QQYWSNPPT	FGGGTKLEIK	33
SC27.105	DVQMTQSPSSLSASLGERVSLTC	QASQSVSNNLN	WYQQTPGKAPRLLIY	GASKLED	GVSSRFSGTGYGTDFTFTISSLEEEDVATYFC	LQHRYLWT	FGGGTKLEIK	37
SC27.106	DIQMTQSSSSFSVSLGDRVTITC	KASEDIYNRLA	WYQQKPGNAPRLLIC	GATSLET	GVPSRFSGSGSGKDYTLSITSLQTEDVATYYC	QQYWSTPLT	FGAGTKLELK	41
SC27.108	EIVLTQSPALMAASPGEKVTITC	SVSSSISSSNLH	WYQQKSGTSPKLWIY	GTSNLAS	GVPVRFSGSGSGTSYSLTISNMEAEDAATYYC	QQWSSYPHT	FGGGTKLEIK	45
SC27.201	DIQMTQSSSSFSVSLGDRVTITC	KASEDIYNRLA	WYQQKPGNAPRLLIS	GATSLEA	GVPSGFSGSGSGKDYTLSITSLQTEDVATYYC	QQYWSTPPT	FGGGTKLELK	49
SC27.203	DIQMTQSSSSFSVSLGDRVTITC	KASEDIYNRLA	WYQQNPGNTPRLLMS	GATSLET	GVPSRFSGSGSGKDYTLSITSLQIEDVSTYYC	QQYWSTPPT	FGGGTRLEIK	53
SC27.204	DIVMTQSQKFMSTSVGDRVSVAC	KAGQNVGTSVA	WYQQKPGHSPKSLIY	SASYRYS	GVPNRFTGSGSGTDFTLTISNVQSEDLADYFC	QQYITYPYT	FGGGTKLEII	57

FIG. 5A

Anti-CLDN Humanized Antibody Light Chain Variable Region Amino Acid Sequences

Name	FR1	CDRL1	FR2	CDRL2	FR3	CDRL3	FR4	SEQ ID NO
hSC27.1	DIQMTQSPSSVSASVGDRVTITC	KASEDIYNRLA	WYQQKPGKAPKLLIY	GATSLET	GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC	QQYWSTPLT	FGQGTKLEIK	61
hSC27.22	DIVMTQSPDSLAVSLGERATINC	RASQTVSTSSYSYMH	WYQQKPGQPPKLLIY	FASNVES	GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC	QHSWEIPWT	FGQGTKLEIK	65
hSC27.108	EIVLTQSPATLSLSPGERATLSC	SVSSSISSSNLH	WYQQKPGQAPRLLIY	GTSNLAS	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QQWSSYPHT	FGGGTKVEIK	69
hSC27.204	DIQMTQSPSSLSASVGDRVTITC	KAGQNVGTSVA	WFQQKPGKAPKSLIY	SASYRYS	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQYITYPYT	FGGGTKVEIK	73
hSC27.108v1	EIVLTQSPDFQSVTPKEKVTITC	SVSSSISSSNLH	WYQQKPDQSPKLWIY	GTSNLAS	GVPSRFSGSGSGTDFTLTINSLEAEDAATYYC	QQWSSYPHT	FGGGTKVEIK	77

FIG. 5A Cont.

Anti-CLDN Mouse Antibody Heavy Chain Variable Region Amino Acid Sequences

Name	FR1	CDRH1	FR2	CDRH2	FR3	CDRH3	FR4	SEQ ID NO
SC27.1	EVQLQESRPELVKPGASVKISCKTSGYTFT	EYTLH	WVKQSHGKSLEWIG	GINPNNGDTIYNQKFKG	KATLTVDKSSSTAYMELRSLTSEYSAVYYCAR	RAITVYAMDY	WGQGTSVTVSS	23
SC27.22	QVQLQQPGAELVRPGASVKLSCKASGYTFT	SYWMN	WVKQRPGQGLEWIA	MIHPSDSEIRLNQKFKD	KATLTVDRSSSTAYMQLSSPTSEDSAVYYCAR	IDSYYGYLFYFDY	WGQGTTLTVSS	27
SC27.103	EVHLQQSGPELVKPGGSMKISCKASGYSFT	GYTMN	WVKQSHGKNLEWIG	LFNPYNGGTSYNQKFKG	KATLTVDKSSSTAYMELLSLTSEDSAVYYCAR	CYRYDGLDY	WGQGTTLTVSS	31
SC27.104	EVQLQQSGPELVKPGASVKISCKTSGYTFT	EYTVH	WVKQSHGKSLEWIG	GVYPKNGDTTYNQKFRG	KATLTVDKSSNTAYMELRSLTSEDSAVYYCTG	KDGYDGFAY	WGQGTLVTVSA	35
SC27.105	EVQLQQSGPELVKPGASVKISCKASGYSFT	GYYMN	WVKQSPEKSLEWIG	EINPSTGSTTYNQKFKA	KATLTVDKSSSTAYMQLKSLTSEDSAVYYCAR	RDYYYGSGFYAMDY	WGQGTSVTVSS	39
SC27.106	EVQLQQSGPELVKPGASVKISCKTSGYTFT	EYTMH	WVKQSHGKSLEWIG	GINPNNGGTNYNQKFKG	KATLTVDKSSSTAYMELRSLTSEDSAVYYCAR	RLITYYAMDY	WGQGTSVTVSS	43
SC27.108	QVQMQQSGAELVRPGTSVKVSCKASGYAFT	NYLIE	WVKQRPGQGLEWIG	LINPGSGGTNYNEKFKG	KATLTADKSSTTAYMQLSSLTSDDSAVYFCAR	RSPLGSWIYYAYDGVAY	WGQGTLVTVSA	47
SC27.201	EVQLQQSGPELVKPGASVKISCKTSGYTFT	ENIRH	WVKQSRGKSLEWIG	TINPNNGETRYNQKFKG	KATLTVDKSSSTAYMELRSLTSEDSAVYYCTR	GITKSPYGMDY	WGQGTSITVSS	51
SC27.203	EVQLQQSGPELVKPGASVKISCKTSGYTFT	ENIIH	WVKQSHGKSLEWIG	GINPINGGTSYNQKFKG	KATLTVDKSSSTAYMELRSLTSEDSAVYYCAR	GITTSPYAMDY	WGQGTSVTVSS	55
SC27.204	EVKVLESGGGLVQPGGSLKLSCAASGFDFS	RYWMS	WVRQAPGKGLEWIG	EINPDSSTINYTPSLKA	KFIISRDNAKNTLYLQMSKVRSEDTALYYCTG	PAY	WGQGTLVTVSA	59

FIG. 5B

Anti-CLDN Humanized Antibody Heavy Chain Variable Region Amino Acid Sequences

Name	FR1	CDRH1	FR2	CDRH2	FR3	CDRH3	FR4	SEQ ID NO
hSC27.1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	EYTLH	WVRQAPGQRLEWMG	GINPNNGDTIYNQKFKG	RVTITRDTSASTAYMELSSLRSEDTAVYYCAR	RAITVYAMDY	WGQGTLVTVSS	63
hSC27.22	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYWMN	WVRQAPGQRLEWMG	MIHPSDSEIRLNQKFKD	RVTITRDTSASTAYMELSSLRSEDTAVYYCAR	IDSYYGYLFYFDY	WGQGTTVTVSS	67
hSC27.108	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	NYLIE	WVRQAPGQGLEWMG	LINPGSGGTNYNEKFKG	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR	RSPLGSWIYYAYDGVAY	WGQGTLVTVSS	71
hSC27.204	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	75
hSC27.22 - VH1-8	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYWMN	WVRQATGQGLEWMG	MIHPSDSEIRLNQKFKD	RVTMTRNTSISTAYMELSSLRSEDTAVYYCAR	IDSYYGYLFYFDY	WGQGTTVTVSS	79
hSC27.22 - VH1-46	QVQLVQSGAEVKKPGASVKVSCKASGYTFT	SYWMN	WVRQAPGQGLEWMG	MIHPSDSEIRLNQKFKD	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR	IDSYYGYLFYFDY	WGQGTTVTVSS	81
hSC27.22 - VH1-69	QVQLVQSGAEVKKPGSSVKVSCKASGGTFS	SYWMN	WVRQAPGQGLEWMG	MIHPSDSEIRLNQKFKD	RVTITADESTSTAYMELSSLRSEDTAVYYCAR	IDSYYGYLFYFDY	WGQGTTVTVSS	83
hSC27.204v1	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIKYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	85
hSC27.204v2	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIQYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	87
hSC27.204v3	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYNPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	89
hSC27.204v4	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	91

FIG. 5B Cont.

Anti-CLDN Humanized Antibody Heavy Chain Variable Region Amino Acid Sequences

Name	FR1	CDRH1	FR2	CDRH2	FR3	CDRH3	FR4	SEQ ID NO
hSC27.204v5	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIKYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	93
hSC27.204v6	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIQYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	95
hSC27.204v7	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYNPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCTG	PAY	WGQGTLVTVSS	97
hSC27.204v8	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	99
hSC27.204v9	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIKYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	101
hSC27.204v10	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIQYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	103
hSC27.204v11	EVQLLESGGGLVQPGGSLRLSCAASGFTFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYNPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	105
hSC27.204v12	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	107
hSC27.204v13	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIKYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	109
hSC27.204v14	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTIQYTPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	111
hSC27.204v15	EVQLLESGGGLVQPGGSLRLSCAASGFDFS	RYWMS	WVRQAPGKGLEWVS	EINPDSSTINYNPSLKA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAG	PAY	WGQGTLVTVSS	113

FIG. 5B Cont.

Anti-CLDN Mouse Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
SC27.1	Light Chain	GACATCCAGATGACACAATCTTCATCCTCCTTTTCTGTATCTCTAGGAGACAGAGTCACCATTACTTGCAAGGCAAGTGAAGACATATATAATCGGTTAGCCTGGTATCAGCAGAAACCAGGAAA TGCTCCCAGGCTCTTAATATCTGGTGCAACCAGTTTGGAAACTGGGACTCCTTCAAGATTCAGTGGCAGTGGATCTGGAAAGGATTACACTCTCAGTATTACCAGTCTTCGGACTGAAGATGCTG CTACTTATTACTGTCAACAATATTGGAGTACTCCACTCACGTTCGGTACTGGGACCAAGCTGGAGCTGAAA	20
SC27.1	Heavy Chain	GAGGTCCAGCTGCAAGAGTCTAGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGACTTCTGGATACACATTCACTGAATACACCTTGCACTGGGTGAAGCAGAGTCATGG AAAGAGCCTTGAGTGGATTGGAGGTATTAATCCTAACAATGGTGATACTATCTACAACCAGAAATTCAAGGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCC GCAGCCTGACATCTGAATATTCTGCAGTCTATTACTGTGCAAGAAGGGCGATTACGGTCTATGCTATGGACTACTGGGGTCAAGGTACCTCAGTCACCGTCTCCTCA	22
SC27.22	Light Chain	GACATTGTGCTGACACAGTCTCCTGCTTCCTTAGCTGTATCTCTGGGGCAGAGGGCCACCATCTCATGCAGGGCCAGCCAGACTGTCAGTACATCTAGCTATAGTTATATGCACTGGTTCCAACA GAAACCAGGACAGCCACCCAAACTCCTCATCAAGTTTGCATCCAACGTAGAATCTGGGGTCCCTGCCAGATTCAGTGGCAGTGGGTCTGGGACAGACTTCACCCTCAACATCCATCCTGTGGAGG AGGAGGATATTTCAACATATTACTGTCAGCACAGTTGGGAGATTCCGTGGAGGCACCAAGCTGGAAATCAAA	24
SC27.22	Heavy Chain	CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTGGTGAGGCCTGGAGCTTCAGTGAAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACCAGCTACTGGATGAACTGGGTGAAGCAGAGGCCTGG ACAAGGCCTTGAATGGATTGGCCATGATTCATCCTTCCGATAGTGAAATTAGGTTAAATCAGAAGTTCAAGGACAAGGCCACATTGACTGTAGACAGATCCTCCAGCACAGCCTACATGCAACTCA GCAGCCCGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAATTGATAGTTATTATGGTTACCTGTTTTACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA	26
SC27.103	Light Chain	CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCTAGGGGAACGGGTCACCATGACCTGCAGCTCAAGTGTAAGTTCCAGTTACTTGCACTGGTACCAGCAGAAGCCAGG ATCCTCCCCCACACTCTGGATTTATAGGACATCCGACCTGGCTTCTGGAGTCCCAGCTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTACTCTCTCACAATCAGCAGCATGGAGGCTGAAGATG CTGCCACTTATTACTGCCAACCAGTATCATCGTTCCCCGTGGACGTTCGGTGGAGGCACCAGGCTGGAAATCAAA	28
SC27.103	Heavy Chain	GAGGTCCACCTGCAACAGTCTGGACCTGAGCTAGTGAAGCCTGGAGGTTCAATGAAGATATCCTGCAAGGCTTCTGGTTACTCATTCACTGGCTACACCATGAACTGGGTGAAGCAGAGGCCATGG AAAGAACCTTGAGTGGATTGGACTTTTTAATCCTTACAATGGTGGTACTAGTTATAACCAGAAGTTCAAGGGCAAGGCCACATTAACTGTAGACAAGTCATCCAGCACAGCCTACATGGAGCTCC TCAGTCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCAAGATGCTATAGGTACGACGGTCTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA	30

FIG. 5C

Anti-CLDN Mouse Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
SC27.104	Light Chain	GACATCCAGATGACACAATCTTCATCCTCCTTTTCTGTATCTCTAGGAGACAGAGTCACCATTACTTGCAAGGCAAGTGAGGACATATATAATCGGTTAGCCTGGTATCAGCAGAAACCAGGAAA TGCTCCCAGGCTCTTAATATCTGGTGCAACCAGTTTGGAAACTGGGGTTCCTTCAAGATTCAGTGGCAGTGGATCTGGAAAGGATTACACTCTCAGCATTACCAGTCTTCAGACTGAAGATGTTG CTACTTATTACTGTCAACAGTATTGGAGTAATCCTCCGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAA	32
SC27.104	Heavy Chain	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGACTTCTGGATACACATTCACTGAATACACCGTGCACTGGGTGAAGCAGAGCCATGG AAAGAGCCTTGAGTGGATTGGAGGTGTTTATCCTAAGAATGGTGATACTACCTACAACCAGAAGTTCAGGGGCAAGGCCACACTTGACTGTAGACAAGTCCTCCAACACAGCCTATATGGAACTCC GCAGCCTGACATCTGAGGATTCTGCAGTCTATTACTGTACAGGAAAGGATGGGTACGACGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA	34
SC27.105	Light Chain	GATGTTCAAATGACCCAGTCTCCATCCTCCCTGTCTGCATCTTTGGGAGAGAAGAGTCTCCCTGACTTGCCAGGCAAGTCAGAGTGTTAGCAATAATTTAAACTGGTATCAGCAAACACCAGGGAA AGCTCCTAGGCTCTTGATCTATGGTGCAAGCAAATTGGGAAGATGGGGTCTCTTCAAGGTTCAGTGGCACTGGATATGGGACAGATTTCACTTTCACCATCAGCAGCCTGGAGGAAGAATGTGG CAACTTATTTTTGTCTACAGCATAGGTATCTGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAA	36
SC27.105	Heavy Chain	GAGGTCCAGCTGCAGCAGTCTGGACCTGAGTTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGGCTTCTGGTTACTCATTCACTGGCTACTACATGAACTGGGTGAAGCAAAGTCCTGA AAAGAGCCTTGAGTGGATTGGAGAGATTAATCCTAGCACTGGTAGTACTACTTACAACCAGAAGTTCAAGGGCCACATTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAGCTCA AGAGCCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCAAGAAGGGATTATTACTACGGTAGTGGTTTCTATGCTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	38
SC27.106	Light Chain	GACATCCAGATGACACAATCTTCATCCTCCTTTTCTGTATCTCTAGGAGACAGAGTCACCATTACTTGCAAGGCAAGTGAGGACATATATAATCGGTTAGCCTGGTATCAGCAGAAACCAGGAAA TGCTCCTAGGCTCTTAATATGTGGTGCAACCAGTTTGGAAACTGGGGTTCCTTCAAGATTCAGTGGCAGTGGATCTGGAAAGGATTACACTCTCAGCATTACCAGTCTTCAGACTGAAGATGTTG CTACTTATTACTGTCAACAGTATTGGAGTACTCCGCTCACGTTCGGTGCTGGGACCAAACTGGAGCTGAAA	40
SC27.106	Heavy Chain	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGACTTCTGGATACACATTCACTGAATACACCATGCACTGGGTGAAGCAGAGCCATGG AAAGAGCCTTGAGTGGATTGGAGGTATTAATCCTAACAATGGTGGTACTAACTACAACCAGAAGTTCAAGGGCAAGGCCACACTTGACTGTTGACAAGTCCTCCAGCACAGCCTACATGGAGCTCC GCAGCCTGACATCTGAGGATTCTGCAGTCTATTACTGTGCAAGAAGGCTTATTACTTACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	42

FIG. 5C Cont.

Anti-CLDN Mouse Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
SC27.108	Light Chain	GAAATTGTGCTCACCCAGTCTCCAGCACTCATGGCTGCATCTCCAGGGGAGAAGGTCACCATCACCTGCAGTGTCAGCTCAAGTATAAGTTCCAGCAACTTGCACTGGTACCAGCAGAAGTCAGG AACCTCCCCCAAACTCTGGATTTATGGCACATCCAACCTGGCTTCTGGAGTCCCTGTTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTATTCTCTCACAATCAGCAACATGGAGGCTGAAGATG CTGCCACTTATTACTGTCAACAGTGGAGTAGTTACCCACACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA	44
SC27.108	Heavy Chain	CAGGTCCAAATGCAGCAGTCTGGAGCTGAGCTGGTAAGGCCTGGGACTTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACGCCTTCACTAATTACTTGATAGAGTGGGTAAAGCAGAGGCCTGG ACAGGGCCTTGAGTGGATTGGACTGATTAATCCTGGAAGTGGTGGTACTAATTACAATGAGAAGTTCAAGGGCAAGGCAACACTGACTGCAGACAAATCCTCCACCACTGCCTACATGCAGCTCA GCAGCCTGACATCTGATGACTCTGCGGTTTATTTCTGTGCAAGACGGTCCCCTCTAGGGAGTTGGATCTACTATGCTTACGACGGTGTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCT GCA	46
SC27.201	Light Chain	GACATCCAGATGACACAATCTTCATCCTCCTTTTCTGTCTCTCTGGGAGACAGAGTCACTATTACTTGCAAGGCAAGTGAGGACATCTATAATCGGTTAGCCTGGTATCAACAGAAACCAGGAAA TGCTCCTAGGCTCTTAATATCTGGTGCAACCAGTTTGGAAGCTGGGGTTCCTTCAGGATTCAGTGGCAGTGGATCTGGAAAGGATTACACTCTCAGCATTACCAGTCTTCAGACTGAAGATGTTG CTACTTATTACTGTCAACAGTATTGGAGTACTCCTCCGACGTTCGGTGGAGGCACCAAGCTGGAACTCAAG	48
SC27.201	Heavy Chain	GAGGTCCAGCTGCAACAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGACTTCTGGATACACATTCACTGAAAACATCAGACACTGGGTGAAGCAGAGCCGAGG AAAGAGCCTTGAGTGGATTGGTACTATTAATCCTAATAATGGTGAGACTAGGTACAATCAGAAGTTCAAGGGCAAGGCCACACTTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCC GCAGCCTGACATCTGAGGATTCTGCAGTCTATTACTGTACAAGGGGGATTACAAAGTCCCCTTATGGTATGGACTACTGGGGTCAAGGAACCTCAATCACCGTCTCCTCA	50
SC27.203	Light Chain	GACATCCAGATGACACAATCTTCATCCTCCTTTTCTGTATCTCTAGGAGACAGAGTCACCATCACTTGCAAGGCAAGTGAGGACATATATAATCGGTTAGCCTGGTATCAGCAGAATCCAGGAAA TACTCCTAGGCTCTTAATGTCTGGTGCAACCAGTTTGGAAACTGGGGTTCCTTCAAGATTCAGTGGCAGTGGATCTGGAAAGGATTACACTCTCAGCATTACCAGTCTTCAGATTGAAGATGTTT CTACTTATTACTGTCAACAATATTGGAGTACTCCTCCGACGTTCGGTGGAGGCACCAGGCTGGAAATCAAA	52
SC27.203	Heavy Chain	GAGGTCCAGCTGCAACAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTGCAAGACTTCTGGATACACATTCACTGAAAACATCATACACTGGGTGAAGCAGAGCCATGG AAAGAGCCTTGAGTGGATTGGAGGTATTAATCCTATCAATGGTGGTACTAGCTACAACCAGAAGTTCAAGGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCC GTAGCCTGACATCTGAGGATTCTGCAGTCTATTACTGTGCAAGGGGGATTACTACGTCCCCTTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	54
SC27.204	Light Chain	GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCAGCGTCGCCTGCAAGGCCGGTCAGAATGTGGGTACTAGTGTAGCCTGGTATCAACAGAAACCAGGACA TTCTCCTAAATCACTGATTTACTCGGCATCCTACCGGTACAGTGGAGTCCCTAATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAATGTGCAGTCTGAAGACTTGG CAGACTATTTCTGTCAGCAATATATCACCTATCCGTACACGTTCGGAGGGGGGACCAAGCTGGAAATAATA	56
SC27.204	Heavy Chain	GAGGTGAAGGTTCTCGAGTCTGGAGGTGGCCTGGTGCAGCCTGGAGGATCCCTGAAACTCTCCTGTGCAGCCTCAGGATTCGATTTTAGTAGATACTGGATGAGTTGGGTCCGGCAGGCTCCAGG GAAAGGCCTAGAATGGATTGGAGAAATTAATCCAGATAGCAGTACGATAAACTATACGCCATCTCTAAAGGCTAAATTCATCATCTCCAGAGACAACGCCAAAAATACGCTGTACCTGCAAATGA GCAAAGTGAGATCTGAGGACACAGCCCTTTATTACTGTACAGGACCAGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA	58

FIG. 5C Cont.

Anti-CLDN Humanized Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
hSC27.1	Light Chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTAAGGCGAGTGAGGATATTTACAACCGGTTAGCCTGGTATCAGCAGAAACCA GGGAAAGCCCCTAAGCTCCTGATCTATGGTGCAACCAGTTTGGAAACTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTACACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGTATTGGAGTACTCCACTCACGTTCGGTCAAGGGACCAAGCTGGAGATTAAA	60
hSC27.1	Heavy Chain	CAGGTCCAGCTTGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGGCTTCTGGATACACCTTCACTGAGTATACTCTGCATTGGGTGCGCCAGGCC CCCGGACAAAGGCTTGAGTGGATGGGAGGGATCAACCCTAACAATGGTGACACAATATATAACCAGAAGTTCAAGGGCAGAGTCACCATTACCAGGGACACATCCGCGAGCACAGCCTAC ATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTGTATTACTGTGCGAGAAGGGCGATTACGGTCTATGCTATGGACTACTGGGGTCAAGGTACCCTAGTCACCGTCTCGAGC	62
hSC27.22	Light Chain	GACATTGTCATGACCCAGTCCCCTGACAGTTTGGCCGTTAGCTTGGGGGAGCGTGCCACCATCAACTGTAGGGCTAGTCAAACTGTTTCTACATCCTCCTACTCTTACATGCATTGGTAT CAGCAGAAACCTGGTCAGCCTCCAAAACTGCTGATTTATTTCGCATCTAACGTCGAGTCCGGAGTTCCTGACCGGTTCAGCGGATCAGGAAGCGGTACAGATTTTACACTTACCATCTCA TCTCTGCAAGCAGAAGATGTGGCCGTGTACTATTGTCAGCATTCCTGGGAGATCCCCTGGACCTTCGGGCAGGGAACCAAGCTCGAGATTAAA	64
hSC27.22	Heavy Chain	CAGGTGCAGTTGGTGCAGAGGCGGCGCCGAAGTCAAGAAACCAGGAGCTTCTGTCAAAGTCTCCTGTAAAGCCTCCGGATATACCTTCACCAGCTACTGGATGAATTGGGTAAGACAGGCC CCCGGACAGAGGCTTGAGTGGATGGGAATGATCCATCCTCTGACAGCGAGATTCGGCTCAACCAGAAGTTTAAAGACCGAGTGACTATCACAGCGGATACCAGTGCTAGCACAGCCTAC ATGGAGTTGAGTTCTCTTCGTAGCGAGGACACTGCCGTGTATTATTGCGCCCGCATCGACTCATATTATGGTTATCTGTTCTACTTCGACTATTGGGGCCAGGGGACCACCGTGACTGTG TCTTCC	66
hSC27.108	Light Chain	GAAATCGTGCTTACACAATCCCCTGCCACTCTGAGCCTTTCTCCAGGCGAGCGAGCAACCCTTTCCTCTGCAGTGTTTCCTCTTCAATCAGTTCCAGCAATTTGCACTGGTACCAGCAGAAG CCTGGTCAGGCACCCCGATTGTTGATCTATGGCACATCTAACCTGGCCAGCGGCATCCCTGCTCGGTTCAGTGGATCTGGCTCCGGAACAGATTTCACTCTCACTATCAGCTCCCTTGAG CCTGAAGATTTTGCCGTGTACTACTGTCAGCAATGGAGTTCCTACCCCCACACCTTTGGCGGCGGGACAAAGGTCGAGATAAAA	68
hSC27.108	Heavy Chain	CAGGTACAGCTGGTCCAGTCCGGCGCTGAGGTTAAGAAGCCCGGTGCCTCCGTGAAGGTATCTTGTAAGGCCTCAGGTTACACCTTTACAAATTATCTGATCGAATGGGTGAGACAGGCC CCAGGTCAGGGTCTGGAATGGATGGGACTCATCAACCCTGGGGAGTGGCGGGGACCAACTACAACGAAAAGTTTAAGGGGAGAGTGACAATGACCAGTACCTCCACCGCATAT ATGGAGCTGCGAAGCTTGAGGTCCGATGACACTGCTGTGTACTATTGCGCCCGTAGAAGCCCACTCGGGTCTTGGATCTATTACGCATACGATGGTGTGGGCCTATTGGGGCCAGGGCACC CTGGTGACAGTCAGCTCC	70
hSC27.204	Light Chain	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGTGGGCGACAGAGTGACCATCACATGCAAGGCCGGCCAGAACGTGGGCACCTCTGTGGCCTGGTTCCAGCAGAAGCCT GGCAAGGCCCCCAAGTCCCTGATCTACTCCGCGCGTCCCCTCCAGATTCTCCGGCTCTGGCTCTGGCACCGACTTTACCCTGACCATCAGCTCCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGTACATCACCTACCCCTACACCTTCGGCGGAGGCACCAAGGTGGAAATCAAG	72
hSC27.204	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTACCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	74

FIG. 5C Cont.

Anti-CLDN Humanized Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
hSC27.108v1	Light Chain	GAAATCGTGCTGACTCAGTCTCCCGATTTCCAGTCCGTCACACCCAAGGAGAAAGTCACCATCACTTGTTCTGTCTCCTCCAAGCATCTCTTCTAGTAACCTGCACTGGTATCAGCAGAAG CCTGATCAGTCCCCTAAGCTTTGGATATACGGCACCTCAAACCTGCCTCCGGAGTTCCTTCAAGGTTTTCAGGTAGTGGATCTGGAACCGATTTCACCCTTACAATAAACAGTCTTGAG GCCGAGGACGCCGCCACTTACTACTGCCAGCAGTGGAGTTCTTACCCCCACACATTTGGGGGCGGCACCAAAGTGGAGATCAAA	76
hSC27.22 - VH1 - 8	Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACACCTTTACCAGCTACTGGATGAACTGGGTGCGACAGGCT ACCGGCCAGGGCCTGGAATGGATGGGCATGATCGACTCCGAGATCCGGCTGAACCAGAAATTCAAGGACAGAGTGACCATGACCCGGAACACCTCCATCTCCACCGCCTAC ATGGAACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTACTGCGCCCGGATCGACTCCTACTACGGCTACCTGTTCTACTTCGACTACTGGGGCCAGGGCACCACCGTGACCGTG TCATCT	78
hSC27.22 - VH1 - 46	Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCTGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCTACACCTTTACCAGCTACTGGATGAACTGGGTGCGACAGGCC CCTGGACAGGGCCTGGAATGGATGGGCATGATCGACTCCGAGATCCGGCTGAACCAGAAATTCAAGGACCGCGTGACCATGACCCGGGACACCTCCATCTCCACCGCCTAC ATGGAACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTACTGCGCCCGGATCGACTCCTACTACGGCTACCTGTTCTACTTCGACTACTGGGGCCAGGGCACCACCGTGACCGTG TCATCT	80
hSC27.22 - VH1 - 69	Heavy Chain	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCCGGCTCCTCCGTGAAGGTGTCCTGCAAGGCTTCCGGCGGCACCTTCTCCAGCTACTGGATGAACTGGGTGCGACAGGCC CCTGGACAGGGCCTGGAATGGATGGGCATGATCGACTCCGAGATCCGGCTGAACCAGAAATTCAAGGACAGAGTGACCATCACCGCCGACGAGTCCACCTCCACCGCCTAC ATGGAACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTACTGCGCCCGGATCGACTCCTACTACGGCTACCTGTTCTACTTCGACTACTGGGGCCAGGGCACCACCGTGACCGTG TCATCT	82
hSC27.204v1	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAAGTACACCCCCAGCCTGAAGGACCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCAGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	84
hSC27.204v2	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCCAGTACACCCCCAGCCTGAAGGACCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCAGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	86
hSC27.204v3	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCCAGCCTGAAGGACCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCAGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	88

FIG. 5C Cont.

Anti-CLDN Humanized Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
hSC27.204v4	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTACCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	90
hSC27.204v5	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAAGTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTACCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	92
hSC27.204v6	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAGTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTACCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	94
hSC27.204v7	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTACCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	96
hSC27.204v8	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	98
hSC27.204v9	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAAGTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	100
hSC27.204v10	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAGCTACACCCCCAGCCTGAAGGACCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	102

FIG. 5C Cont.

Anti-CLDN Humanized Antibody Variable Region Nucleic Acid Sequences

Name	Chain	Nucleic Acid Sequence	SEQ ID NO
hSC27.204v11	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	104
hSC27.204v12	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	106
hSC27.204v13	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	108
hSC27.204v14	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCCAGTACACCCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	110
hSC27.204v15	Heavy Chain	GAAGTGCAGCTGCTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCTCCGGCTTCGACTTCTCCCGGTACTGGATGTCCTGGGTGCGACAGGCT CCTGGCAAGGGCCTGGAATGGGTGTCCGAGATCAACCCCGACTCCTCCACCATCAACTACACCCCAGCCTGAAGGCCCGGTTCACCATCTCTCGGGACAACTCCAAGAACACCCTGTAC CTGCAGATGAACTCCCTGCGGGCCGAGGACACCGCCGTGTACTACTGTGCCGGCCCTGCTTATTGGGGCCAGGGCACCCTCGTGACCGTGTCCTCT	112

FIG. 5C Cont.

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.1	Light Chain	DIQMTQSPSSVSASVGDRVTITCKASEDIYNRLAWYQQKPGKAPKLLIYGATSLETGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQYWSTPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	114
hSC27.1	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTLHWVRQAPGQRLEWMGGINPNNGDTIYNQKFKGRVTITRDTSASTAYMELSSLRSEDTAVYYCARRAITVYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG	115
hSC27.22	Light Chain	DIVMTQSPDSLAVSLGERATINCRASQTVSTSSYSYMHWYQQKPGQPPKLLIYFASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSWEIPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	116
hSC27.22	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	117
hSC27.108	Light Chain	EIVLTQSPATLSLSPGERATLSCSVSSSISSSNLHWYQQKPGQAPRLLIYGTSNLASGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQWSSYPHTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	118
hSC27.108	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYLIEWVRQAPGQGLEWMGLINPGSGGTNYNEKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARRSPLGSWIYYAYDGVAYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	119
hSC27.204	Light Chain	DIQMTQSPSSLSASVGDRVTITCKAQNVGTSVAWFQQKPGKAPKSLIYSASYRYSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYITYPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	120
hSC27.204	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	121

FIG. 5D

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.22ss1	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	122
hSC27.22 - VH1 - 8	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQATGQGLEWMGMIHPSDSEIRLNQKFKDRVTMTRNTSISTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	123
hSC27.22 - VH1 - 46	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGMIHPSDSEIRLNQKFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	124
hSC27.22 - VH1 - 69	Heavy Chain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYWMNWVRQAPGQGLEWMGMIHPSDSEIRLNQKFKDRVTITADESTSTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	125
hSC27.22 IgG2	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG	126

FIG. 5D Cont.

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.22 IgG4 R409K	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	127
hSC27.22 IgG4 S228P	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	128
hSC27.22 IgG4 S228P K370E R409K	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	129
hSC27.22 IgG4 K370E	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	130
hSC27.22 IgG4 S228P K370E	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	131
hSC27.22 IgG4 C127S S228P	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	132

FIG. 5D Cont.

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.22 IgG4 C127S K370E	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	133
hSC27.22 IgG4 C127S S228P K370E	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQRLEWMGMIHPSDSEIRLNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARIDSYYGYLFYFDYWGQGTTVTVSSASTKGPSVFPLAPSSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVEGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSLSLG	134
hSC27.108v1	Light Chain	EIVLTQSPDFQSVTPKEKVTITCSVSSSISSSNLHWYQQKPDQSPKLWIYGTSNLASGVPSRFSGSGSGTDFTLTINSLEAEDAATYYCQQWSSYPHTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	135
hSC27.204v1	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTIKYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	136
hSC27.204v2	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTIQYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	137
hSC27.204v3	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYNPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	138

FIG. 5D Cont.

SUBSTITUTE SHEET (RULE 26)

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.204v4	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	139
hSC27.204v5	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTIKYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	140
hSC27.204v6	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTIQYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	141
hSC27.204v7	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYNPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCTGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	142
hSC27.204v8	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	143
hSC27.204 v9	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTIKYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	144

FIG. 5D Cont.

Anti-CLDN Humanized Antibody Full Length Amino Acid Sequences

Name	Chain	Full Sequence	SEQ ID NO
hSC27.204v10	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTIQYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	145
hSC27.204v11	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYNPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	146
hSC27.204v12	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	147
hSC27.204v13	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTIKYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	148
hSC27.204v14	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTIQYTPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	149
hSC27.204v15	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFDFSRYWMSWVRQAPGKGLEWVSEINPDSSTINYNPSLKARFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGPAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG	150

FIG. 5D Cont.

CDRs of hSC27.1 Light and Heavy Chain Variable Regions
Light Chain
Heavy Chain
Insertion
Unusual residue(<1% of sequences)

FIG. 5E

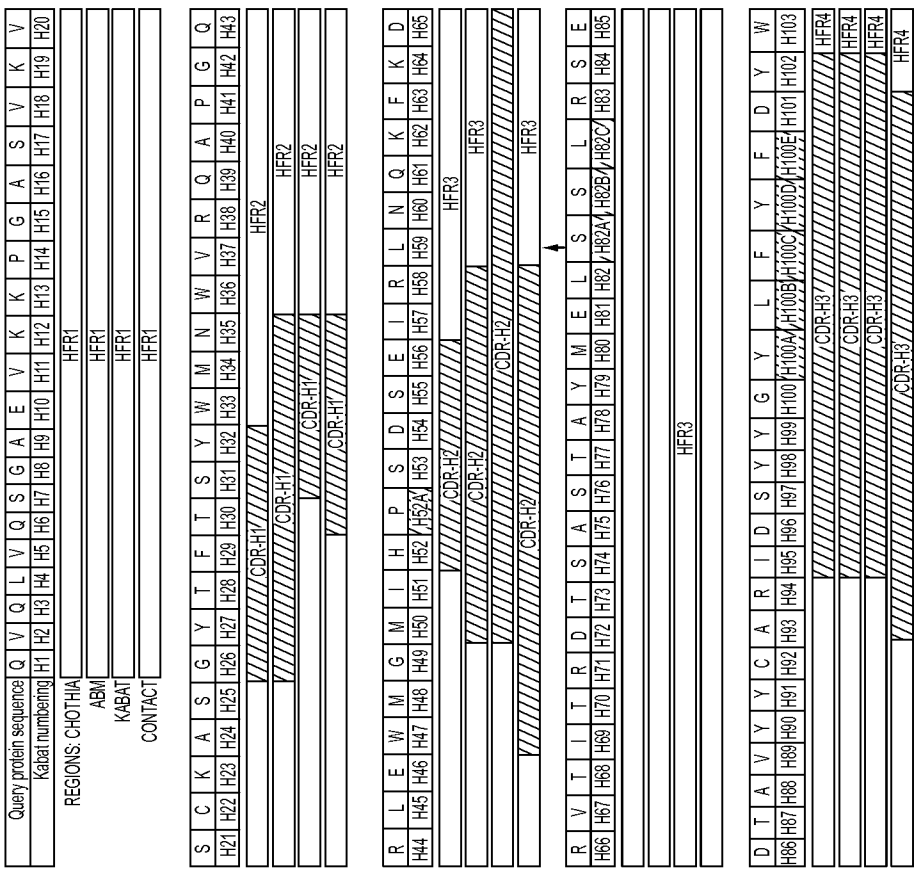
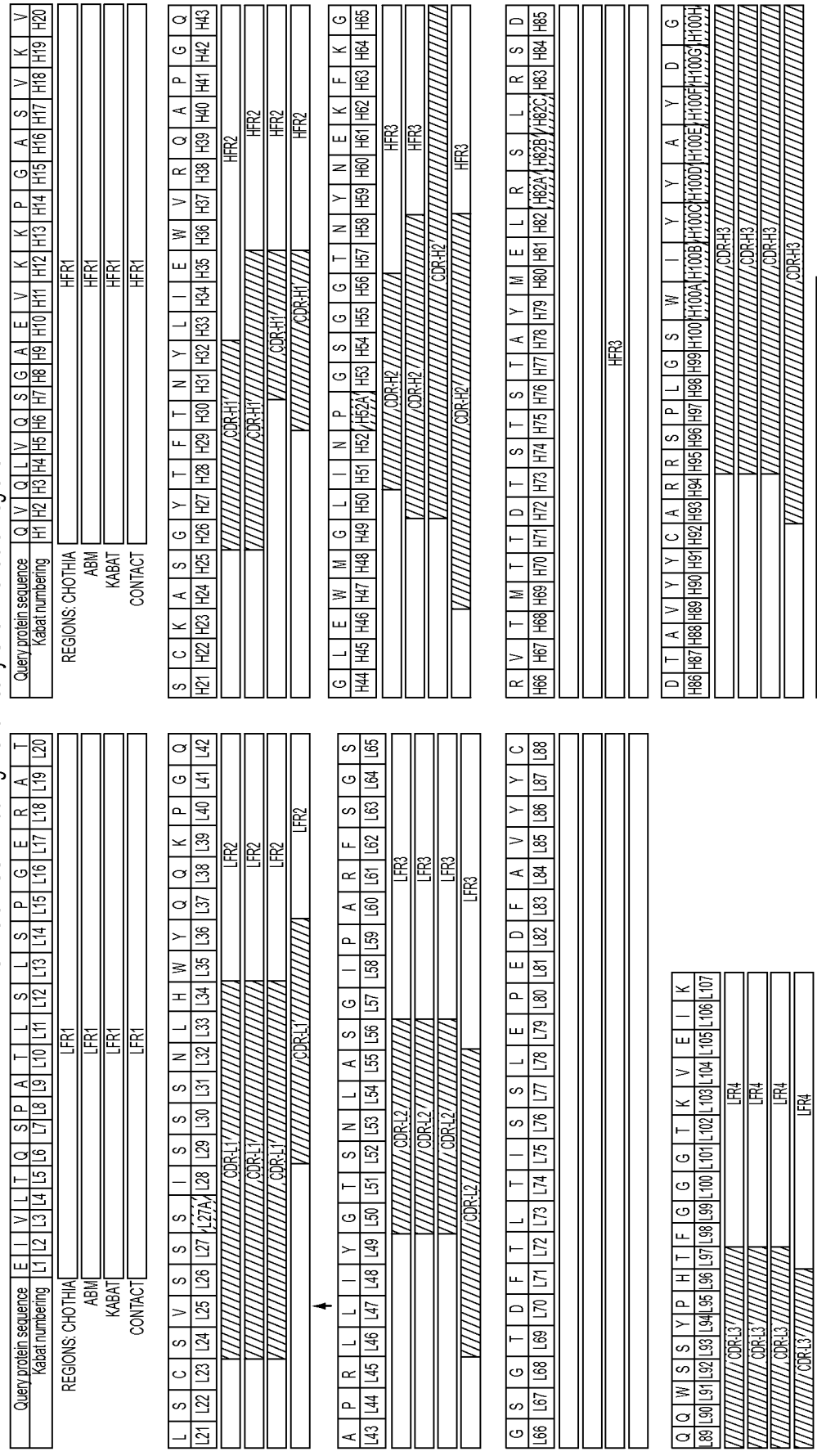
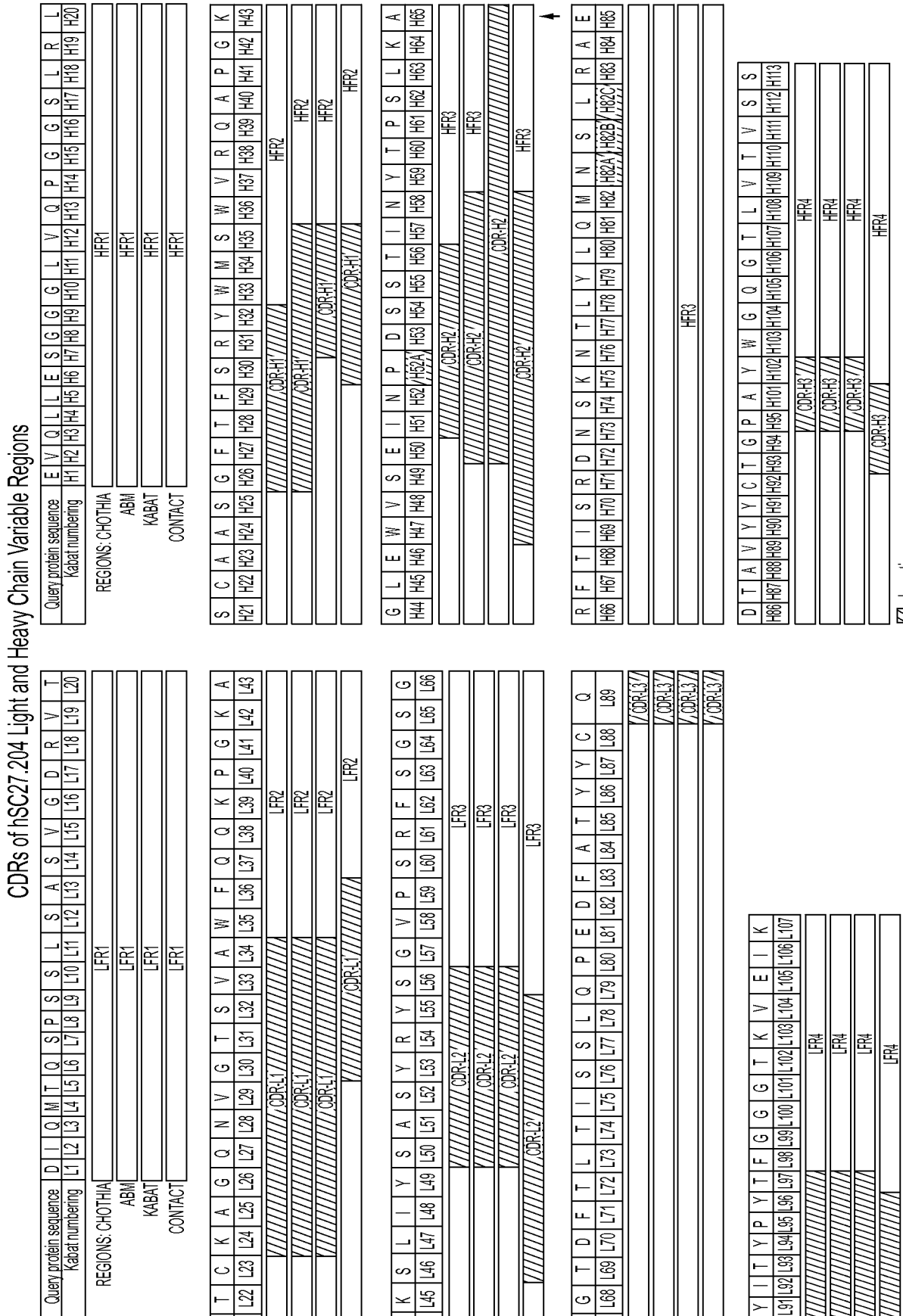

CDRs of hSC27.22 Light and Heavy Chain Variable Regions
Light Chain
Heavy Chain
Insertion
Unusual residue(<1% of sequences)

FIG. 5F


CDRs of hSC27.108 Light and Heavy Chain Variable Regions
Light Chain
Heavy Chain
Insertion
Unusual residue(<1% of sequences)
FIG. 5G


CDRs of hSC27.204 Light and Heavy Chain Variable Regions
Query protein sequence
Kabat numbering
REGIONS: CHOTHIA
ABM
KABAT
CONTACT
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CDR-L1
LFR2
CDR-L2
LFR3
CDR-L3
LFR4
HFR1
CDR-H1
HFR2
CDR-H2
HFR3
CDR-H3
HFR4
Insertion
Unusual residue(<1% of sequences)
Light Chain
Heavy Chain

FIG. 5H

Multireactive Anti-CLDN Antibody Characteristics

	ΔMFI	
	SC27.1	**SC27.22**
hCLDN6	60349	68358
hCLDN9	27276	35051
hCLDN4	59786	10914

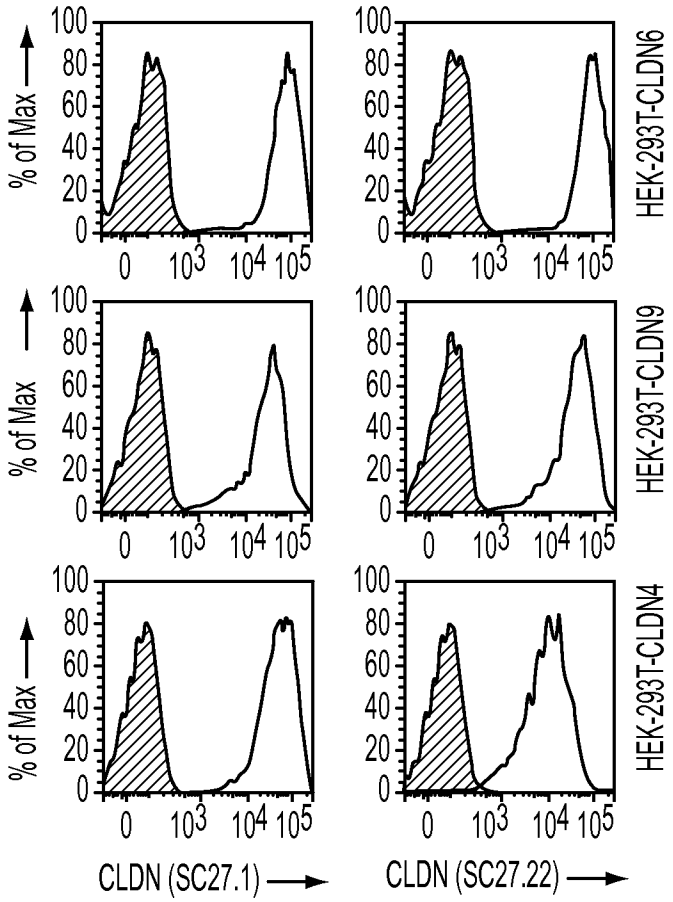


FIG. 6A

Anti-CLDN Antibodies Bind HEK-293T Cells Over-expressing hCLDN6, CLDN4 and CLDN9

Antibody	CLDN6 (MFI)	CLDN4 (MFI)	CLDN9 (MFI)
SC27.102	38709	818	265
SC27.103	99568	75	12118
SC27.104	39175	22618	7227
SC27.105	82961	69	80
SC27.106	55760	1987	595
SC27.108	99745	88	86
SC27.201	29895	23145	7101
SC27.203	47431	2977	587
SC27.204	106271	79	23048
mIgG2b control	84	73	81

FIG. 6B

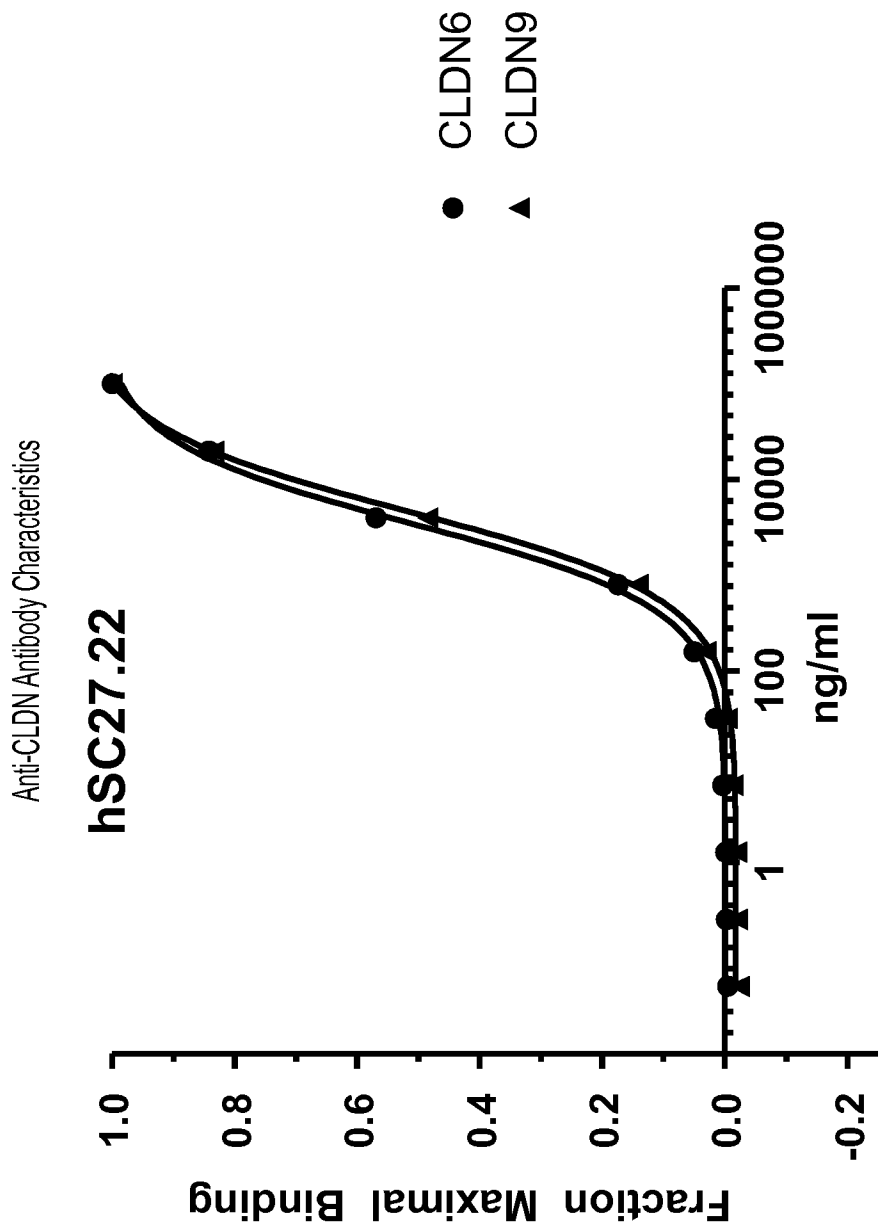

Anti-CLDN Antibody Characteristics
hSC27.22
CLDN6
CLDN9
Fraction Maximal Binding
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
100
10000
1000000
ng/ml

FIG. 6C

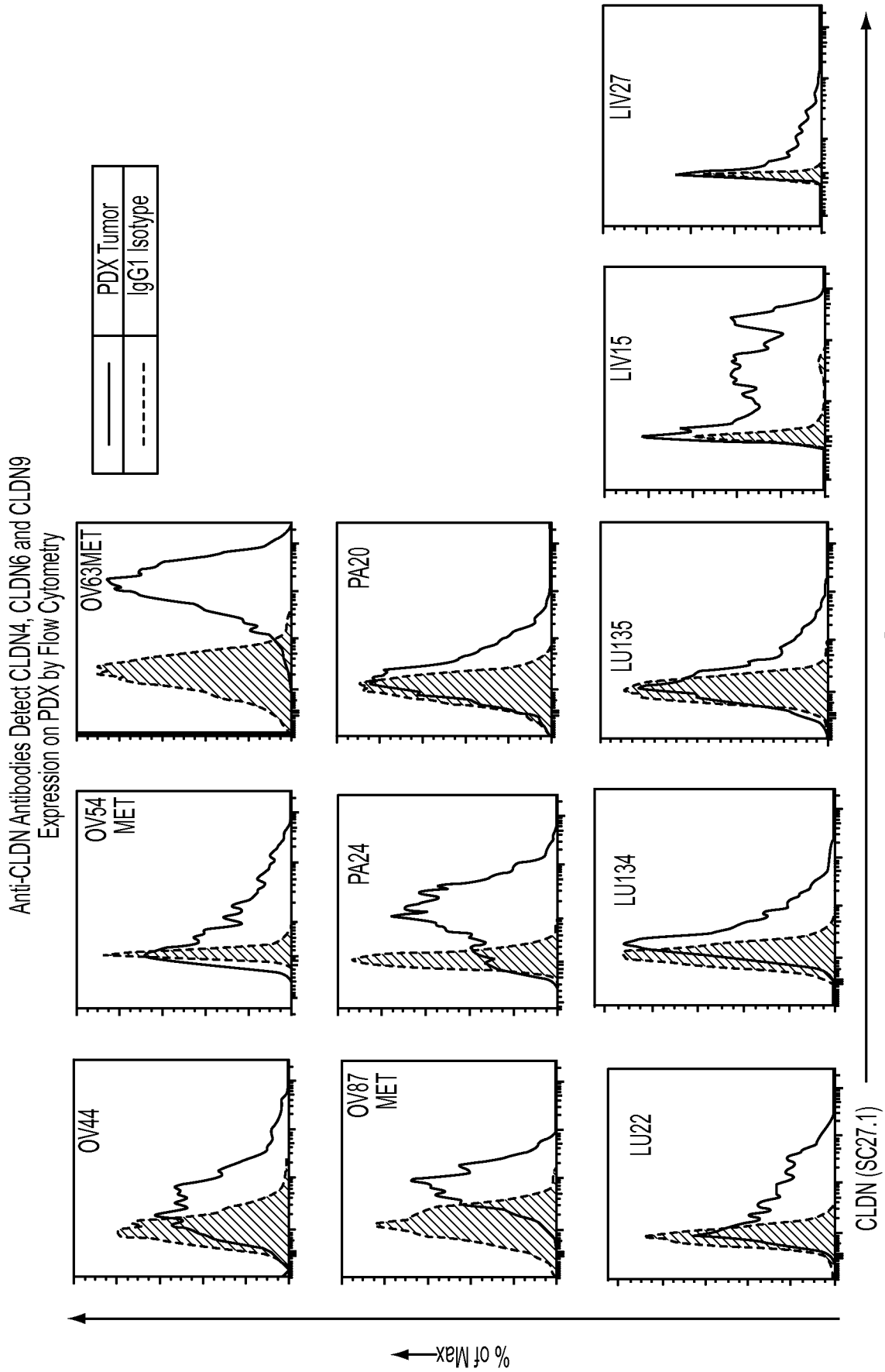
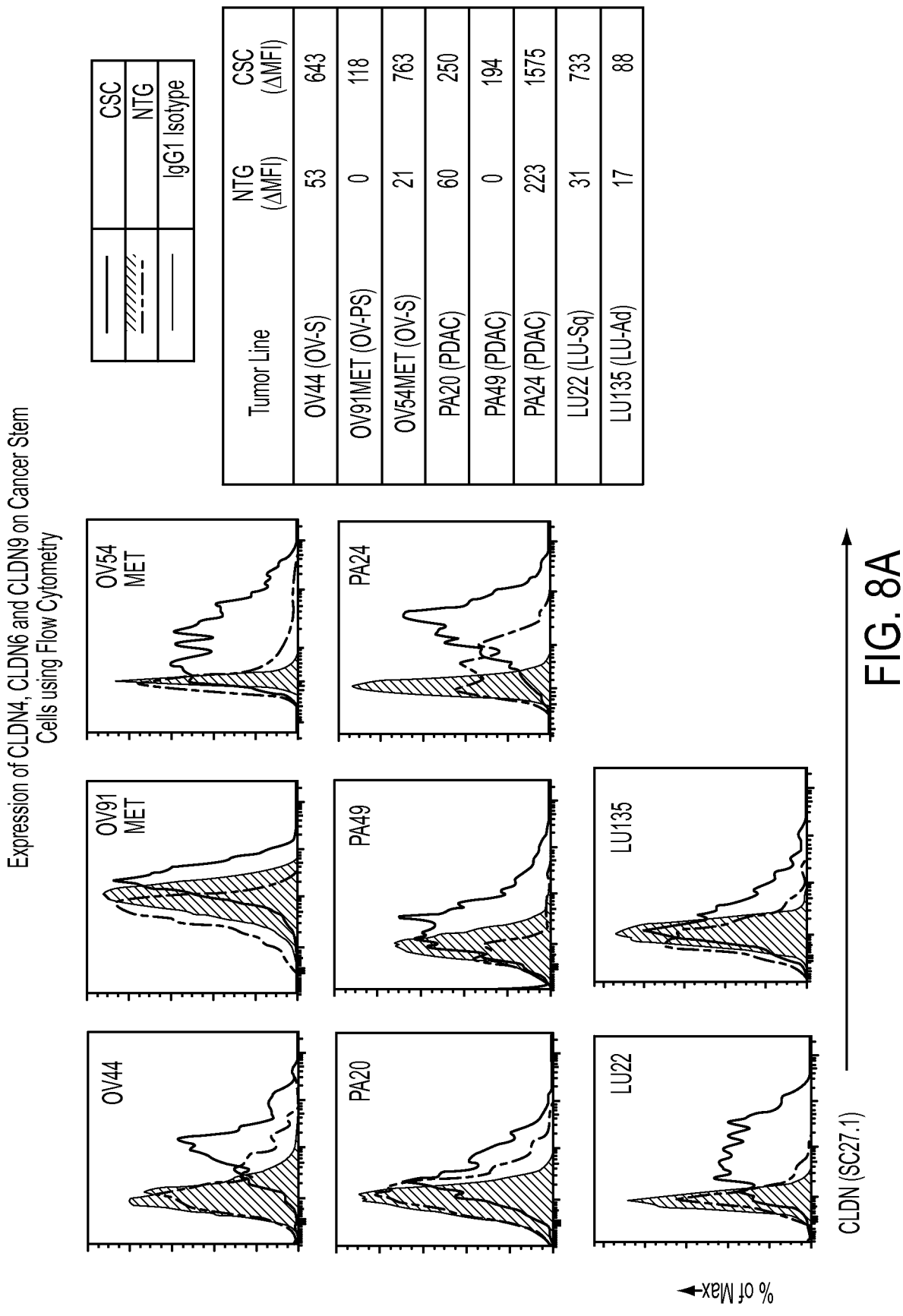

Anti-CLDN Antibodies Detect CLDN4, CLDN6 and CLDN9 Expression on PDX by Flow Cytometry
PDX Tumor
IgG1 Isotype
OV44
OV54 MET
OV63MET
OV87 MET
PA24
PA20
LU22
LU134
LU135
LIV15
LIV27
% of Max
CLDN (SC27.1)

FIG. 7



Tumor Line	NTG (ΔMFI)	CSC (ΔMFI)
OV44 (OV-S)	53	643
OV91MET (OV-PS)	0	118
OV54MET (OV-S)	21	763
PA20 (PDAC)	60	250
PA49 (PDAC)	0	194
PA24 (PDAC)	223	1575
LU22 (LU-Sq)	31	733
LU135 (LU-Ad)	17	88

FIG. 8A

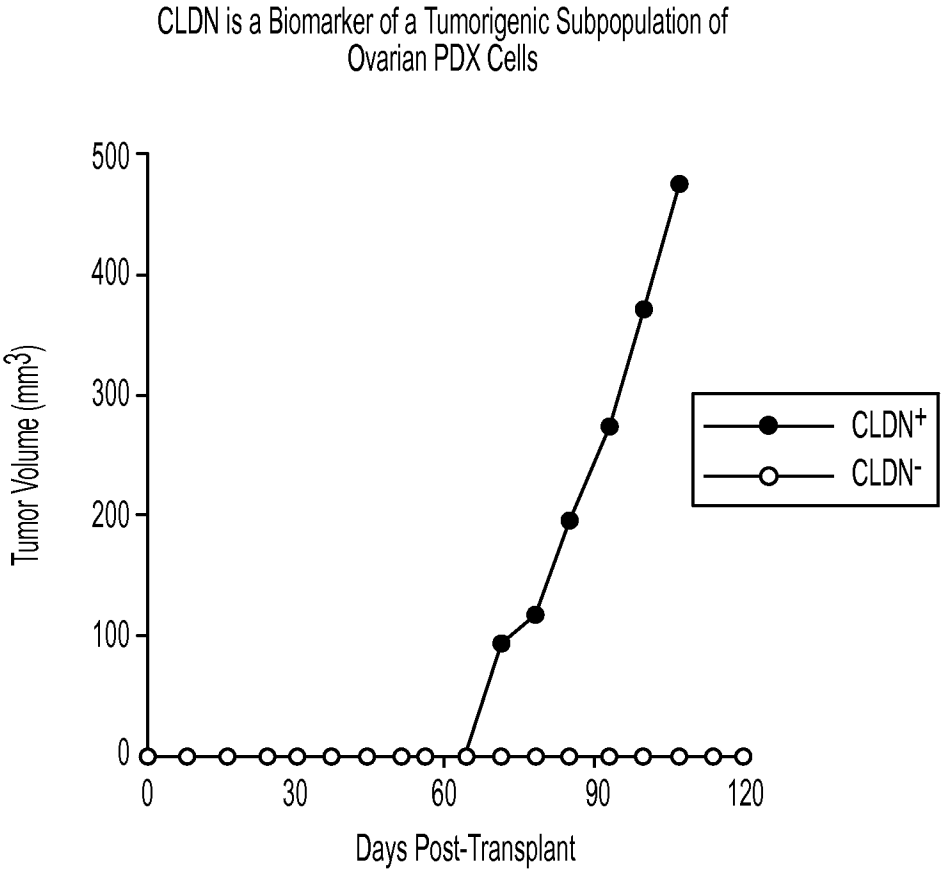

CLDN is a Biomarker of a Tumorigenic Subpopulation of Ovarian PDX Cells
Tumor Volume (mm3)
500
400
300
200
100
0
0
30
60
90
120
Days Post-Transplant
CLDN+
CLDN-

FIG. 8B

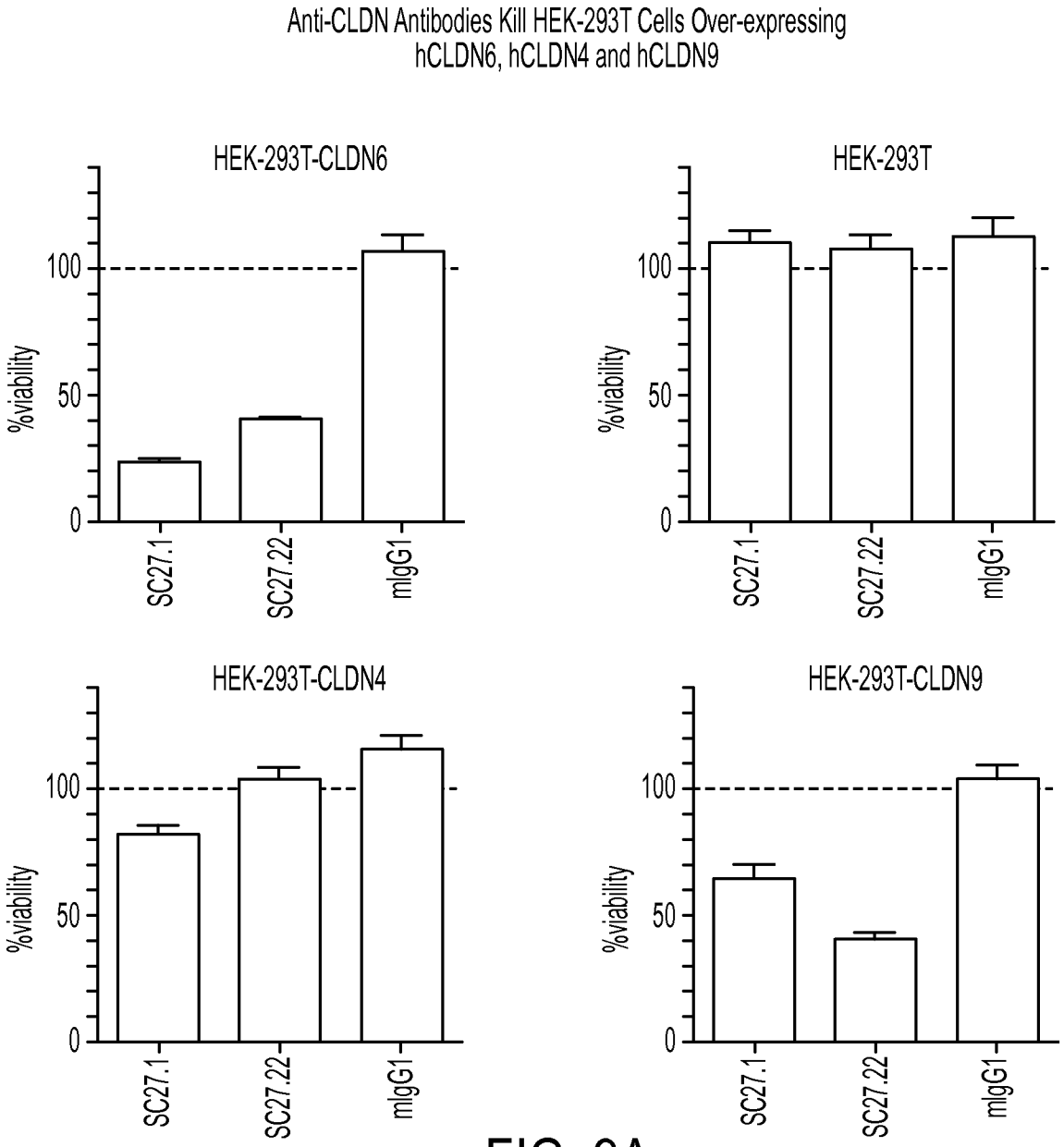

Anti-CLDN Antibodies Kill HEK-293T Cells Over-expressing hCLDN6, hCLDN4 and hCLDN9
HEK-293T-CLDN6
HEK-293T
HEK-293T-CLDN4
HEK-293T-CLDN9
%viability
100
50
0
SC27.1
SC27.22
mIgG1

FIG. 9A

Anti-CLDN Antibodies Kill HEK-293T Cells Over-expressing hCLDN6, hCLDN4 and hCLDN9

Antibody	CLDN6 (IC_{50})	CLDN4 (IC_{50})	CLDN9 (IC_{50})	HEK-T293T-naïve (IC_{50})
SC27.103	57.7	NK	465.9	NK
SC27.104	284.2	969.2	NK	NK
SC27.105	234.9	NK	NK	NK
SC27.108	101.9	NK	NK	NK
SC27.201	48.2	69.7	155.1	NK
SC27.204	25.2	NK	16.9	NK
mIgG1 control	NK	NK	NK	NK

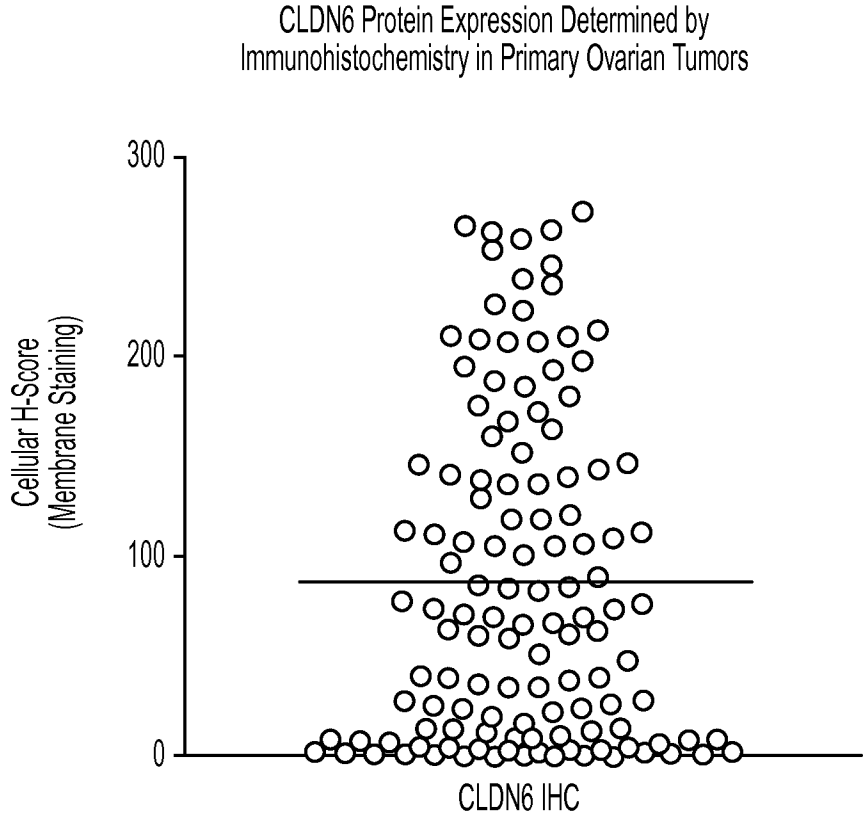
IC_{50} units – nM
NK = no killing

FIG. 9B

CLDN6 Protein Expression Determined by Immunohistochemistry in PDX Tumor Cell Lines

PDX Line	CLDN6
LU123p1	-
LU134p4	++, 90%
LU134p1	+/++, 80%
LU135p3	++, 90%
LU123p2	-
LU141p2	-
BR36p3	++, 90%
BR36p4	++, 90%
OV25p3	++, 70%
OV25p4	++, 70%
OV39p2	++, 70%
OV39p6	++, 80%
OV46p3	++, 90%
OV46p4	++, 90%
OV79p1	++, 20%
OV79p3	++, 30%
OV27p2	+/++, 10%
OV27p3MET	++, 60%
OV27p6MET	++, 30%
OV44p1	+/++, 90%
OV54p1	+, 1%
OV72p3MET	++, 60%
OV78p3	++, 90%
OV87p2MET	++/+++, 90%
OV89p3	++/+++, 20%

FIG. 10A



	H-Score				
	0-15 Negative	16-100 Low	101-200 Medium	201-300 High	Percent Positive
CLDN6 Expression	37	39	32	17	88/125 = 70%

FIG. 10B

SEQUENCE LISTING

<110> Stem CentRx, LLC

<120> NOVEL ANTI-CLAUDIN ANTIBODIES AND METHODS OF USE

<130> sc2701.pct // S69697 1040WO

<150> 61/900,916
<151> 2013-11-06

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<170> PatentIn version 3.5

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20 25 30

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35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
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Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
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275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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Gln Lys Ser Leu Ser Leu Ser Pro Gly
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ggaaatgctc ccaggctctt aatatctggt gcaaccagtt tggaaactgg gactccttca 180

agattcagtg gcagtggatc tggaaaggat tacactctca gtattaccag tcttcggact 240

gaagatgctg ctacttatta ctgtcaacaa tattggagta ctccactcac gttcggtact 300

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20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Thr Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Arg Thr
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Leu
85 90 95

Thr Phe Gly Thr Gly Thr Lys Leu Glu Leu Lys
100 105

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catggaaaga gccttgagtg gattggaggt attaatccta acaatggtga tactatctac 180

aaccagaaat tcaagggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaatat tctgcagtct attactgtgc aagaagggcg 300

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Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Leu His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Asp Thr Ile Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Tyr Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Ile Thr Val Tyr Ala Met Asp Tyr Trp Gly Gln Gly
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caacagaaac caggacagcc acccaaactc ctcatcaagt ttgcatccaa cgtagaatct 180

ggggtccctg ccagattcag tggcagtggg tctgggacag acttcaccct caacatccat 240

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20 25 30

Ser Tyr Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Lys Phe Ala Ser Asn Val Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

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85 90 95

Glu Ile Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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<400> 26
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tcctgcaagg cttctggcta caccttcacc agctactgga tgaactgggt gaagcagagg 120

cctggacaag gccttgaatg gattgccatg attcatcctt ccgatagtga aattaggtta 180

aatcagaagt tcaaggacaa ggccacattg actgtagaca gatcctccag cacagcctac 240

atgcaactca gcagcccgac atctgaggac tctgcggtct attactgtgc aagaattgat 300

agttattatg gttacctgtt ttactttgac tactggggcc aaggcaccac tctcacagtc 360

tcctca 366

<210> 27
<211> 122
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.22 Heavy Chain Variable Region

<400> 27

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Ala Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Arg Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 28
<211> 324
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature

<223> SC27.103 Light Chain Variable Region

<400> 28
caaattgttc tcacccagtc tccagcaatc atgtctgcat ctctagggga acgggtcacc 60

atgacctgca ctgccagctc aagtgtaagt tccagttact tgcactggta ccagcagaag 120

ccaggatcct cccccacact ctggatttat aggacatccg acctggcttc tggagtccca 180

gctcgcttca gtggcagtgg atctgggacc tcttactctc tcacaatcag cagcatggag 240

gctgaagatg ctgccactta ttactgccac cagtatcatc gttccccgtg gacgttcggt 300

ggaggcacca ggctggaaat caaa 324

<210> 29
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.103 Light Chain Variable Region

<400> 29

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Thr Leu Trp
35 40 45

Ile Tyr Arg Thr Ser Asp Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Tyr His Arg Ser Pro
85 90 95

Trp Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 30
<211> 354
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.103 Heavy Chain Variable Region

<400> 30
gaggtccacc tgcaacagtc tggacctgag ctagtgaagc ctggaggttc aatgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt tttaatcctt acaatggtgg tactagttat 180

aaccagaagt tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc aagatgctat 300

aggtacgacg gtcttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 31
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.103 Heavy Chain Variable Region

<400> 31

Glu Val His Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35 40 45

Gly Leu Phe Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Cys Tyr Arg Tyr Asp Gly Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 32
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.104 Light Chain Variable Region

<400> 32
gacatccaga tgacacaatc ttcatcctcc ttttctgtat ctctaggaga cagagtcacc 60

attacttgca aggcaagtga ggacatatat aatcggttag cctggtatca gcagaaacca 120

ggaaatgctc ccaggctctt aatatctggt gcaaccagtt tggaaactgg ggttccttca 180

agattcagtg gcagtggatc tggaaaggat tacactctca gcattaccag tcttcagact 240

gaagatgttg ctacttatta ctgtcaacag tattggagta atcctccgac gttcggtgga 300

ggcaccaagc tggaaatcaa a 321

<210> 33
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.104 Light Chain Variable Region

<400> 33

Asp Ile Gln Met Thr Gln Ser Ser Ser Ser Phe Ser Val Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Asn Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 34
<211> 354
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.104 Heavy Chain Variable Region

<400> 34
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaaga cttctggata cacattcact gaatacaccg tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggaggt gtttatccta agaatggtga tactacctac 180

aaccagaagt tcaggggcaa ggccacattg actgtagaca agtcctccaa cacagcctat 240

atggaactcc gcagcctgac atctgaggat tctgcagtct attactgtac aggaaaggat 300

gggtacgacg ggtttgctta ctggggccaa gggactctgg tcactgtctc tgca 354

<210> 35
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.104 Heavy Chain Variable Region

<400> 35

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Val His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Val Tyr Pro Lys Asn Gly Asp Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Arg Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Lys Asp Gly Tyr Asp Gly Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 36
<211> 318
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.105 Light Chain Variable Region

<400> 36
gatgttcaaa tgacccagtc tccatcctcc ctgtctgcat ctttgggaga gagtctccc 60

ctgacttgcc aggcaagtca gagtgttagc aataatttaa actggtatca gcaaacacca 120

gggaaagctc ctaggctctt gatctatggt gcaagcaaat tggaagatgg ggtctcttca 180

aggttcagtg gcactggata tgggacagat ttcactttca ccatcagcag cctggaggaa 240

gaagatgtgg caacttattt ttgtctacag cataggtatc tgtggacgtt cggtggaggc 300

accaagctgg aaatcaaa 318

<210> 37
<211> 106
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.105 Light Chain Variable Region

<400> 37

Asp Val Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Thr Cys Gln Ala Ser Gln Ser Val Ser Asn Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Lys Leu Glu Asp Gly Val Ser Ser Arg Phe Ser Gly
50 55 60

Thr Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Glu
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His Arg Tyr Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 38
<211> 369
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.105 Heavy Chain Variable Region

<400> 38
gaggtccagc tgcagcagtc tggacctgag ttggtgaagc ctggggcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctactaca tgaactgggt gaagcaaagt 120

cctgaaaaga gccttgagtg gattggagag attaatccta gcactggtag tactacttac 180

aaccagaagt tcaaggccaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagaagggat 300

tattactacg gtagtggttt ctatgctatg gactactggg gtcaaggaac ctcagtcacc 360

gtctcctca 369

<210> 39
<211> 123
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.105 Heavy Chain Variable Region

<400> 39

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser Pro Glu Lys Ser Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Thr Gly Ser Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Ala Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Lys Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Tyr Tyr Gly Ser Gly Phe Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 40
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.106 Light Chain Variable Region

<400> 40
gacatccaga tgacacaatc ttcatcctcc ttttctgtat ctctaggaga cagagtcacc 60

attacttgca aggcaagtga ggacatatat aatcggttag cctggtatca gcagaaacca 120

ggaaatgctc ctaggctctt aatatgtggt gcaaccagtt tggaaactgg ggttccttca 180

agattcagtg gcagtggatc tggaaaggat tacactctca gcattaccag tcttcagact 240

gaagatgttg ctacttatta ctgtcaacag tattggagta ctccgctcac gttcggtgct 300

gggaccaaac tggagctgaa a 321

<210> 41
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.106 Light Chain Variable Region

<400> 41

Asp Ile Gln Met Thr Gln Ser Ser Ser Ser Phe Ser Val Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Cys Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 42
<211> 357
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.106 Heavy Chain Variable Region

<400> 42
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaaga cttctggata cacattcact gaatacacca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggaggt attaatccta acaatggtgg tactaactac 180

aaccagaagt tcaagggcaa ggccacattg actgttgaca agtcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggat tctgcagtct attactgtgc aagaaggctt 300

attacttact atgctatgga ctactggggt caaggaacct cagtcaccgt ctcctca 357

<210> 43
<211> 119
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.106 Heavy Chain Variable Region

<400> 43

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Gly Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Leu Ile Thr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Ser
115

<210> 44
<211> 324
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.108 Light Chain Variable Region

<400> 44
gaaattgtgc tcacccagtc tccagcactc atggctgcat ctccagggga gaaggtcacc 60

atcacctgca gtgtcagctc aagtataagt tccagcaact tgcactggta ccagcagaag 120

tcaggaacct cccccaaact ctggatttat ggcacatcca acctggcttc tggagtccct 180

gttcgcttca gtggcagtgg atctgggacc tcttattctc tcacaatcag caacatggag 240

gctgaagatg ctgccactta ttactgtcaa cagtggagta gttacccaca cacgttcgga 300

gggggggacca agctggaaat aaaa 324

<210> 45
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.108 Light Chain Variable Region

<400> 45

Glu Ile Val Leu Thr Gln Ser Pro Ala Leu Met Ala Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
20 25 30

Asn Leu His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Asn Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95

His Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 46
<211> 378
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.108 Heavy Chain Variable Region

<400> 46
caggtccaaa tgcagcagtc tggagctgag ctggtaaggc ctgggacttc agtgaaggtg 60

tcctgcaagg cttctggata cgccttcact aattacttga tagagtgggt aaagcagagg 120

cctggacagg gccttgagtg gattggactg attaatcctg gaagtggtgg tactaattac 180

aatgagaagt tcaagggcaa ggcaacactg actgcagaca aatcctccac cactgcctac 240

atgcagctca gcagcctgac atctgatgac tctgcggttt atttctgtgc aagacggtcc 300

cctctaggga gttggatcta ctatgcttac gacggtgttg cttactgggg ccaagggact 360

ctggtcactg tctctgca 378

<210> 47
<211> 126
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.108 Heavy Chain Variable Region

<400> 47

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Gln Val Gln Met Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr
            20                  25                  30

Leu Ile Glu Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Arg Ser Pro Leu Gly Ser Trp Ile Tyr Tyr Ala Tyr Asp Gly
            100                 105                 110

Val Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
        115                 120                 125
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<210> 48
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.201 Light Chain Variable Region

<400> 48

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gacatccaga tgacacaatc ttcatcctcc ttttctgtct ctctgggaga cagagtcact       60

attacttgca aggcaagtga ggacatctat aatcggttag cctggtatca acagaaacca      120

ggaaatgctc ctaggctctt aatatctggt gcaaccagtt tggaagctgg ggttccttca      180

ggattcagtg gcagtggatc tggaaaggat tacactctca gcattaccag tcttcagact      240

gaagatgttg ctacttatta ctgtcaacag tattggagta ctcctccgac gttcggtgga      300

ggcaccaagc tggaactcaa g                                                321
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<210> 49
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.201 Light Chain Variable Region

<400> 49

Asp Ile Gln Met Thr Gln Ser Ser Ser Ser Phe Ser Val Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Ala Gly Val Pro Ser Gly Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 50
<211> 360
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.201 Heavy Chain Variable Region

<400> 50
gaggtccagc tgcaacagtc tggacctgaa ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaaga cttctggata cacattcact gaaaacatca gacactgggt gaagcagagc 120

cgaggaaaga gccttgagtg gattggtact attaatccta ataatggtga gactaggtac 180

aatcagaagt tcaagggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240

atggagctcc gcagcctgac atctgaggat tctgcagtct attactgtac aaggggggatt 300

acaaagtccc cttatggtat ggactactgg ggtcaaggaa cctcaatcac cgtctcctca 360

<210> 51
<211> 120
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.201 Heavy Chain Variable Region

<400> 51

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Asn
20 25 30

Ile Arg His Trp Val Lys Gln Ser Arg Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Thr Ile Asn Pro Asn Asn Gly Glu Thr Arg Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Ile Thr Lys Ser Pro Tyr Gly Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Ile Thr Val Ser Ser
115 120

<210> 52
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.203 Light Chain Variable Region

<400> 52
gacatccaga tgacacaatc ttcatcctcc ttttctgtat ctctaggaga cagagtcacc 60

atcacttgca aggcaagtga ggacatatat aatcggttag cctggtatca gcagaatcca 120

ggaaatactc ctaggctctt aatgtctggt gcaaccagtt tggaaactgg ggttccttca 180

agattcagtg gcagtggatc tggaaaggat tacactctca gcattaccag tcttcagatt 240

gaagatgttt ctacttatta ctgtcaacaa tattggagta ctcctccgac gttcggtgga 300

ggcaccaggc tggaaatcaa a 321

<210> 53
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.203 Light Chain Variable Region

<400> 53

Asp Ile Gln Met Thr Gln Ser Ser Ser Ser Phe Ser Val Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

Leu Ala Trp Tyr Gln Gln Asn Pro Gly Asn Thr Pro Arg Leu Leu Met
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Ile
65 70 75 80

Glu Asp Val Ser Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 54
<211> 360
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.203 Heavy Chain Variable Region

<400> 54
gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc agtgaagata 60

tcctgcaaga cttctggata cacattcact gaaaacatca tacactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggaggt attaatccta tcaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctccag cacagcctac 240

atggagctcc gtagcctgac atctgaggat tctgcagtct attactgtgc aaggggggatt 300

actacgtccc cttatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

<210> 55
<211> 120
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE

<223> SC27.203 Heavy Chain Variable Region

<400> 55

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Asn
20 25 30

Ile Ile His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Gly Ile Asn Pro Ile Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ile Thr Thr Ser Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 56
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.204 Light Chain Variable Region

<400> 56
gacattgtga tgacccagtc tcaaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcgcctgca aggccggtca gaatgtgggt actagtgtag cctggtatca acagaaacca 120

ggacattctc ctaaatcact gatttactcg gcatcctacc ggtacagtgg agtccctaat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagactattt ctgtcagcaa tatatcacct atccgtacac gttcggaggg 300

gggaccaagc tggaaataat a 321

<210> 57
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE

<223> SC27.204 Light Chain Variable Region

<400> 57

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Ala Cys Lys Ala Gly Gln Asn Val Gly Thr Ser
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys Ser Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asn Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ile Thr Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Ile
100 105

<210> 58
<211> 336
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<223> SC27.204 Heavy Chain Variable Region

<400> 58
gaggtgaagg ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc 60

tcctgtgcag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

ccagggaaag gcctagaatg gattggagaa attaatccag atagcagtac gataaactat 180

acgccatctc taaaggctaa attcatcatc tccagagaca acgccaaaaa tacgctgtac 240

ctgcaaatga gcaaagtgag atctgaggac acagcccttt attactgtac aggaccagct 300

tactggggcc aagggactct ggtcactgtc tctgca 336

<210> 59
<211> 112
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<223> SC27.204 Heavy Chain Variable Region

<400> 59

Glu Val Lys Val Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
100 105 110

<210> 60
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.1 Light Chain Variable Region

<400> 60
gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgta aggcgagtga ggatatttac aaccggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatggt gcaaccagtt tggaaactgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat tacactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag tattggagta ctccactcac gttcggtcaa 300

gggaccaagc tggagattaa a 321

<210> 61
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 Light Chain Variable Region

<400> 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 62
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.1 Heavy Chain Variable Region

<400> 62
caggtccagc ttgtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg cttctggata caccttcact gagtatactc tgcattgggt gcgccaggcc 120

cccggacaaa ggcttgagtg gatgggaggg atcaacccta acaatggtga cacaatatat 180

aaccagaagt tcaagggcag agtcaccatt accagggaca catccgcgag cacagcctac 240

atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagaagggcg 300

attacggtct atgctatgga ctactggggt caaggtaccc tagtcaccgt ctcgagc 357

<210> 63
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 Heavy Chain Variable Region

<400> 63

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Thr Leu His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Gly Ile Asn Pro Asn Asn Gly Asp Thr Ile Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Ile Thr Val Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 64
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.22 Light Chain Variable Region

<400> 64
gacattgtca tgacccagtc ccctgacagt ttggccgtta gcttggggga gcgtgccacc 60

atcaactgta gggctagtca aactgtttct acatcctcct actcttacat gcattggtat 120

cagcagaaac ctggtcagcc tccaaaactg ctgatttatt tcgcatctaa cgtcgagtcc 180

ggagttcctg accggttcag cggatcagga agcggtacag attttacact taccatctca 240

tctctgcaag cagaagatgt ggccgtgtac tattgtcagc attcctggga gatcccctgg 300

accttcgggc agggaaccaa gctcgagatt aaa 333

<210> 65
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 Light Chain Variable Region

<400> 65

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Thr Val Ser Thr Ser
20 25 30

Ser Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Phe Ala Ser Asn Val Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His Ser Trp
85 90 95

Glu Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 66
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.22 Heavy Chain Variable Region

<400> 66
caggtgcagt tggtgcagag cggcgccgaa gtcaagaaac caggagcttc tgtcaaagtc 60

tcctgtaaag cctccggata taccttcacc agctactgga tgaattgggt aagacaggcc 120

cccggacaga ggcttgagtg gatgggaatg atccatccct ctgacagcga gattcggctc 180

aaccagaagt ttaaagaccg agtgactatc acacgcgata ccagtgctag cacagcctac 240

atggagttga gttctcttcg tagcgaggac actgccgtgt attattgcgc ccgcatcgac 300

tcatattatg gttatctgtt ctacttcgac tattggggcc aggggaccac cgtgactgtg 360

tcttcc 366

<210> 67
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 Heavy Chain Variable Region

<400> 67

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 68
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.108 Light Chain Variable Region

<400> 68
gaaatcgtgc ttacacaatc ccctgccact ctgagccttt ctccaggcga gcgagcaacc 60

ctttcctgca gtgtttcctc ttcaatcagt tccagcaatt tgcactggta ccagcagaag 120

cctggtcagg caccccgatt gttgatctat ggcacatcta acctggccag cggcatccct 180

gctcggttca gtggatctgg ctccggaaca gatttcactc tcactatcag ctcccttgag 240

cctgaagatt ttgccgtgta ctactgtcag caatggagtt cctaccccca cacctttggc 300

ggcgggacaa aggtcgagat aaaa 324

<210> 69
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 Light Chain Variable Region

<400> 69

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
20 25 30

Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95

His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 70
<211> 378

<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.108 Heavy Chain Variable Region

<400> 70
caggtacagc tggtccagtc cggcgctgag gttaagaagc ccggtgcctc cgtgaaggta 60

tcttgtaagg cctcaggtta cacctttaca aattatctga tcgaatgggt gagacaggcc 120

ccaggtcagg gtctggaatg gatgggactc atcaaccctg ggagtggcgg gaccaactac 180

aacgaaaagt ttaaggggag agtgacaatg accacagata ccagtacctc caccgcatat 240

atggagctgc gaagcttgag gtccgatgac actgctgtgt actattgcgc ccgtagaagc 300

ccactcgggt cttggatcta ttacgcatac gatggtgtgg cctattgggg ccagggcacc 360

ctggtgacag tcagctcc 378

<210> 71
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 Heavy Chain Variable Region

<400> 71

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Leu Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Pro Leu Gly Ser Trp Ile Tyr Tyr Ala Tyr Asp Gly
100 105 110

Val Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 72
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204 Light Chain Variable Region

<400> 72
gacatccaga tgacccagtc cccctccagc ctgtctgctt ccgtgggcga cagagtgacc 60

atcacatgca aggccggcca gaacgtgggc acctctgtgg cctggttcca gcagaagcct 120

ggcaaggccc ccaagtccct gatctactcc gcctcctaca gatactccgg cgtgccctcc 180

agattctccg gctctggctc tggcaccgac tttaccctga ccatcagctc cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag tacatcacct acccctacac cttcggcgga 300

ggcaccaagg tggaaatcaa g 321

<210> 73
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 Light Chain Variable Region

<400> 73

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Gly Gln Asn Val Gly Thr Ser
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Thr Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 74
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204 Heavy Chain Variable Region

<400> 74
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 75
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 Heavy Chain Variable Region

<400> 75

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 76
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.108v1 Light Chain Variable Region

<400> 76
gaaatcgtgc tgactcagtc tcccgatttc agtccgtca cacccaagga gaaagtcacc 60

atcacttgtt ctgtctcctc aagcatctct tctagtaacc tgcactggta tcagcagaag 120

cctgatcagt cccctaagct ttggatatac ggcacctcaa acctcgcctc cggagttcct 180

tcaaggtttt caggtagtgg atctggaacc gatttcaccc ttacaataaa cagtcttgag 240

gccgaggacg ccgccactta ctactgccag cagtggagtt cttaccccca cacatttggg 300

ggcggcacca aagtggagat caaa 324

<210> 77
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108v1 Light Chain Variable Region

<400> 77

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
20 25 30

Asn Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
85 90 95

His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 78
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.22-VH1-8 Heavy Chain Variable Region

<400> 78
caggtgcagc tggtgcagtc tggcgccgaa gtgaagaaac ctggcgcctc cgtgaaggtg 60

tcctgcaagg cctccggcta cacctttacc agctactgga tgaactgggt gcgacaggct 120

accggccagg gcctggaatg gatgggcatg atccacccct ccgactccga gatccggctg 180

aaccagaaat tcaaggacag agtgaccatg acccggaaca cctccatctc caccgcctac 240

atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc ccggatcgac 300

tcctactacg gctacctgtt ctacttcgac tactggggcc agggcaccac cgtgaccgtg 360

tcatct 366

<210> 79
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22-VH1-8 Heavy Chain Variable Region

<400> 79

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 80
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.22-VH1-46 Heavy Chain Variable Region

<400> 80
caggtgcagc tggtgcagtc tggcgccgaa gtgaagaaac ctggcgcctc cgtgaaggtg 60

tcctgcaagg cctccggcta cacctttacc agctactgga tgaactgggt gcgacaggcc 120

cctggacagg gcctggaatg gatgggcatg atccaccct ccgactccga gatccggctg 180

aaccagaaat tcaaggaccg cgtgaccatg accagagaca cctccaccag caccgtgtac 240

atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc ccggatcgac 300

tcctactacg gctacctgtt ctacttcgac tactggggcc agggcaccac cgtgaccgtg 360

tcatct 366

<210> 81
<211> 122
<212> PRT
<213> Artificial Sequence

<220>

<223> hSC27.22-VH1-46 Heavy Chain Variable Region

<400> 81

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 82
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.22-VH1-69 Heavy Chain Variable Region

<400> 82
caggtgcagc tggtgcagtc tggcgccgaa gtgaagaaac ccggctcctc cgtgaaggtg 60

tcctgcaagg cttccggcgg caccttctcc agctactgga tgaactgggt gcgacaggcc 120

cctggacagg gcctggaatg gatgggcatg atccaccccct ccgactccga gatccggctg 180

aaccagaaat tcaaggacag agtgaccatc accgccgacg agtccacctc caccgcctac 240

atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc ccggatcgac 300

tcctactacg gctacctgtt ctacttcgac tactggggcc agggcaccac cgtgaccgtg 360

tcatct 366

<210> 83
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22-VH1-69 Heavy Chain Variable Region

<400> 83

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 84
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v1 Heavy Chain Variable Region

<400> 84
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 85
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v1 Heavy Chain Variable Region

<400> 85

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 86
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v2 Heavy Chain Variable Region

<400> 86
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catccagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 87
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v2 Heavy Chain Variable Region

<400> 87

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 88
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v3 Heavy Chain Variable Region

<400> 88
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

aaccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 89
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v3 Heavy Chain Variable Region

<400> 89

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 90
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v4 Heavy Chain Variable Region

<400> 90
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 91
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v4 Heavy Chain Variable Region

<400> 91

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 92
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v5 Heavy Chain Variable Region

<400> 92
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 93
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v5 Heavy Chain Variable Region

<400> 93

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 94
<211> 336
<212> DNA
<213> Artificial Sequence

<220>

<223> hSC27.204v6 Heavy Chain Variable Region

<400> 94
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catccagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 95
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v6 Heavy Chain Variable Region

<400> 95

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 96
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v7 Heavy Chain Variable Region

<400> 96
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

aaccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtac cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 97
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v7 Heavy Chain Variable Region

<400> 97

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 98
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v8 Heavy Chain Variable Region

<400> 98
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 99
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v8 Heavy Chain Variable Region

<400> 99

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 100
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v9 Heavy Chain Variable Region

<400> 100
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 101
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v9 Heavy Chain Variable Region

<400> 101

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 102
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v10 Heavy Chain Variable Region

<400> 102
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catccagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 103
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v10 Heavy Chain Variable Region

<400> 103

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 104
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v11 Heavy Chain Variable Region

<400> 104
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt caccttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

aaccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 105
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v11 Heavy Chain Variable Region

<400> 105

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 106
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v12 Heavy Chain Variable Region

<400> 106
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 107
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v12 Heavy Chain Variable Region

<400> 107

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 108
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v13 Heavy Chain Variable Region

<400> 108
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 109
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v13 Heavy Chain Variable Region

<400> 109

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 110
<211> 336

<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v14 Heavy Chain Variable Region Variable Region

<400> 110
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catccagtac 180

acccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 111
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v14 Heavy Chain Variable Region

<400> 111

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 112
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> hSC27.204v15 Heavy Chain Variable Region

<400> 112
gaagtgcagc tgctggaatc tggcggcgga ctggtgcagc ctggcggatc tctgagactg 60

tcttgtgccg cctccggctt cgacttctcc cggtactgga tgtcctgggt gcgacaggct 120

cctggcaagg gcctggaatg ggtgtccgag atcaaccccg actcctccac catcaactac 180

aaccccagcc tgaaggcccg gttcaccatc tctcgggaca actccaagaa caccctgtac 240

ctgcagatga actccctgcg ggccgaggac accgccgtgt actactgtgc cggccctgct 300

tattggggcc agggcaccct cgtgaccgtg tcctct 336

<210> 113
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v15 Heavy Chain Variable Region

<400> 113

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

<210> 114
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 Light Chain

<400> 114

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Glu Asp Ile Tyr Asn Arg
20 25 30

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Thr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210>  115
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.1 Heavy Chain

<400>  115

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
            20                  25                  30

Thr Leu His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45
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Gly Gly Ile Asn Pro Asn Asn Gly Asp Thr Ile Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Ala Ile Thr Val Tyr Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320
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Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210>  116
<211>  218
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 Light Chain

<400>  116

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Thr Val Ser Thr Ser
            20                  25                  30

Ser Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Phe Ala Ser Asn Val Glu Ser Gly Val Pro Asp
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65                  70                  75                  80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His Ser Trp
                85                  90                  95
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Glu Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110


Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125


Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140


Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190


His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  117
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 Heavy Chain

<400>  117

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45


Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110
```

```
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445


Ser Pro Gly
    450


<210>  118
<211>  215
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.108 Light Chain

<400>  118

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
            20                  25                  30


Asn Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
                85                  90                  95


His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110


Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125


Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140
```

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 119
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 Heavy Chain

<400> 119

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Leu Ile Glu Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Pro Leu Gly Ser Trp Ile Tyr Tyr Ala Tyr Asp Gly
100 105 110

Val Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

```
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
                165                 170                 175

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
            180                 185                 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
        195                 200                 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
    210                 215                 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225                 230                 235                 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
                245                 250                 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            260                 265                 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        275                 280                 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    290                 295                 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305                 310                 315                 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                325                 330                 335

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            340                 345                 350

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
        355                 360                 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    370                 375                 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385                 390                 395                 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                405                 410                 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            420                 425                 430
```

```
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        435                 440                 445


Ser Leu Ser Leu Ser Pro Gly
    450                 455


<210>  120
<211>  214
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204 Light Chain

<400>  120

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Lys Ala Gly Gln Asn Val Gly Thr Ser
            20                  25                  30


Val Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45


Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Thr Tyr Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110


Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125


Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190
```

```
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210>  121
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204 Heavy Chain

<400>  121

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205
```

```
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 122
<211> 451
<212> PRT
<213> Artificial Sequence

<220>

<223> hSC27.22ss1 Heavy Chain

<400> 122

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255
```

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270


His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285


Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300


Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320


Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335


Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350


Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445


Ser Pro Gly
    450


<210>  123
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22-VH1-8 Heavy Chain

<400>  123

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
```

```
Trp Met Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300
```

```
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210>  124
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22-VH1-46 Heavy Chain

<400>  124

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335
```

```
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly
    450


<210>  125
<211>  451
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22-VH1-69 Heavy Chain

<400>  125

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110
```

```
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445


Ser Pro Gly
    450


<210>  126
<211>  447
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 IgG2 Heavy Chain

<400>  126

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45


Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125


Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140
```

```
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
    210                 215                 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415
```

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 127
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 IgG4 R409K Heavy Chain

<400> 127

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 128
<211> 448
<212> PRT
<213> Artificial Sequence

<220>

<223> hSC27.22 IgG4 S228P Heavy Chain

<400> 128

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255
```

```
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445


<210>  129
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 IgG4 S228P K370E R409K Heavy Chain

<400>  129

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45
```

```
Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320
```

```
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445


<210>  130
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 IgG4 K370E Heavy Chain

<400>  130

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365
```

```
Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445


<210>  131
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 IgG4 S228P K370E Heavy Chain

<400>  131

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160
```

```
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430
```

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

<210> 132
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 IgG4 C127S S228P Heavy Chain

<400> 132

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

```
His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445
```

<210> 133
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 IgG4 C127S K370E Heavy Chain

<400> 133

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270
```

```
Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445


<210>  134
<211>  448
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.22 IgG4 C127S S228P K370E Heavy Chain

<400>  134

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45
```

```
Gly Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320
```

```
Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Glu Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445


<210>  135
<211>  215
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.108v1 Heavy Chain

<400>  135

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Ser Val Ser Ser Ser Ile Ser Ser Ser
            20                  25                  30

Asn Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Trp
        35                  40                  45

Ile Tyr Gly Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu
65                  70                  75                  80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro
                85                  90                  95

His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110
```

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 136
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v1 Heavy Chain

<400> 136

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
50 55 60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105 110

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380
```

```
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400


Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430


Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  137
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v2 Heavy Chain

<400>  137

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 138
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v3 Heavy Chain

<400> 138

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220
```

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  139
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v4 Heavy Chain

<400>  139

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  140
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v5 Heavy Chain

<400>  140

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
    50                  55                  60
```

```
Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335
```

```
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350


Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365


Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400


Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430


Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  141
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v6 Heavy Chain

<400>  141

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125
```

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400
```

```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430


Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  142
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v7 Heavy Chain

<400>  142

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175
```

```
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 143
<211> 441
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v8 Heavy Chain

<400> 143

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220


Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240
```

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  144
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v9 Heavy Chain

<400>  144

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285
```

```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  145
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v10 Heavy Chain

<400>  145

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350
```

```
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  146
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v11 Heavy Chain

<400>  146

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125
```

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Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400
```

```
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430


Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  147
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v12 Heavy Chain

<400>  147

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190
```

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440
```

<210> 148
<211> 441

<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v13 Heavy Chain

<400> 148

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30


Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu
    50                  55                  60


Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110


Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220


Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240
```

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  149
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v14 Heavy Chain

<400>  149

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30
```

```
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300
```

```
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  150
<211>  441
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.204v15 Heavy Chain

<400>  150

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ala Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Pro Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            100                 105                 110

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        115                 120                 125

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    130                 135                 140

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
145                 150                 155                 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                165                 170                 175

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            180                 185                 190

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        195                 200                 205

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
            340                 345                 350
```

```
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
        355                 360                 365


Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400


Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
                405                 410                 415


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430


Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440


<210>  151
<211>  11
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.1 CDRL1

<400>  151

Lys Ala Ser Glu Asp Ile Tyr Asn Arg Leu Ala
1               5                   10


<210>  152
<211>  7
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.1 CDRL2

<400>  152

Gly Ala Thr Ser Leu Glu Thr
1               5


<210>  153
<211>  9
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  hSC27.1 CDRL3

<400>  153

Gln Gln Tyr Trp Ser Thr Pro Leu Thr
1               5


<210>  154
<211>  5
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<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 CDRH1

<400> 154

Glu Tyr Thr Leu His
1 5

<210> 155
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 CDRH2

<400> 155

Gly Ile Asn Pro Asn Asn Gly Asp Thr Ile Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 156
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.1 CDRH3

<400> 156

Arg Ala Ile Thr Val Tyr Ala Met Asp Tyr
1 5 10

<210> 157
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRL1

<400> 157

Arg Ala Ser Gln Thr Val Ser Thr Ser Ser Tyr Ser Tyr Met His
1 5 10 15

<210> 158
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRL2

<400> 158

Phe Ala Ser Asn Val Glu Ser
1 5

<210> 159
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRL3

<400> 159

Gln His Ser Trp Glu Ile Pro Trp Thr
1 5

<210> 160
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRH1

<400> 160

Ser Tyr Trp Met Asn
1 5

<210> 161
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRH2

<400> 161

Met Ile His Pro Ser Asp Ser Glu Ile Arg Leu Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> 162
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.22 CDRH3

<400> 162

Ile Asp Ser Tyr Tyr Gly Tyr Leu Phe Tyr Phe Asp Tyr
1 5 10

<210> 163
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRL1

<400> 163

Ser Val Ser Ser Ser Ile Ser Ser Ser Asn Leu His
1 5 10

<210> 164
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRL2

<400> 164

Gly Thr Ser Asn Leu Ala Ser
1 5

<210> 165
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRL3

<400> 165

Gln Gln Trp Ser Ser Tyr Pro His Thr
1 5

<210> 166
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRH1

<400> 166

Asn Tyr Leu Ile Glu
1 5

<210> 167
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRH2

<400> 167

Leu Ile Asn Pro Gly Ser Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> 168
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.108 CDRH3

<400> 168

Arg Ser Pro Leu Gly Ser Trp Ile Tyr Tyr Ala Tyr Asp Gly Val Ala
1 5 10 15

Tyr

<210> 169
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 CDRL1

<400> 169

Lys Ala Gly Gln Asn Val Gly Thr Ser Val Ala
1 5 10

<210> 170
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 CDRL2

<400> 170

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 171
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 CDRL3

<400> 171

Gln Gln Tyr Ile Thr Tyr Pro Tyr Thr
1 5

<210> 172
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> hSC27.204 CDRH1

<400> 172

Arg Tyr Trp Met Ser
1 5

<210> 173
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 CDRH2

<400> 173

Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Thr Pro Ser Leu Lys
1 5 10 15

Ala

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204 CDRH3

<400> 174

Pro Ala Tyr
1

<210> 175
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v1, hSC27.204v5 and hSC27.405v13 CDRH2

<400> 175

Glu Ile Asn Pro Asp Ser Ser Thr Ile Lys Tyr Thr Pro Ser Leu Lys
1 5 10 15

Ala

<210> 176
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v2, hSC27.204v6 and hSC27.405v14 CDRH2

<400> 176

Glu Ile Asn Pro Asp Ser Ser Thr Ile Gln Tyr Thr Pro Ser Leu Lys
1 5 10 15

Ala

<210> 177
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> hSC27.204v3, hSC27.204v7 and hSC27.405v15 CDRH2

<400> 177

Glu Ile Asn Pro Asp Ser Ser Thr Ile Asn Tyr Asn Pro Ser Leu Lys
1 5 10 15

Ala

<210> 178
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Codon optimized hSC27.22ss1 full length HC DNA

<400> 178
caagtgcagc tcgtccagtc cggtgccgaa gtcaagaagc cgggcgcatc agtgaaagtg 60

tcgtgcaaag cctccgggta caccttcacc tcatactgga tgaactgggt ccgccaagcc 120

ccgggacaga gactggagtg gatgggcatg attcacccat ccgattccga gatccggctg 180

aaccagaagt tcaaggaccg cgtgaccatc acccgggaca ccagcgccag cactgcctac 240

atggaattga gctcgctgcg gtccgaggat accgctgtgt actattgcgc gaggatcgac 300

tcctactacg gctacctttt ctacttcgac tactggggac aagggacgac cgtgactgtg 360

tcgagc 366